Tricyclic Quinolone BCL6 Bifunctional Degraders

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application Serial Nos. 63/580,207, filed September 1, 2023; 63/607,009, filed December 6, 2023; 63/572,811, filed April 1, 2024; and 63/665,613, filed June 28, 2024; each of which is hereby incorporated by reference in its entirety.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in XML format and is hereby incorporated by reference in its entirety. Said XML file, created on August 26, 2024, is named TLS-054WO_SL.xml and is 2,685 bytes in size.

TECHNICAL FIELD

This disclosure provides compounds of Formula (**I**) (e.g., Formula (**I-1**), Formula (**I-2**), Formula (**I-a**) (e.g., Formula (**I-a-1**), (**I-a-2**), (**I-a-3**), or (**I-a-4**)), Formula (**I-b**) (e.g., Formula (**I-b-1**), (**I-b-2**), (**I-b-3**), or (**I-b-4**)), Formula (**I-c**) (e.g., Formula (**I-c-1**) or (**I-c-2**)), Formula (**I-d**) (e.g., Formula (**I-d-1**)), or Formula (**I-e**) (e.g., Formula (**I-e-1**) or (**I-e-2**))), Formula (**II**), or Formula (**II-a**) (e.g., Formula (**II-a-1**)), or pharmaceutically acceptable salts thereof, that induce degradation of a BCL6 protein. These compounds are useful, for example, for treating cancer in a subject (e.g., a human). This disclosure also provides compositions containing compounds of Formula (**I**) (e.g., Formula (**I-1**), Formula (**I-2**), Formula (**I-a**) (e.g., Formula (**I-a-1**), (**I-a-2**), (**I-a-3**), or (**I-a-4**)), Formula (**I-b**) (e.g., Formula (**I-b-1**), (**I-b-2**), (**I-b-3**), or (**I-b-4**)), Formula (**I-c**) (e.g., Formula (**I-c-1**) or (**I-c-2**)), Formula (**I-d**) (e.g., Formula (**I-d-1**)), or Formula (**I-e**) (e.g., Formula (**I-e-1**) or (**I-e-2**))), Formula (**II**), or Formula (**II-a**) (e.g., Formula (**II-a-1**)), or pharmaceutically acceptable salts thereof, as well as methods of using and making the same.

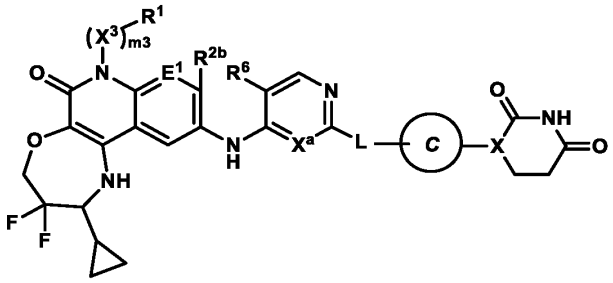
BACKGROUND

B-cell lymphoma 6 (BCL6) protein is a transcriptional repressor involved in the formation and maintenance of germinal centers (GCs) within lymphoid follicles. It controls the

functions of the GC and coordinates the activities of signaling mediators in the maturation of GC B cells. There are over 1000 known or putative BCL6 target genes, including *MYC*, *BCL2*, genes related to DNA damage response (e.g., *ATR*, *TP53*), and cell cycle checkpoint control (e.g., *CDKN1A*, *CDKN1B*). BCL6 is expressed in the dark zone cells of GCs, where somatic hypermutation is allowed to occur to generate high-affinity B-cell receptors. Overexpression or loss of control of BCL6, for example by translocation, can permit maintenance of the pro-hypermutation functions and abrogation of the antitumor functions of BCL6.

SUMMARY

Provided herein are compounds of Formula (**I**):



Formula (**I**)

or pharmaceutically acceptable salts thereof, wherein:

$\mathbf{E^1}$ is $C\mathbf{R^{2a}}$ or N;

$\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are independently selected from the group consisting of: H, halo, cyano, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, and C_{1-3} haloalkoxy;

m3 is 0 or 1;

$\mathbf{X^3}$ is C_{1-3} alkylene optionally substituted with 1-3 $\mathbf{R^c}$;

$\mathbf{R^1}$ is selected from the group consisting of: H, halo, and $\mathbf{R^{b1}}$;

$\mathbf{X^a}$ is selected from the group consisting of: N and $C\mathbf{R^{Xa}}$;

$\mathbf{R^6}$ and $\mathbf{R^{Xa}}$ are independently selected from the group consisting of: H, halo, C_{1-2} alkyl, C_{1-2} haloalkyl, C_{1-2} alkoxy, CN, and C≡CH;

L is $-(\mathbf{L^A})_{n1}-$, wherein:

n1 is an integer from 1 to 5; and

each $\mathbf{L^A}$ is independently selected from the group consisting of: $\mathbf{L^{A1}}$, $\mathbf{L^{A3}}$, and $\mathbf{L^{A4}}$, wherein:

0-2 of $\mathbf{L^A}$ is $\mathbf{L^{A1}}$;

0-2 of $\mathbf{L^A}$ is $\mathbf{L^{A3}}$; and

1-3 of $\mathbf{L^A}$ is $\mathbf{L^{A4}}$,

each $\mathbf{L^{A1}}$ is independently selected from the group consisting of: CH_2, $CH\mathbf{R^L}$, and $C(\mathbf{R^L})_2$, wherein:

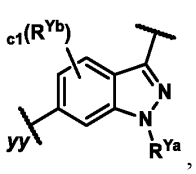
each $\mathbf{R^L}$ is independently selected from the group consisting of: halo, cyano, OH, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -(C_{0-3} alkylene)-(C_{3-5} cycloalkyl), -(C_{0-3} alkylene)-(4-6 membered heterocyclyl), and C_{1-6} alkyl optionally substituted with 1-6 $\mathbf{R^c}$;

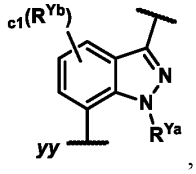
each $\mathbf{L^{A3}}$ is independently selected from the group consisting of: $N(\mathbf{R^d})$, $N(\mathbf{R^b})$, O, $S(O)_{0-2}$, and C(=O);

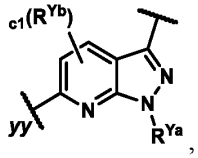
each $\mathbf{L^{A4}}$ is independently selected from the group consisting of:

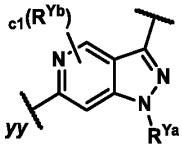
(a) C_{3-15} cycloalkylene or 4-15 membered heterocyclylene, each of which is optionally substituted with 1-6 substituents independently selected from the group consisting of: $\mathbf{R^a}$ and $\mathbf{R^b}$; and

(b) phenylene or 5-6 membered heteroarylene, each of which is optionally substituted with 1-3 substituents independently selected from the group consisting of: $\mathbf{R^a}$ and $\mathbf{R^b}$;

Ring C is selected from the group consisting of: 

, 

, 

, and 

, wherein:

c1 is 0, 1, or 2;

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of $\mathbf{R^a}$ and $\mathbf{R^b}$;

$\mathbf{R^{Ya}}$ is selected from the group consisting of: H, $\mathbf{R^a}$, and $\mathbf{R^b}$; and

yy represents the point of attachment to **L**;

X is CH or N;

each $\mathbf{R^a}$ is independently selected from the group consisting of:

(a) halo;

(b) cyano;

(c) OH;

(d) oxo;

(e) C_{1-6} alkoxy optionally substituted with 1-6 $\mathbf{R^c}$;

(f) $N\mathbf{R^d}\mathbf{R^e}$;

(g) $C(=O)C_{1-6}$ alkyl;

(h) $C(=O)OC_{1-6}$ alkyl;

(i) $C(=O)N(\mathbf{R^f})_2$;

(j) $S(O)_{0-2}(C_{1-6}$ alkyl);

(k) $S(O)_{0-2}(C_{1-6}$ haloalkyl); and

(l) C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, each optionally substituted with 1-6 $\mathbf{R^c}$;

each $\mathbf{R^b}$ is independently selected from the group consisting of: $\mathbf{-(L^b)_b-R^{b1}}$ and $\mathbf{R^{b1}}$, wherein:

each **b** is independently 1, 2, or 3;

each $\mathbf{L^b}$ is independently selected from the group consisting of: O, N(H), $N(C_{1-3}$ alkyl), $S(O)_{0-2}$, C(=O), and C_{1-3} alkylene; and

each $\mathbf{R^{b1}}$ is independently selected from the group consisting of: C_{3-6} cycloalkyl and 4-8 membered heterocyclyl, each of which is optionally substituted with 1-3 $\mathbf{R^g}$;

each $\mathbf{R^c}$ is independently selected from the group consisting of: halo, cyano, OH, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $N\mathbf{R^d}\mathbf{R^e}$, $C(=O)C_{1-6}$ alkyl, $C(=O)OC_{1-6}$ alkyl, $C(=O)N(\mathbf{R^f})_2$, $S(O)_{0-2}(C_{1-6}$ alkyl), and $S(O)_{0-2}(C_{1-6}$ haloalkyl);

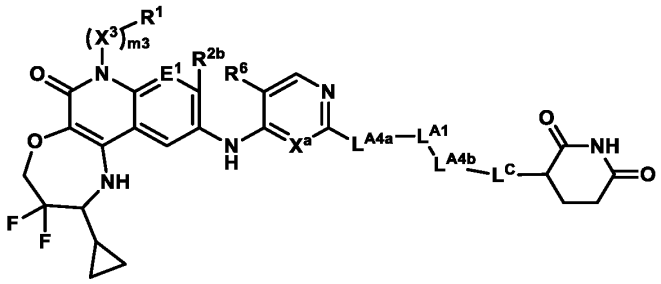
each $\mathbf{R^d}$ and $\mathbf{R^e}$ is independently selected from the group consisting of: H, $C(=O)C_{1-6}$ alkyl, $C(=O)C_{1-6}$ haloalkyl, $C(=O)OC_{1-6}$ alkyl, $C(=O)OC_{1-6}$ haloalkyl, $C(=O)N(\mathbf{R^f})_2$, $S(O)_{1-2}(C_{1-6}$ alkyl), $S(O)_{1-2}(C_{1-6}$ haloalkyl), $S(O)_{1-2}N(\mathbf{R^f})_2$, and C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^h}$;

each $\mathbf{R^f}$ is independently selected from the group consisting of: H and C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^h}$;

each R^g is independently selected from the group consisting of: R^h, oxo, C_{1-3} alkyl, and C_{1-3} haloalkyl; and

each R^h is independently selected from the group consisting of: halo, cyano, OH, -(C_{0-3} alkylene)-C_{1-6} alkoxy, -(C_{0-3} alkylene)-C_{1-6} haloalkoxy, -(C_{0-3} alkylene)-NH_2, -(C_{0-3} alkylene)-N(H)(C_{1-3} alkyl), and –(C_{0-3} alkylene)-N(C_{1-3} alkyl)$_2$.

Also provided herein are compounds of Formula (**II-a**):



Formula (**II-a**)

or pharmaceutically acceptable salts thereof, wherein:

E^1 is CR^{2a} or N;

R^{2a} and R^{2b} are independently selected from the group consisting of: H, halo, cyano, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, and C_{1-3} haloalkoxy;

m3 is 0 or 1;

X^3 is C_{1-3} alkylene optionally substituted with 1-3 R^c;

R^1 is selected from the group consisting of: H, halo, and R^{b1};

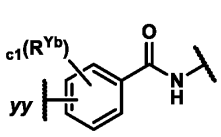
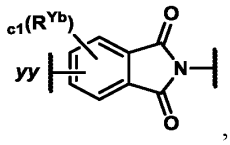
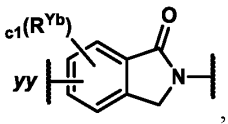
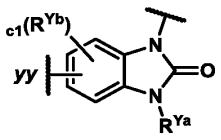
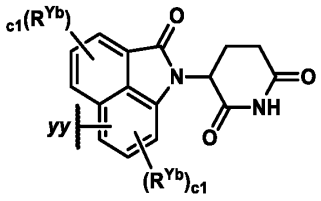
X^a is selected from the group consisting of: N and CR^{Xa};

R^6 and R^{Xa} are independently selected from the group consisting of: H, halo, C_{1-2} alkyl, C_{1-2} haloalkyl, C_{1-2} alkoxy, CN, and C≡CH;

L^{A4a} and L^{A4b} are independently 4-12 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 R^a;

L^{A1} is CH_2, CHR^L, or $C(R^L)_2$, and

each R^L is independently selected from the group consisting of: F, OH, and C_{1-3} alkyl optionally substituted with 1-3 R^c;

$\mathbf{L^C}$ is selected from the group consisting of: , , , , and ;

each **c1** is independently 0, 1, or 2;

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of $\mathbf{R^a}$ and $\mathbf{R^b}$;

$\mathbf{R^{Ya}}$ is selected from the group consisting of: H, $\mathbf{R^a}$, and $\mathbf{R^b}$; and

yy represents the point of attachment to $\mathbf{L^{A4b}}$;

each $\mathbf{R^a}$ is independently selected from the group consisting of:

(a) halo;

(b) cyano;

(c) OH;

(d) oxo;

(e) C_{1-6} alkoxy optionally substituted with 1-6 $\mathbf{R^c}$;

(f) $N\mathbf{R^d}\mathbf{R^e}$;

(g) $C(=O)C_{1-6}$ alkyl;

(h) $C(=O)OC_{1-6}$ alkyl;

(i) $C(=O)N(\mathbf{R^f})_2$;

(j) $S(O)_{0-2}(C_{1-6}$ alkyl);

(k) $S(O)_{0-2}(C_{1-6}$ haloalkyl); and

(l) C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, each optionally substituted with 1-6 $\mathbf{R^c}$;

each $\mathbf{R^b}$ is independently selected from the group consisting of: $\mathbf{-(L^b)_b-R^{b1}}$ and $\mathbf{R^{b1}}$, wherein:

each **b** is independently 1, 2, or 3;

each $\mathbf{L^b}$ is independently selected from the group consisting of: O, N(H), $N(C_{1-3}$ alkyl), $S(O)_{0-2}$, C(=O), and C_{1-3} alkylene; and

each $\mathbf{R^{b1}}$ is independently selected from the group consisting of: C_{3-6} cycloalkyl and 4-8 membered heterocyclyl, each of which is optionally substituted with 1-3 $\mathbf{R^g}$;

each $\mathbf{R^c}$ is independently selected from the group consisting of: halo, cyano, OH, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $N\mathbf{R^d}\mathbf{R^e}$, $C(=O)C_{1-6}$ alkyl, $C(=O)OC_{1-6}$ alkyl, $C(=O)N(\mathbf{R^f})_2$, $S(O)_{0-2}(C_{1-6}$ alkyl), and $S(O)_{0-2}(C_{1-6}$ haloalkyl);

each $\mathbf{R^d}$ and $\mathbf{R^e}$ is independently selected from the group consisting of: H, $C(=O)C_{1-6}$ alkyl, $C(=O)C_{1-6}$ haloalkyl, $C(=O)OC_{1-6}$ alkyl, $C(=O)OC_{1-6}$ haloalkyl, $C(=O)N(\mathbf{R^f})_2$, $S(O)_{1-2}(C_{1-6}$ alkyl), $S(O)_{1-2}(C_{1-6}$ haloalkyl), $S(O)_{1-2}N(\mathbf{R^f})_2$, and C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^h}$;

each $\mathbf{R^f}$ is independently selected from the group consisting of: H and C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^h}$;

each $\mathbf{R^g}$ is independently selected from the group consisting of: $\mathbf{R^h}$, oxo, C_{1-3} alkyl, and C_{1-3} haloalkyl; and

each $\mathbf{R^h}$ is independently selected from the group consisting of: halo, cyano, OH, $-(C_{0-3}$ alkylene)-C_{1-6} alkoxy, $-(C_{0-3}$ alkylene)-C_{1-6} haloalkoxy, $-(C_{0-3}$ alkylene)-NH_2, $-(C_{0-3}$ alkylene)-$N(H)(C_{1-3}$ alkyl), and $-(C_{0-3}$ alkylene)-$N(C_{1-3}$ alkyl)$_2$.

Also provided herein are pharmaceutical compositions comprising a compound of Formula (**I**) (e.g., Formula (**I-1**), Formula (**I-2**), Formula (**I-a**) (e.g., Formula (**I-a-1**), (**I-a-2**), (**I-a-3**), or (**I-a-4**)), Formula (**I-b**) (e.g., Formula (**I-b-1**), (**I-b-2**), (**I-b-3**), or (**I-b-4**)), Formula (**I-c**) (e.g., Formula (**I-c-1**) or (**I-c-2**)), Formula (**I-d**) (e.g., Formula (**I-d-1**)), or Formula (**I-e**) (e.g., Formula (**I-e-1**) or (**I-e-2**))), Formula (**II**), or Formula (**II-a**) (e.g., Formula (**II-a-1**)), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Provided herein are methods for treating cancer in a subject in need thereof, the methods comprising administering to the subject a therapeutically effective amount of a compound of Formula (**I**) (e.g., Formula (**I-1**), Formula (**I-2**), Formula (**I-a**) (e.g., Formula (**I-a-1**), (**I-a-2**), (**I-a-3**), or (**I-a-4**)), Formula (**I-b**) (e.g., Formula (**I-b-1**), (**I-b-2**), (**I-b-3**), or (**I-b-4**)), Formula (**I-c**) (e.g., Formula (**I-c-1**) or (**I-c-2**)), Formula (**I-d**) (e.g., Formula (**I-d-1**)), or Formula (**I-e**) (e.g., Formula (**I-e-1**) or (**I-e-2**))), Formula (**II**), or Formula (**II-a**) (e.g., Formula (**II-a-1**)), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein.

Also provided herein are BCL6 proteins non-covalently bound with a compound of Formula (**I**) (e.g., Formula (**I-1**), Formula (**I-2**), Formula (**I-a**) (e.g., Formula (**I-a-1**), (**I-a-2**), (**I-a-3**), or (**I-a-4**)), Formula (**I-b**) (e.g., Formula (**I-b-1**), (**I-b-2**), (**I-b-3**), or (**I-b-4**)), Formula (**I-c**) (e.g., Formula (**I-c-1**) or (**I-c-2**)), Formula (**I-d**) (e.g., Formula (**I-d-1**)), or Formula (**I-e**) (e.g., Formula (**I-e-1**) or (**I-e-2**))), Formula (**II**), or Formula (**II-a**) (e.g., Formula (**II-a-1**)), or

a pharmaceutically acceptable salt thereof.

Also provided herein are ternary complexes comprising a BCL6 protein, a compound of Formula (**I**) (e.g., Formula (**I-1**), Formula (**I-2**), Formula (**I-a**) (e.g., Formula (**I-a-1**), (**I-a-2**), (**I-a-3**), or (**I-a-4**)), Formula (**I-b**) (e.g., Formula (**I-b-1**), (**I-b-2**), (**I-b-3**), or (**I-b-4**)), Formula (**I-c**) (e.g., Formula (**I-c-1**) or (**I-c-2**)), Formula (**I-d**) (e.g., Formula (**I-d-1**)), or Formula (**I-e**) (e.g., Formula (**I-e-1**) or (**I-e-2**))), Formula (**II**), or Formula (**II-a**) (e.g., Formula (**II-a-1**)), or a pharmaceutically acceptable salt thereof, and a cereblon (CRBN) E3 ligase protein (also referred to herein as a CRBN protein), or a portion thereof.

To facilitate understanding of the disclosure set forth herein, a number of additional terms are provided. Generally, the nomenclature used herein and the laboratory procedures in organic chemistry, medicinal chemistry, and pharmacology described are those well-known and commonly employed in the art. Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Each of the patents, applications, published applications, and other publications that are mentioned throughout the specification and the attached appendices are incorporated herein by reference in their entireties. In the case of conflict between the present disclosure and any content incorporated by reference, the present disclosure controls.

The details of one or more embodiments of the invention are set forth in the accompanying drawings and the description below. Other features and advantages of the invention will be apparent from the description and drawings, and from the claims.

DETAILED DESCRIPTION

This disclosure provides compounds of Formula (**I**) (e.g., Formula (**I-1**), Formula (**I-2**), Formula (**I-a**) (e.g., Formula (**I-a-1**), (**I-a-2**), (**I-a-3**), or (**I-a-4**)), Formula (**I-b**) (e.g., Formula (**I-b-1**), (**I-b-2**), (**I-b-3**), or (**I-b-4**)), Formula (**I-c**) (e.g., Formula (**I-c-1**) or (**I-c-2**)), Formula (**I-d**) (e.g., Formula (**I-d-1**)), or Formula (**I-e**) (e.g., Formula (**I-e-1**) or (**I-e-2**))), Formula (**II**), or Formula (**II-a**) (e.g., Formula (**II-a-1**)), or pharmaceutically acceptable salts thereof, that induce degradation of a BCL6 protein. These compounds are useful, e.g., for treating a cancer. This disclosure also provides compositions containing compounds of Formula (**I**) (e.g., Formula (**I-1**), Formula (**I-2**), Formula (**I-a**) (e.g., Formula (**I-a-1**), (**I-a-2**), (**I-a-3**), or (**I-a-4**)), Formula (**I-b**) (e.g., Formula (**I-b-1**), (**I-b-2**), (**I-b-3**), or (**I-b-4**)), Formula (**I-c**) (e.g., Formula (**I-c-1**) or (**I-c-2**)), Formula (**I-d**) (e.g., Formula (**I-d-1**)), or Formula (**I-e**)

(e.g., Formula (**I-e-1**) or (**I-e-2**))), Formula (**II**), or Formula (**II-a**) (e.g., Formula (**II-a-1**)), or pharmaceutically acceptable salts thereof, as well as methods of using and making the same.

Upon antigen challenge, germinal centers (GCs) are formed in lymphoid follicles, and B-cells in the dark zone of GCs undergo rapid proliferation and somatic hypermutation, both of their immunoglobin variable genes to generate high-affinity B-cell receptors, as well as of other genes including *BCL6*. BCL6 is often considered to be a 'master regulator' of the GC reaction. In some cancers, BCL6 can be mutated, translocated, and/or BCL6 expression can be upregulated. See, e.g., Leeman-Neill and Bhagat, *Expert Opinion on Therapeutic Targets* 22.2 (2018): 143-152, doi: 10.1080/14728222.2018.1420782; Mlynarczyk and Melnick. *Immunological Reviews* 288.1 (2019): 214-239, doi: 10.1111/imr.12755.

The BCL6 protein has multiple domains, including a BTB domain, an RD2 domain, and a DNA binding domain. The N-terminal BTB domain is the site of homodimerization of BCL6, and the interface of the monomers forms the "lateral groove", which is a binding site for endogenous co-repressors of *BCL6*, such as SMRT, NCOR, and BCOR. See, e.g., Cardenas, Mariano G., et al. *Clinical Cancer Research* 23.4 (2017): 885-893, doi: 10.1158/1078-0432.CCR-16-2071.

Compounds that induce degradation of a target protein are sometimes referred to as heterobifunctional compounds, PROTACs, or degraders. Such compounds generally include a moiety that binds to the target protein and a moiety that binds to a ubiquitin E3 ligase (sometimes referred to as an E3 ligase or simply an E3), these two moieties being optionally separated by a linker. To induce degradation, heterobifunctional compounds are believed to induce formation of a ternary complex between the target protein, the compound, and an E3 ligase. Formation of the ternary complex is then followed by ubiquitination of the target protein and degradation of the ubiquitinated target protein by a proteosome. Several E3 ligases have been used as the partner E3 ligase for heterobifunctional degraders. Herein, the cereblon (CRBN) E3 ligase (also referred to herein as a CRBN protein) is used.

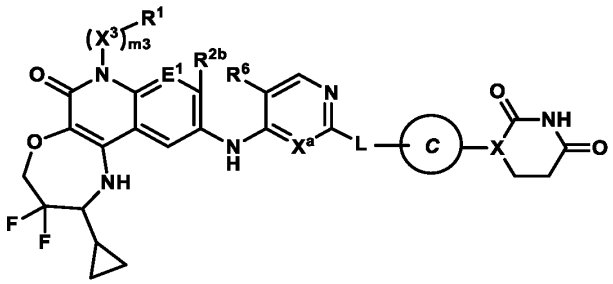
A degradation approach for a target protein can have potential advantages compared to, e.g., small molecule inhibition of the target protein. One potential advantage is that the duration of effect of a heterobifunctional compound is generally based on the resynthesis rate of the target protein. Another potential advantage is that many heterobifunctional compounds are believed to be released from the ubiquitinated target protein-E3 ligase complex and made available for formation of further ternary complexes; this is sometimes referred to as "catalytic" turnover of the heterobifunctional compound. Degradation of a target protein can also be advantageous over small molecule inhibition in some cases, as degradation can impair a

scaffolding function of a target protein, whereas a small molecule might not. It is also generally believed that for formation of a ternary complex, high affinity to the target protein is not always required.

Heterobifunctional compounds are further described in, for example, International Publication Nos. WO 2021/077010; WO 2022/221673; WO 2024/086759; WO 2024/151557; WO 2023/232133; WO 2023/212147; WO 2023/114460; McCoull, William, et al., *ACS Chemical Biology* 13.11 (2018): 3131-3141, doi: 10.1021/acschembio.8b00698; Chamberlain and Hamann, *Nature Chemical Biology* 15.10 (2019): 937-944, doi: 10.1038/s41589-019-0362-y; Li and Song, *Journal of Hematology & Oncology* 13 (2020), doi: 10.1186/s13045-020-00885-3; Wu, et al. *Nature Structural & Molecular Biology* 27.7 (2020): 605-614, doi: 10.1038/s41594-020-0438-0; Dong, et al., *Journal of Medicinal Chemistry* 64.15 (2021): 10606-10620, doi: 10.1021/acs.jmedchem.1c00895; Yang, et al., *Targeted Oncology* 16.1 (2021): 1-12, doi: 10.1007/s11523-020-00782-2.

Compound Embodiments

Provided herein are compounds of Formula (**I**):



Formula (**I**)

or pharmaceutically acceptable salts thereof, wherein:

$\mathbf{E^1}$ is $C\mathbf{R^{2a}}$ or N;

$\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are independently selected from the group consisting of: H, halo, cyano, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, and C_{1-3} haloalkoxy;

m3 is 0 or 1;

$\mathbf{X^3}$ is C_{1-3} alkylene optionally substituted with 1-3 $\mathbf{R^c}$;

$\mathbf{R^1}$ is selected from the group consisting of: H, halo, and $\mathbf{R^{b1}}$;

$\mathbf{X^a}$ is selected from the group consisting of: N and $C\mathbf{R^{Xa}}$;

$\mathbf{R^6}$ and $\mathbf{R^{Xa}}$ are independently selected from the group consisting of: H, halo, C_{1-2} alkyl, C_{1-2} haloalkyl, C_{1-2} alkoxy, CN, and C≡CH;

L is $-(\mathbf{L^A})_{\mathbf{n1}}-$, wherein:

n1 is an integer from 1 to 5; and

each $\mathbf{L^A}$ is independently selected from the group consisting of: $\mathbf{L^{A1}}$, $\mathbf{L^{A3}}$, and $\mathbf{L^{A4}}$, wherein:

0-2 of $\mathbf{L^A}$ is $\mathbf{L^{A1}}$;

0-2 of $\mathbf{L^A}$ is $\mathbf{L^{A3}}$; and

1-3 of $\mathbf{L^A}$ is $\mathbf{L^{A4}}$,

each $\mathbf{L^{A1}}$ is independently selected from the group consisting of: CH_2, $CH\mathbf{R^L}$, and $C(\mathbf{R^L})_2$, wherein:

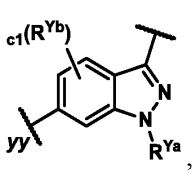
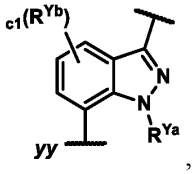
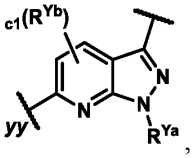
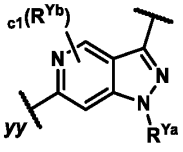
each $\mathbf{R^L}$ is independently selected from the group consisting of: halo, cyano, OH, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -(C_{0-3} alkylene)-(C_{3-5} cycloalkyl), -(C_{0-3} alkylene)-(4-6 membered heterocyclyl), and C_{1-6} alkyl optionally substituted with 1-6 $\mathbf{R^c}$;

each $\mathbf{L^{A3}}$ is independently selected from the group consisting of: $N(\mathbf{R^d})$, $N(\mathbf{R^b})$, O, $S(O)_{0-2}$, and C(=O);

each $\mathbf{L^{A4}}$ is independently selected from the group consisting of:

(a) C_{3-15} cycloalkylene or 4-15 membered heterocyclylene, each of which is optionally substituted with 1-6 substituents independently selected from the group consisting of: $\mathbf{R^a}$ and $\mathbf{R^b}$; and

(b) phenylene or 5-6 membered heteroarylene, each of which is optionally substituted with 1-3 substituents independently selected from the group consisting of: $\mathbf{R^a}$ and $\mathbf{R^b}$;

Ring C is selected from the group consisting of: , , , and , wherein:

c1 is 0, 1, or 2;

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of $\mathbf{R^a}$ and $\mathbf{R^b}$;

$\mathbf{R^{Ya}}$ is selected from the group consisting of: H, $\mathbf{R^a}$, and $\mathbf{R^b}$; and

yy represents the point of attachment to **L**;

X is CH or N;

each $\mathbf{R^a}$ is independently selected from the group consisting of:

(a) halo;

(b) cyano;

(c) OH;

(d) oxo;

(e) C_{1-6} alkoxy optionally substituted with 1-6 $\mathbf{R^c}$;

(f) $N\mathbf{R^d}\mathbf{R^e}$;

(g) $C(=O)C_{1-6}$ alkyl;

(h) $C(=O)OC_{1-6}$ alkyl;

(i) $C(=O)N(\mathbf{R^f})_2$;

(j) $S(O)_{0-2}(C_{1-6}$ alkyl);

(k) $S(O)_{0-2}(C_{1-6}$ haloalkyl); and

(l) C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, each optionally substituted with 1-6 $\mathbf{R^c}$;

each $\mathbf{R^b}$ is independently selected from the group consisting of: $\mathbf{-(L^b)_b-R^{b1}}$ and $\mathbf{R^{b1}}$, wherein:

each **b** is independently 1, 2, or 3;

each $\mathbf{L^b}$ is independently selected from the group consisting of: O, N(H), $N(C_{1-3}$ alkyl), $S(O)_{0-2}$, C(=O), and C_{1-3} alkylene; and

each $\mathbf{R^{b1}}$ is independently selected from the group consisting of: C_{3-6} cycloalkyl and 4-8 membered heterocyclyl, each of which is optionally substituted with 1-3 $\mathbf{R^g}$;

each $\mathbf{R^c}$ is independently selected from the group consisting of: halo, cyano, OH, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $N\mathbf{R^d}\mathbf{R^e}$, $C(=O)C_{1-6}$ alkyl, $C(=O)OC_{1-6}$ alkyl, $C(=O)N(\mathbf{R^f})_2$, $S(O)_{0-2}(C_{1-6}$ alkyl), and $S(O)_{0-2}(C_{1-6}$ haloalkyl);

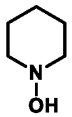
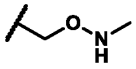
each $\mathbf{R^d}$ and $\mathbf{R^e}$ is independently selected from the group consisting of: H, $C(=O)C_{1-6}$ alkyl, $C(=O)C_{1-6}$ haloalkyl, $C(=O)OC_{1-6}$ alkyl, $C(=O)OC_{1-6}$ haloalkyl, $C(=O)N(\mathbf{R^f})_2$, $S(O)_{1-2}(C_{1-6}$ alkyl), $S(O)_{1-2}(C_{1-6}$ haloalkyl), $S(O)_{1-2}N(\mathbf{R^f})_2$, and C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^h}$;

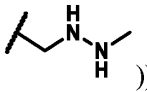
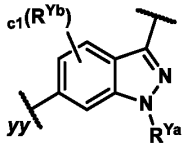
each $\mathbf{R^f}$ is independently selected from the group consisting of: H and C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^h}$;

each $\mathbf{R^g}$ is independently selected from the group consisting of: $\mathbf{R^h}$, oxo, C_{1-3} alkyl, and C_{1-3} haloalkyl; and

each $\mathbf{R^h}$ is independently selected from the group consisting of: halo, cyano, OH, $-(C_{0-3}$ alkylene)-C_{1-6} alkoxy, $-(C_{0-3}$ alkylene)-C_{1-6} haloalkoxy, $-(C_{0-3}$ alkylene)-NH_2, $-(C_{0-3}$ alkylene)-$N(H)(C_{1-3}$ alkyl), and $-(C_{0-3}$ alkylene)-$N(C_{1-3}$ alkyl)$_2$.

Certain combinations of heteroatoms (e.g., N, O, S, or halo) define compounds which are less stable under physiological conditions. Examples include (**1**) compounds containing acetal or animal linkages; (**2**) compounds containing acyclic N-O, N-N, or $N\text{-}S(O)_0$ bonds; and (**3**) compounds containing O-O, $O\text{-}S(O)_{0-2}$, N-halo, O-halo, and $S(O)_{0-2}$-halo bonds. Accordingly, such compounds are less preferred.

As used herein, "acyclic bonds" mean chemical bonds that are not part of a ring. Examples include the N-O bond in  and . For avoidance of doubt, acyclic N-O, N-N, or $N\text{-}S(O)_0$ bonds (i.e., those bonds that are not part of a ring (e.g., in  or


)) are less preferred, but Formula (**I**) compounds can include N-O, N-N, or N-S(O)$_0$ bonds that form part of a ring (e.g., the N-N bond in 

).

In some embodiments of Formula (**I**):

$\mathbf{E^1}$ is $C\mathbf{R^{2a}}$ or N;

$\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are independently selected from the group consisting of: H, halo, cyano, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, and C_{1-3} haloalkoxy;

m3 is 0 or 1;

$\mathbf{X^3}$ is C_{1-3} alkylene optionally substituted with 1-3 $\mathbf{R^c}$;

$\mathbf{R^1}$ is selected from the group consisting of: H and halo;

$\mathbf{X^a}$ is selected from the group consisting of: N and $C\mathbf{R^{Xa}}$;

$\mathbf{R^6}$ and $\mathbf{R^{Xa}}$ are independently selected from the group consisting of: H, halo, C_{1-2} alkyl, C_{1-2} haloalkyl, C_{1-2} alkoxy, CN, and C≡CH;

L is $-(\mathbf{L^A})_{n1}-$, wherein:

n1 is an integer from 1 to 5; and

each $\mathbf{L^A}$ is independently selected from the group consisting of: $\mathbf{L^{A1}}$, $\mathbf{L^{A3}}$, and $\mathbf{L^{A4}}$, wherein:

0-2 of $\mathbf{L^A}$ is $\mathbf{L^{A1}}$;

0-2 of $\mathbf{L^A}$ is $\mathbf{L^{A3}}$; and

1-3 of $\mathbf{L^A}$ is $\mathbf{L^{A4}}$,

each $\mathbf{L^{A1}}$ is independently selected from the group consisting of: CH_2, $CH\mathbf{R^L}$, and $C(\mathbf{R^L})_2$, wherein:

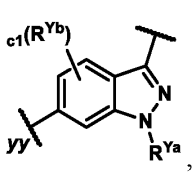
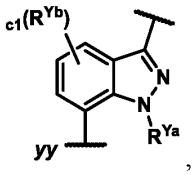
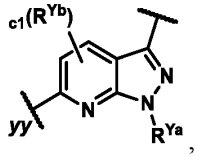
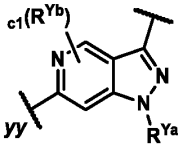
each $\mathbf{R^L}$ is independently selected from the group consisting of: halo, cyano, OH, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -(C_{0-3} alkylene)-(C_{3-5} cycloalkyl), -(C_{0-3} alkylene)-(4-6 membered heterocyclyl), and C_{1-6} alkyl optionally substituted with 1-6 $\mathbf{R^c}$;

each $\mathbf{L^{A3}}$ is independently selected from the group consisting of: N($\mathbf{R^d}$), N($\mathbf{R^b}$), O, $S(O)_{0-2}$, and C(=O);

each $\mathbf{L^{A4}}$ is independently selected from the group consisting of:

(a) C_{3-15} cycloalkylene or 4-15 membered heterocyclylene, each of which is optionally substituted with 1-6 substituents independently selected from the group consisting of: $\mathbf{R^a}$ and $\mathbf{R^b}$; and

(b) phenylene or 5-6 membered heteroarylene, each of which is optionally substituted with 1-3 substituents independently selected from the group consisting of: $\mathbf{R^a}$ and $\mathbf{R^b}$;

Ring C is selected from the group consisting of: , , , and , wherein:

c1 is 0, 1, or 2;

each $\mathbf{R^{Ya}}$ and $\mathbf{R^{Yb}}$ is independently selected from the group consisting of $\mathbf{R^a}$ and $\mathbf{R^b}$; and

yy represents the point of attachment to **L**;

X is CH or N;

each $\mathbf{R^a}$ is independently selected from the group consisting of:

(a) halo;

(b) cyano;

(c) OH;

(d) oxo;

(e) C_{1-6} alkoxy optionally substituted with 1-6 $\mathbf{R^c}$;

(f) $N\mathbf{R^dR^e}$;

(g) $C(=O)C_{1-6}$ alkyl;

(h) $C(=O)OC_{1-6}$ alkyl;

(i) $C(=O)N(\mathbf{R^f})_2$;

(j) $S(O)_{0-2}(C_{1-6}$ alkyl);

(k) $S(O)_{0-2}(C_{1-6}$ haloalkyl); and

(l) C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, each optionally substituted with 1-6 $\mathbf{R^c}$;

each $\mathbf{R^b}$ is independently selected from the group consisting of: $\mathbf{-(L^b)_b-R^{b1}}$ and $\mathbf{R^{b1}}$, wherein:

each **b** is independently 1, 2, or 3;

each $\mathbf{L^b}$ is independently selected from the group consisting of: O, N(H), $N(C_{1-3}$ alkyl), $S(O)_{0-2}$, C(=O), and C_{1-3} alkylene; and

each $\mathbf{R^{b1}}$ is independently selected from the group consisting of: C_{3-6} cycloalkyl and 4-8 membered heterocyclyl, each of which is optionally substituted with 1-3 $\mathbf{R^g}$;

each $\mathbf{R^c}$ is independently selected from the group consisting of: halo, cyano, OH, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $N\mathbf{R^dR^e}$, $C(=O)C_{1-6}$ alkyl, $C(=O)OC_{1-6}$ alkyl, $C(=O)N(\mathbf{R^f})_2$, $S(O)_{0-2}(C_{1-6}$ alkyl), and $S(O)_{0-2}(C_{1-6}$ haloalkyl);

each $\mathbf{R^d}$ and $\mathbf{R^e}$ is independently selected from the group consisting of: H, $C(=O)C_{1-6}$ alkyl, $C(=O)C_{1-6}$ haloalkyl, $C(=O)OC_{1-6}$ alkyl, $C(=O)OC_{1-6}$ haloalkyl, $C(=O)N(\mathbf{R^f})_2$, $S(O)_{1-2}(C_{1-6}$ alkyl), $S(O)_{1-2}(C_{1-6}$ haloalkyl), $S(O)_{1-2}N(\mathbf{R^f})_2$, and C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^h}$;

each $\mathbf{R^f}$ is independently selected from the group consisting of: H and C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^h}$;

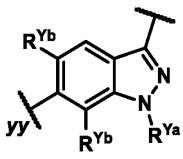
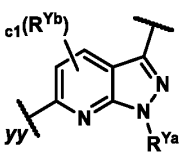
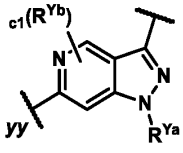
each $\mathbf{R^g}$ is independently selected from the group consisting of: $\mathbf{R^h}$, oxo, C_{1-3} alkyl, and C_{1-3} haloalkyl; and

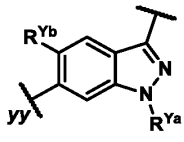
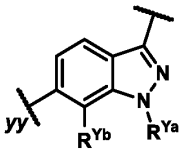
each $\mathbf{R^h}$ is independently selected from the group consisting of: halo, cyano, OH, $-(C_{0-3}$ alkylene)-C_{1-6} alkoxy, $-(C_{0-3}$ alkylene)-C_{1-6} haloalkoxy, $-(C_{0-3}$ alkylene)-NH_2, $-(C_{0-3}$ alkylene)-$N(H)(C_{1-3}$ alkyl), and $-(C_{0-3}$ alkylene)-$N(C_{1-3}$ alkyl)$_2$.

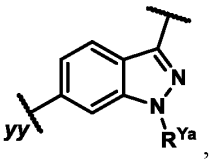
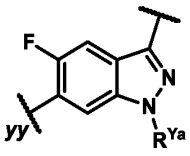
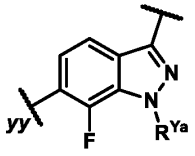
In some embodiments of Formula (**I**), one or more of **(1)-(5)** applies:

(1) $\mathbf{R^{2b}}$ is selected from the group consisting of: halo, cyano, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, and C_{1-3} haloalkoxy;

(2) $\mathbf{E^1}$ is N;

(3) Ring C is selected from the group consisting of: , , , and ;

(4) Ring C is selected from the group consisting of:  and , wherein $\mathbf{R^{Yb}}$ is $C_{1\text{-}3}$ alkyl optionally substituted with 1-3 F; and/or

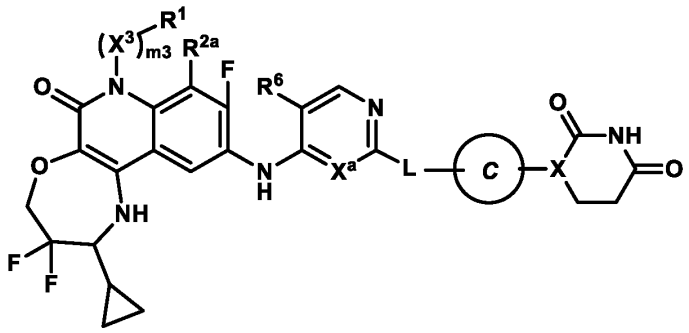
(5) Ring C is selected from the group consisting of: , , and , wherein $\mathbf{R^{Ya}}$ is $-(C_{0\text{-}3}$ alkylene)-$\mathbf{R^{b1}}$ or $C_{2\text{-}4}$ alkyl optionally substituted with 1-3 $\mathbf{R^{c}}$.

In some embodiments of Formula (**I**), $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are each independently H or F.

In some embodiments of Formula (**I**), $\mathbf{E^1}$ is $C\mathbf{R^{2a}}$; and each of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ is H.

In some embodiments of Formula (**I**), $\mathbf{E^1}$ is $C\mathbf{R^{2a}}$; one of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ is F; and the other of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ is H.

In some embodiments, the compounds of Formula (**I**) are compounds of Formula (**I-1**):

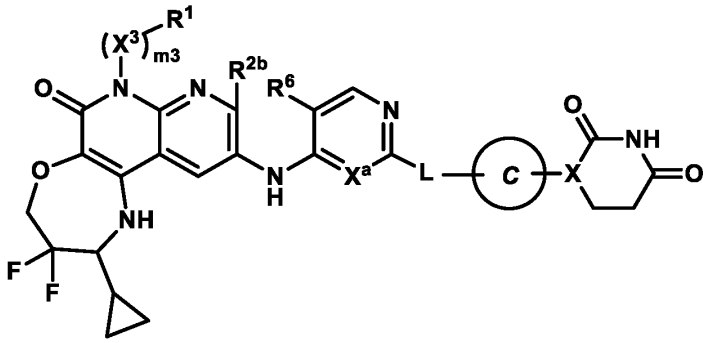


Formula (**I-1**)

or pharmaceutically acceptable salts thereof.

In some embodiments of Formula (**I-1**), $\mathbf{R^{2a}}$ is H.

In some embodiments, the compounds of Formula (**I**) are compounds of Formula (**I-2**):



Formula (**I-2**)

or pharmaceutically acceptable salts thereof.

In some embodiments of Formula (**I-2**), $\mathbf{R^{2b}}$ is H.

In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), $\mathbf{R^1}$ is selected from the group consisting of: H and halo.

In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), **m3** is 1; and $\mathbf{R^1}$ is H.

In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), $-(\mathbf{X^3})_{\mathbf{m3}}\text{-}\mathbf{R^1}$ is $C_{1\text{-}3}$ alkyl. For example, $-(\mathbf{X^3})_{\mathbf{m3}}\text{-}\mathbf{R^1}$ can be methyl.

In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), **m3** is 0; and $\mathbf{R^1}$ is H.

In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), $\mathbf{R^1}$ is $\mathbf{R^{b1}}$. In some embodiments, $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl optionally substituted with 1-3 $\mathbf{R^g}$ (e.g., C_{3-6} cycloalkyl optionally substituted with 1-3 F).

In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), **m3** is 1; and $\mathbf{R^1}$ is $\mathbf{R^{b1}}$. In some embodiments, $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl optionally substituted with 1-3 $\mathbf{R^g}$ (e.g., C_{3-6} cycloalkyl optionally substituted with 1-3 F).

In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), $-(\mathbf{X^3})_{\mathbf{m3}}-\mathbf{R^1}$ is $-CH_2-\mathbf{R^{b1}}$.

In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), **m3** is 0; and $\mathbf{R^1}$ is $\mathbf{R^{b1}}$. In some embodiments, $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl optionally substituted with 1-3 $\mathbf{R^g}$ (e.g., C_{3-6} cycloalkyl optionally substituted with 1-3 F).

In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), $-(\mathbf{X^3})_{\mathbf{m3}}-\mathbf{R^1}$ is selected from the group consisting of:

a) H;

b) C_{1-3} alkyl;

c) $\mathbf{R^{b1}}$; and

d) $-CH_2\mathbf{R^{b1}}$, wherein:

$\mathbf{R^{b1}}$ is a C_{3-6} cycloalkyl optionally substituted with 1-3 $\mathbf{R^g}$ (e.g., C_{3-6} cycloalkyl optionally substituted with 1-3 F).

In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), $-(\mathbf{X^3})_{\mathbf{m3}}-\mathbf{R^1}$ is selected from the group consisting of: H and methyl.

In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), $\mathbf{R^6}$ is Cl or F. For example, $\mathbf{R^6}$ can be Cl.

In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), $\mathbf{X^a}$ is N.

In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), $\mathbf{X^a}$ is N; and $\mathbf{R^6}$ is Cl.

In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), **L** is $-(\mathbf{L^A})_{\mathbf{n1}}-$, wherein:

n1 is an integer from 2 to 4; and

each $\mathbf{L^A}$ is independently selected from the group consisting of: $\mathbf{L^{A1}}$, $\mathbf{L^{A3}}$, and $\mathbf{L^{A4}}$, wherein:

0-2 (e.g., 0 or 1) of $\mathbf{L^A}$ is $\mathbf{L^{A1}}$;

0-2 (e.g., 0) of $\mathbf{L^A}$ is $\mathbf{L^{A3}}$; and

2-3 of $\mathbf{L^A}$ are $\mathbf{L^{A4}}$, wherein:

each $\mathbf{L^{A4}}$ is independently a C_{3-10} cycloalkylene or a 4-12 membered heterocyclylene, each of which is optionally substituted with 1-3 $\mathbf{R^a}$, wherein:

each $\mathbf{R^a}$ present on $\mathbf{L^{A4}}$ is independently selected from the group consisting of: F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F; and

each $\mathbf{R^L}$ is independently selected from the group consisting of: F, OH, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$ (e.g., C_{1-3} alkyl optionally substituted with 1-3 F).

In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), **L** is selected from the group consisting of:

$\mathbf{-L^{A4a}-L^{A1}-L^{A4b}-}$*bb*;

$\mathbf{-L^{A4a}-L^{A3}-L^{A4b}-}$*bb*;

$\mathbf{-L^{A4a}-L^{A4b}-}$*bb*;

$\mathbf{-L^{A4a}-L^{A3}-L^{A4c}-\ L^{A4b}-}$*bb*; and

$\mathbf{-L^{A4a}-L^{A4c}-L^{A3}-L^{A4b}-}$*bb*, wherein:

$\mathbf{L^{A4a}}$, $\mathbf{L^{A4b}}$, and $\mathbf{L^{A4c}}$ are each an independently selected $\mathbf{L^{A4}}$,

$\mathbf{L^{A3}}$ is selected from the group consisting of: O and N($\mathbf{R^d}$), and

bb represents the point of attachment to **Ring C**.

In some embodiments, $\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ are independently 4-12 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R^a}$; $\mathbf{L^{A4c}}$ is a C_{3-10} cycloalkylene optionally substituted with 1-3 $\mathbf{R^a}$; and each $\mathbf{R^L}$ is independently selected from the group consisting of: F, OH, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$ (e.g., C_{1-3} alkyl optionally substituted with 1-3 F). In some embodiments, $\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ each contain 1-2 ring nitrogen atoms and no additional ring heteroatoms. In some embodiments, each $\mathbf{R^a}$ present on $\mathbf{L^{A4a}}$, $\mathbf{L^{A4b}}$, and/or $\mathbf{L^{A4c}}$ is independently selected from the group consisting of: F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F. In some embodiments, each $\mathbf{R^a}$ present on $\mathbf{L^{A4a}}$, $\mathbf{L^{A4b}}$, and/or $\mathbf{L^{A4c}}$ is independently selected from the group consisting of: F and C_{1-3} alkyl optionally substituted with 1-3 F. For example, each $\mathbf{R^a}$ present on $\mathbf{L^{A4a}}$, $\mathbf{L^{A4b}}$, and/or $\mathbf{L^{A4c}}$ can be F, Me, or CF_3 (e.g., F or Me).

In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), **L** is selected from the group consisting of:

$\mathbf{-L^{A4a}-L^{A1}-L^{A4b}-}$*bb*;

-$\mathbf{L}^{A4a}$-$\mathbf{L}^{A3}$-$\mathbf{L}^{A4b}$-*bb*; and

-$\mathbf{L}^{A4a}$-$\mathbf{L}^{A4b}$-*bb*; wherein:

$\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ are each an independently selected $\mathbf{L}^{A4}$,

$\mathbf{L}^{A3}$ is selected from the group consisting of: O and N($\mathbf{R}^{d}$), and

bb represents the point of attachment to **Ring C**.

In some embodiments, $\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ are independently 4-12 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R}^{a}$; and each $\mathbf{R}^{L}$ is independently selected from the group consisting of: F, OH, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R}^{c}$ (e.g., C_{1-3} alkyl optionally substituted with 1-3 F). In some embodiments, $\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ each contain 1-2 ring nitrogen atoms and no additional ring heteroatoms. In some embodiments, each $\mathbf{R}^{a}$ present on $\mathbf{L}^{A4a}$ and/or $\mathbf{L}^{A4b}$ is independently selected from the group consisting of: F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F. In some embodiments, each $\mathbf{R}^{a}$ present on $\mathbf{L}^{A4a}$ and/or $\mathbf{L}^{A4b}$ is independently selected from the group consisting of: F and C_{1-3} alkyl optionally substituted with 1-3 F. For example, each $\mathbf{R}^{a}$ present on $\mathbf{L}^{A4a}$ and/or $\mathbf{L}^{A4b}$ can be F, Me, or CF_3 (e.g., F or Me).

In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), **L** is:

-$\mathbf{L}^{A4a}$-$\mathbf{L}^{A1}$-$\mathbf{L}^{A4b}$-*bb*, wherein:

$\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ are independently 4-12 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R}^{a}$; and

each $\mathbf{R}^{L}$ is independently selected from the group consisting of: F, OH, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R}^{c}$ (e.g., C_{1-3} alkyl optionally substituted with 1-3 F).

In some embodiments, $\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ are independently monocyclic 4-6 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R}^{a}$. In some embodiments, one of $\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ is a 1,4-piperidinylene; and the other of $\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ is independently selected from the group consisting of: 1,4-piperidinylene and 1,4-piperazinylene, wherein each of the 1,4-piperidinylene or 1,4-piperazinylene is optionally substituted with 1-2 $\mathbf{R}^{a}$. In some embodiments, $\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ each contain 1-2 ring nitrogen atoms and no additional ring heteroatoms. In some embodiments, each $\mathbf{R}^{a}$ present on $\mathbf{L}^{A4a}$ and/or $\mathbf{L}^{A4b}$ is independently selected from the group consisting of: F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F. In some embodiments, each $\mathbf{R}^{a}$ present on $\mathbf{L}^{A4a}$ and/or $\mathbf{L}^{A4b}$ is independently selected from the group consisting of: F and C_{1-3} alkyl optionally substituted with 1-3 F. For example, each $\mathbf{R}^{a}$ present on $\mathbf{L}^{A4a}$ and/or $\mathbf{L}^{A4b}$ can be F, Me, or CF_3 (e.g., F or Me).

In some embodiments, one of $\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ is a monocyclic 4-6 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R^a}$; and the other of $\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ is a bicyclic spirocyclic 6-12 (e.g., 10-12) membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R^a}$. In some embodiments, $\mathbf{L^{A4b}}$ is a monocyclic 4-6 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R^a}$; and $\mathbf{L^{A4a}}$ is a bicyclic spirocyclic 6-12 (e.g., 10-12) membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R^a}$. In some embodiments, $\mathbf{L^{A4b}}$ is 1,4-piperidinylene optionally substituted with 1-2 $\mathbf{R^a}$; and $\mathbf{L^{A4a}}$ is a bicyclic spirocyclic 10-12 membered nitrogen-containing heterocyclylene optionally substituted with 1-2 $\mathbf{R^a}$. In some embodiments, $\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ each contain 1-2 ring nitrogen atoms and no additional ring heteroatoms. In some embodiments, each $\mathbf{R^a}$ present on $\mathbf{L^{A4a}}$ and/or $\mathbf{L^{A4b}}$ is independently selected from the group consisting of: F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F. In some embodiments, each $\mathbf{R^a}$ present on $\mathbf{L^{A4a}}$ and/or $\mathbf{L^{A4b}}$ is independently selected from the group consisting of: F, and C_{1-3} alkyl optionally substituted with 1-3 F. For example, each $\mathbf{R^a}$ present on $\mathbf{L^{A4a}}$ and/or $\mathbf{L^{A4b}}$ can be F, Me, or CF_3 (e.g., F or Me).

In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), $\mathbf{L^{A1}}$ is CH_2.

In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), **L** is: $\mathbf{-L^{A4a}\text{-}L^{A1}\text{-}L^{A4b}}$-*bb*; and $\mathbf{L^{A1}}$ is CH_2.

In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), $\mathbf{L^{A1}}$ is $CH\mathbf{R^L}$, wherein $\mathbf{R^L}$ is C_{1-3} alkyl optionally substituted with 1-3 F (e.g., $\mathbf{R^L}$ is methyl or CF_3).

In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), **L** is: $\mathbf{-L^{A4a}\text{-}L^{A1}\text{-}L^{A4b}}$-*bb*; and $\mathbf{L^{A1}}$ is $CH\mathbf{R^L}$, wherein $\mathbf{R^L}$ is C_{1-3} alkyl optionally substituted with 1-3 F (e.g., $\mathbf{R^L}$ is methyl or CF_3).

In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), **L** is $-(\mathbf{L^A})_{\mathbf{n1}}-$, wherein:

n1 is 1, 2, or 3; and

each $\mathbf{L^A}$ is independently selected from the group consisting of: $\mathbf{L^{A1}}$, $\mathbf{L^{A3}}$, and $\mathbf{L^{A4}}$, wherein:

0-1 of $\mathbf{L^A}$ is $\mathbf{L^{A1}}$;

0-1 of $\mathbf{L^A}$ is $\mathbf{L^{A3}}$; and

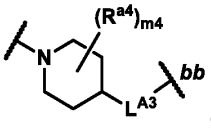
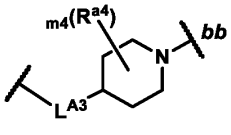
one $\mathbf{L^A}$ is $\mathbf{L^{A4}}$, wherein:

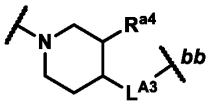
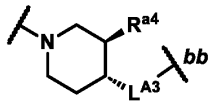
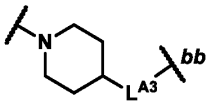
$\mathbf{L^{A4}}$ is a 4-12 membered heterocyclylene optionally substituted with 1-3 $\mathbf{R^a}$, wherein:

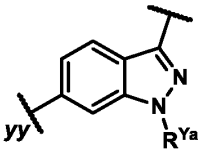
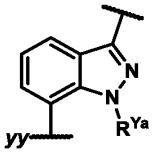
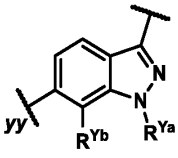
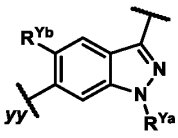
each $\mathbf{R^a}$ present on $\mathbf{L^{A4}}$ is independently selected from the group consisting of: F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F; and

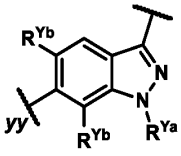
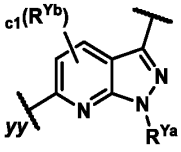
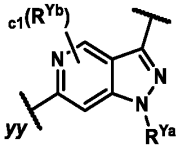
each $\mathbf{R^L}$ is independently selected from the group consisting of: F, OH, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$ (e.g., C_{1-3} alkyl optionally substituted with 1-3 F). In some embodiments, $\mathbf{L^{A4}}$ is a monocyclic 4-6 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R^a}$. In some embodiments, $\mathbf{L^{A3}}$ is N(H).

In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), **L** is selected from the group consisting of: $\mathbf{-L^{A4}\text{-}L^{A3}}$-*bb* and $\mathbf{-L^{A3}\text{-}L^{A4}}$-*bb*, wherein ***bb*** represents the point of attachment to **Ring C**. In some embodiments, $\mathbf{L^{A4}}$ is a monocyclic 4-6 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R^a}$. In some embodiments, $\mathbf{L^{A3}}$ is N(H).

In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), **L** is selected from the group consisting of:  and , wherein **m4** is 0, 1, or 2; each $\mathbf{R^{a4}}$ is independently selected from the group consisting of: F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F; and ***bb*** represents the point of attachment to **Ring C**. In some embodiments, $\mathbf{L^{A3}}$ is N(H); and each $\mathbf{R^{a4}}$ is independently C_{1-3} alkyl optionally substituted with 1-3 F (e.g., methyl).

In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), **L** is selected from the group consisting of:  (e.g., ) and , wherein $\mathbf{R^{a4}}$ is selected from the group consisting of: F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F (e.g., $\mathbf{R^{a4}}$ is C_{1-3} alkyl optionally substituted with 1-3 F); and ***bb*** represents the point of attachment to **Ring C**. In some embodiments, $\mathbf{L^{A3}}$ is N(H); and each $\mathbf{R^{a4}}$ is independently C_{1-3} alkyl optionally substituted with 1-3 F (e.g., methyl).

In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), **Ring C** is selected from the group consisting of: , , , and .

In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), **Ring C** is selected from the group consisting of: , , and .

In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), $\mathbf{R^{Ya}}$ is selected from the group consisting of: $\mathbf{R^a}$ and $\mathbf{R^b}$.

In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), $\mathbf{R^{Ya}}$ is selected from the group consisting of:

(a) H;

(b) C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$; and

(c) –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$ (e.g., C_{3-6} cycloalkyl optionally substituted with 1-3 F); and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$ (e.g., C_{1-3} alkyl optionally substituted with 1-3 F).

In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), $\mathbf{R^{Ya}}$ is H or C_{1-3} alkyl optionally substituted with 1-3 F (e.g., C_{1-3} alkyl (e.g., methyl)); and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: F and C_{1-3} alkyl optionally substituted with 1-3 F.

In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), $\mathbf{R^{Ya}}$ is selected from the group consisting of:

(a) C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$; and

(b) –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$ (e.g., C_{3-6} cycloalkyl optionally substituted with 1-3 F); and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$ (e.g., C_{1-3} alkyl optionally substituted with 1-3 F).

In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), $\mathbf{R^{Ya}}$ is C_{1-3} alkyl optionally substituted with 1-3 F (e.g., C_{1-3} alkyl (e.g., methyl)); and

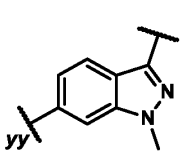
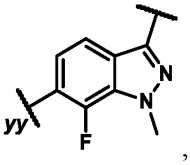
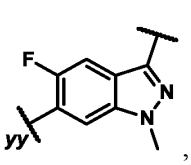
each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: F and C_{1-3} alkyl optionally substituted with 1-3 F.

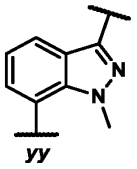
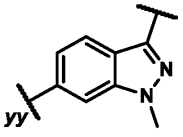
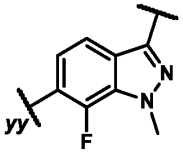
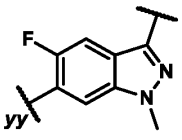
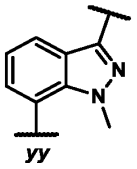
In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), **c1** is 1 or 2; and each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$ (e.g., C_{1-3} alkyl optionally substituted with 1-3 F). For example, **c1** can be 1; and $\mathbf{R^{Yb}}$ can be selected from the group consisting of: F and C_{1-3} alkyl optionally substituted with 1-3 F.

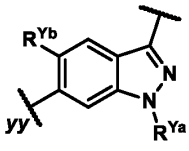
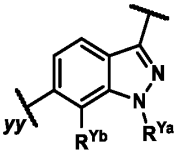
In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), **c1** is 1 or 2; and each $\mathbf{R^{Yb}}$ is F. In some embodiments, **c1** is 2; and each $\mathbf{R^{Yb}}$ is F.

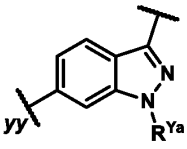
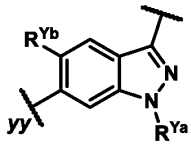
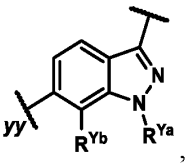
In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), $\mathbf{R^{Ya}}$ is C_{1-3} alkyl optionally substituted with 1-3 F; and each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: F and C_{1-3} alkyl optionally substituted with 1-3 F.

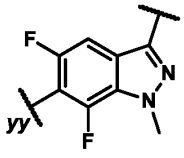
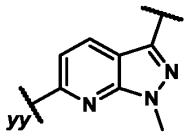
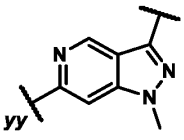
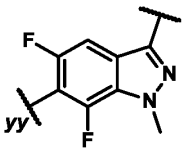
In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), $\mathbf{R^{Ya}}$ is methyl; and each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: F, Me, and CF_3 (e.g., each $\mathbf{R^{Yb}}$ is F).

In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), **Ring C** is selected from the group consisting of: , , , and

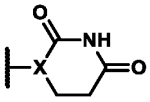
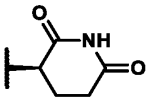

. For example, **Ring C** can be 
. For example, **Ring C** can be 
. For example, **Ring C** can be 
. For example, **Ring C** can be 
.

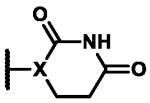
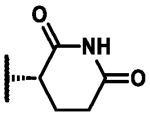
In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), **Ring C** is selected from the group consisting of: 
and 
, wherein $\mathbf{R^{Yb}}$ is C_{1-3} alkyl optionally substituted with 1-3 F. In some embodiments, $\mathbf{R^{Ya}}$ is methyl. In some embodiments, $\mathbf{R^{Yb}}$ is methyl or CF_3.

In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), **Ring C** is selected from the group consisting of: 
, 
, and 
, wherein $\mathbf{R^{Ya}}$ is $-(C_{0-3}$ alkylene)-$\mathbf{R^{b1}}$ or C_{2-4} alkyl optionally substituted with 1-3 $\mathbf{R^{c}}$. In some embodiments, $\mathbf{R^{Yb}}$ is F or C_{1-3} alkyl optionally substituted with 1-3 F.

In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), **Ring C** is selected from the group consisting of: , , and . For example, **Ring C** can be .

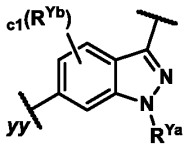
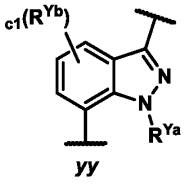
In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), **X** is CH.

In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), the  moiety is .

In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), the  moiety is .

In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), **X** is N.

In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), **X** is CH; and

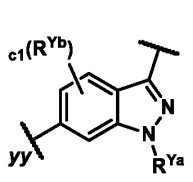
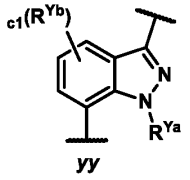
Ring C is selected from the group consisting of:  and , wherein:

$\mathbf{R^{Ya}}$ is H, $\mathbf{R^{b1}}$, -CH_2-$\mathbf{R^{b1}}$, or C_{1-3} alkyl optionally substituted with 1-3 F,

wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl optionally substituted with 1-3 F, and

each R^{Yb} is independently selected from the group consisting of: F and C_{1-3} alkyl optionally substituted with 1-3 F. In some embodiments, R^{Ya} is methyl; and each R^{Yb} is F. In some embodiments, **c1** is 1. In some embodiments, **c1** is 2.

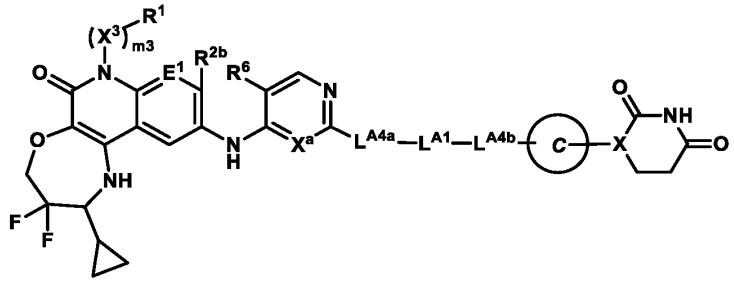
In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), **X** is CH; and

Ring C is selected from the group consisting of:  and , wherein:

R^{Ya} is C_{1-3} alkyl optionally substituted with 1-3 F (e.g., C_{1-3} alkyl (e.g., methyl)); and

each R^{Yb} is independently selected from the group consisting of: F and C_{1-3} alkyl optionally substituted with 1-3 F. In some embodiments, R^{Ya} is methyl; and each R^{Yb} is F. In some embodiments, **c1** is 1. In some embodiments, **c1** is 2.

In some embodiments, the compounds of Formula (**I**) are compounds of Formula (**I-a**):



Formula (**I-a**)

or pharmaceutically acceptable salts thereof, wherein:

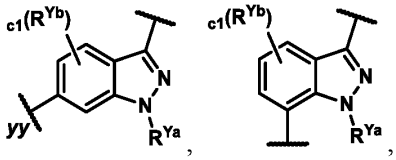
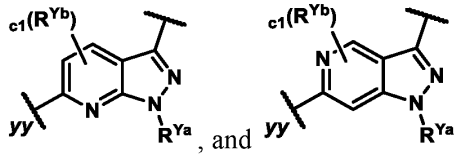
E^1 is CR^{2a} or N;

R^{2a} and R^{2b} are each independently selected from the group consisting of: H and F;

L^{A4a} and L^{A4b} are independently 4-12 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 R^a;

L^{A1} is CH_2 or CHR^L, and

R^L is selected from the group consisting of: F, OH, and C_{1-3} alkyl optionally substituted with 1-3 R^c; and

Ring C is selected from the group consisting of: , , and , wherein:

c1 is 0, 1, or 2;

$\mathbf{R^{Ya}}$ is selected from the group consisting of:

(a) H;

(b) C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$; and

(c) –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$;

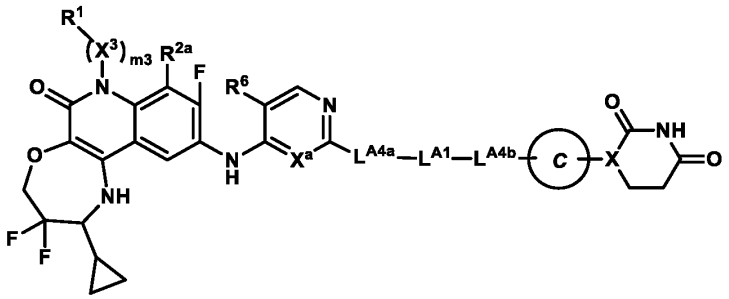
each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$ (e.g., C_{1-3} alkyl optionally substituted with 1-3 F); and

yy represents the point of attachment to $\mathbf{L^{A4b}}$.

In some embodiments of Formula (**I-a**), $\mathbf{E^1}$ is $C\mathbf{R^{2a}}$; and each of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ is H.

In some embodiments of Formula (**I-a**), $\mathbf{E^1}$ is $C\mathbf{R^{2a}}$; one of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ is F; and the other of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ is H.

In some embodiments, the compounds of Formula (**I-a**) are compounds of Formula (**I-a-1**):

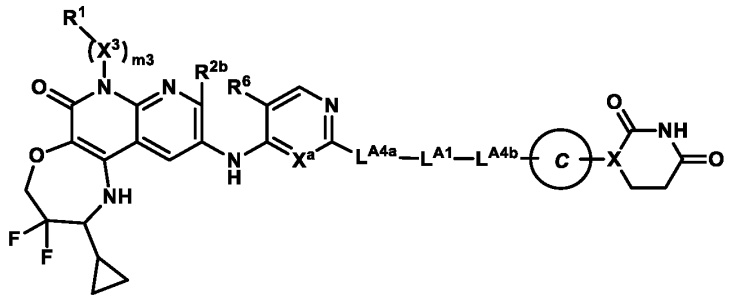


Formula (**I-a-1**)

or pharmaceutically acceptable salts thereof.

In some embodiments of Formula (**I-a-1**), $\mathbf{R^{2a}}$ is H.

In some embodiments, the compounds of Formula (**I-a**) are compounds of Formula (**I-a-2**):



Formula (**I-a-2**)

or pharmaceutically acceptable salts thereof.

In some embodiments of Formula (**I-a-2**), $\mathbf{R^{2b}}$ is H.

In some embodiments of Formula (**I-a**) (e.g., Formula (**I-a-1**) or Formula (**I-a-2**)), $\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ are independently monocyclic 4-6 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R^a}$.

In some embodiments of Formula (**I-a**) (e.g., Formula (**I-a-1**) or Formula (**I-a-2**)), $\mathbf{L^{A4b}}$ is a monocyclic 4-6 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R^a}$; and

$\mathbf{L^{A4a}}$ is a bicyclic spirocyclic 10-12 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R^a}$.

In some embodiments of Formula (**I-a**) (e.g., Formula (**I-a-1**) or Formula (**I-a-2**)), $\mathbf{R^L}$ is $C_{1\text{-}3}$ methyl optionally substituted with 1-3 F;

each $\mathbf{R^a}$ present on $\mathbf{L^{A4a}}$ and/or $\mathbf{L^{A4b}}$ is independently selected from the group consisting of: F, CN, $C_{1\text{-}3}$ alkoxy, OH, and $C_{1\text{-}3}$ alkyl optionally substituted with 1-3 F; and

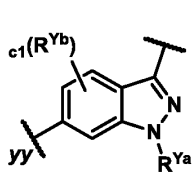
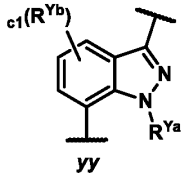
$\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ each contain 1-2 ring nitrogen atoms and no additional ring heteroatoms.

In some embodiments of Formula (**I-a**) (e.g., Formula (**I-a-1**) or Formula (**I-a-2**)), $\mathbf{R^L}$ is $C_{1\text{-}3}$ methyl optionally substituted with 1-3 F;

each $\mathbf{R^a}$ present on $\mathbf{L^{A4a}}$ and/or $\mathbf{L^{A4b}}$ is independently selected from the group consisting of: F and $C_{1\text{-}3}$ alkyl optionally substituted with 1-3 F; and

L^{A4a} and L^{A4b} each contain 1-2 ring nitrogen atoms and no additional ring heteroatoms.

In some embodiments of Formula (**I-a**) (e.g., Formula (**I-a-1**) or Formula (**I-a-2**)), **X** is CH; and

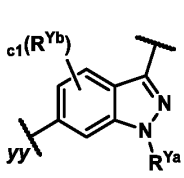
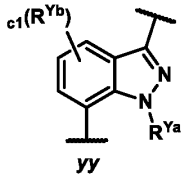
Ring C is selected from the group consisting of:  and , wherein:

R^{Ya} is H, R^{b1}, -CH_2-R^{b1}, or C_{1-3} alkyl optionally substituted with 1-3 F,

wherein R^{b1} is C_{3-6} cycloalkyl optionally substituted with 1-3 F, and

each R^{Yb} is independently selected from the group consisting of: F and C_{1-3} alkyl optionally substituted with 1-3 F. In some embodiments, R^{Ya} is methyl; and each R^{Yb} is F.

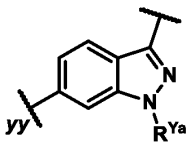
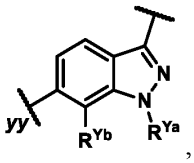
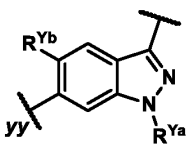
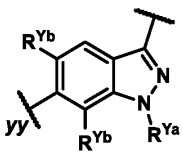
In some embodiments of Formula (**I-a**) (e.g., Formula (**I-a-1**) or Formula (**I-a-2**)), **X** is CH; and

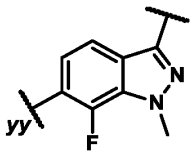
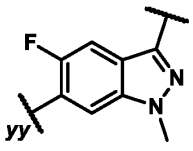
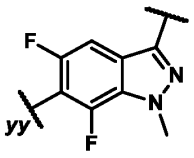
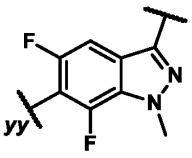
Ring C is selected from the group consisting of:  and , wherein:

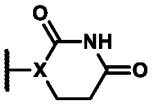
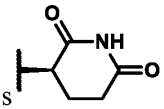
c1 is 0, 1, or 2;

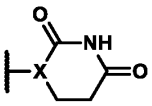
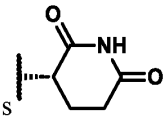
R^{Ya} is C_{1-3} alkyl optionally substituted with 1-3 F (e.g., C_{1-3} alkyl (e.g., methyl)); and

each R^{Yb} is independently selected from the group consisting of: F and C_{1-3} alkyl optionally substituted with 1-3 F. In some embodiments, R^{Ya} is methyl; and each R^{Yb} is F.

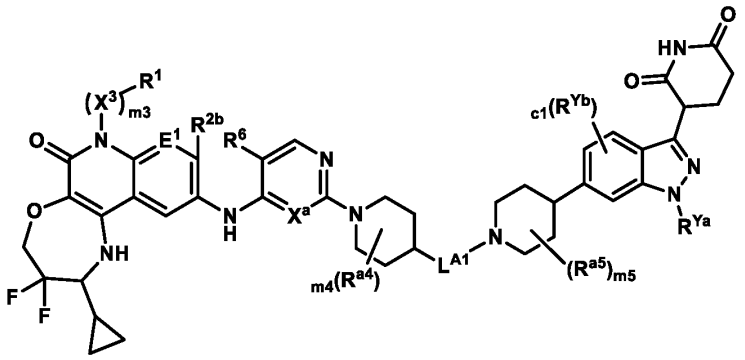
In some embodiments of Formula (**I-a**) (e.g., Formula (**I-a-1**) or Formula (**I-a-2**)), **Ring C** is selected from the group consisting of: , , , and .

In some embodiments of Formula (**I-a**) (e.g., Formula (**I-a-1**) or Formula (**I-a-2**)), **Ring C** is selected from the group consisting of:, , , and . For example, **Ring C** can be .

In some embodiments of Formula (**I-a**) (e.g., Formula (**I-a-1**) or Formula (**I-a-2**)), the  moiety is .

In some embodiments of Formula (**I-a**) (e.g., Formula (**I-a-1**) or Formula (**I-a-2**)), the  moiety is .

In some embodiments, the compounds of Formula (**I**) (e.g., Formula (**I-a**)) are compounds of Formula (**I-b**):



Formula (**I-b**)

or pharmaceutically acceptable salts thereof, wherein:

$\mathbf{E^1}$ is $\mathbf{CR^{2a}}$ or N;

$\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are each independently selected from the group consisting of: H and F;

m4 and **m5** are independently 0, 1, or 2;

each $\mathbf{R^{a4}}$ and $\mathbf{R^{a5}}$ is independently selected from the group consisting of: F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F;

$\mathbf{L^{A1}}$ is CH_2 or $CH\mathbf{R^L}$, and

$\mathbf{R^L}$ is C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$;

c1 is 0, 1, or 2;

$\mathbf{R^{Ya}}$ is selected from the group consisting of:

(a) H;

(b) C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$; and

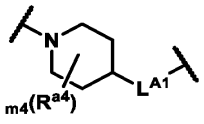
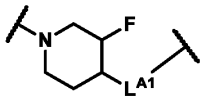
(c) –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$; and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$.

In some embodiments of Formula (**I-b**), one or more of **(1)-(6)** applies:

(1) $\mathbf{R^{2b}}$ is F;

(2) $\mathbf{E^1}$ is N;

(3) the  moiety is: ;

(4) $\mathbf{R^{Ya}}$ is selected from the group consisting of: C_{2-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$, and –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$;

(5) c1 is 2; and/or

(6) c1 is 1, and $\mathbf{R^{Yb}}$ is C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$ (e.g., C_{1-3} alkyl optionally substituted with 1-3 F).

In some embodiments of Formula (**I-b**), two or more of **(1)-(4)** apply:

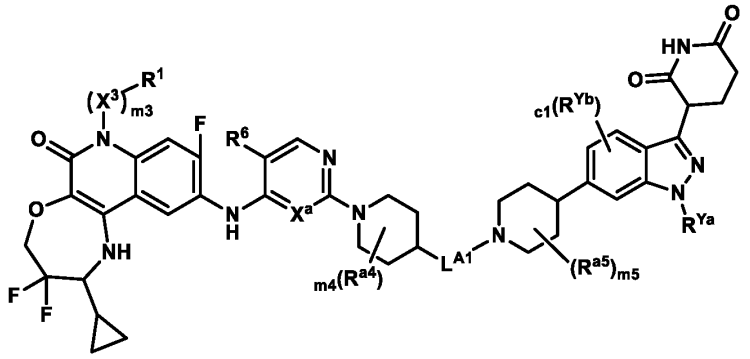
(1) m4 is 1 or 2;

(2) m5 is 1 or 2;

(3) $\mathbf{L^{A1}}$ is $CH\mathbf{R^L}$; and/or

(4) c1 is 1 or 2.

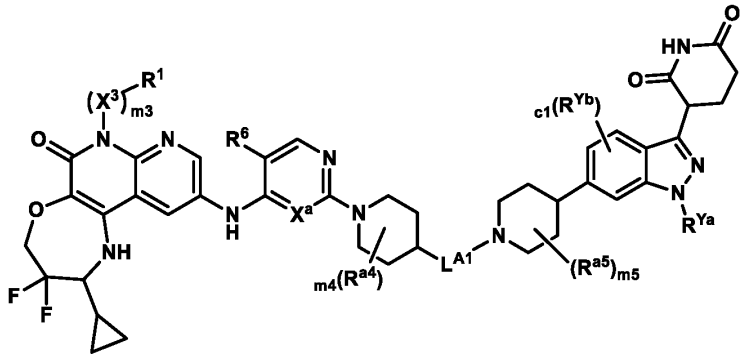
In some embodiments, the compounds of Formula (**I-b**) are compounds of Formula (**I-b-1**):



Formula (**I-b-1**)

or pharmaceutically acceptable salts thereof.

In some embodiments, the compounds of Formula (**I-b**) are compounds of Formula (**I-b-2**):



Formula (**I-b-2**)

or pharmaceutically acceptable salts thereof.

In some embodiments of Formula (**I-b**) (e.g., Formula (**I-b-1**) or Formula (**I-b-2**)), $\mathbf{R^{Ya}}$ is selected from the group consisting of:

(a) C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$; and

(b) –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$ (e.g.,C_{3-6} cycloalkyl optionally substituted with 1-3 F); and

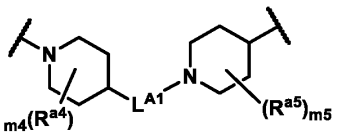
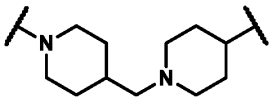
each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$.

In some embodiments of Formula (**I-b**) (e.g., Formula (**I-b-1**) or Formula (**I-b-2**)), $\mathbf{R^{Ya}}$ is C_{1-3} alkyl optionally substituted with 1-3 F (e.g., C_{1-3} alkyl (e.g., methyl)), and

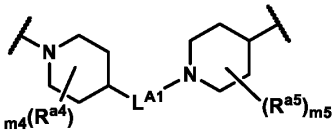
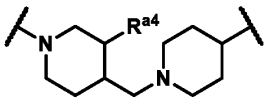
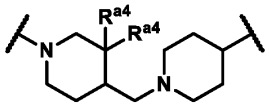
each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: F and C_{1-3} alkyl optionally substituted with 1-3 F.

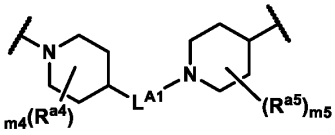
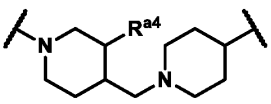
In some embodiments of Formula (**I-b**) (e.g., Formula (**I-b-1**) or Formula (**I-b-2**)), $\mathbf{L^{A1}}$ is CH_2.

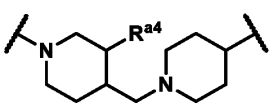
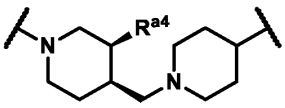
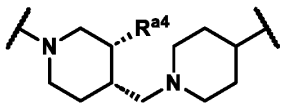
In some embodiments of Formula (**I-b**) (e.g., Formula (**I-b-1**) or Formula (**I-b-2**)), each $\mathbf{R^{a4}}$ and $\mathbf{R^{a5}}$ is independently selected from the group consisting of: F and C_{1-3} alkyl optionally substituted with 1-3 F.

In some embodiments of Formula (**I-b**) (e.g., Formula (**I-b-1**) or Formula (**I-b-2**)), **m4** is 0; and **m5** is 0. For example, the  moiety can be .

In some embodiments of Formula (**I-b**) (e.g., Formula (**I-b-1**) or Formula (**I-b-2**)), **m4** is 1 or 2; and **m5** is 0, wherein each $\mathbf{R^{a4}}$ is independently selected from the group consisting of: F, Me, and CF_3.

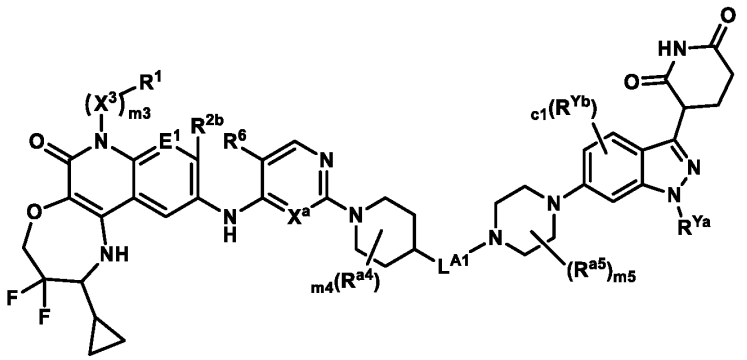
In some embodiments of Formula (**I-b**) (e.g., Formula (**I-b-1**) or Formula (**I-b-2**)), the  moiety is  or . In some embodiments, each $\mathbf{R^{a4}}$ is independently selected from the group consisting of: F, Me, and CF_3.

In some embodiments of Formula (**I-b**) (e.g., Formula (**I-b-1**) or Formula (**I-b-2**)), the  moiety is . In some embodiments, the

 moiety is  or . In some embodiments, $\mathbf{R^{a4}}$ is selected from the group consisting of: F and Me.

In some embodiments of Formula (**I-b**) (e.g., Formula (**I-b-1**) or Formula (**I-b-2**)), **m4** is 0; and **m5** is 1 or 2, wherein each $\mathbf{R^{a5}}$ is independently selected from the group consisting of: F, Me, and CF_3.

In some embodiments, the compounds of Formula (**I**) (e.g., Formula (**I-a**)) are compounds of Formula of Formula (**I-c**):



Formula (**I-c**)

or pharmaceutically acceptable salts thereof, wherein:

$\mathbf{E^1}$ is $C\mathbf{R^{2a}}$ or N;

$\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are each independently selected from the group consisting of: H and F;

m4 and **m5** are independently 0, 1, or 2;

each $\mathbf{R^{a4}}$ is independently selected from the group consisting of: F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F;

each $\mathbf{R^{a5}}$ is independently C_{1-3} alkyl optionally substituted with 1-3 F;

$\mathbf{L^{A1}}$ is CH_2 or $CH\mathbf{R^L}$, and

$\mathbf{R^L}$ is C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$;

c1 is 0, 1, or 2;

$\mathbf{R^{Ya}}$ is selected from the group consisting of:

(a) H;

(b) C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$; and

(c) –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$; and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$.

In some embodiments of Formula (**I-c**), one or more of **(1)-(4)** applies:

(1) $\mathbf{R^{2b}}$ is F;

(2) $\mathbf{E^1}$ is N;

(3) $\mathbf{R^{Ya}}$ is selected from the group consisting of: C_{2-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$, and –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$; and/or

(4) c1 is 2.

In some embodiments of Formula (**I-c**), two or more of **(1)-(4)** apply:

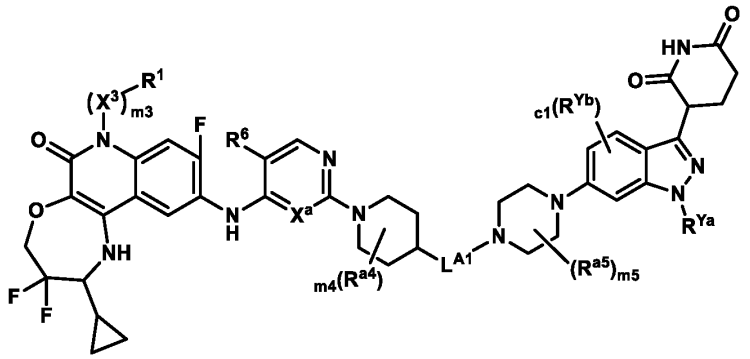
(1) m4 is 2;

(2) m5 is 1 or 2;

(3) $\mathbf{L^{A1}}$ is $CH\mathbf{R^L}$; and/or

(4) c1 is 1 or 2.

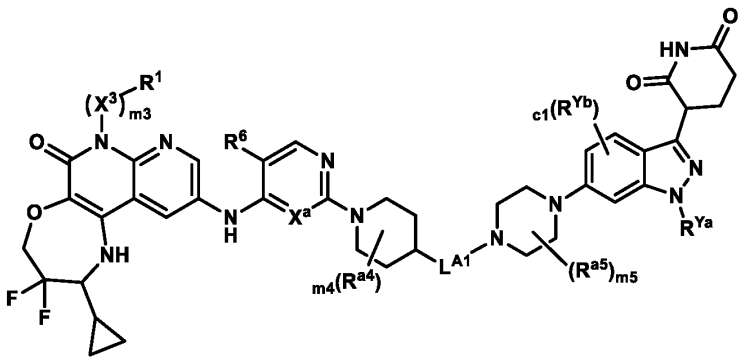
In some embodiments, the compounds of Formula (**I-c**) are compounds of Formula (**I-c-1**):



Formula (**I-c-1**)

or pharmaceutically acceptable salts thereof.

In some embodiments, the compounds of Formula (**I-c**) are compounds of Formula (**I-c-2**):



Formula (**I-c-2**)

or pharmaceutically acceptable salts thereof.

In some embodiments of Formula (**I-c**) (e.g., Formula (**I-c-1**) or Formula (**I-c-2**)), $\mathbf{R^{Ya}}$ is selected from the group consisting of:

(a) C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$; and

(b) –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$ (e.g., C_{3-6} cycloalkyl optionally substituted with 1-3 F); and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$.

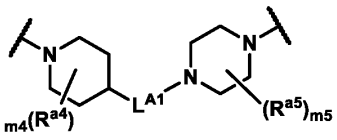
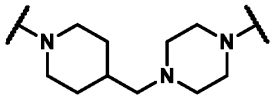
In some embodiments of Formula (**I-c**) (e.g., Formula (**I-c-1**) or Formula (**I-c-2**)), $\mathbf{R^{Ya}}$ is C_{1-3} alkyl optionally substituted with 1-3 F (e.g., C_{1-3} alkyl (e.g., methyl)), and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: F and C_{1-3} alkyl optionally substituted with 1-3 F.

In some embodiments of Formula (**I-c**) (e.g., Formula (**I-c-1**) or Formula (**I-c-2**)), $\mathbf{L^{A1}}$ is CH_2.

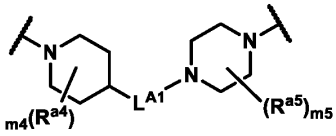
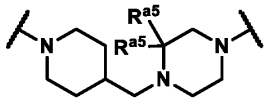
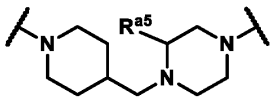
In some embodiments of Formula (**I-c**) (e.g., Formula (**I-c-1**) or Formula (**I-c-2**)), each $\mathbf{R^{a4}}$ is independently selected from the group consisting of: F and C_{1-3} alkyl optionally substituted with 1-3 F; and

each $\mathbf{R^{a5}}$ is independently C_{1-3} alkyl optionally substituted with 1-3 F.

In some embodiments of Formula (**I-c**) (e.g., Formula (**I-c-1**) or Formula (**I-c-2**)), **m4** is 0; and **m5** is 0. For example, the  moiety can be .

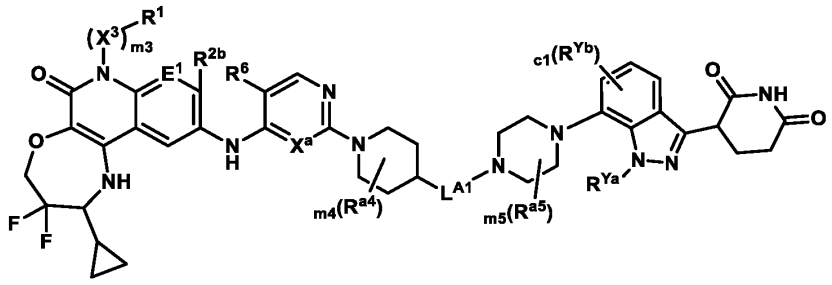
In some embodiments of Formula (**I-c**) (e.g., Formula (**I-c-1**) or Formula (**I-c-2**)), **m4** is 1 or 2; and **m5** is 0, wherein each $\mathbf{R^{a4}}$ is independently selected from the group consisting of: F, Me, and CF_3.

In some embodiments of Formula (**I-c**) (e.g., Formula (**I-c-1**) or Formula (**I-c-2**)), **m4** is 0; and **m5** is 1 or 2, wherein each $\mathbf{R^{a5}}$ is independently selected from the group consisting of Me and CF_3.

In some embodiments of Formula (**I-c**) (e.g., Formula (**I-c-1**) or Formula (**I-c-2**)), the  moiety is  or .

In some embodiments, each $\mathbf{R^{a5}}$ is independently selected from the group consisting of Me and CF_3.

In some embodiments, the compounds of Formula (**I**) (e.g., Formula (**I-a**)) are compounds of Formula (**I-d**):



Formula (**I-d**)

or pharmaceutically acceptable salts thereof, wherein:

$\mathbf{E^1}$ is $C\mathbf{R^{2a}}$ or N;

R^{2a} and R^{2b} are each independently selected from the group consisting of: H and F;

m4 and **m5** are independently 0, 1, or 2;

each R^{a4} is independently selected from the group consisting of: F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F;

each R^{a5} is independently C_{1-3} alkyl optionally substituted with 1-3 F;

L^{A1} is CH_2 or CHR^L, and

R^L is C_{1-3} alkyl optionally substituted with 1-3 R^c;

c1 is 0, 1, or 2;

R^{Ya} is selected from the group consisting of:

(a) H;

(b) C_{1-6} alkyl optionally substituted with 1-3 R^c; and

(c) –(C_{0-3} alkylene)-R^{b1}, wherein R^{b1} is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 R^g; and

each R^{Yb} is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 R^c.

In some embodiments of Formula (**I-d**), one or more of **(1)-(4)** applies:

(1) R^{2b} is F;

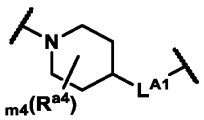
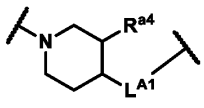
(2) E^1 is N;

(3) R^{Ya} is selected from the group consisting of: C_{2-6} alkyl optionally substituted with 1-3 R^c, and –(C_{0-3} alkylene)-R^{b1}, wherein R^{b1} is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 R^g; and/or

(4) c1 is 2.

In some embodiments of Formula (**I-d**), two or more of **(1)-(5)** apply:

(1) m4 is 2;

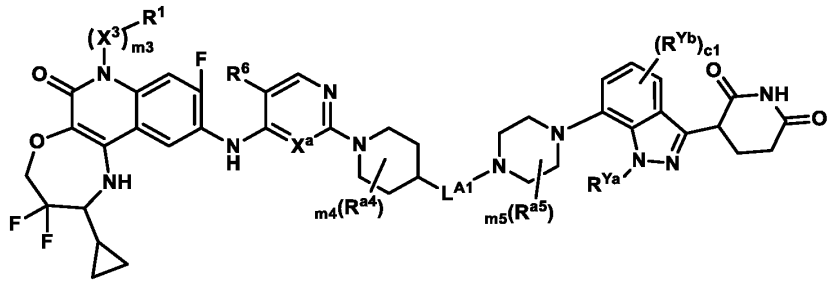
(2) m4 is 1, and the  moiety is: ;

(3) m5 is 1 or 2;

(4) L^{A1} is CHR^L; and/or

(5) c1 is 1 or 2.

In some embodiments, the compounds of Formula (**I-d**) are compounds of Formula (**I-d-1**):



Formula (**I-d-1**)

or pharmaceutically acceptable salts thereof.

In some embodiments of Formula (**I-d**) (e.g., Formula (**I-d-1**)), $\mathbf{R^{Ya}}$ is selected from the group consisting of:

(a) C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$; and

(b) –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$ (e.g., C_{3-6} cycloalkyl optionally substituted with 1-3 F); and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$.

In some embodiments of Formula (**I-d**) (e.g., Formula (**I-d-1**)), $\mathbf{R^{Ya}}$ is C_{1-3} alkyl optionally substituted with 1-3 F (e.g., C_{1-3} alkyl (e.g., methyl)), and

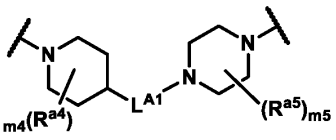
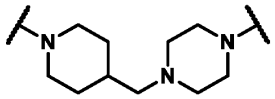
each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: F and C_{1-3} alkyl optionally substituted with 1-3 F.

In some embodiments of Formula (**I-d**) (e.g., Formula (**I-d-1**)), each $\mathbf{R^{a4}}$ is independently selected from the group consisting of: F and C_{1-3} alkyl optionally substituted with 1-3 F; and

each $\mathbf{R^{a5}}$ is independently C_{1-3} alkyl optionally substituted with 1-3 F.

In some embodiments of Formula (**I-d**) (e.g., Formula (**I-d-1**)), $\mathbf{L^{A1}}$ is CH_2.

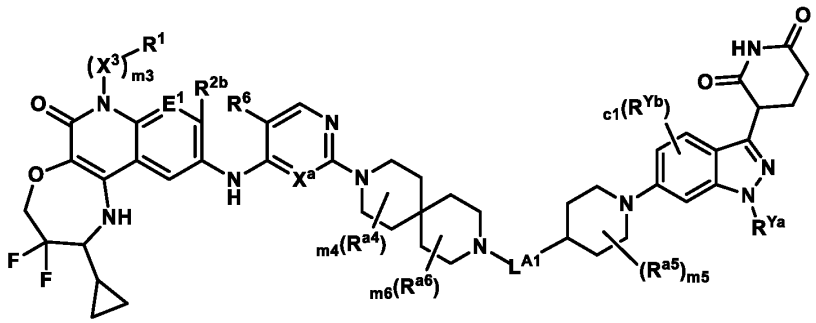
In some embodiments of Formula (**I-d**) (e.g., Formula (**I-d-1**)), **m4** is 0; and **m5** is 0.

For example, the  moiety can be .

In some embodiments of Formula (**I-d**) (e.g., Formula (**I-d-1**)), **m4** is 1 or 2; and **m5** is 0, wherein each $\mathbf{R^{a4}}$ is independently selected from the group consisting of: F, Me, and CF_3.

In some embodiments of Formula (**I-d**) (e.g., Formula (**I-d-1**)), **m4** is 0; and **m5** is 1 or 2, wherein each $\mathbf{R^{a5}}$ is independently selected from the group consisting of: Me and CF_3.

In some embodiments, the compounds of Formula (**I**) (e.g., Formula (**I-a**)) are compounds of Formula (**I-e**):



Formula (**I-e**)

or pharmaceutically acceptable salts thereof, wherein:

$\mathbf{E^1}$ is $C\mathbf{R^{2a}}$ or N;

$\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are each independently selected from the group consisting of: H and F;

m4, **m5**, and **m6** are independently 0, 1, or 2, provided that **m4** + **m6** is 0, 1, 2, or 3;

each $\mathbf{R^{a4}}$, $\mathbf{R^{a5}}$, and $\mathbf{R^{a6}}$ is independently selected from the group consisting of: F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F;

$\mathbf{L^{A1}}$ is CH_2 or $CH\mathbf{R^L}$, and

$\mathbf{R^L}$ is C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$;

c1 is 0, 1, or 2;

$\mathbf{R^{Ya}}$ is selected from the group consisting of:

(a) H;

(b) C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$; and

(c) –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$; and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$.

In some embodiments of Formula (**I-e**), one or more of **(1)-(7)** applies:

(1) $\mathbf{R^{2b}}$ is F;

(2) $\mathbf{E^1}$ is N;

(3) one or more of **m4**, **m5**, and **m6** is independently 1 or 2;

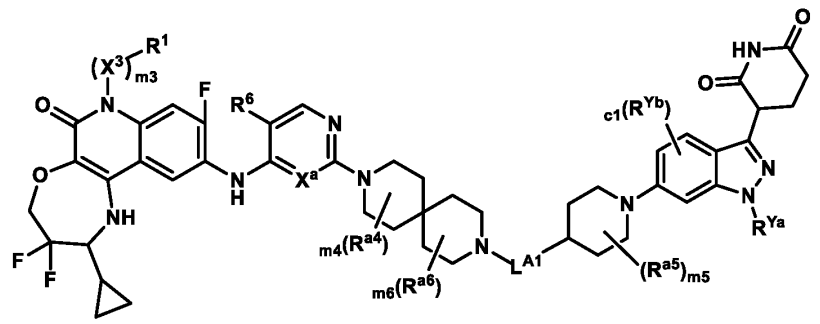
(4) $\mathbf{L^{A1}}$ is $CH\mathbf{R^L}$;

(5) c1 is 1, and $\mathbf{R^{Yb}}$ is C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$;

(6) c1 is 2; and/or

(7) $\mathbf{R^{Ya}}$ is selected from the group consisting of: C_{2-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$, and –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$.

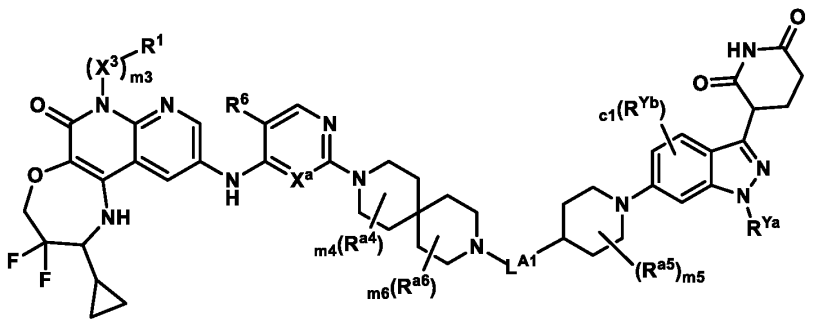
In some embodiments, the compounds of Formula (**I-e**) are compounds of Formula (**I-e-1**):



Formula (**I-e-1**)

or pharmaceutically acceptable salts thereof.

In some embodiments, the compounds of Formula (**I-e**) are compounds of Formula (**I-e-2**):



Formula (**I-e-2**)

or pharmaceutically acceptable salts thereof.

In some embodiments of Formula (**I-e**) (e.g., Formula (**I-e-1**) or Formula (**I-e-2**)), $\mathbf{R^{Ya}}$ is selected from the group consisting of:

(a) C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$; and

(b) –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$ (e.g., C_{3-6} cycloalkyl optionally substituted with 1-3 F); and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$.

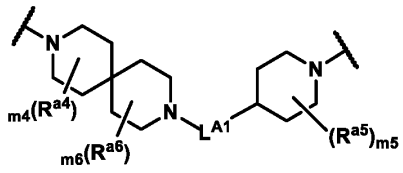
In some embodiments of Formula (**I-e**) (e.g., Formula (**I-e-1**) or Formula (**I-e-2**)), $\mathbf{R^{Ya}}$ is C_{1-3} alkyl optionally substituted with 1-3 F (e.g., C_{1-3} alkyl (e.g., methyl)), and

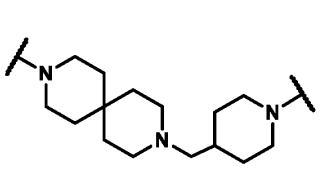
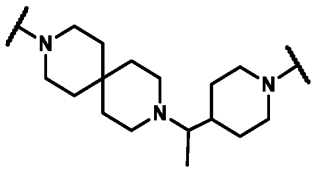
each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: F and C_{1-3} alkyl optionally substituted with 1-3 F.

In some embodiments of Formula (**I-e**) (e.g., Formula (**I-e-1**) or Formula (**I-e-2**)), each $\mathbf{R^{a4}}$, $\mathbf{R^{a5}}$, and $\mathbf{R^{a6}}$ is independently selected from the group consisting of: F and C_{1-3} alkyl optionally substituted with 1-3 F.

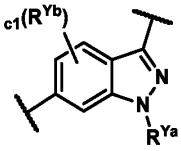
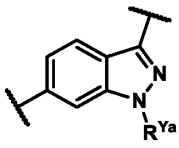
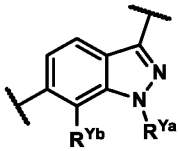
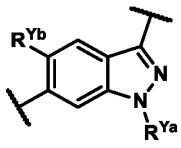
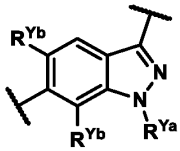
In some embodiments of Formula (**I-e**) (e.g., Formula (**I-e-1**) or Formula (**I-e-2**)), $\mathbf{L^{A1}}$ is CH_2.

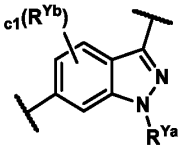
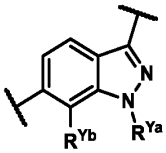
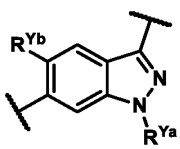
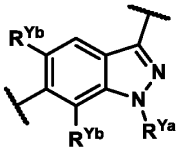
In some embodiments of Formula (**I-e**) (e.g., Formula (**I-e-1**) or Formula (**I-e-2**)), $\mathbf{L^{A1}}$ is CHMe.

In some embodiments of Formula (**I-e**) (e.g., Formula (**I-e-1**) or Formula (**I-e-2**)), **m4** is 0; **m5** is 0; and **m6** is 0. For example, the  moiety can be:

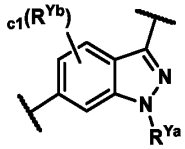
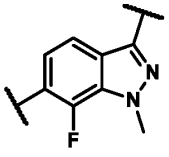
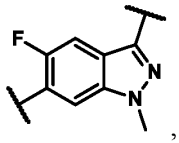
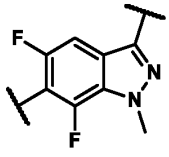
 or .

In some embodiments of Formula (**I-e**) (e.g., Formula (**I-e-1**) or Formula (**I-e-2**)), **m4** is 0; **m6** is 0; and **m5** is 1 or 2, wherein each $\mathbf{R}^{a5}$ is independently selected from the group consisting of: F, Me, and CF_3.

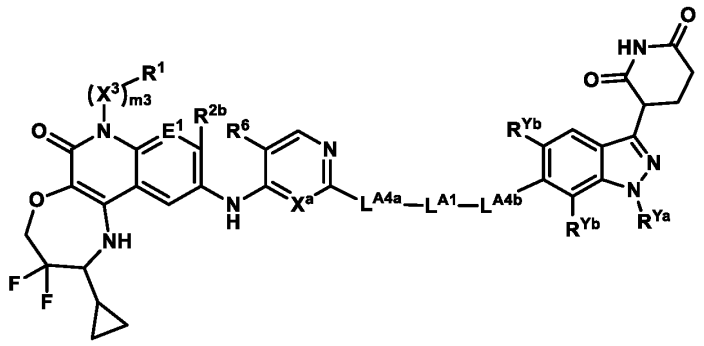
In some embodiments of Formula (**I-a**) (e.g., Formula (**I-a-1**) or (**I-a-2**)), Formula (**I-b**) (e.g., Formula (**I-b-1**) or (**I-b-2**)), Formula (**I-c**) (e.g., Formula (**I-c-1**) or (**I-c-2**)), or Formula (**I-e**) (e.g., Formula (**I-e-1**) or (**I-e-2**)), the  moiety is selected from the group consisting of: , , , and .

In some embodiments of Formula (**I-a**) (e.g., Formula (**I-a-1**) or (**I-a-2**)), Formula (**I-b**) (e.g., Formula (**I-b-1**) or (**I-b-2**)), Formula (**I-c**) (e.g., Formula (**I-c-1**) or (**I-c-2**)), or Formula (**I-e**) (e.g., Formula (**I-e-1**) or (**I-e-2**)), the  moiety is selected from the group consisting of: , , and , wherein each $\mathbf{R}^{Yb}$ is

independently F or C_{1-3} alkyl optionally substituted with 1-3 F; and $\mathbf{R^{Ya}}$ is C_{1-3} alkyl optionally substituted with 1-3 F (e.g., C_{1-3} alkyl (e.g., methyl)).

In some embodiments of Formula (**I-a**) (e.g., Formula (**I-a-1**) or (**I-a-2**)), Formula (**I-b**) (e.g., Formula (**I-b-1**) or (**I-b-2**)), Formula (**I-c**) (e.g., Formula (**I-c-1**) or (**I-c-2**)), or Formula (**I-e**) (e.g., Formula (**I-e-1**) or (**I-e-2**)), the  moiety is selected from the group consisting of: , , and .

In some embodiments, the compounds of Formula (**I-a**) are compounds of Formula (**I-a-3**):



Formula (**I-a-3**)

or pharmaceutically acceptable salts thereof, wherein:

$\mathbf{E^1}$ is $C\mathbf{R^{2a}}$ or N;

$\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are each independently selected from the group consisting of: H and F;

$\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ are independently 4-12 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R^a}$;

$\mathbf{L^{A1}}$ is CH_2 or $CH\mathbf{R^L}$, and

$\mathbf{R^L}$ is selected from the group consisting of: F, OH, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$;

$\mathbf{R^{Ya}}$ is selected from the group consisting of:

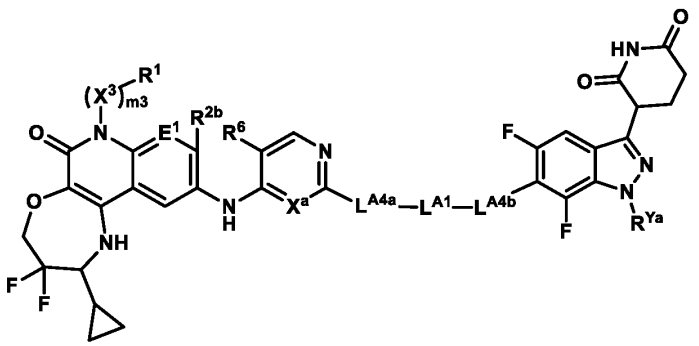
(a) H;

(b) C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$; and

(c) –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$ (e.g., C_{3-6} cycloalkyl optionally substituted with 1-3 F); and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$ (e.g., C_{1-3} alkyl optionally substituted with 1-3 F).

In some embodiments, the compounds of Formula (**I-a**) (e.g., Formula (**I-a-3**)) are compounds of Formula (**I-a-4**):



Formula (**I-a-4**)

or pharmaceutically acceptable salts thereof.

In some embodiments of Formula (**I-a-3**) or (**I-a-4**), $\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ are independently monocyclic 4-6 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R^a}$;

$\mathbf{R^L}$ is C_{1-3} methyl optionally substituted with 1-3 F; and

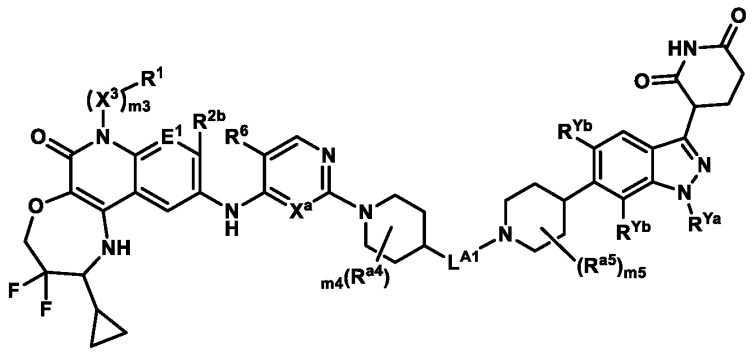
each $\mathbf{R^a}$ present on $\mathbf{L^{A4a}}$ and/or $\mathbf{L^{A4b}}$ is independently selected from the group consisting of: F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F.

In some embodiments of Formula (**I-a-3**) or (**I-a-4**), $\mathbf{E^1}$ is CH; and $\mathbf{R^{2b}}$ is H.

In some embodiments of Formula (**I-a-3**) or (**I-a-4**), $\mathbf{E^1}$ is CH; and $\mathbf{R^{2b}}$ is F.

In some embodiments of Formula (**I-a-3**) or (**I-a-4**), $\mathbf{L^{A1}}$ is CH_2.

In some embodiments, the compounds of Formula (**I-b**) are compounds of Formula (**I-b-3**):



Formula (**I-b-3**)

or pharmaceutically acceptable salts thereof, wherein:

$\mathbf{E^1}$ is $C\mathbf{R^{2a}}$ or N;

$\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are each independently selected from the group consisting of: H and F;

m4 and **m5** are independently 0, 1, or 2;

each $\mathbf{R^{a4}}$ and $\mathbf{R^{a5}}$ is independently selected from the group consisting of: F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F;

$\mathbf{L^{A1}}$ is CH_2 or $CH\mathbf{R^L}$, and

$\mathbf{R^L}$ is C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$;

$\mathbf{R^{Ya}}$ is selected from the group consisting of:

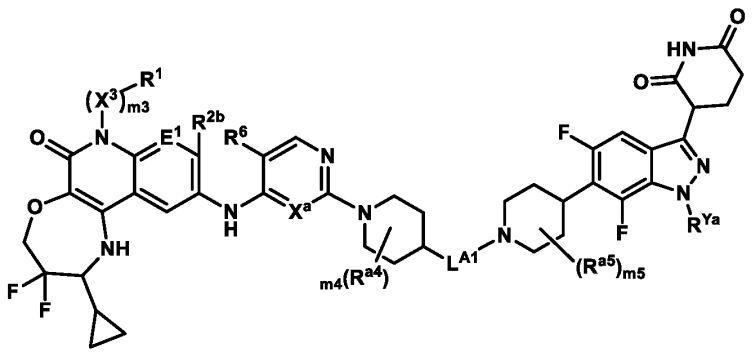
(a) H;

(b) C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$; and

(c) –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$ (e.g., C_{3-6} cycloalkyl optionally substituted with 1-3 F); and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo and C_{1-3} alkyl optionally substituted with 1-3 F.

In some embodiments, the compounds of Formula (**I-b**) (e.g., Formula (**I-b-3**)) are compounds of Formula (**I-b-4**):



Formula (**I-b-4**)

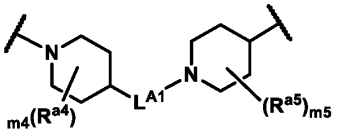
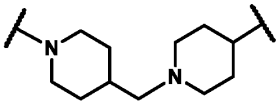
or pharmaceutically acceptable salts thereof.

In some embodiments of Formula (**I-b-3**) or (**I-b-4**), $\mathbf{E^1}$ is CH; and $\mathbf{R^{2b}}$ is H.

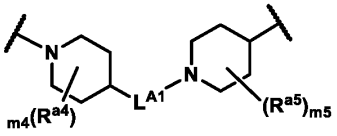
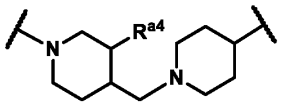
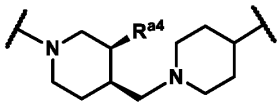
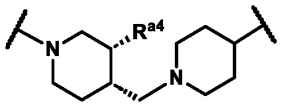
In some embodiments of Formula (**I-b-3**) or (**I-b-4**), $\mathbf{E^1}$ is CH; and $\mathbf{R^{2b}}$ is F.

In some embodiments of Formula (**I-b-3**) or (**I-b-4**), $\mathbf{L^{A1}}$ is CH_2.

In some embodiments of Formula (**I-b-3**) or (**I-b-4**), **m4** is 0; and **m5** is 0.

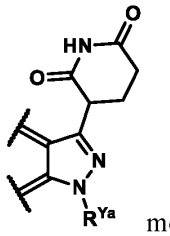
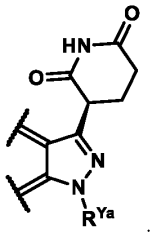
In some embodiments of Formula (**I-b-3**) or (**I-b-4**), the  moiety is .

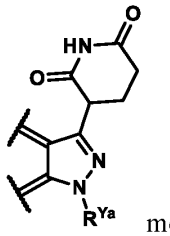
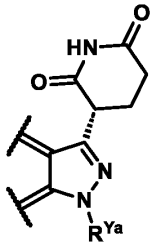
In some embodiments of Formula (**I-b-3**) or (**I-b-4**), **m4** is 1 or 2; and **m5** is 0.

In some embodiments of Formula (**I-b-3**) or (**I-b-4**), the  moiety is  (e.g.,  or ).

In some embodiments of Formula (**I-b-3**) or (**I-b-4**), each $\mathbf{R}^{a4}$ is independently selected from the group consisting of: F and C_{1-3} alkyl optionally substituted with 1-3 F. For example, each $\mathbf{R}^{a4}$ can be independently F or methyl.

In some embodiments of Formula (**I-a-3**), (**I-a-4**), (**I-b-3**), or (**I-b-4**), $\mathbf{R}^{Ya}$ is C_{1-3} alkyl optionally substituted with 1-3 F (e.g., $\mathbf{R}^{Ya}$ is C_{1-3} alkyl (e.g., methyl)).

In some embodiments of Formula (**I-a**) (e.g., Formula (**I-a-1**), (**I-a-2**), (**I-a-3**), or (**I-a-4**)), Formula (**I-b**) (e.g., Formula (**I-b-1**), (**I-b-2**), (**I-b-3**), or (**I-b-4**)), Formula (**I-c**) (e.g., Formula (**I-c-1**) or (**I-c-2**)), Formula (**I-d**) (e.g., Formula (**I-d-1**)), or Formula (**I-e**) (e.g., Formula (**I-e-1**) or (**I-e-2**)), the  moiety is .

In some embodiments of Formula (**I-a**) (e.g., Formula (**I-a-1**), (**I-a-2**), (**I-a-3**), or (**I-a-4**)), Formula (**I-b**) (e.g., Formula (**I-b-1**), (**I-b-2**), (**I-b-3**), or (**I-b-4**)), Formula (**I-c**) (e.g., Formula (**I-c-1**) or (**I-c-2**)), Formula (**I-d**) (e.g., Formula (**I-d-1**)), or Formula (**I-e**) (e.g., Formula (**I-e-1**) or (**I-e-2**)), the  moiety is .

In some embodiments of Formula (**I-a**) (e.g., Formula (**I-a-1**), (**I-a-2**), (**I-a-3**), or (**I-a-4**)), Formula (**I-b**) (e.g., Formula (**I-b-1**), (**I-b-2**), (**I-b-3**), or (**I-b-4**)), Formula (**I-c**) (e.g., Formula (**I-c-1**) or (**I-c-2**)), Formula (**I-d**) (e.g., Formula (**I-d-1**)), or Formula (**I-e**) (e.g., Formula (**I-e-1**) or (**I-e-2**)), $\mathbf{R}^{6}$ is F or Cl; and $\mathbf{X}^{a}$ is N.

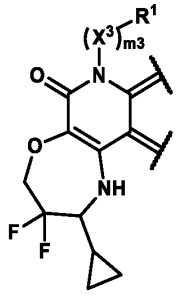
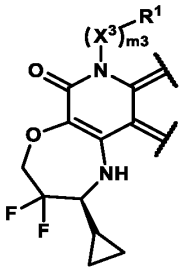
In some embodiments of Formula (**I-a**) (e.g., Formula (**I-a-1**), (**I-a-2**), (**I-a-3**), or (**I-a-4**)), Formula (**I-b**) (e.g., Formula (**I-b-1**), (**I-b-2**), (**I-b-3**), or (**I-b-4**)), Formula (**I-c**) (e.g., Formula (**I-c-1**) or (**I-c-2**)), Formula (**I-d**) (e.g., Formula (**I-d-1**)), or Formula (**I-e**) (e.g., Formula (**I-e-1**) or (**I-e-2**)), $\mathbf{R}^{6}$ is Cl; and $\mathbf{X}^{a}$ is N.

In some embodiments of Formula (**I-a**) (e.g., Formula (**I-a-1**), (**I-a-2**), (**I-a-3**), or (**I-a-4**)), Formula (**I-b**) (e.g., Formula (**I-b-1**), (**I-b-2**), (**I-b-3**), or (**I-b-4**)), Formula (**I-c**) (e.g.,

Formula (**I-c-1**) or (**I-c-2**)), Formula (**I-d**) (e.g., Formula (**I-d-1**)), or Formula (**I-e**) (e.g., Formula (**I-e-1**) or (**I-e-2**)), $-(X^3)_{m3}-R^1$ is C_{1-3} alkyl. For example, $-(X^3)_{m3}-R^1$ can be methyl.

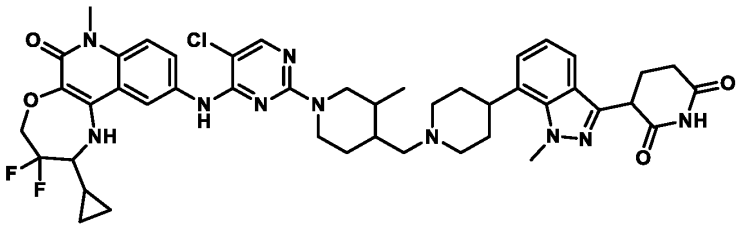
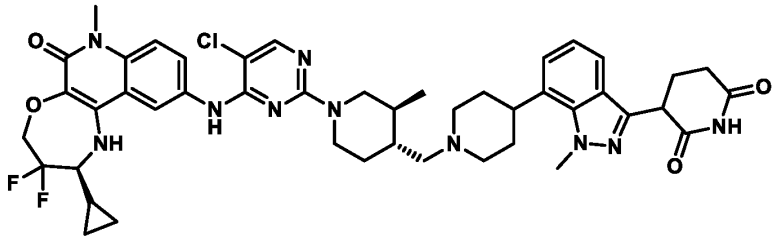
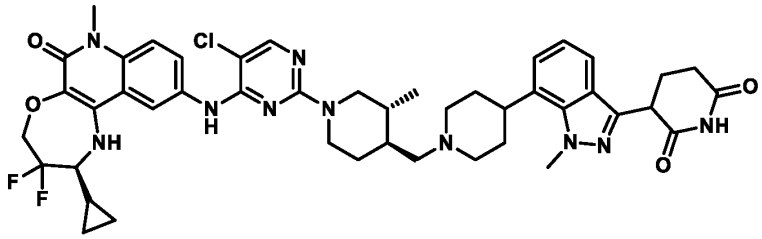
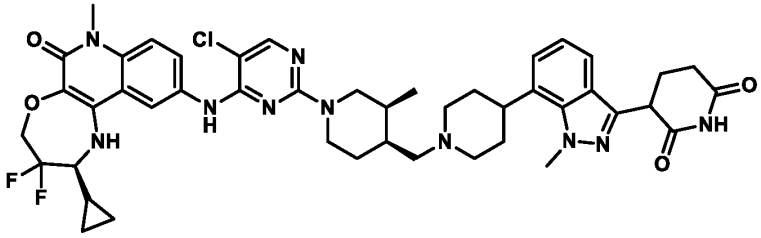
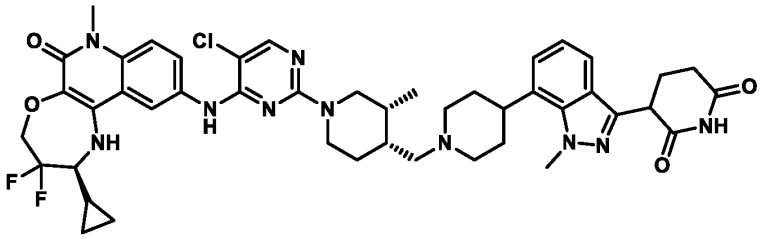
In some embodiments of Formula (**I-a**) (e.g., Formula (**I-a-1**), (**I-a-2**), (**I-a-3**), or (**I-a-4**)), Formula (**I-b**) (e.g., Formula (**I-b-1**), (**I-b-2**), (**I-b-3**), or (**I-b-4**)), Formula (**I-c**) (e.g., Formula (**I-c-1**) or (**I-c-2**)), Formula (**I-d**) (e.g., Formula (**I-d-1**)), or Formula (**I-e**) (e.g., Formula (**I-e-1**) or (**I-e-2**)), $-(X^3)_{m3}-R^1$ is H.

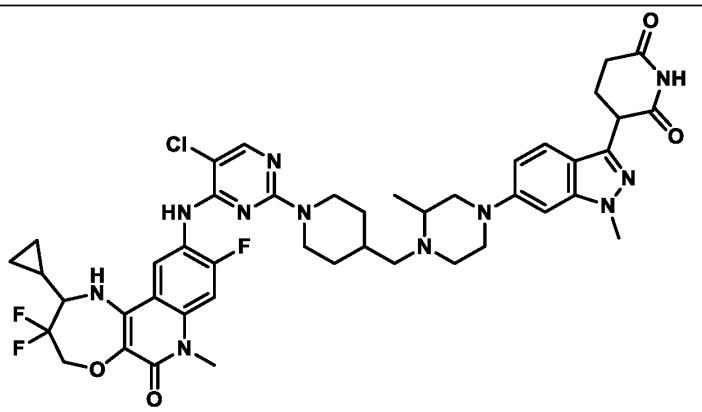
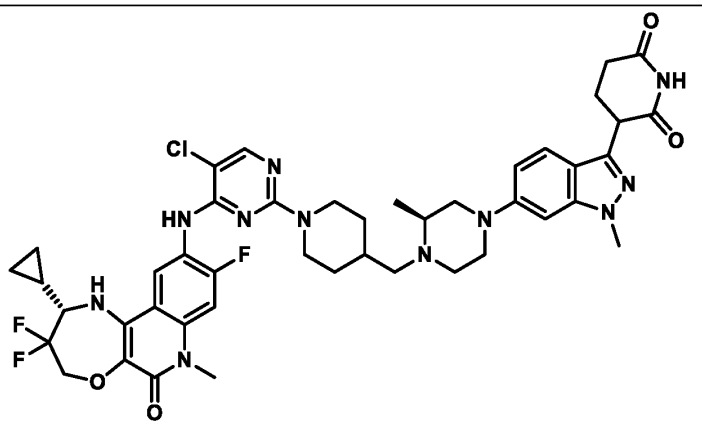
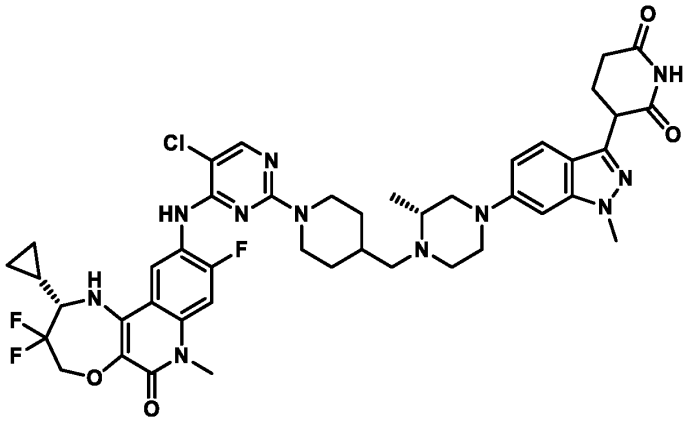
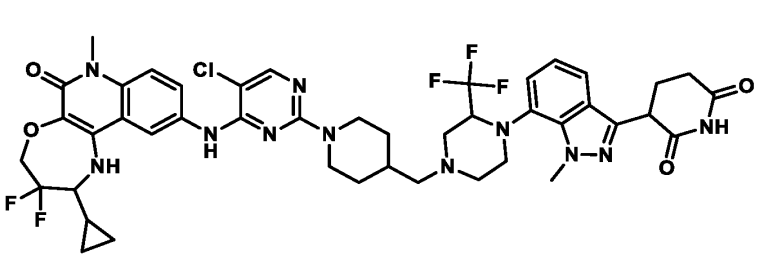
In some embodiments of Formula (**I-a**) (e.g., Formula (**I-a-1**), (**I-a-2**), (**I-a-3**), or (**I-a-4**)), Formula (**I-b**) (e.g., Formula (**I-b-1**), (**I-b-2**), (**I-b-3**), or (**I-b-4**)), Formula (**I-c**) (e.g., Formula (**I-c-1**) or (**I-c-2**)), Formula (**I-d**) (e.g., Formula (**I-d-1**)), or Formula (**I-e**) (e.g., Formula (**I-e-1**) or (**I-e-2**)), $-(X^3)_{m3}-R^1$ is $-R^{b1}$ or $-CH_2-R^{b1}$. In some embodiments, the R^{b1} is C_{3-6} cycloalkyl optionally substituted with 1-3 F.

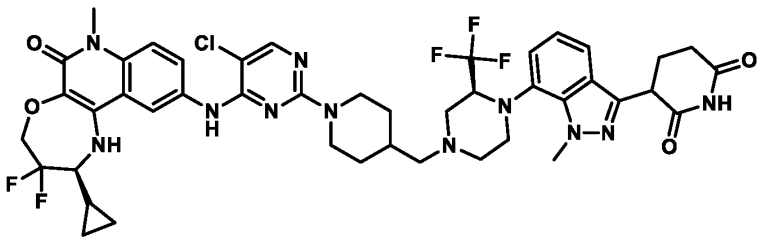
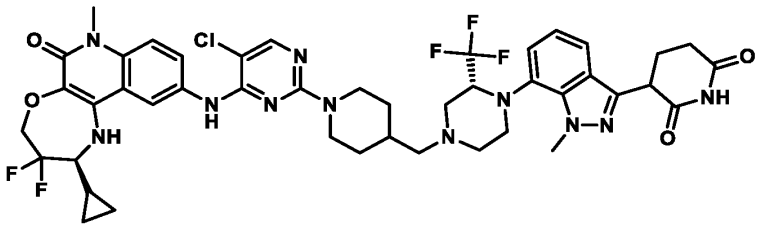
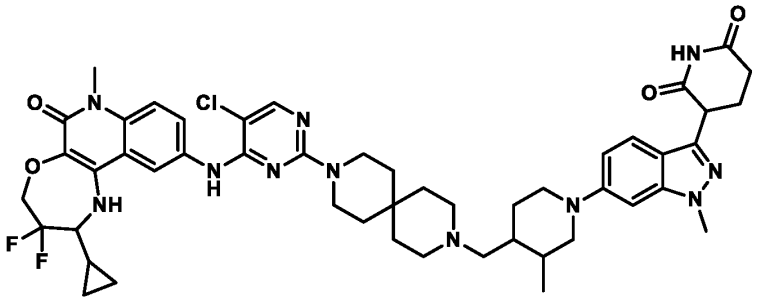
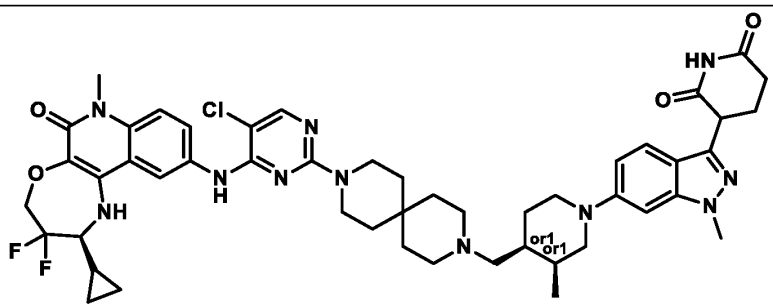
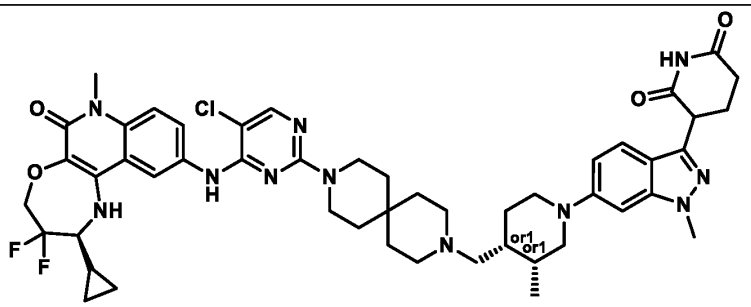
In some embodiments of Formula (**I**) (e.g., Formula (**I-1**) or (**I-2**)), Formula (**I-a**) (e.g., Formula (**I-a-1**), (**I-a-2**), (**I-a-3**), or (**I-a-4**)), Formula (**I-b**) (e.g., Formula (**I-b-1**), (**I-b-2**), (**I-b-3**), or (**I-b-4**)), Formula (**I-c**) (e.g., Formula (**I-c-1**) or (**I-c-2**)), Formula (**I-d**) (e.g., Formula (**I-d-1**)), or Formula (**I-e**) (e.g., Formula (**I-e-1**) or (**I-e-2**)), the  moiety is .

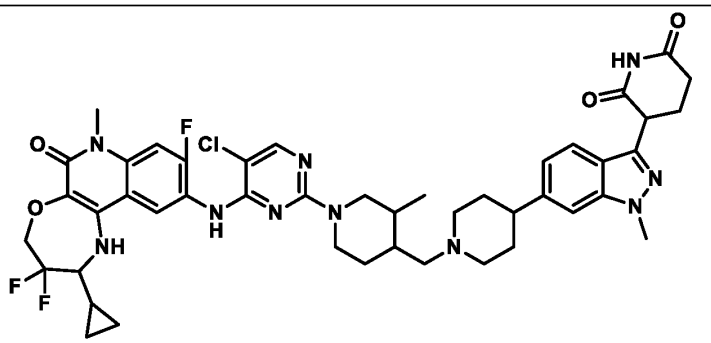
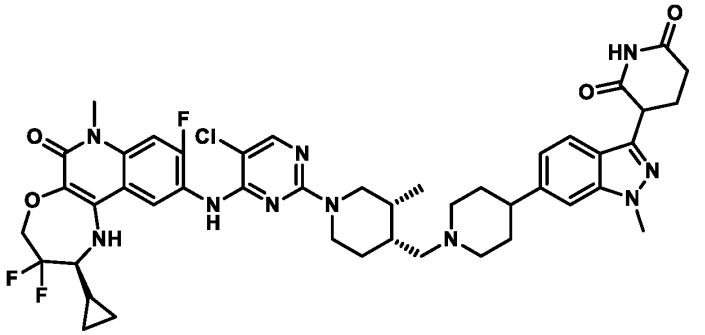
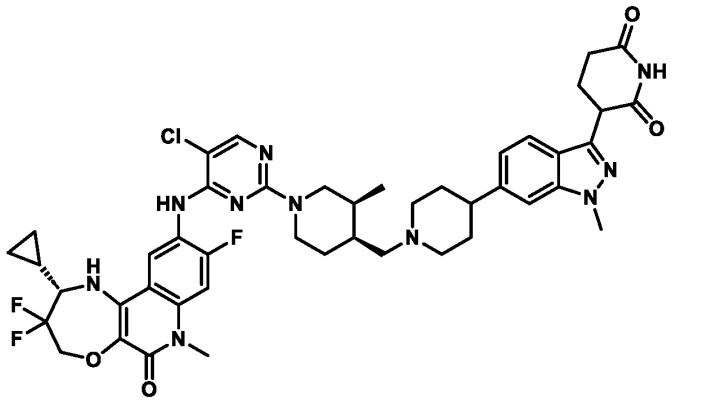
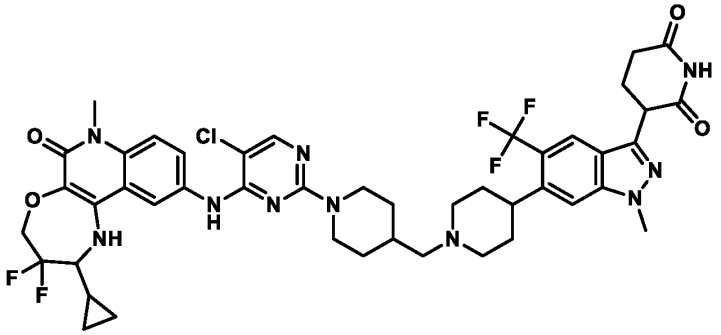
In some embodiments, the compounds of Formula (**I**) are selected from the group consisting of the compounds in **Table C1**, or pharmaceutically acceptable salts thereof.

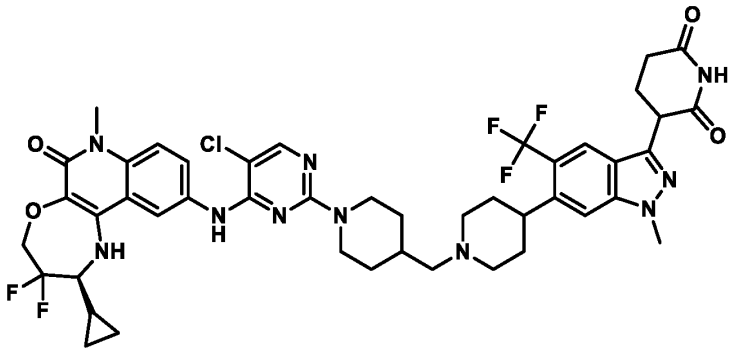
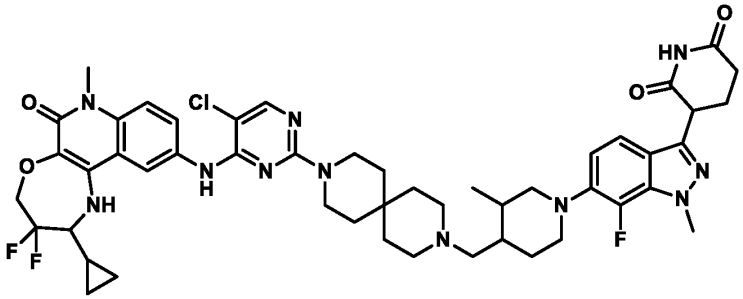
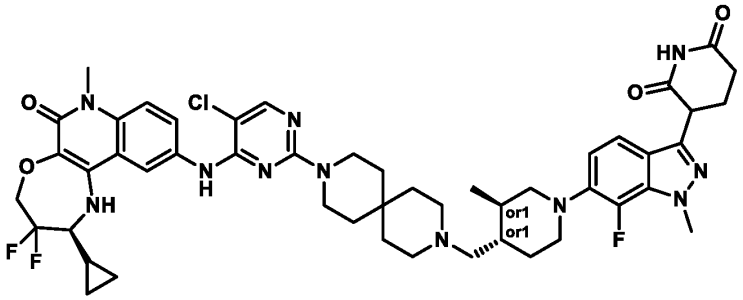
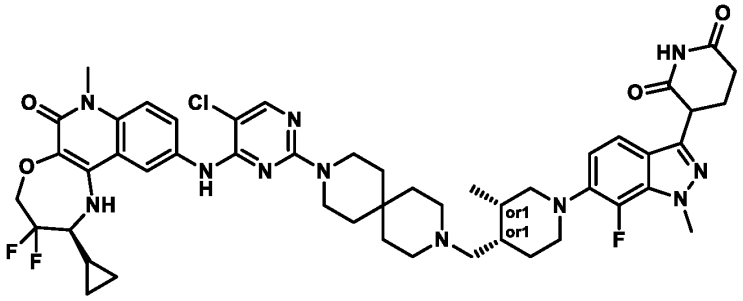
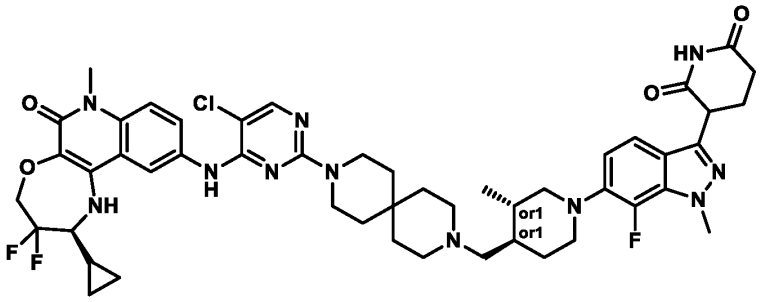
Table C1

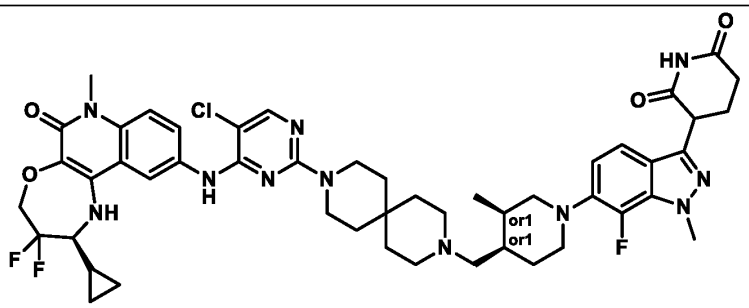
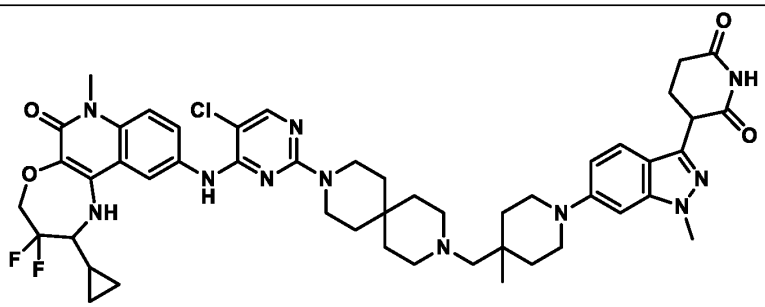
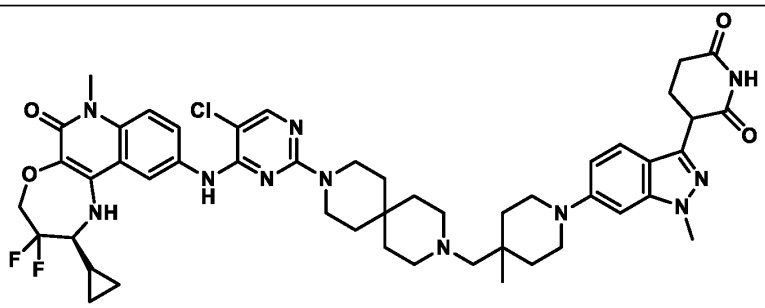
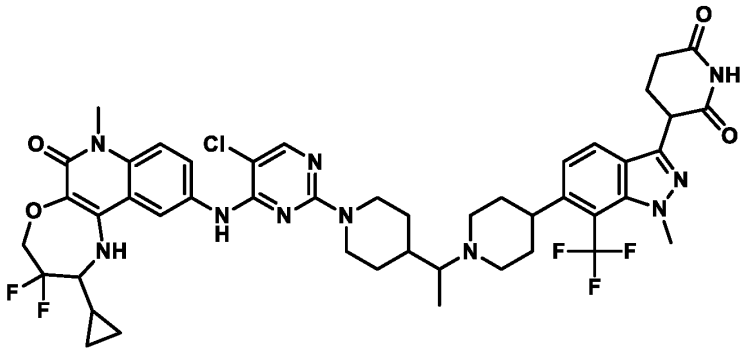
No.	Compound Structure
101	
101a	
101b	
101c	
101d	

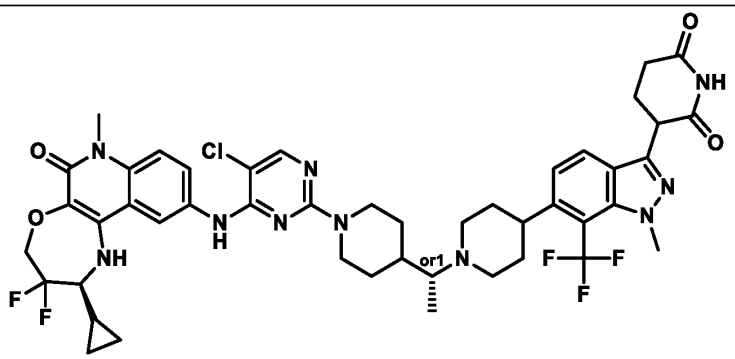
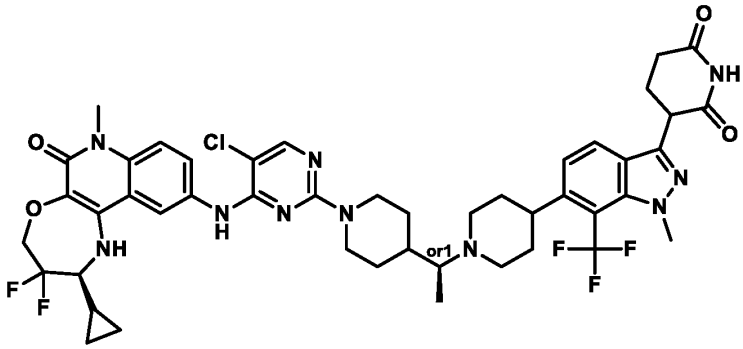
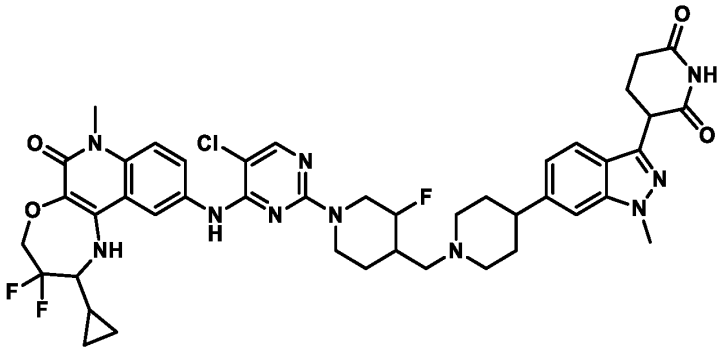
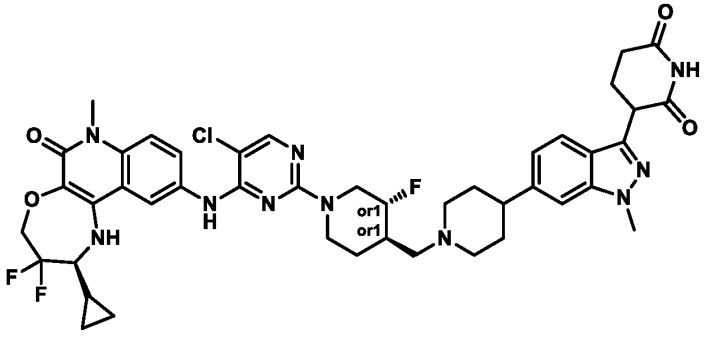
102	
102a	
102b	
103	

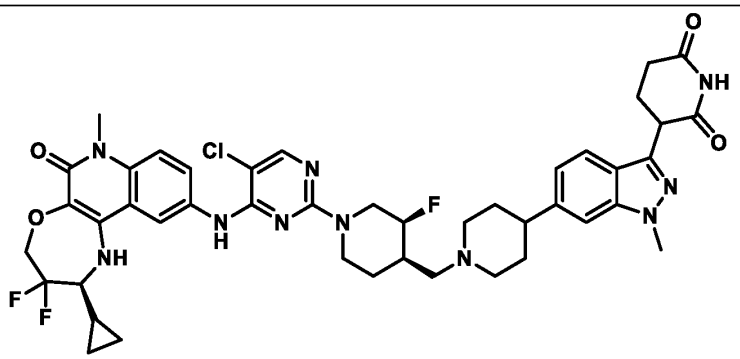
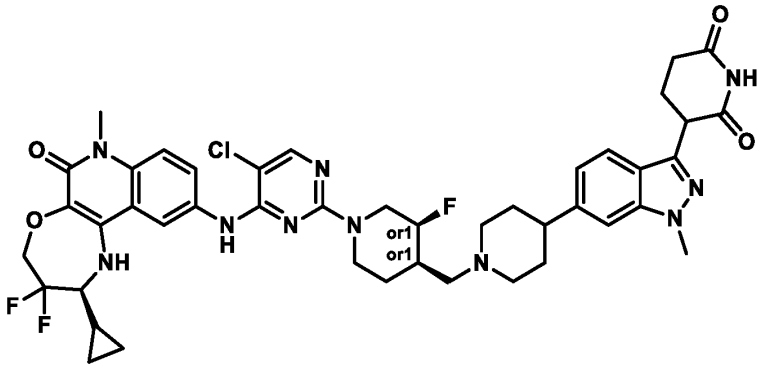
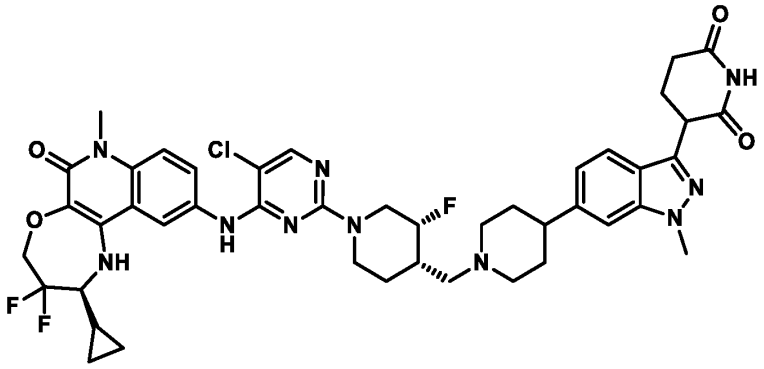
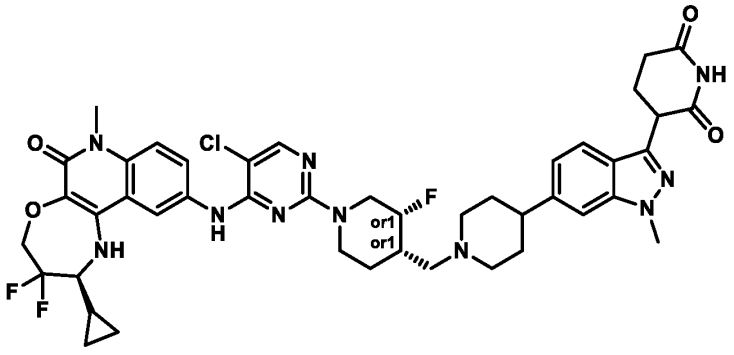
103a	
103b	
104	
104a	
104b	

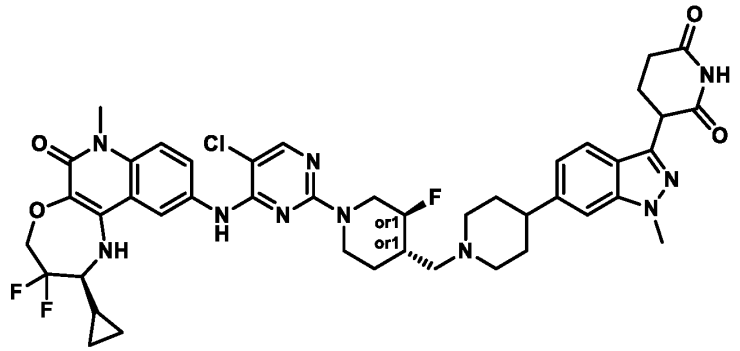
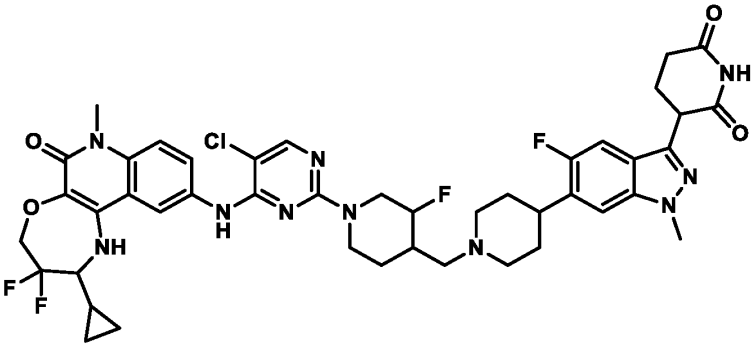
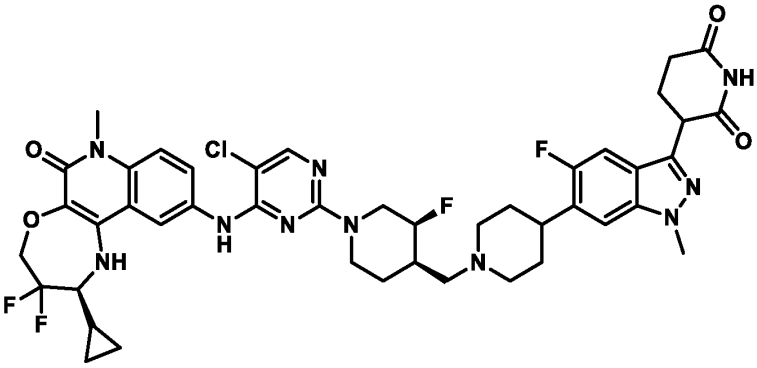
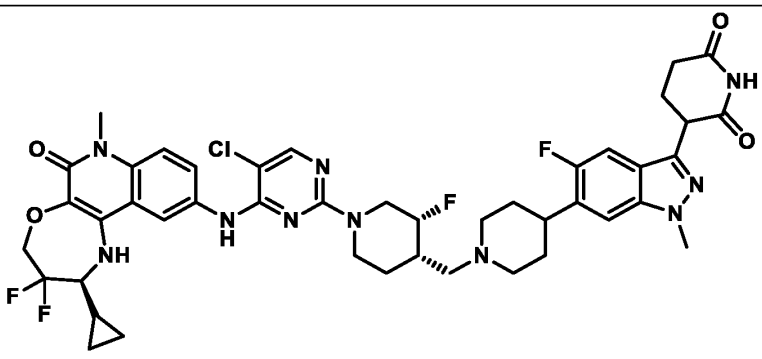
105	
105a	
105b	
106	

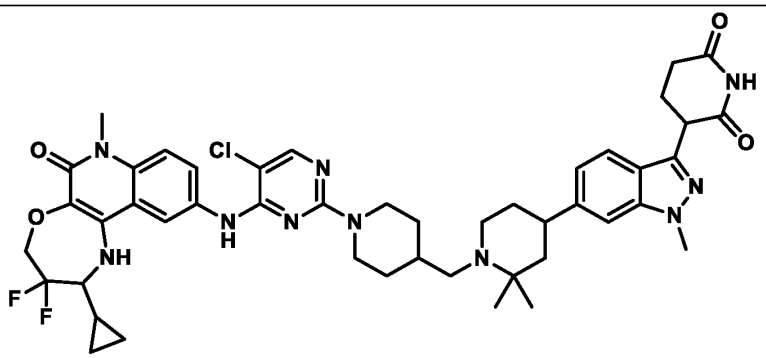
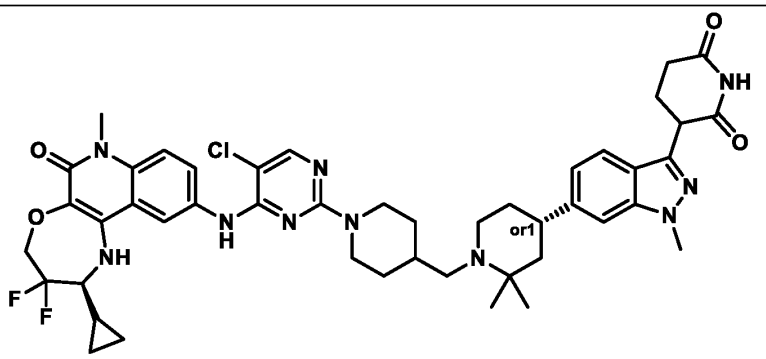
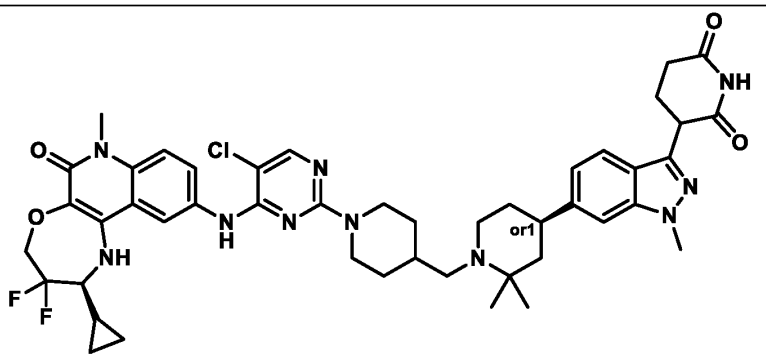
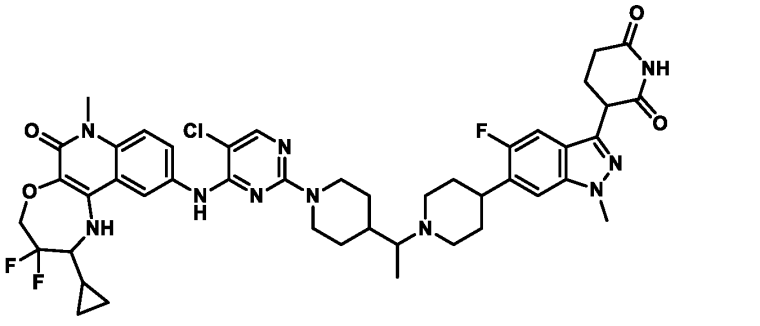
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107	
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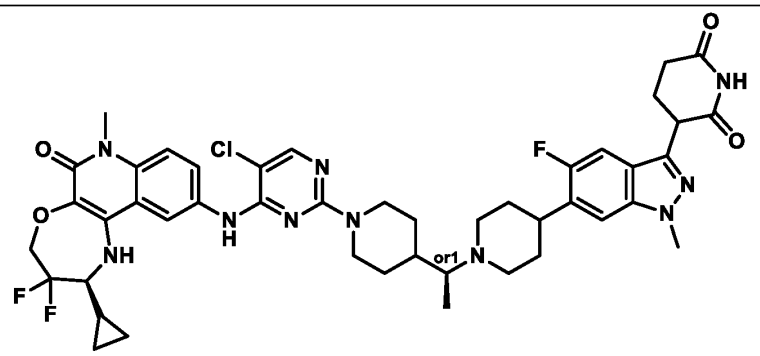
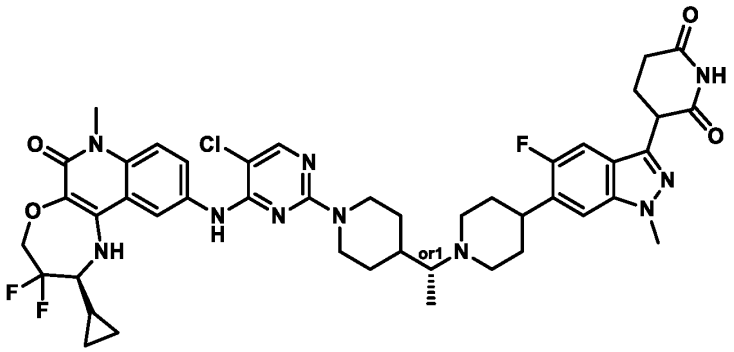
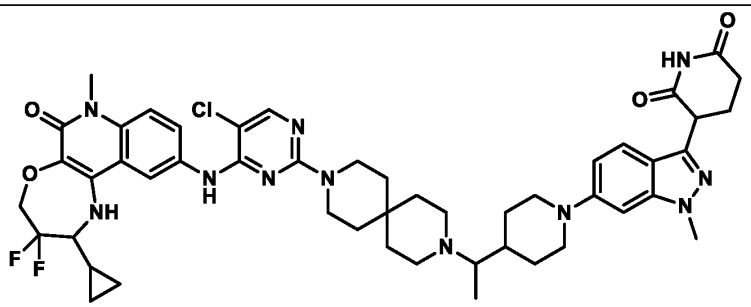
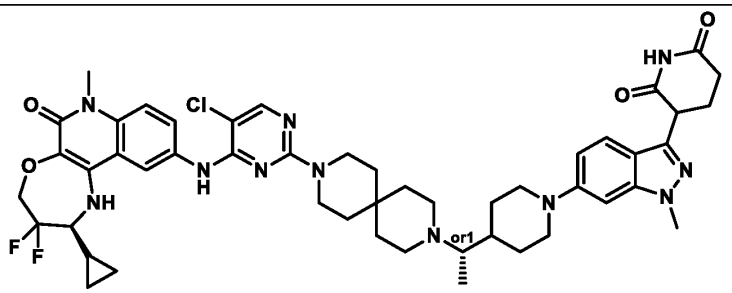
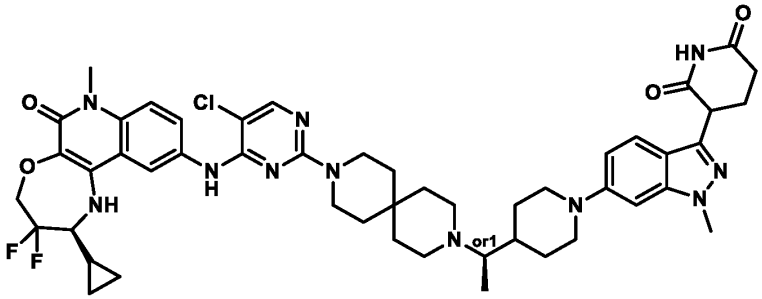
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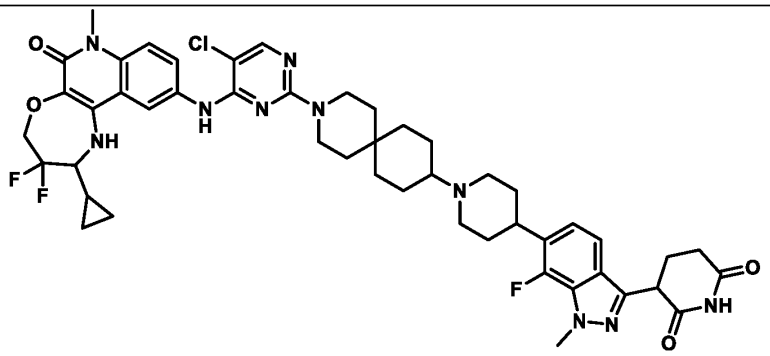
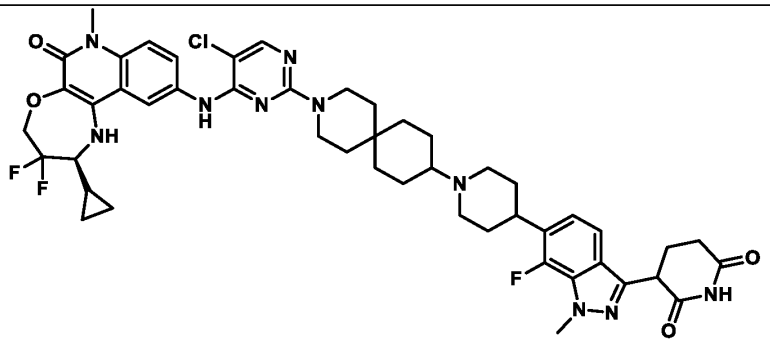
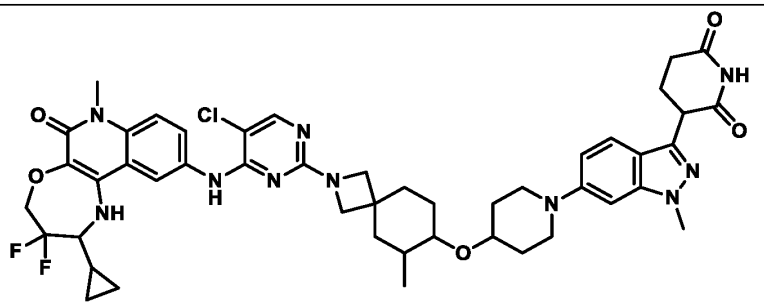
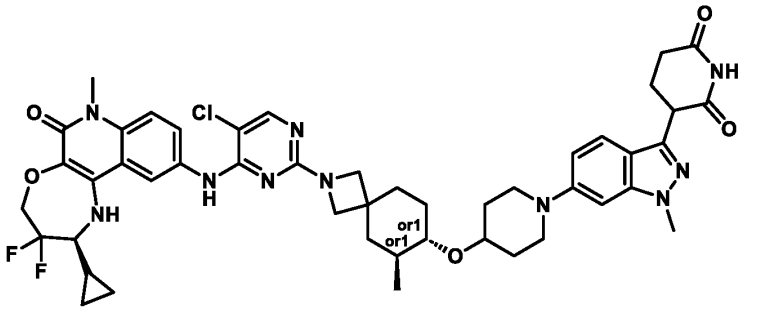
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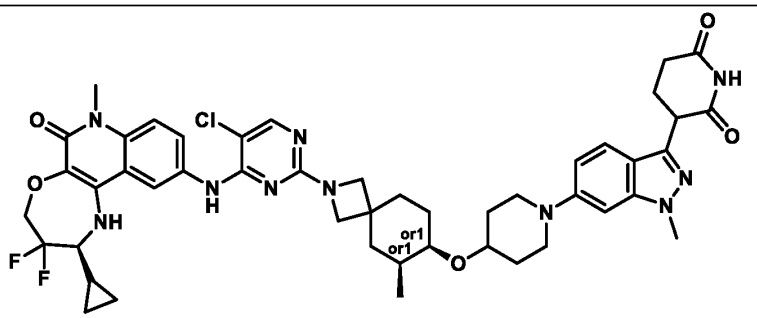
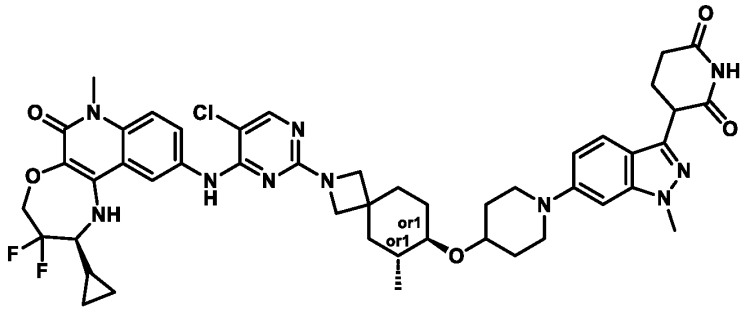
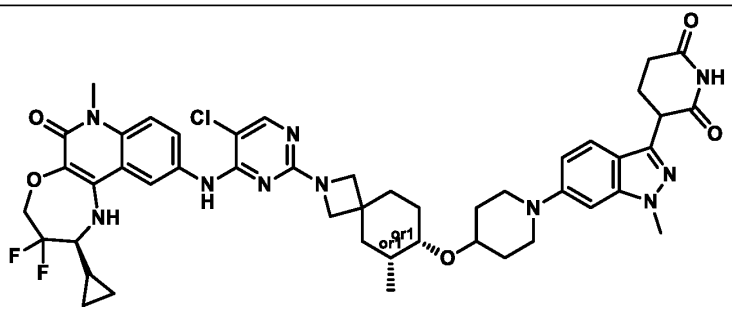
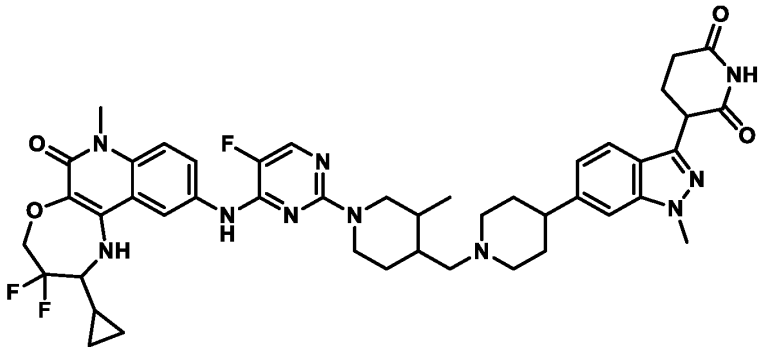
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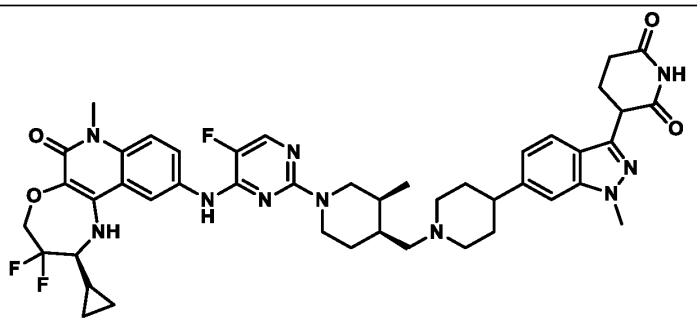
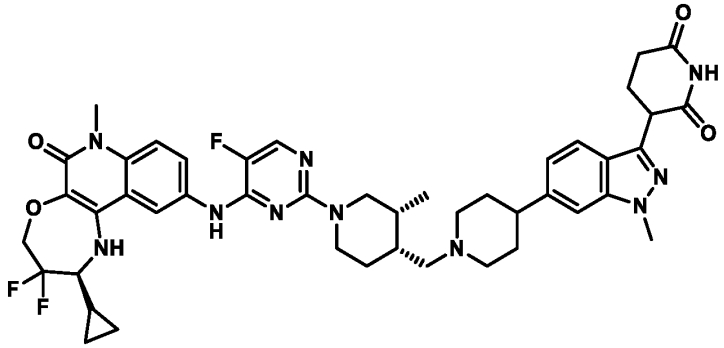
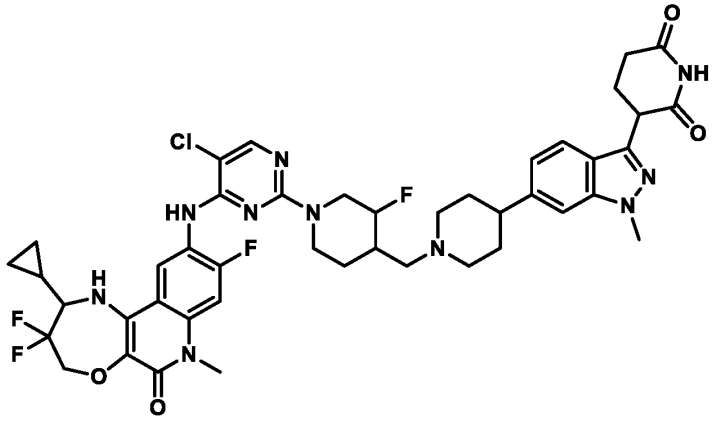
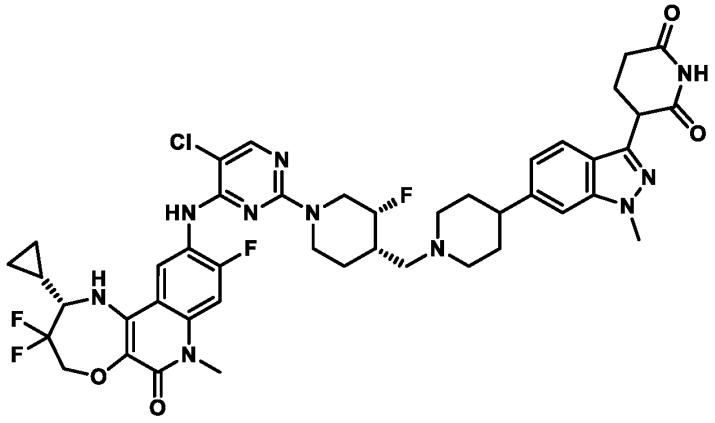
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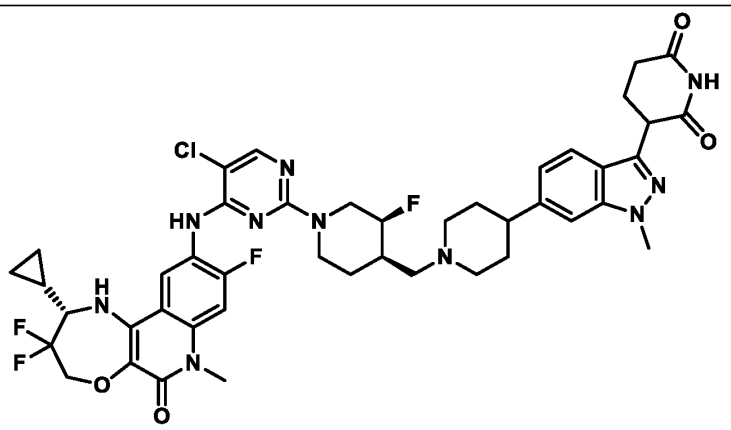
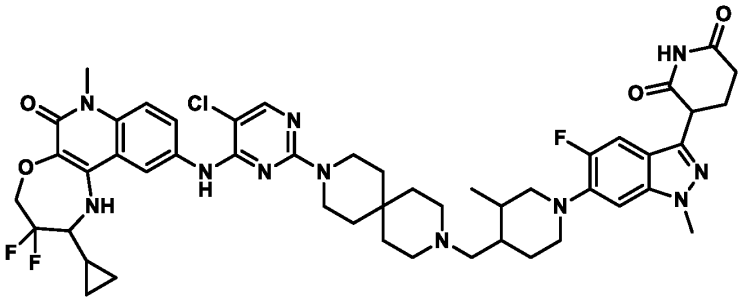
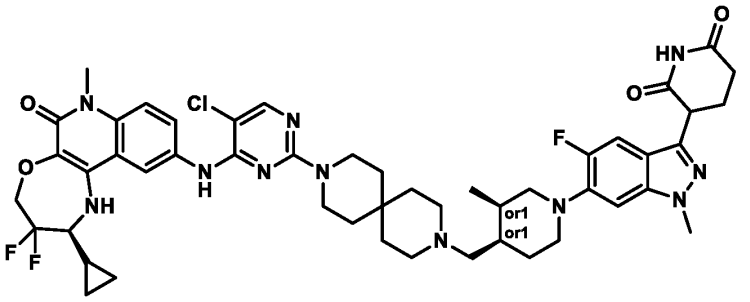
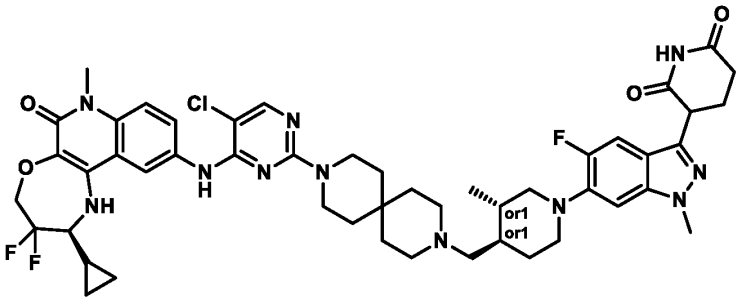
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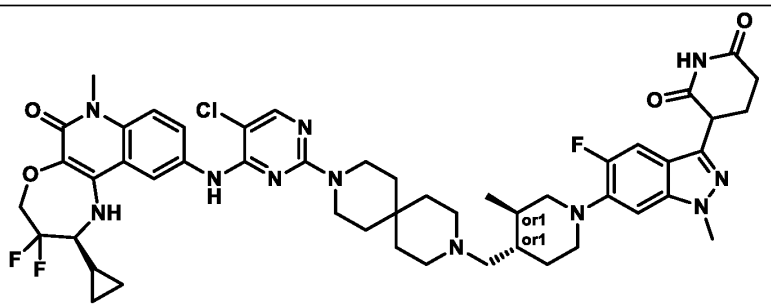
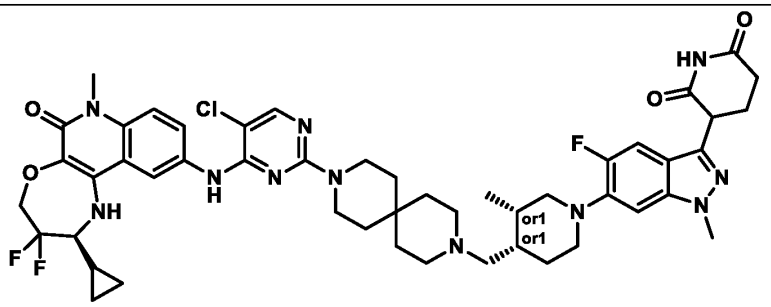
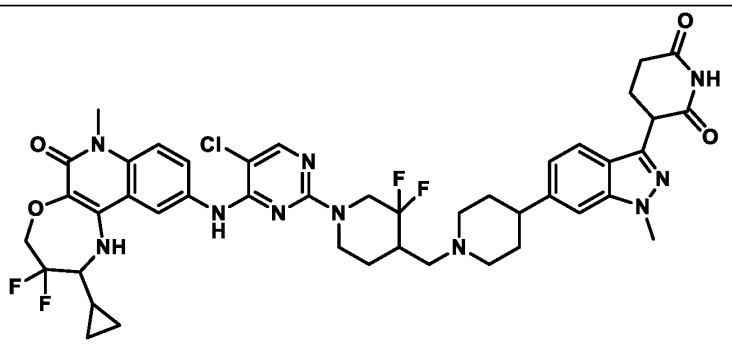
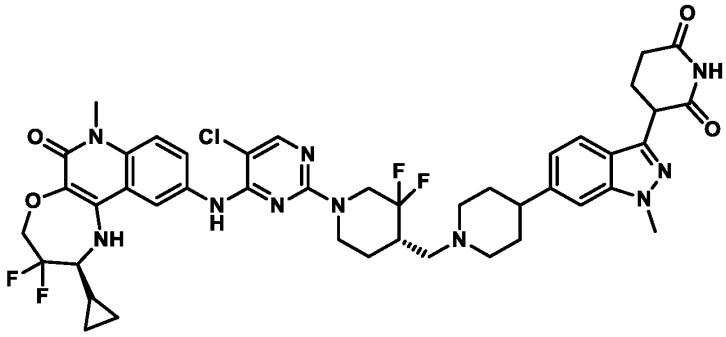
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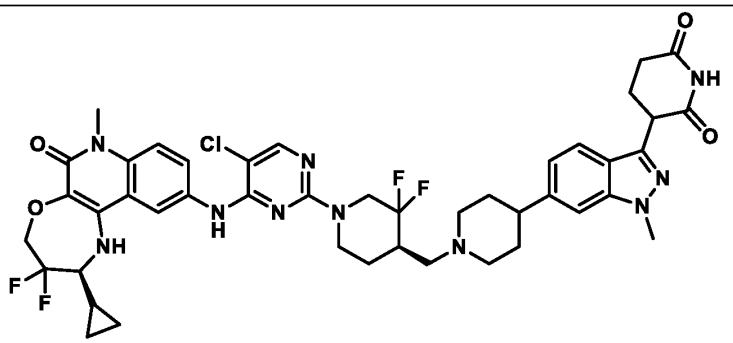
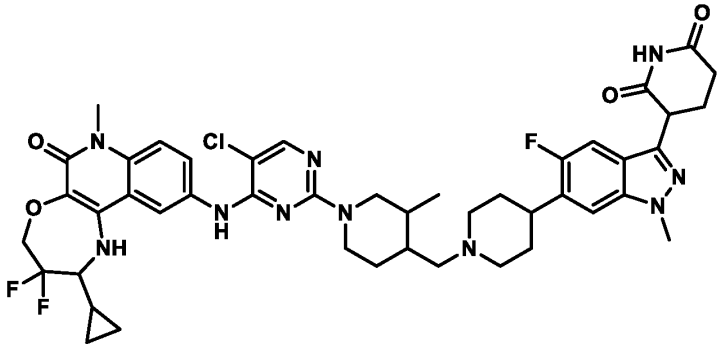
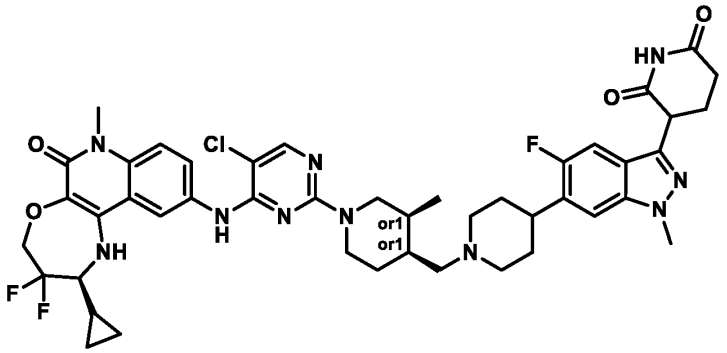
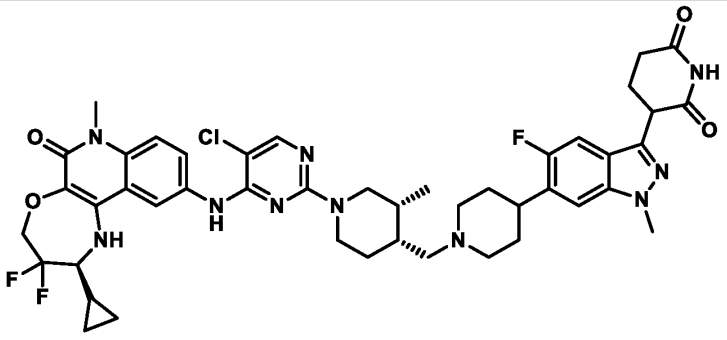
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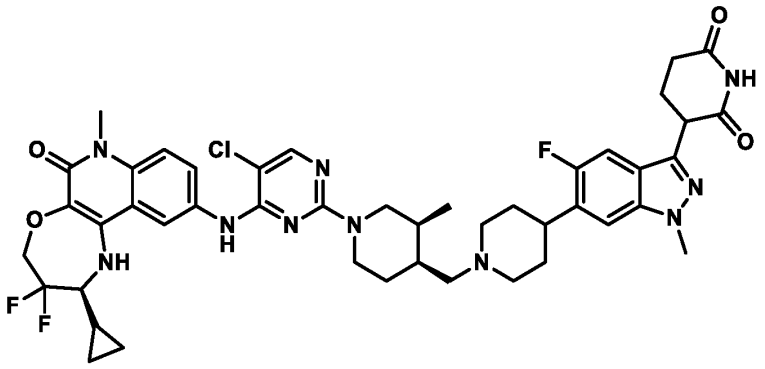
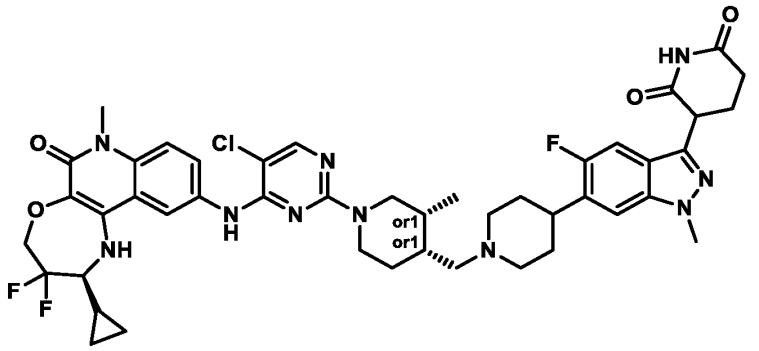
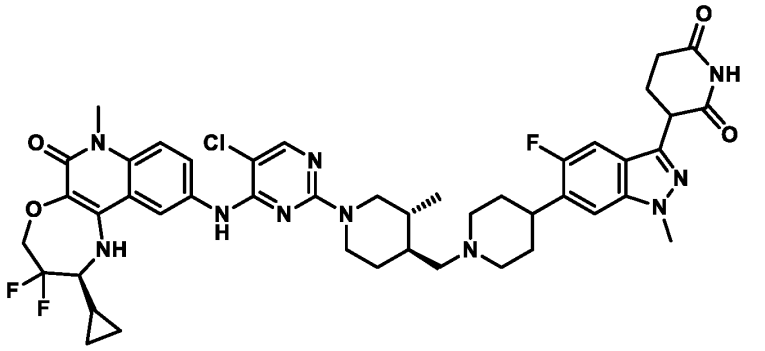
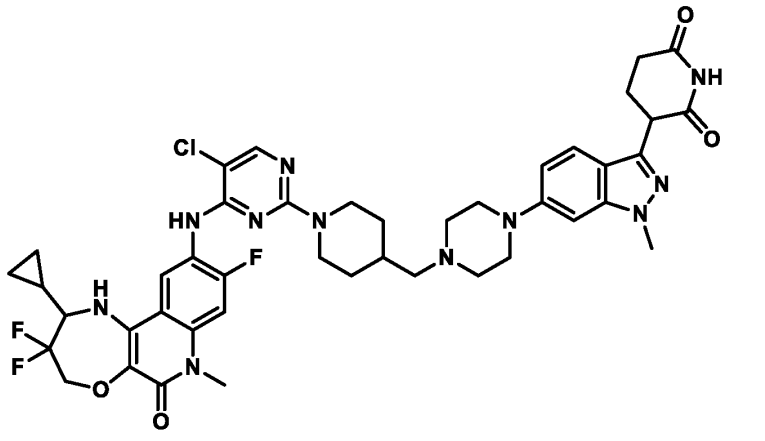
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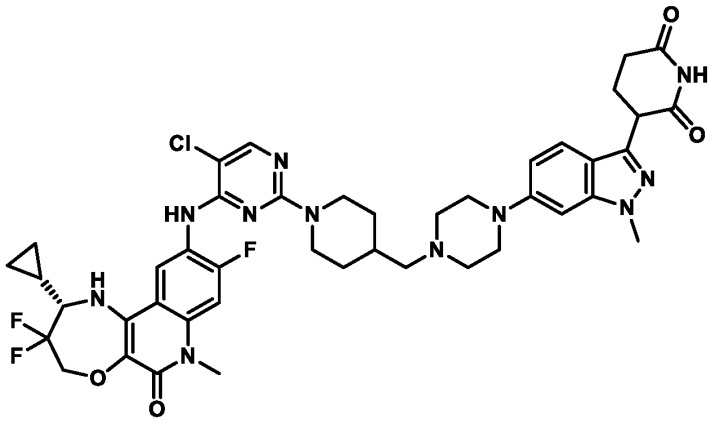
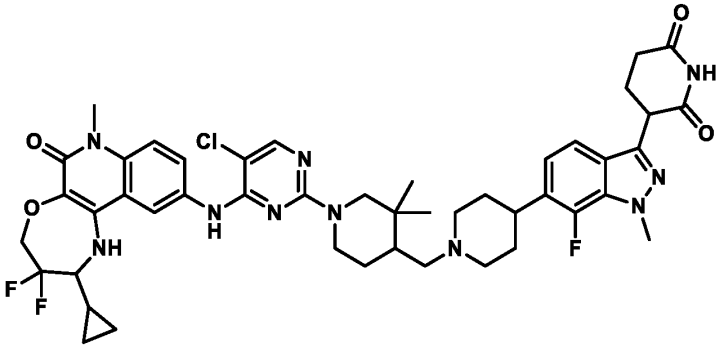
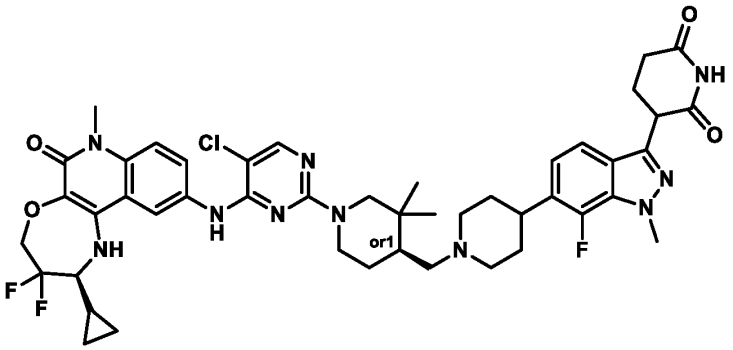
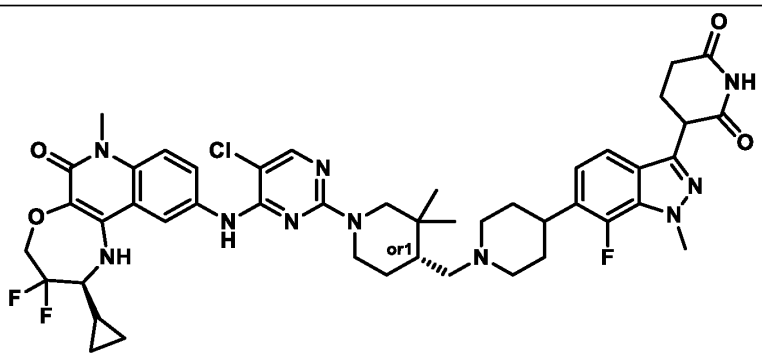
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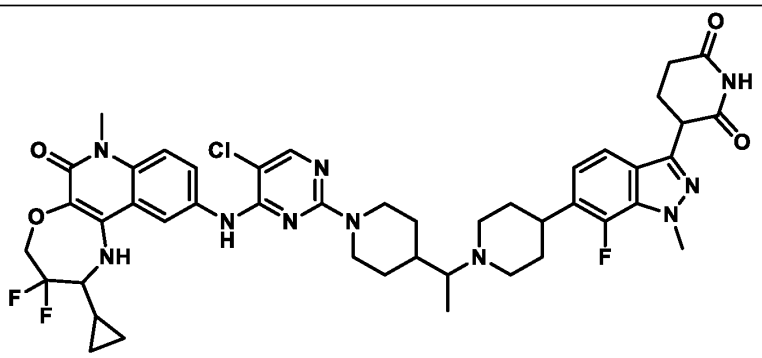
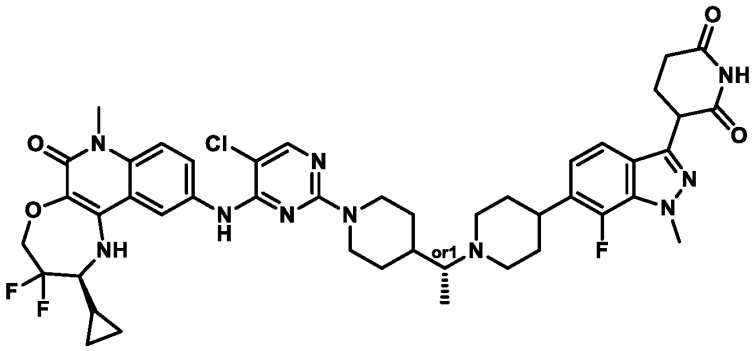
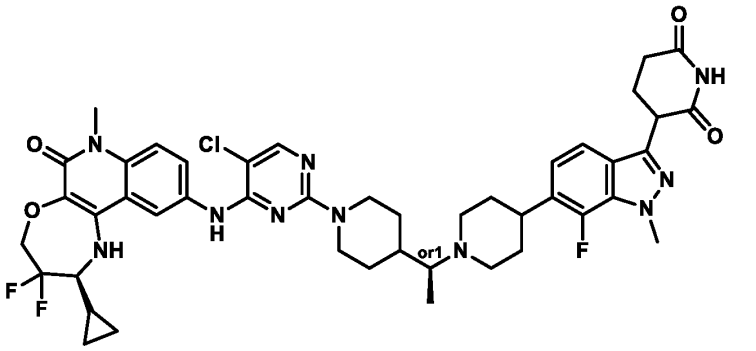
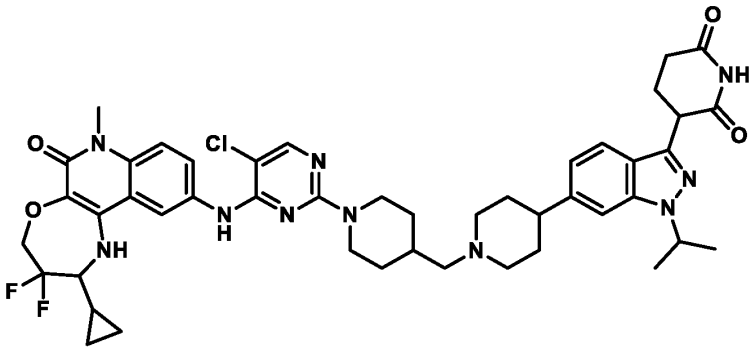
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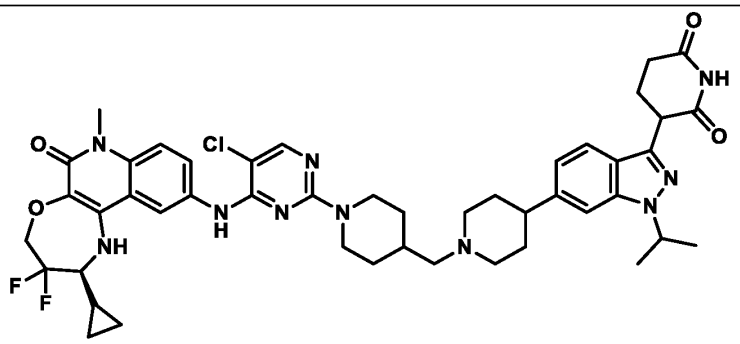
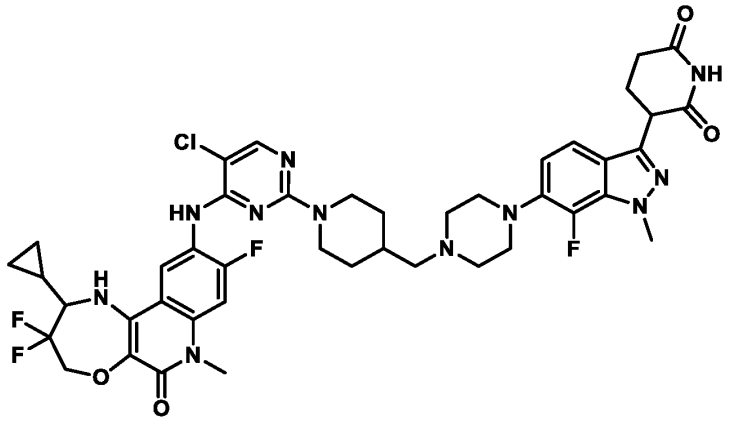
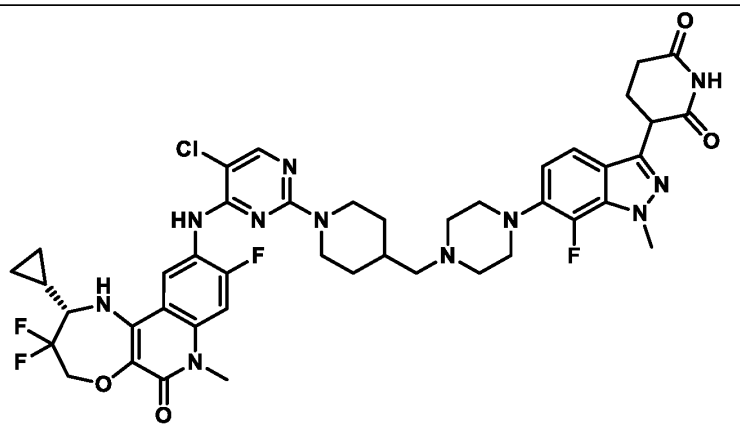
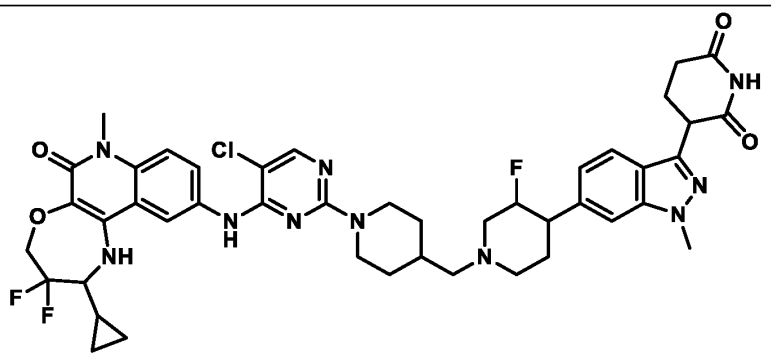
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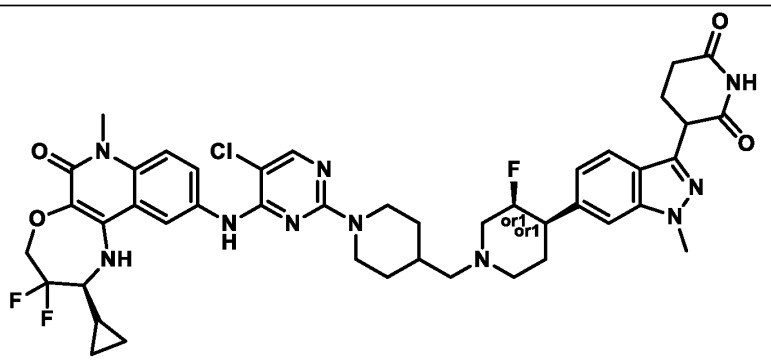
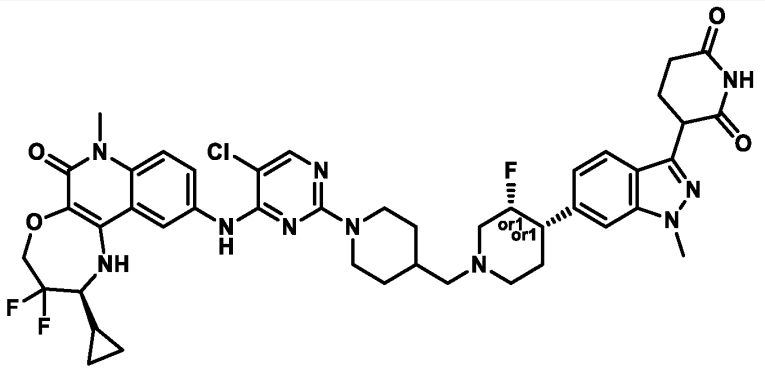
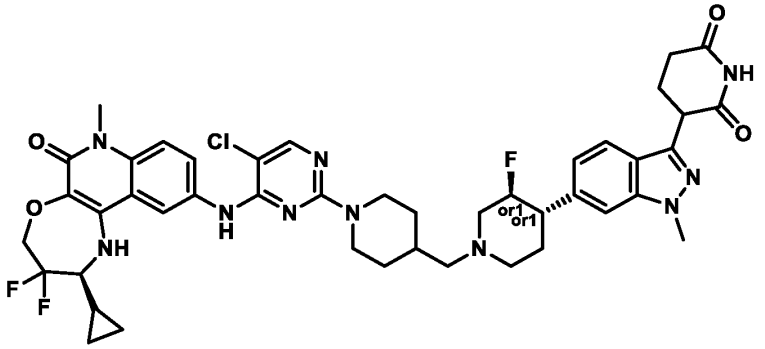
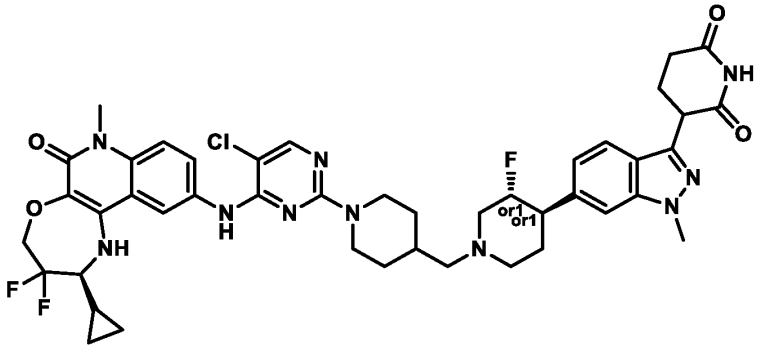
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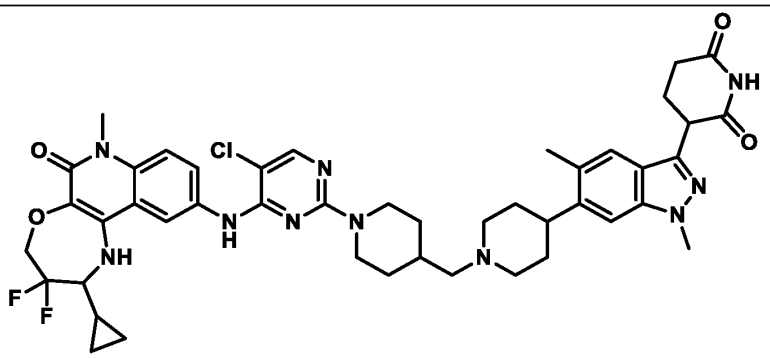
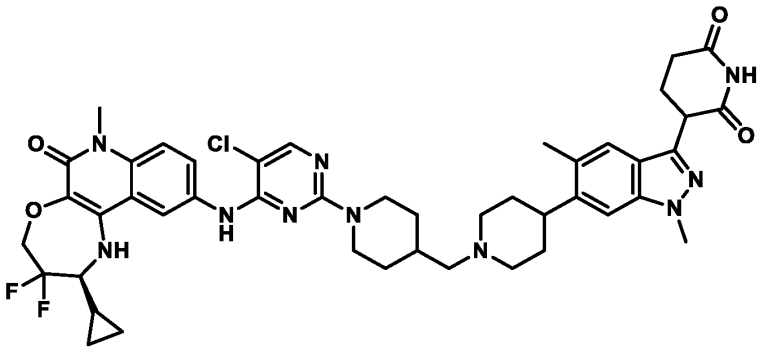
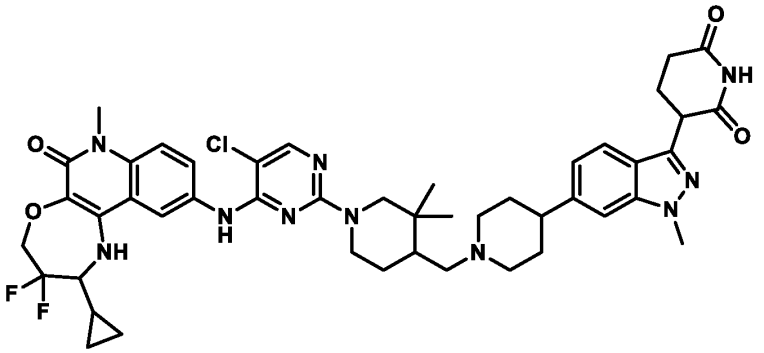
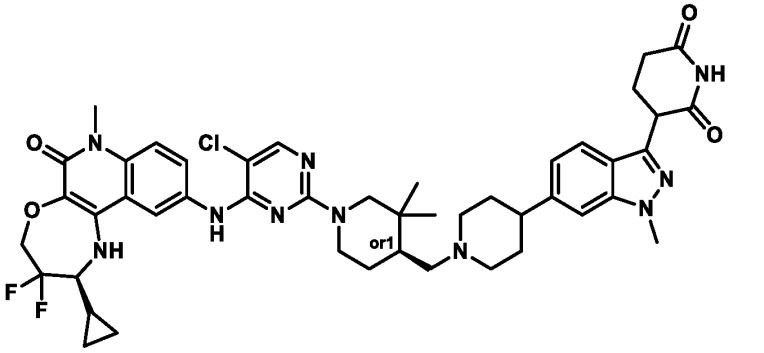
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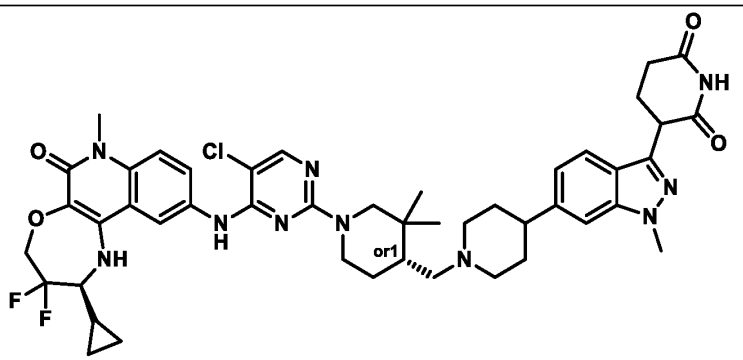
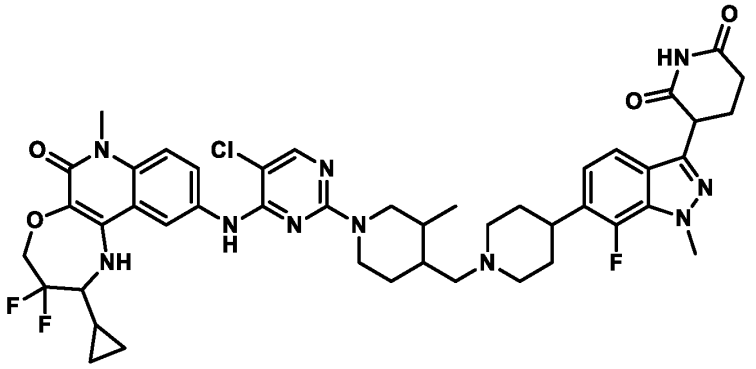
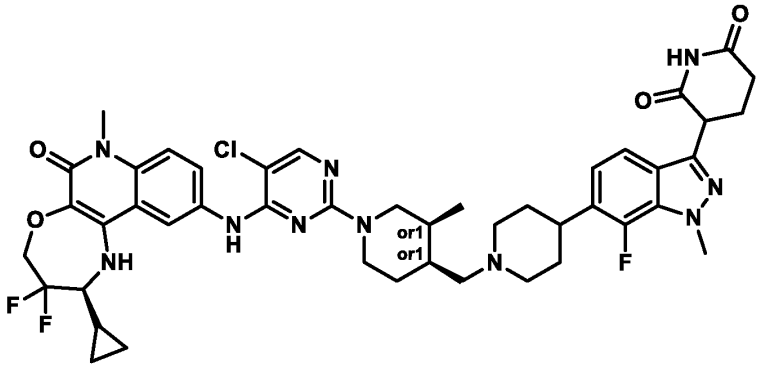
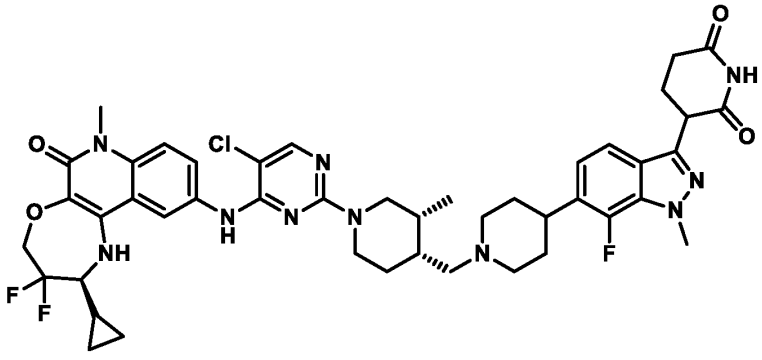
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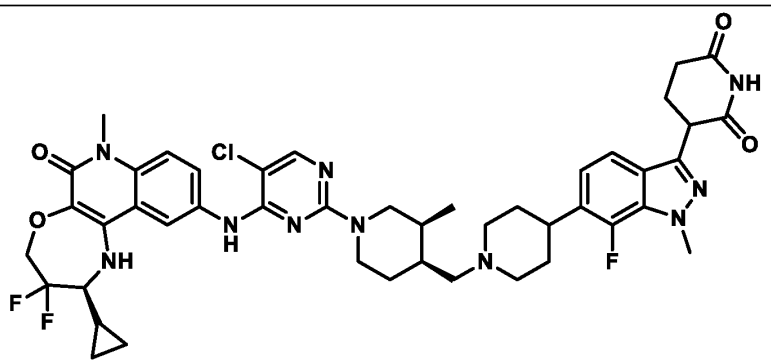
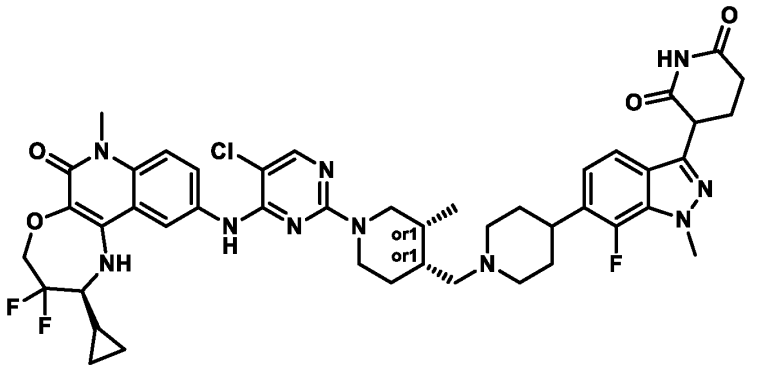
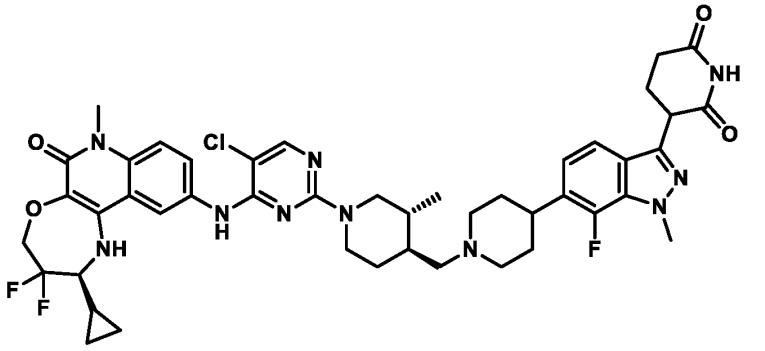
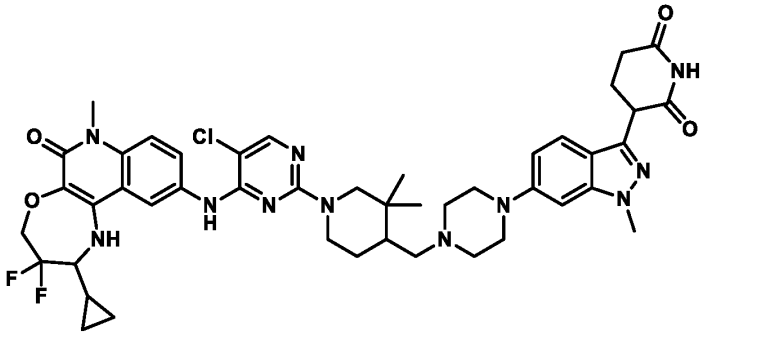
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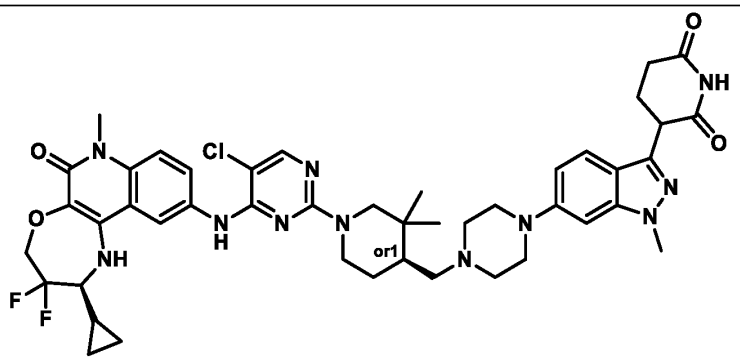
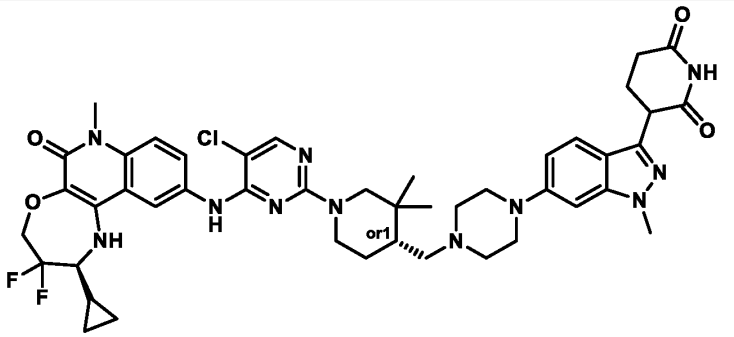
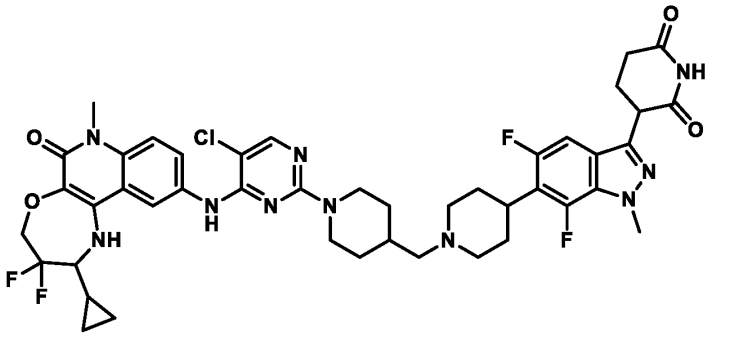
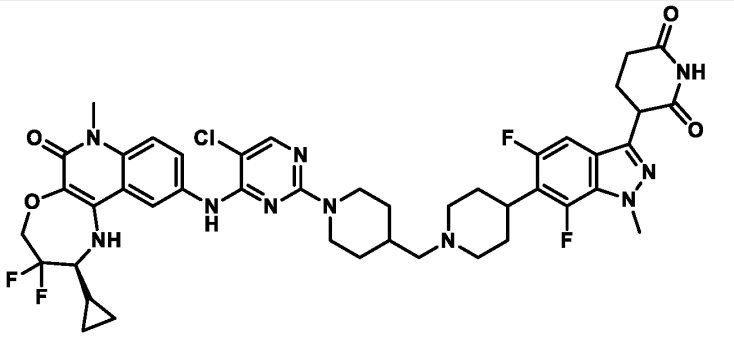
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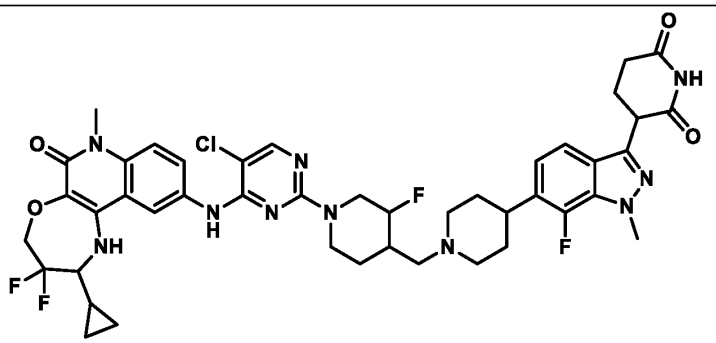
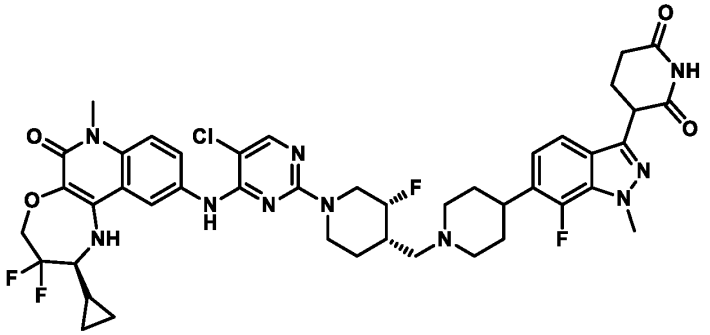
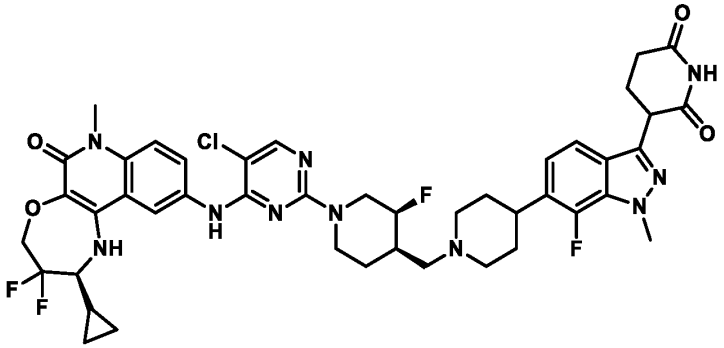
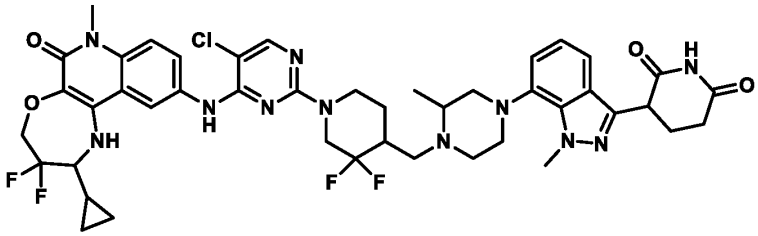
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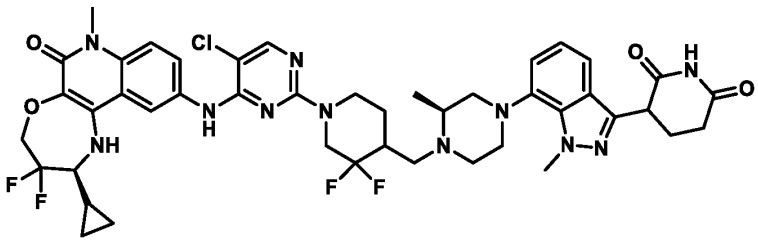
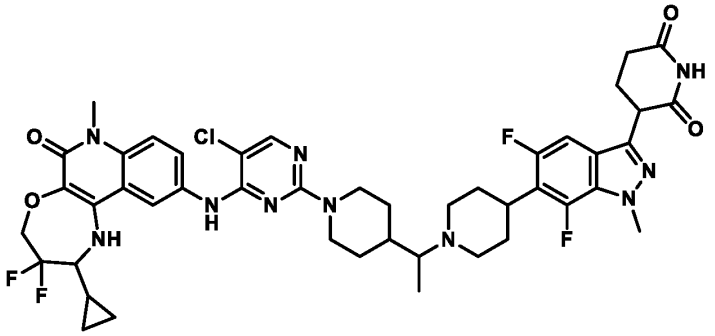
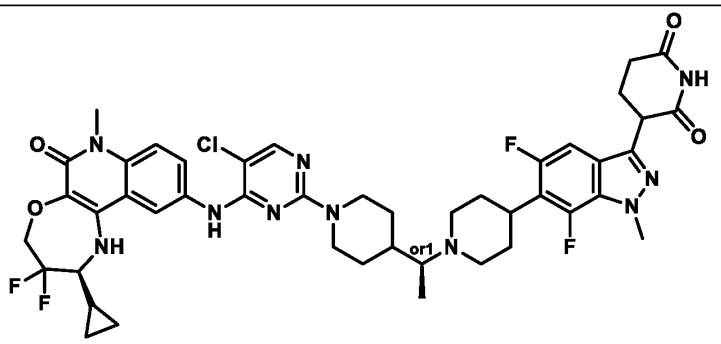
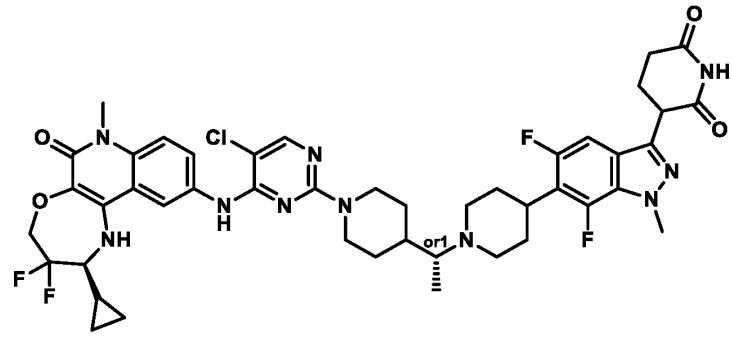
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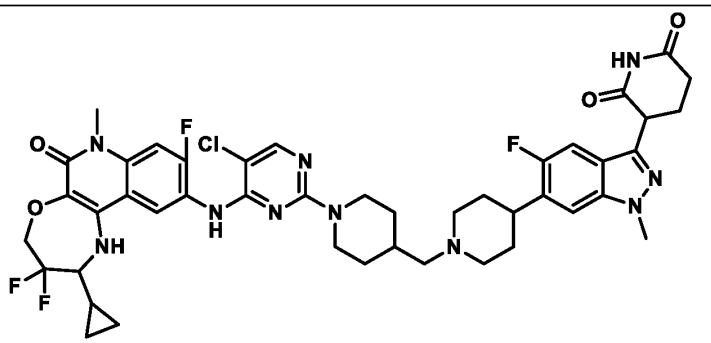
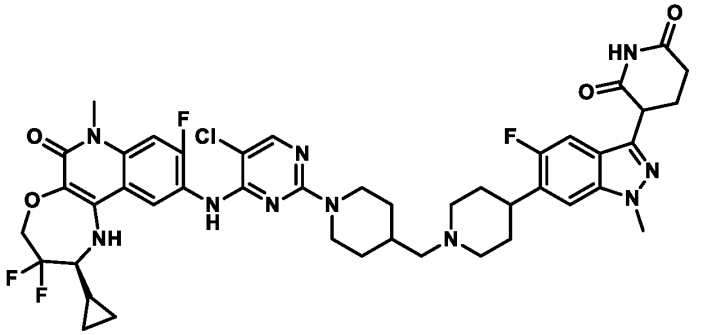
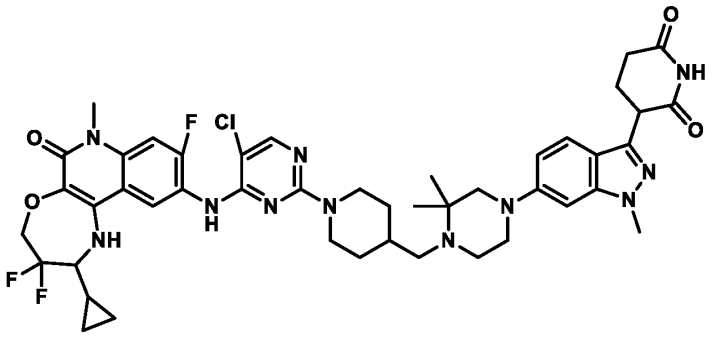
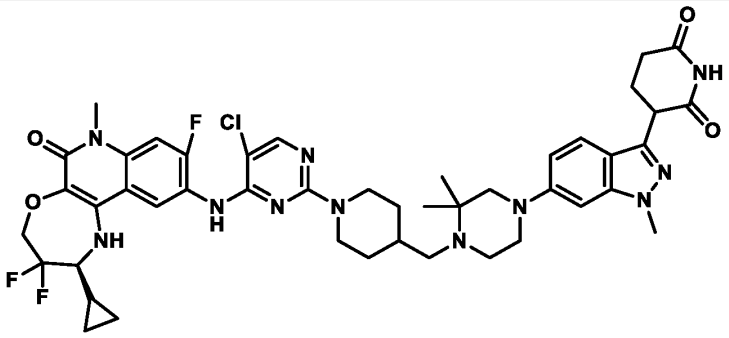
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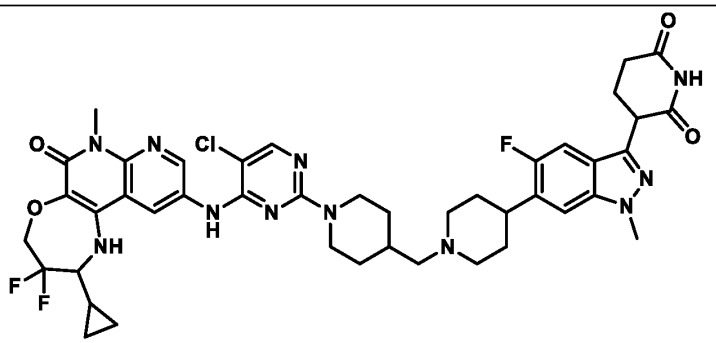
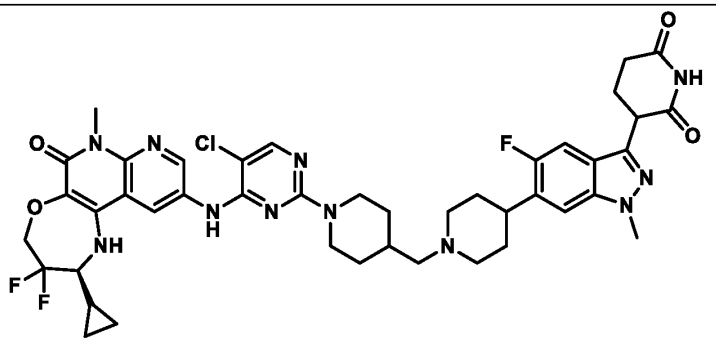
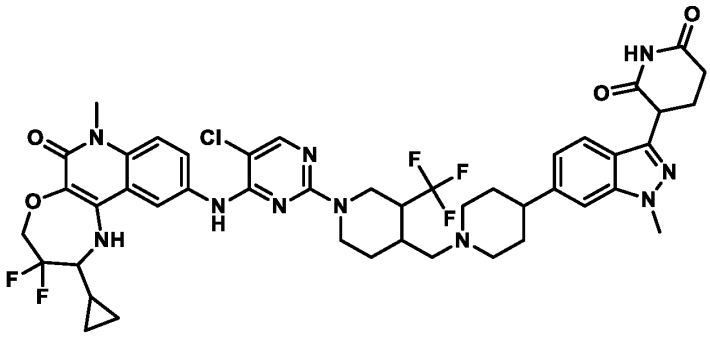
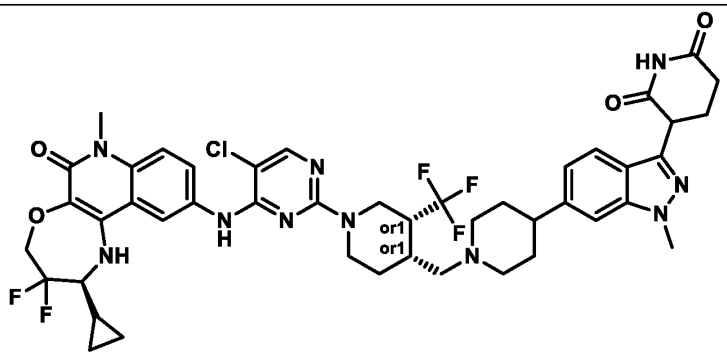
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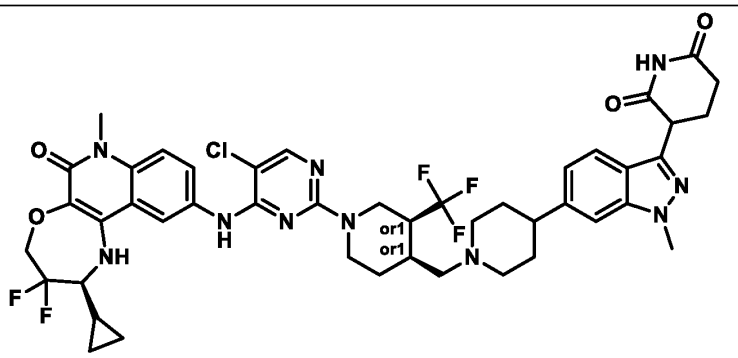
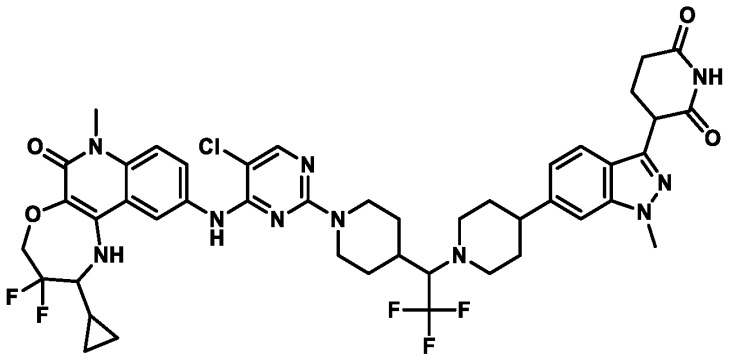
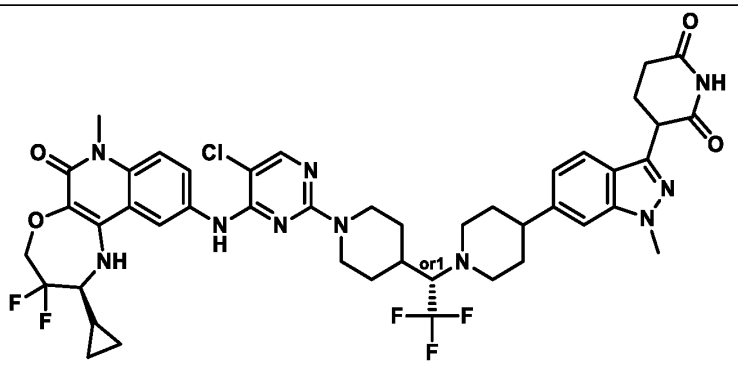
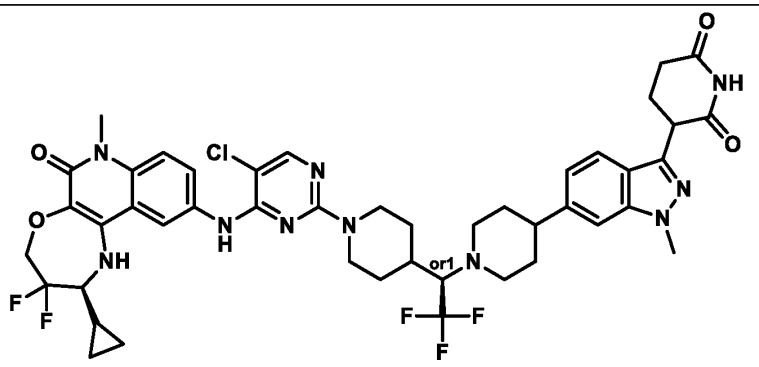
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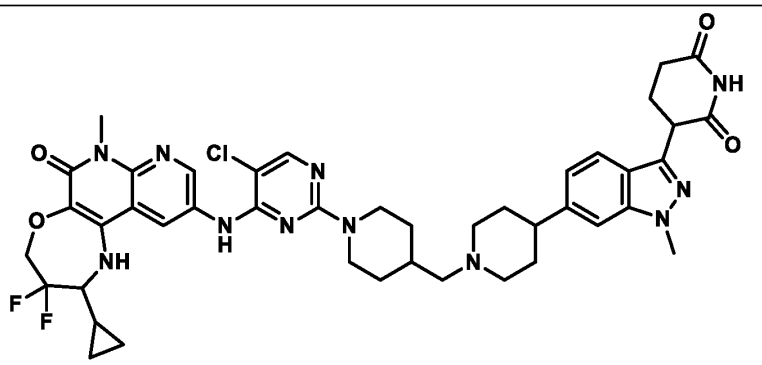
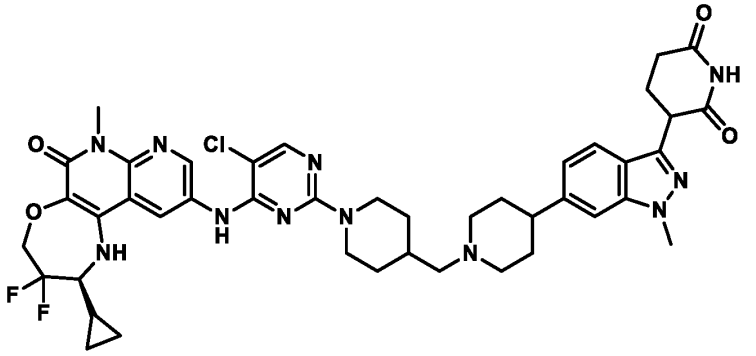
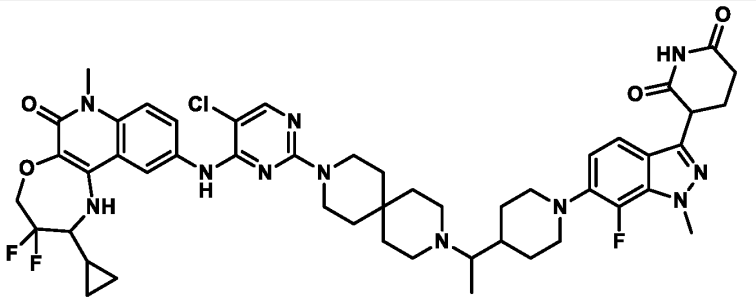
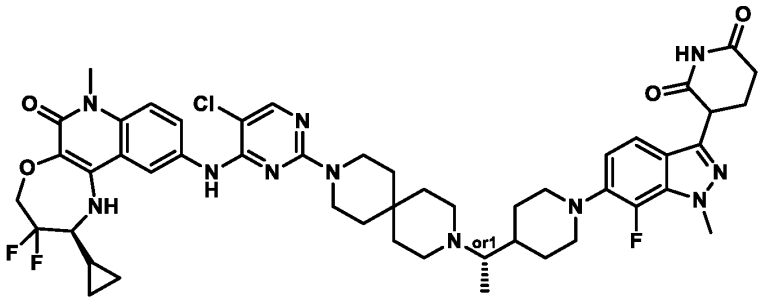
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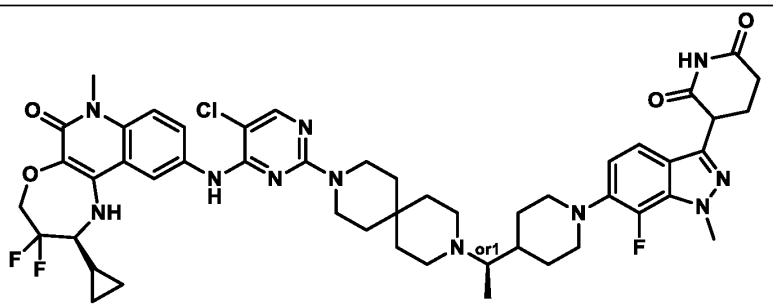
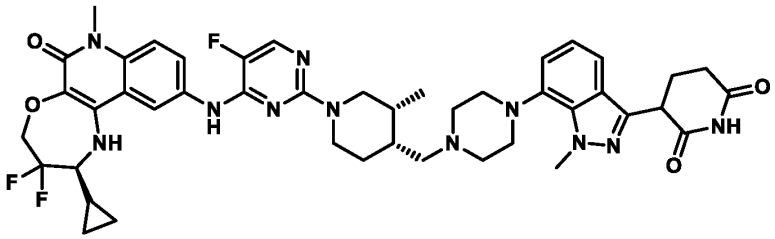
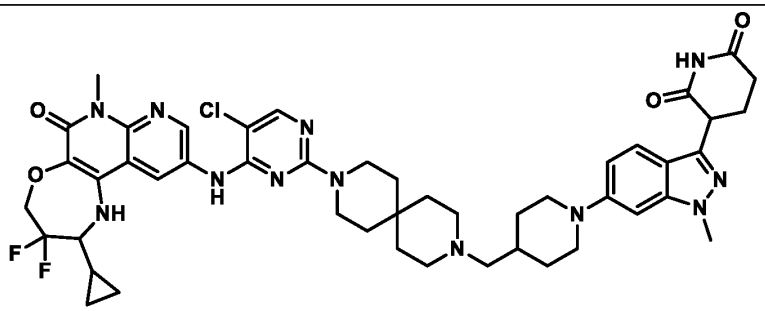
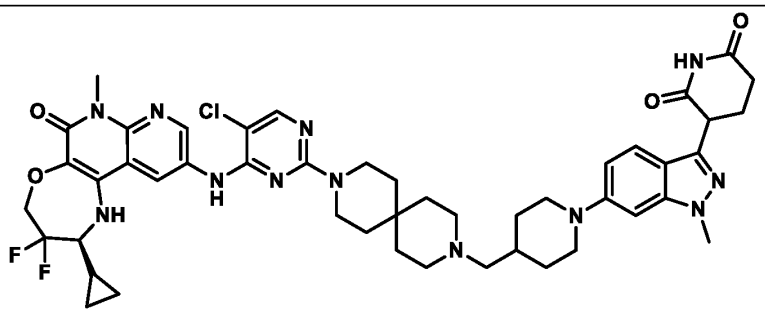
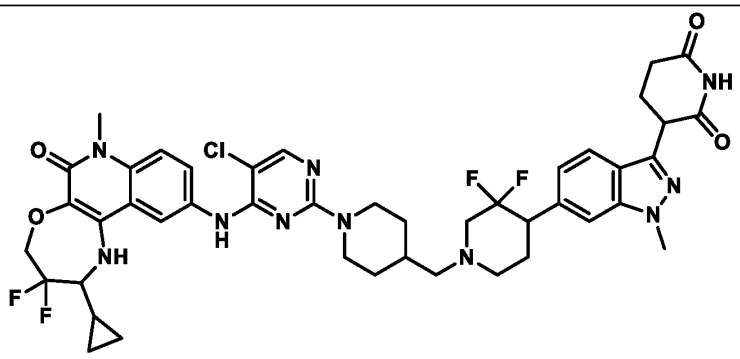
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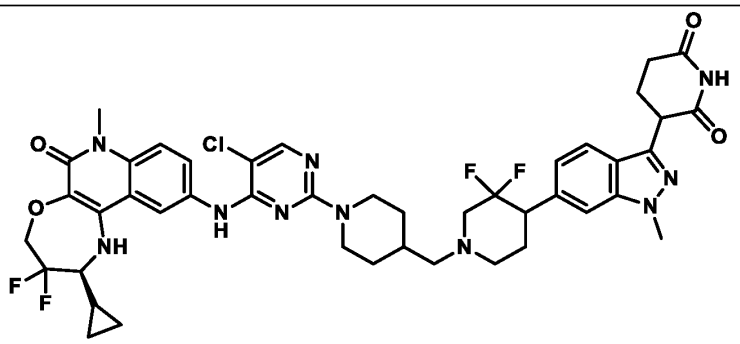
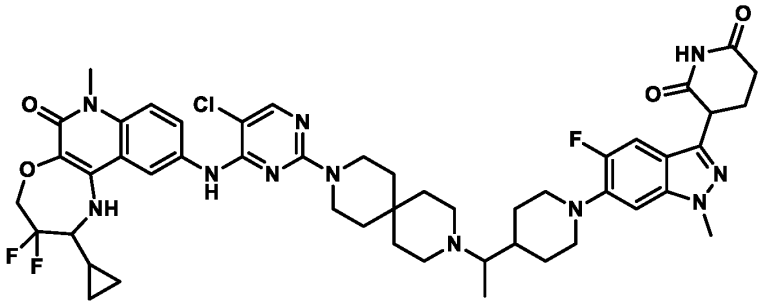
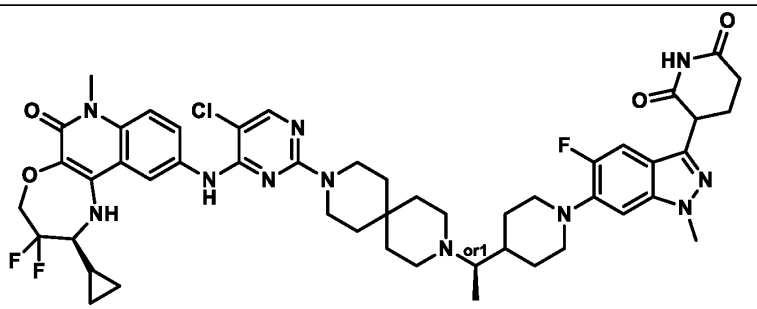
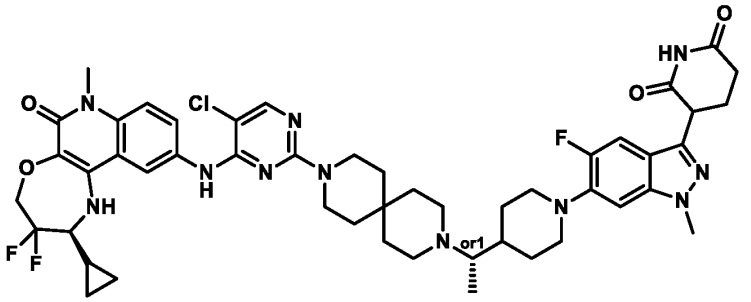
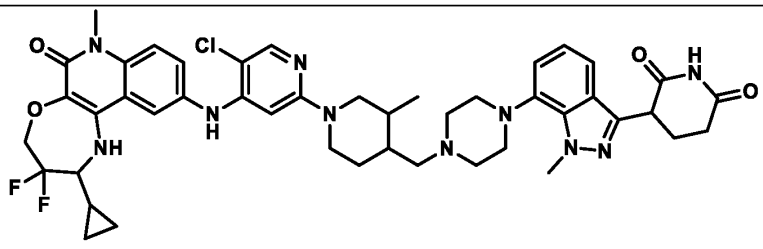
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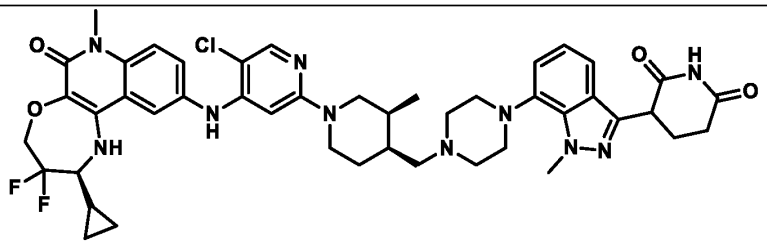
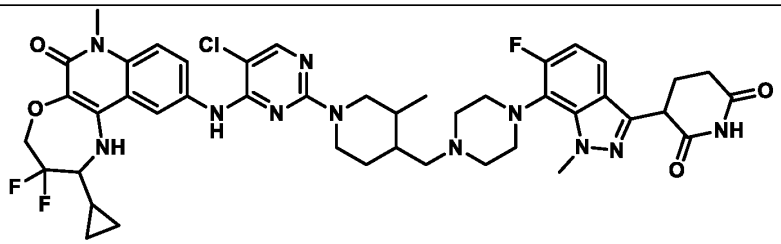
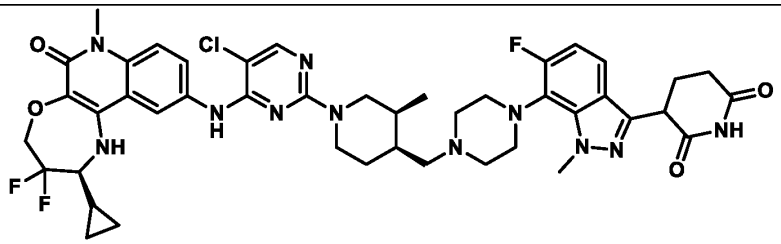
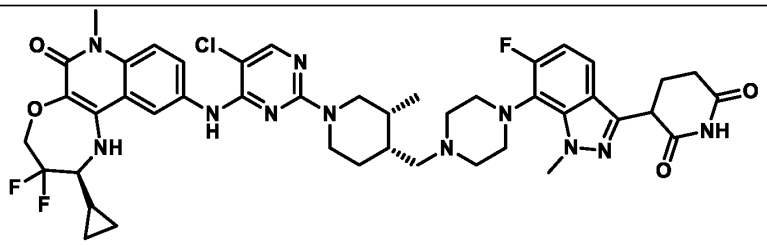
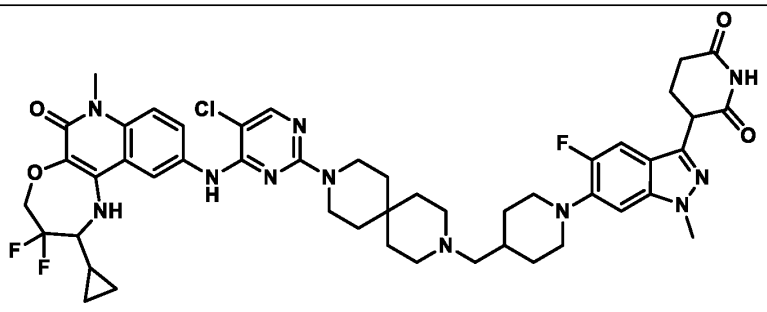
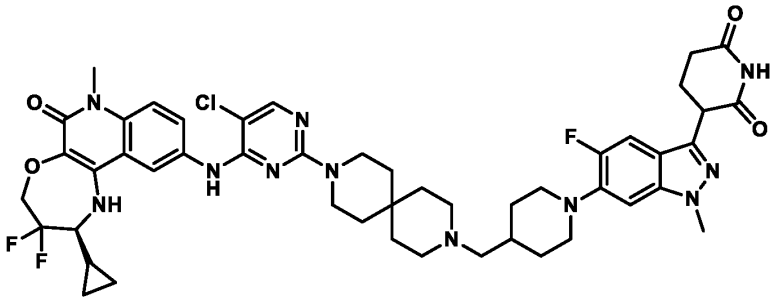
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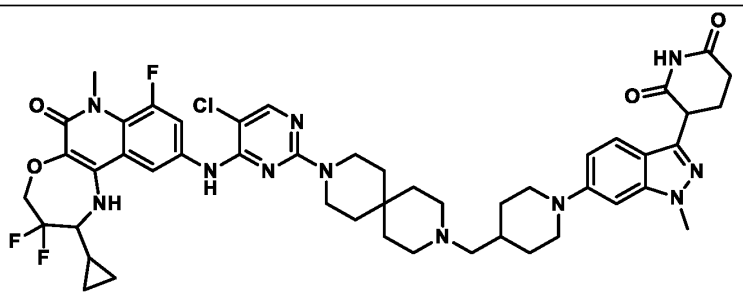
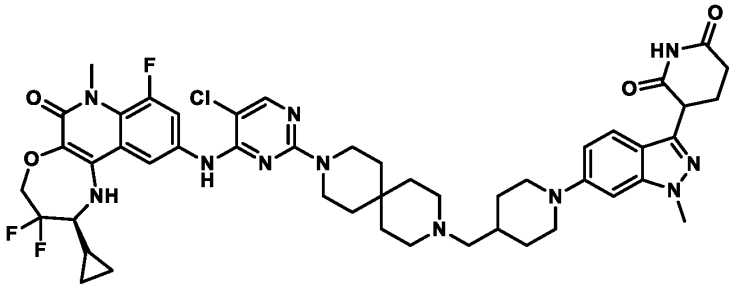
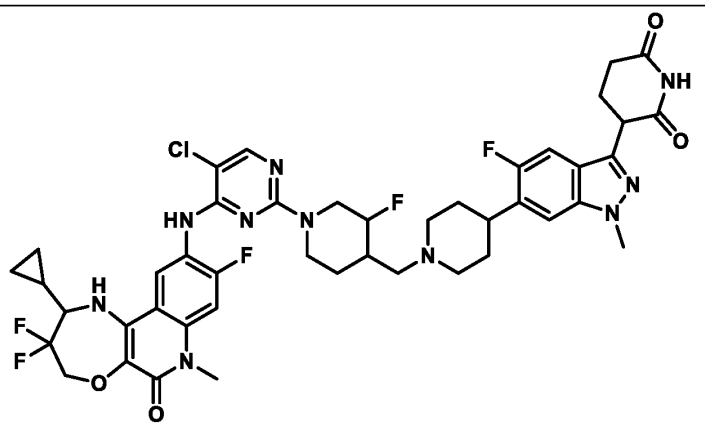
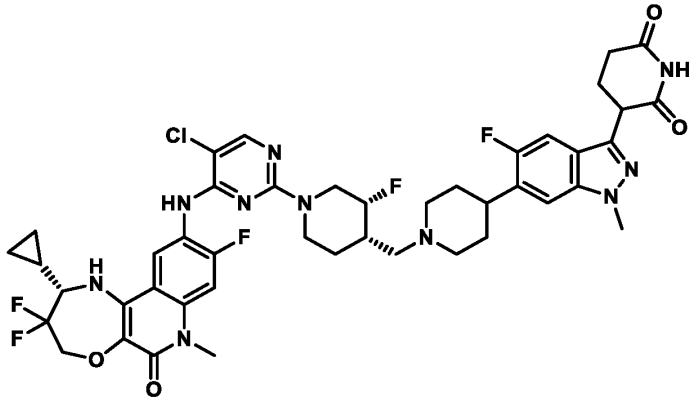
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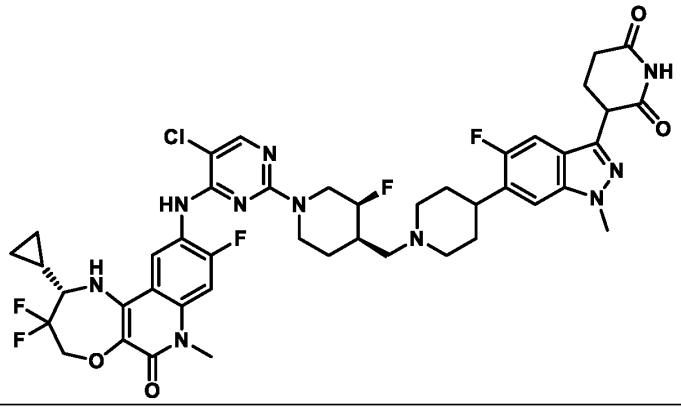
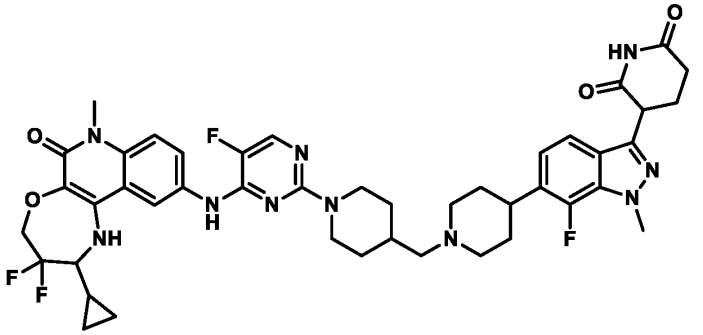
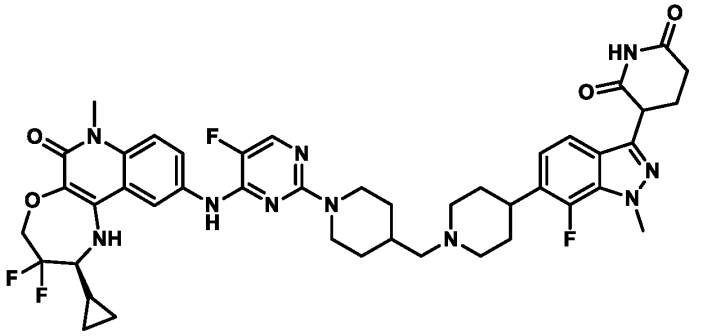
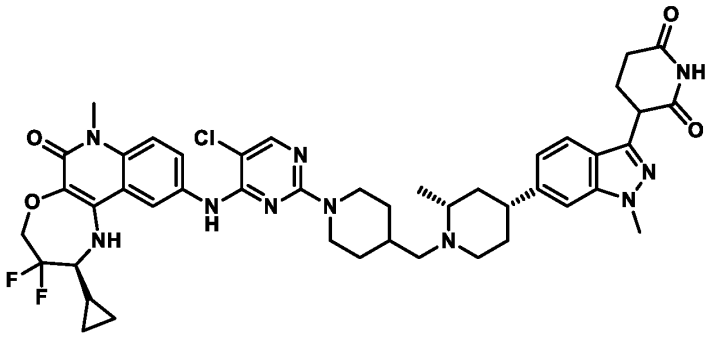
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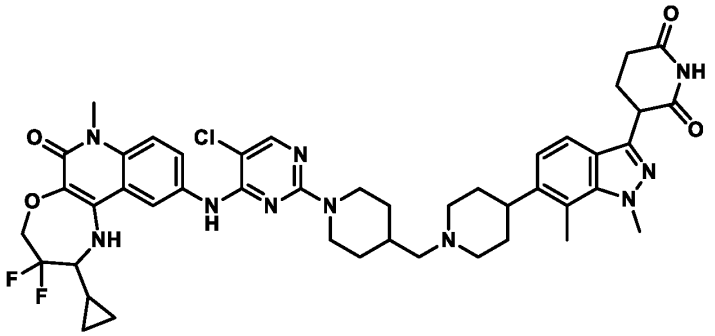
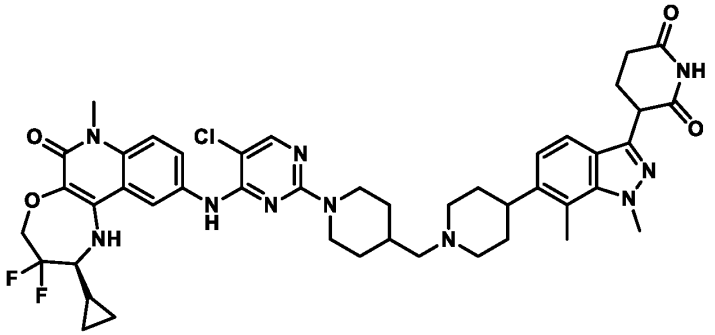
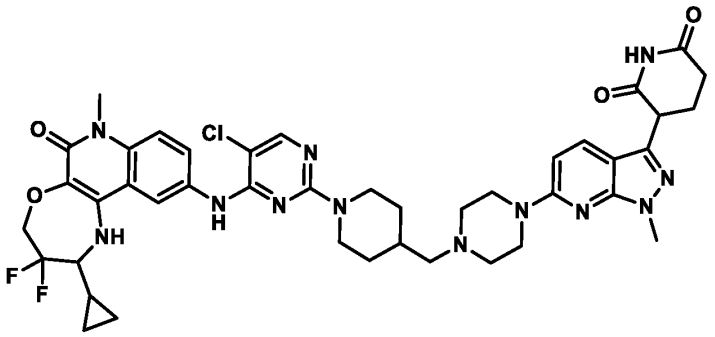
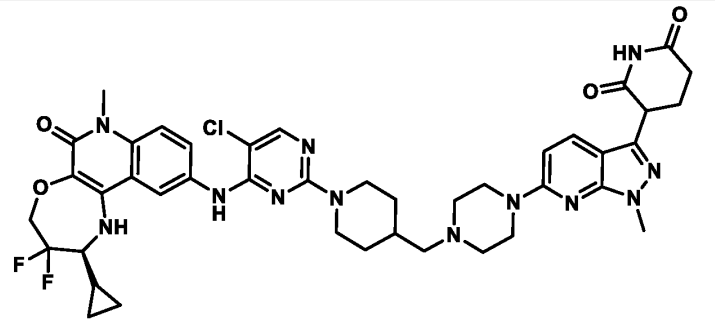
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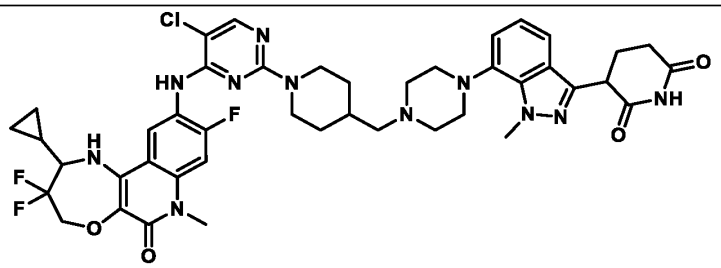
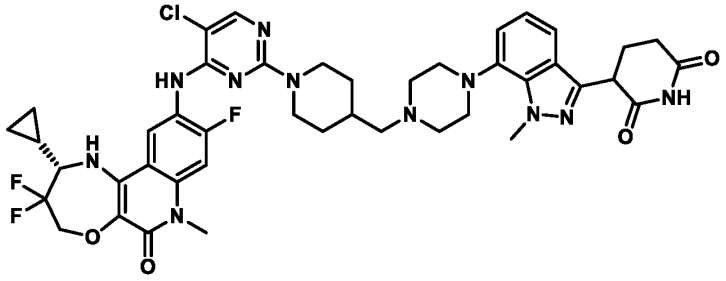
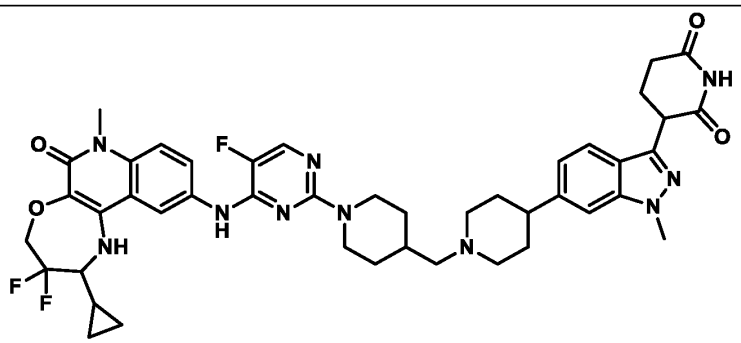
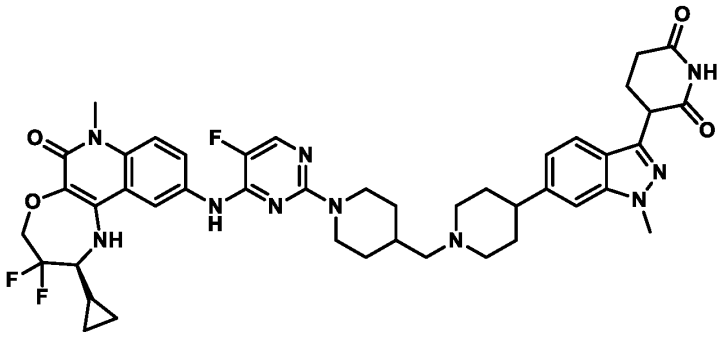
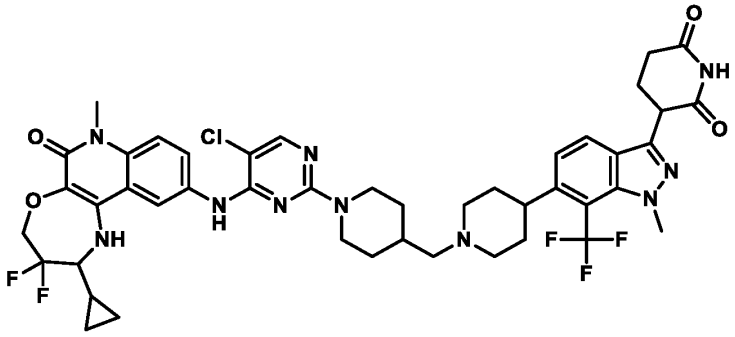
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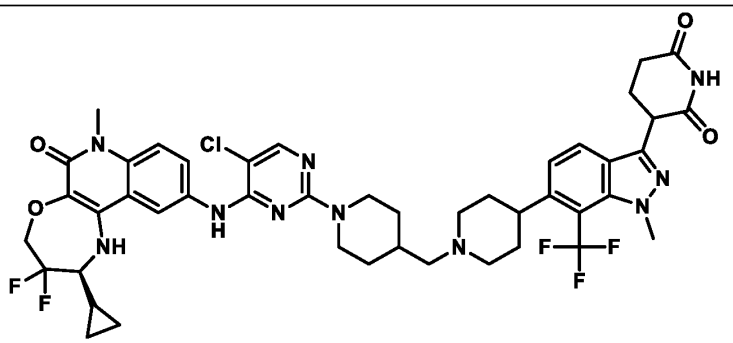
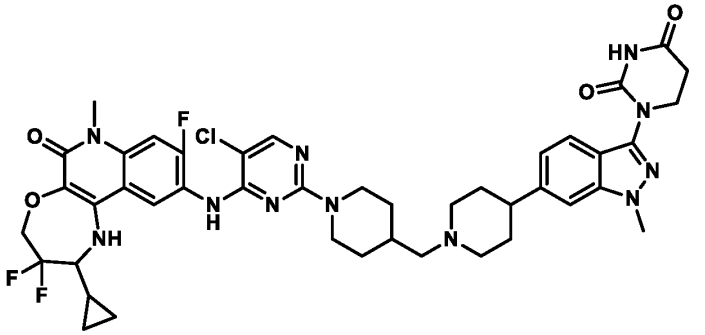
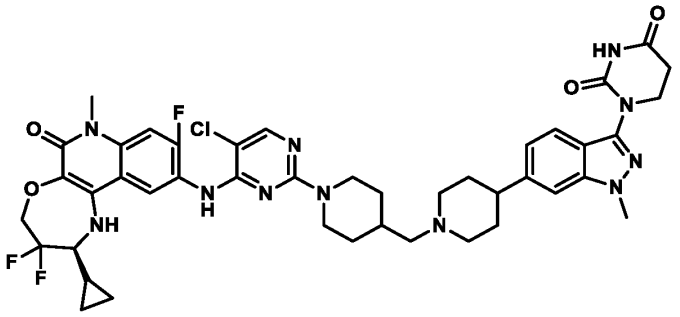
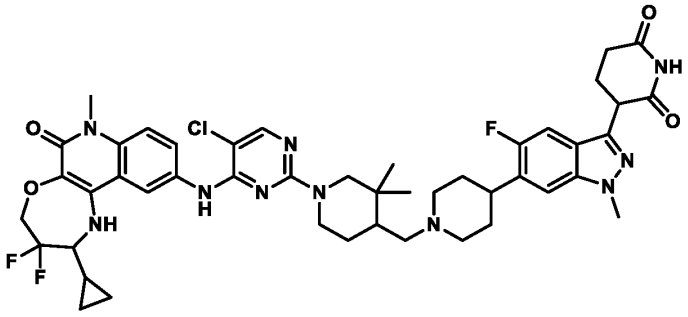
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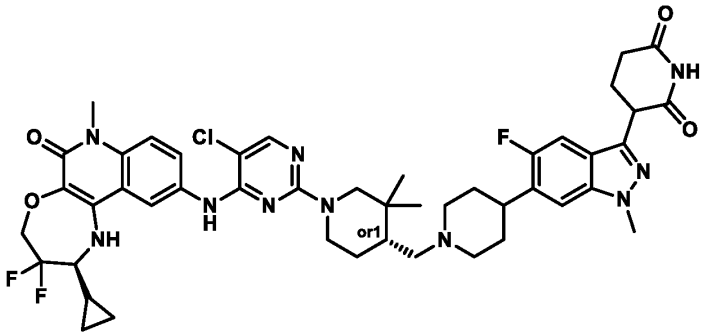
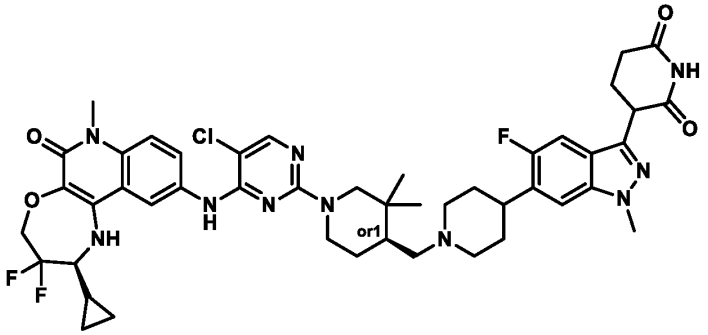
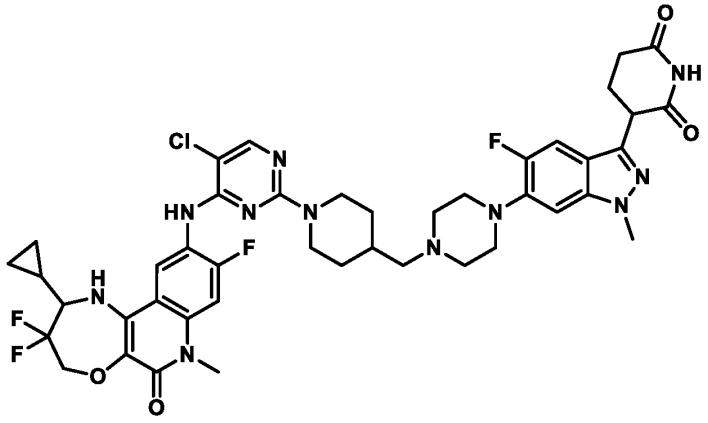
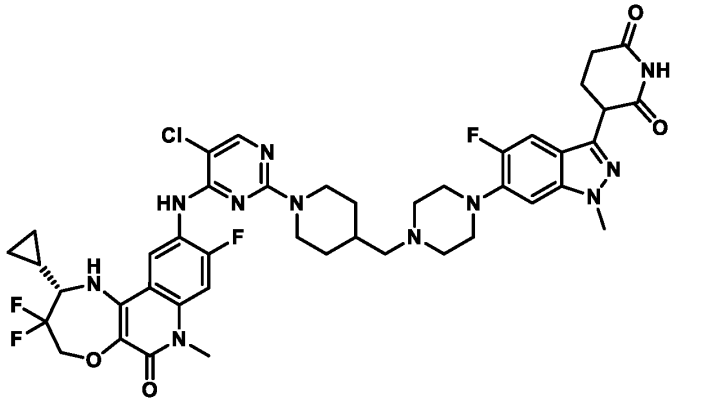
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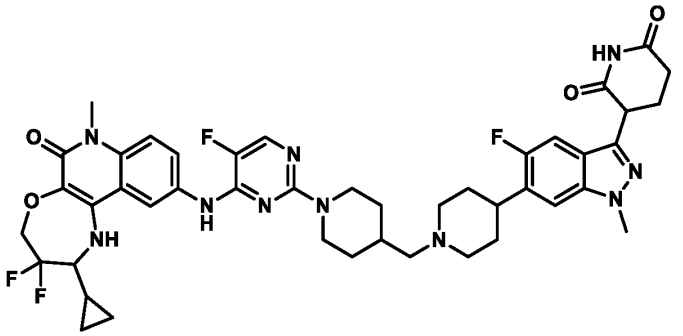
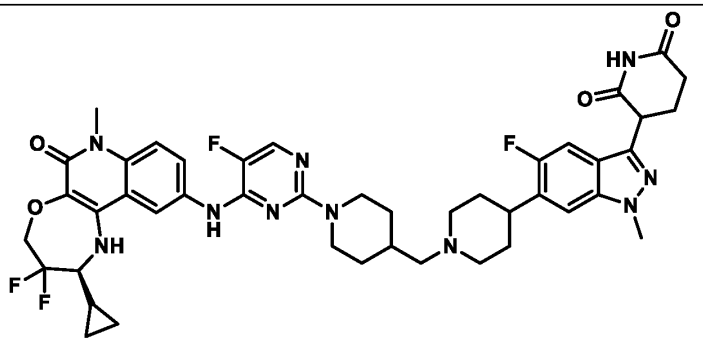
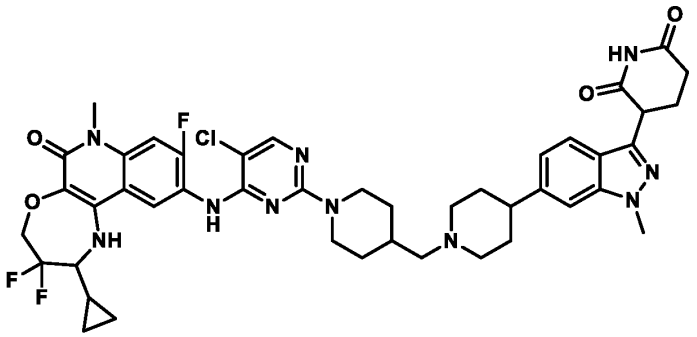
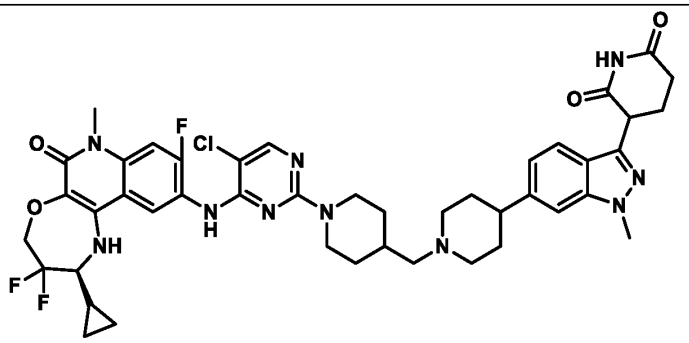
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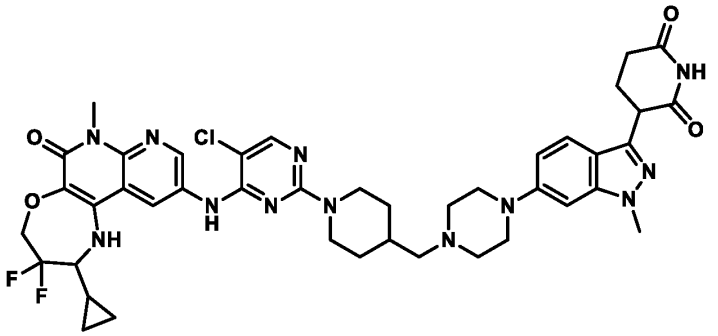
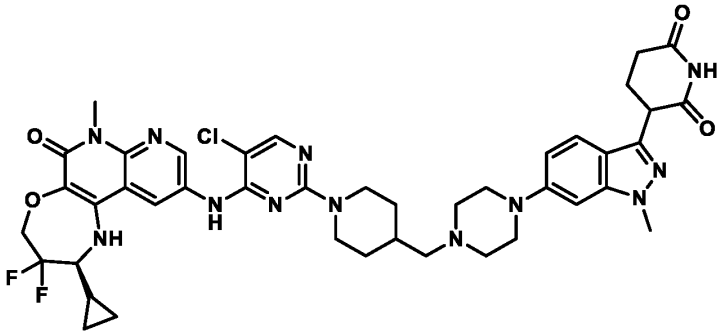
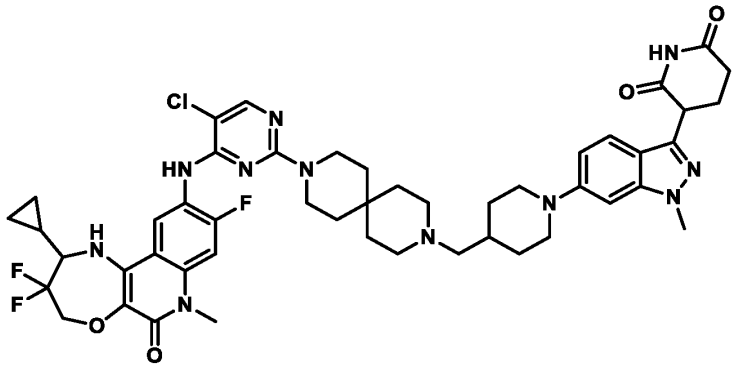
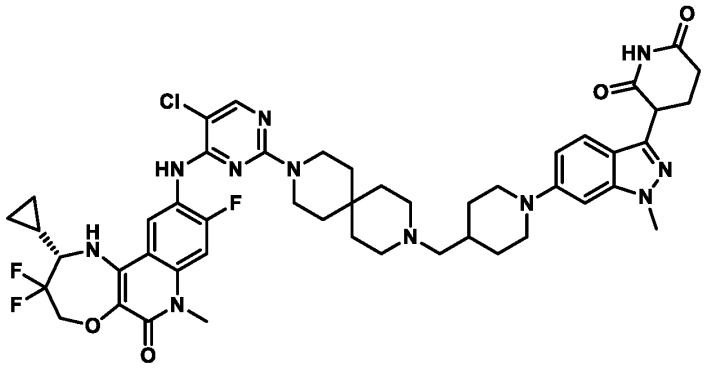
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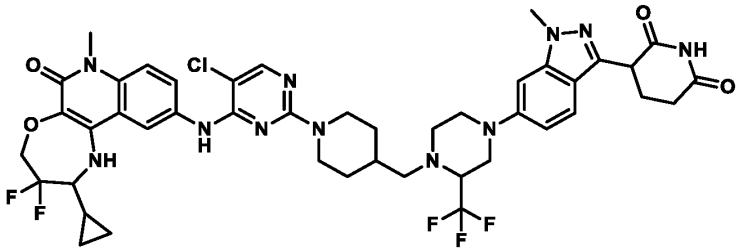
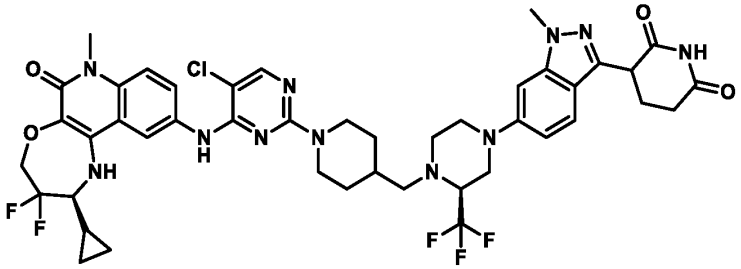
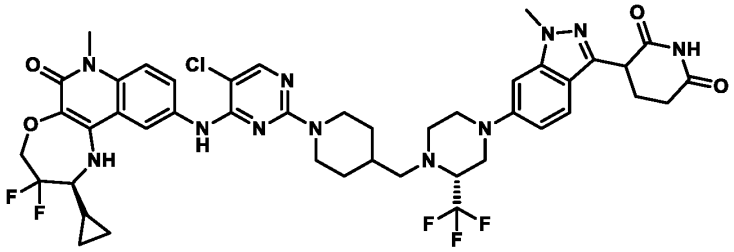
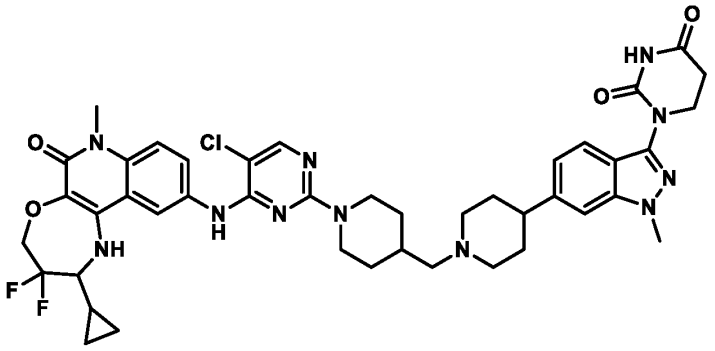
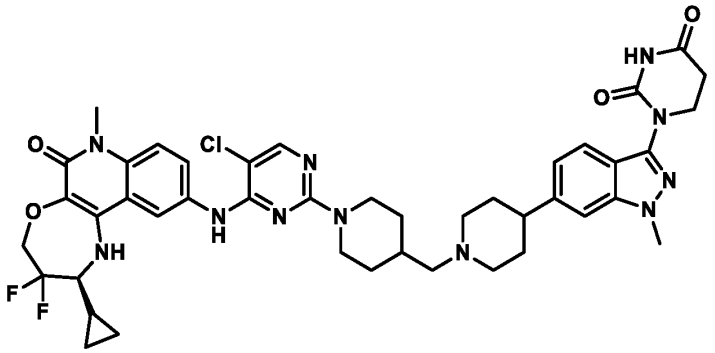
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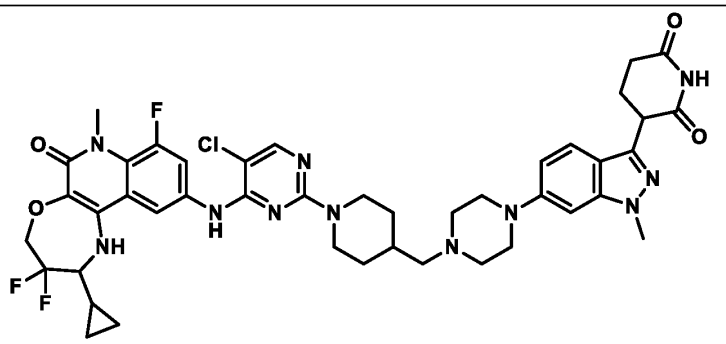
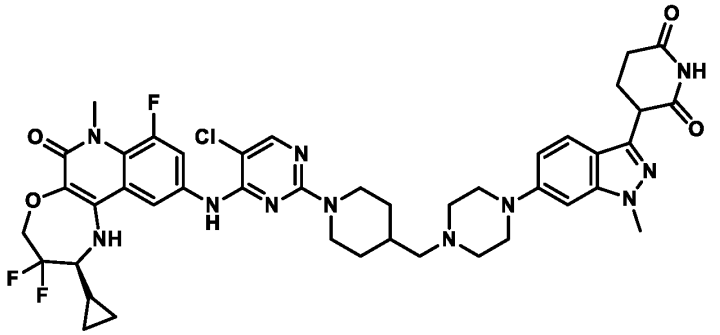
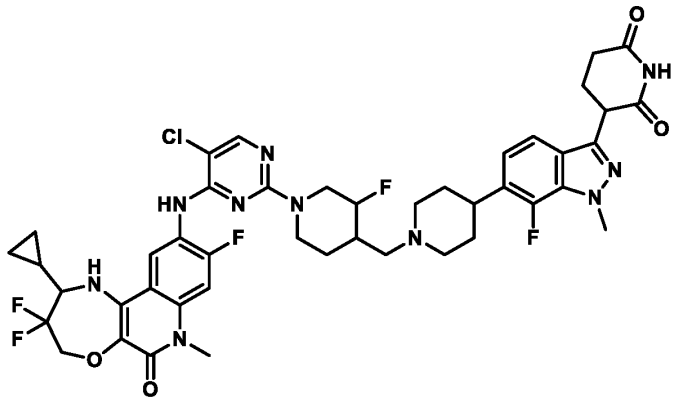
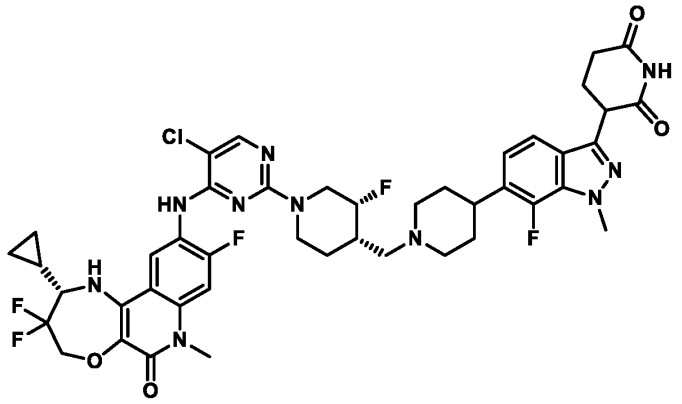
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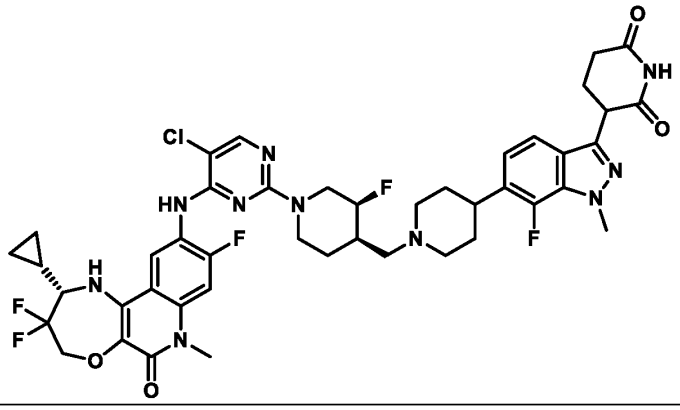
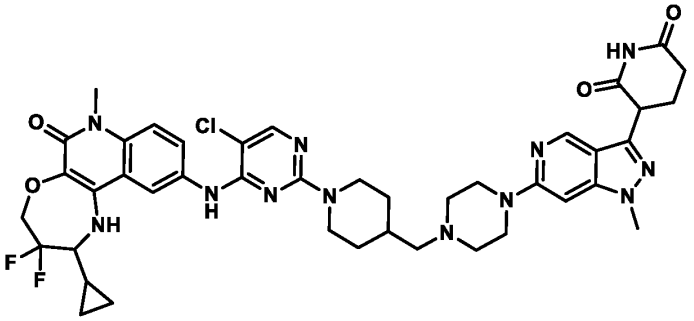
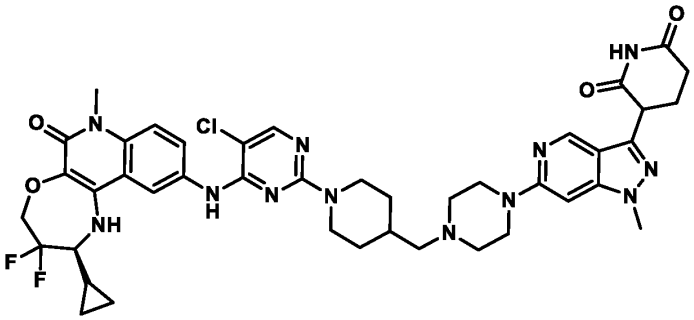
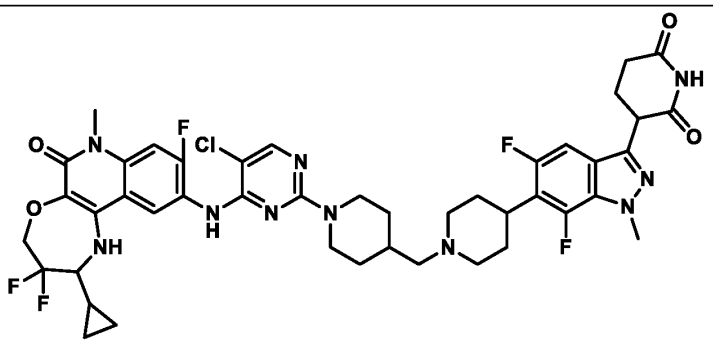
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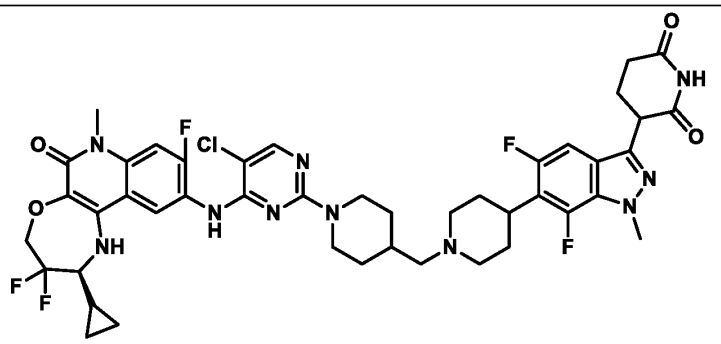
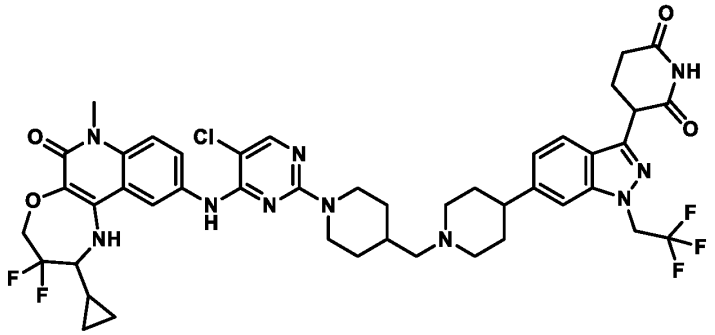
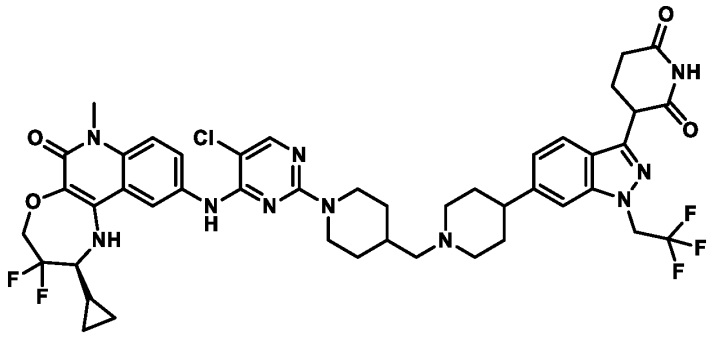
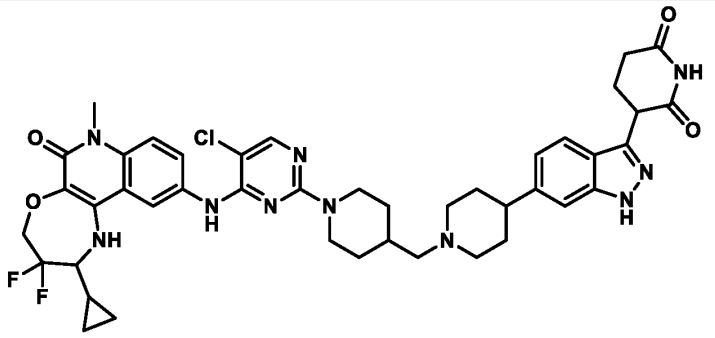
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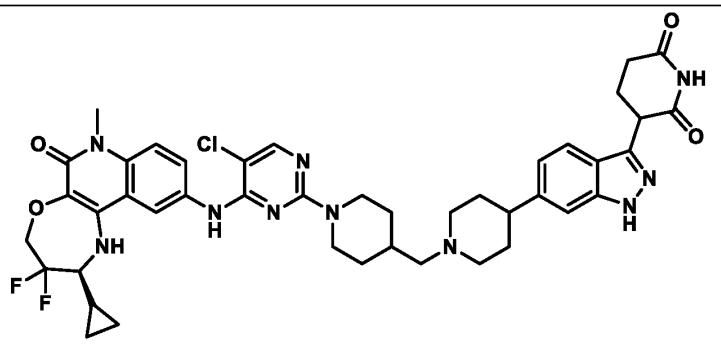
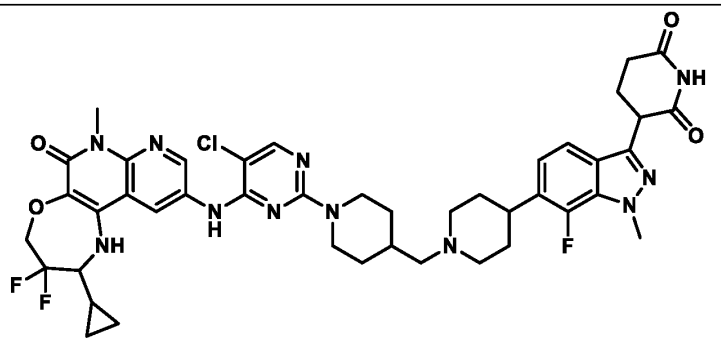
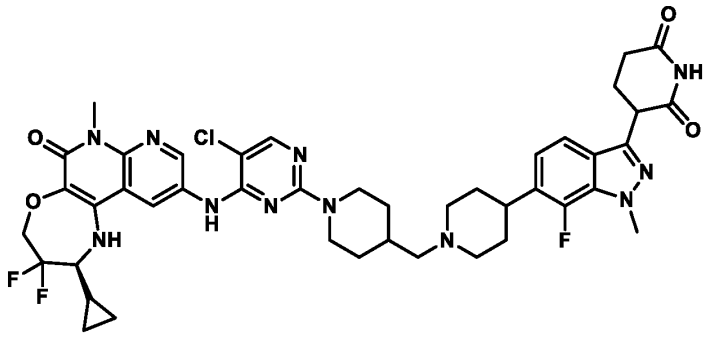
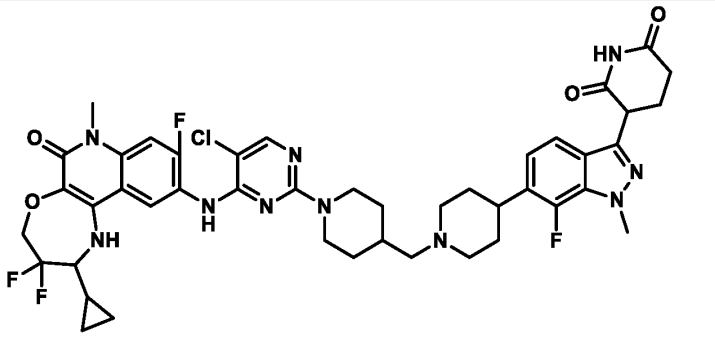
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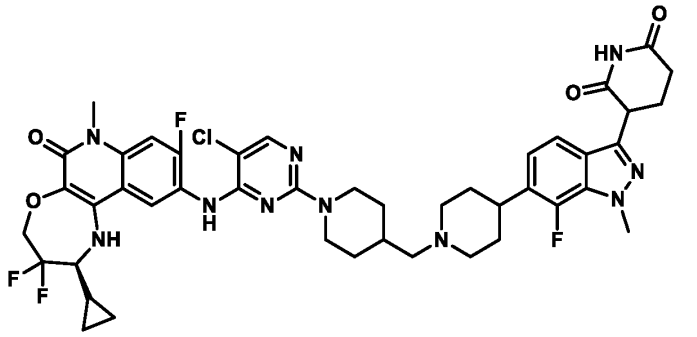
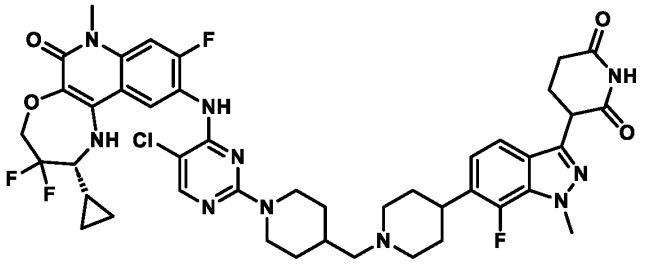
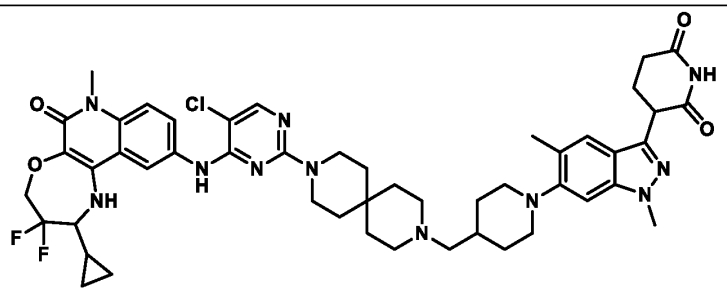
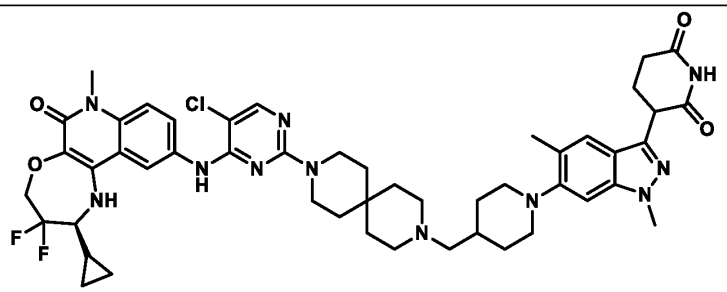
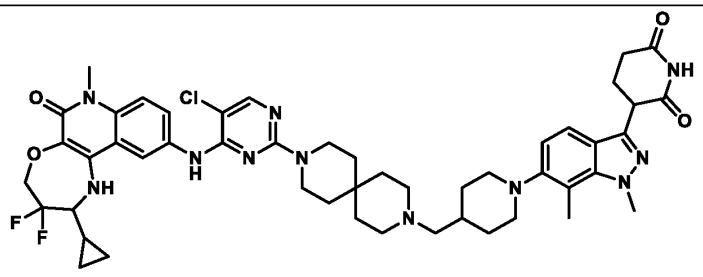
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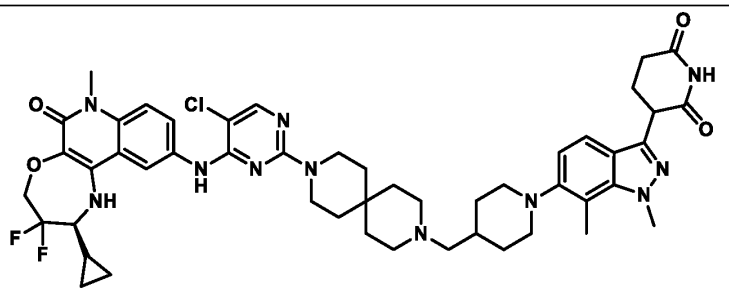
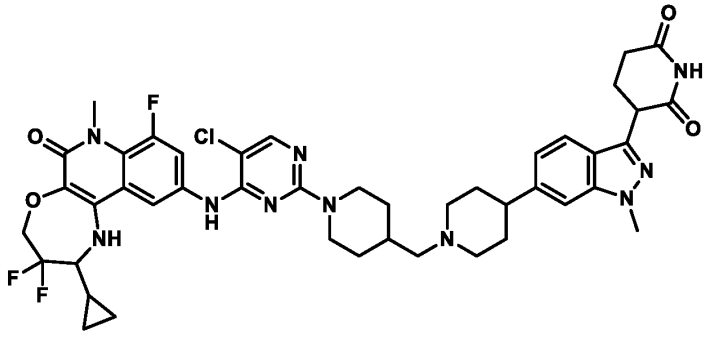
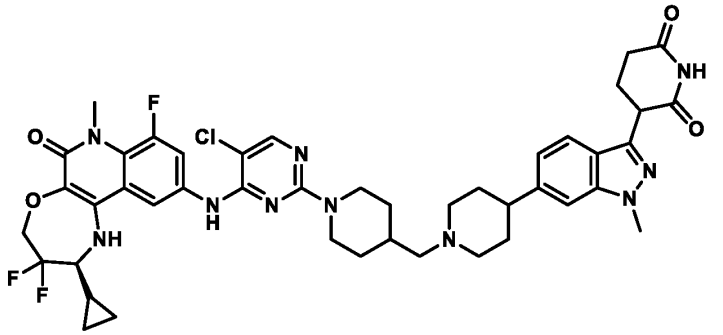
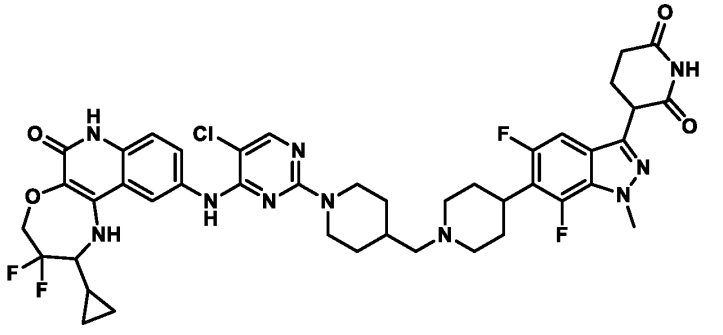
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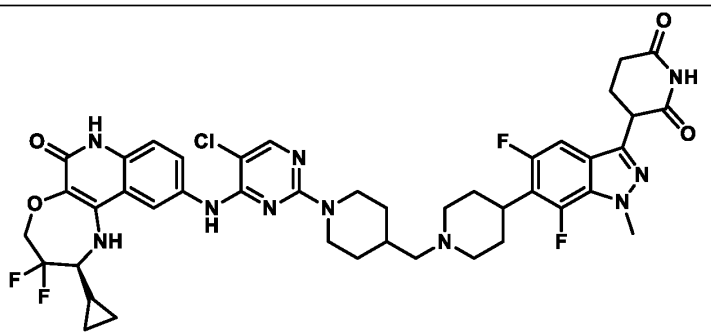
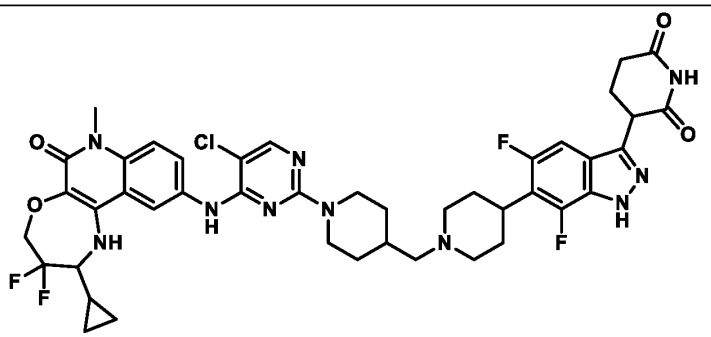
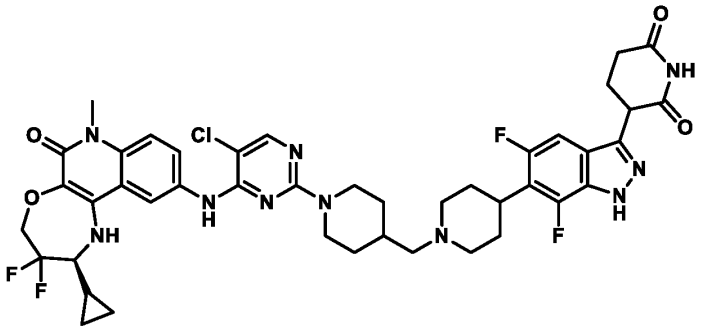
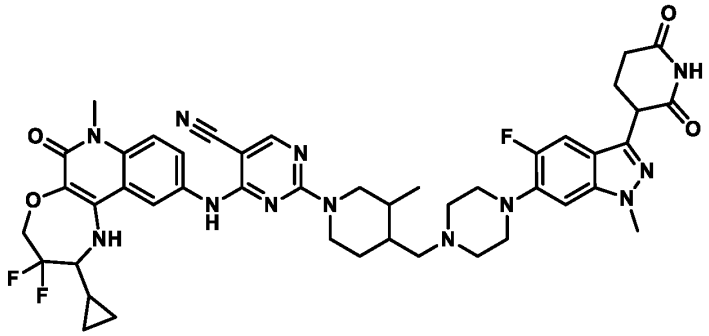
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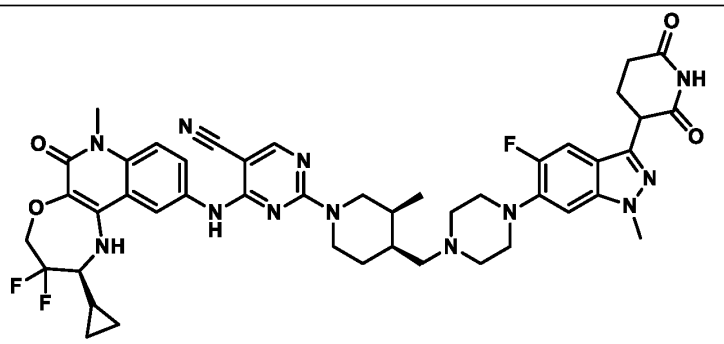
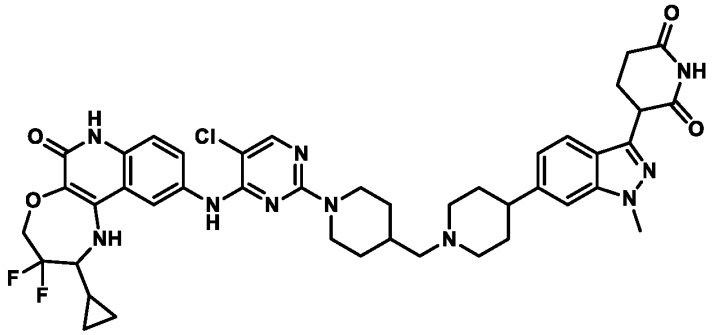
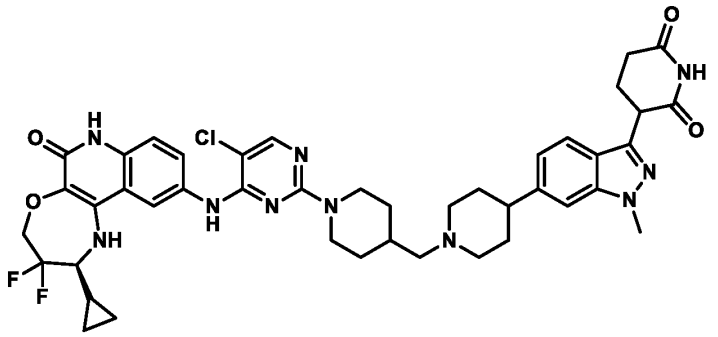
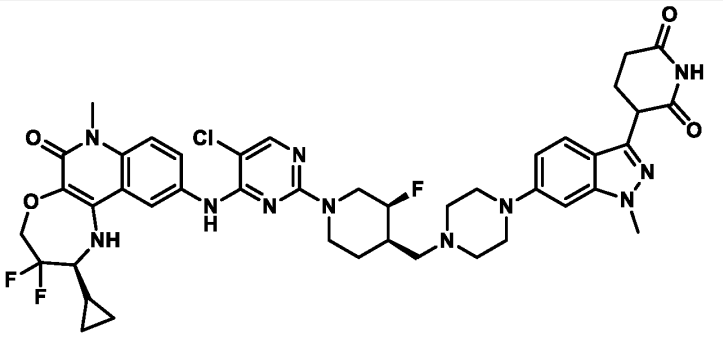
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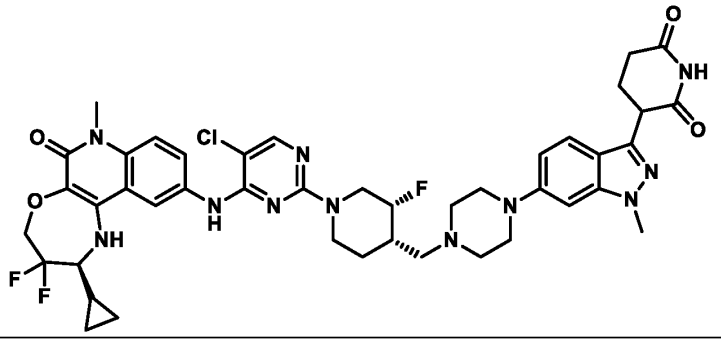
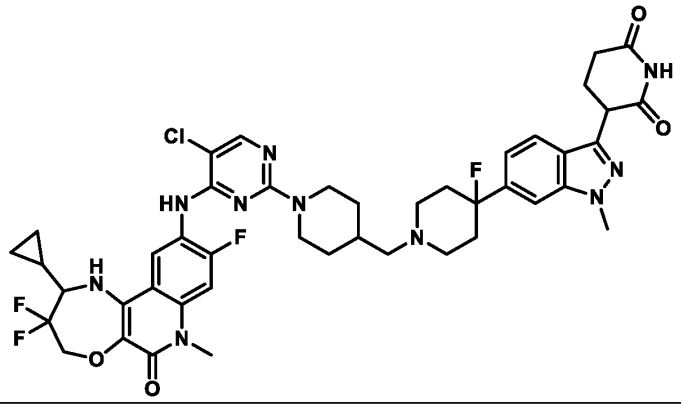
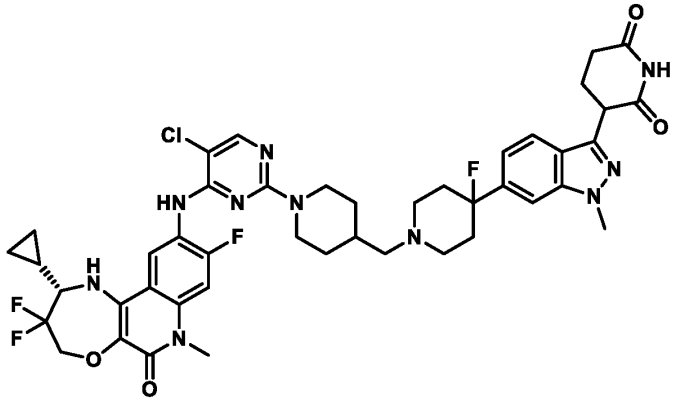
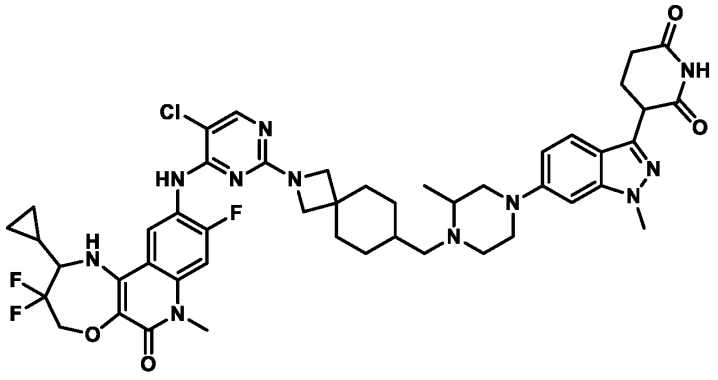
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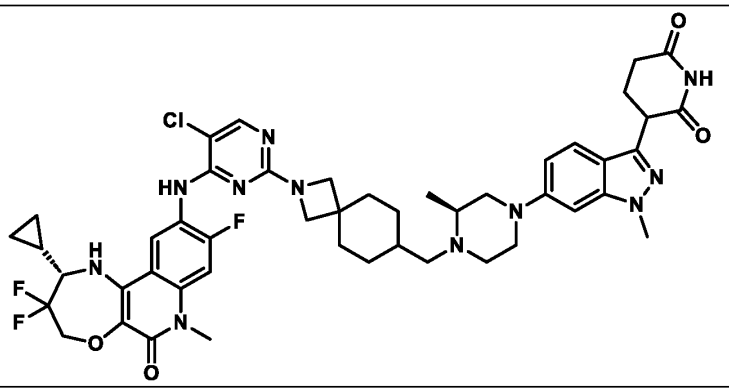
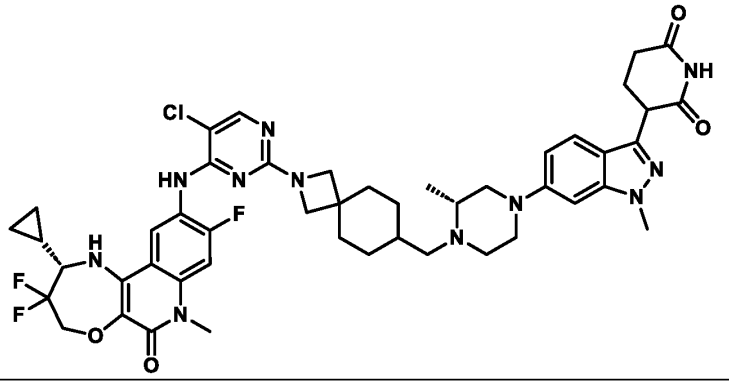
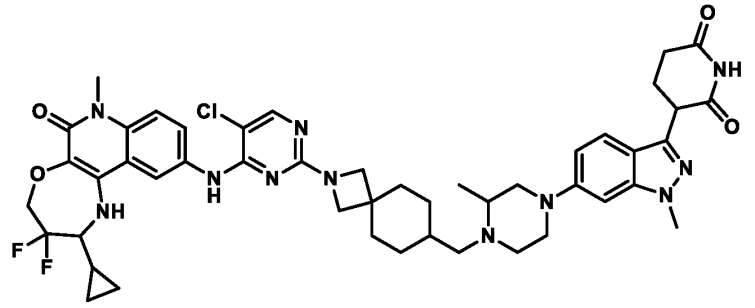
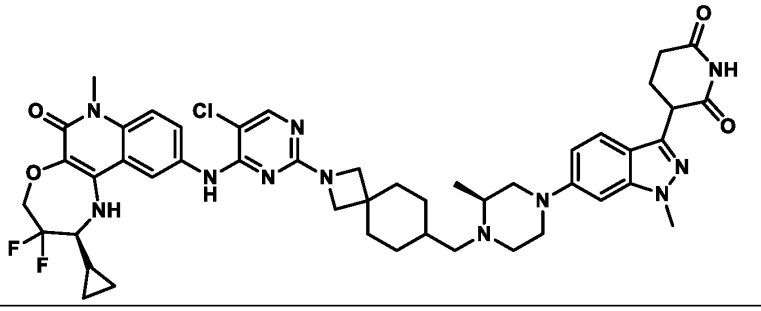
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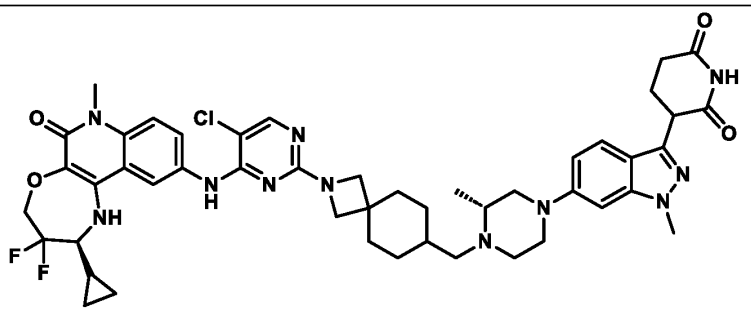
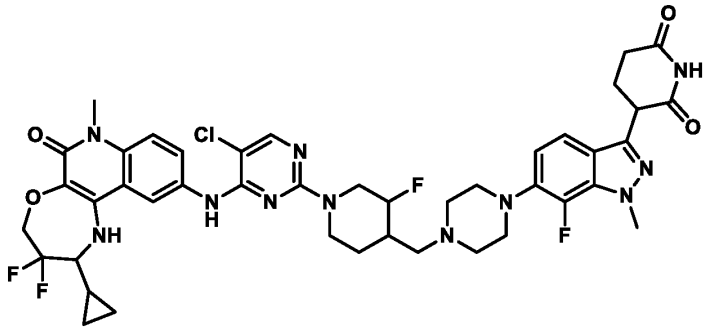
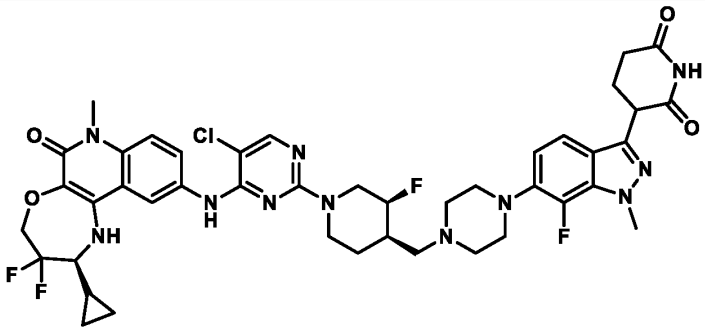
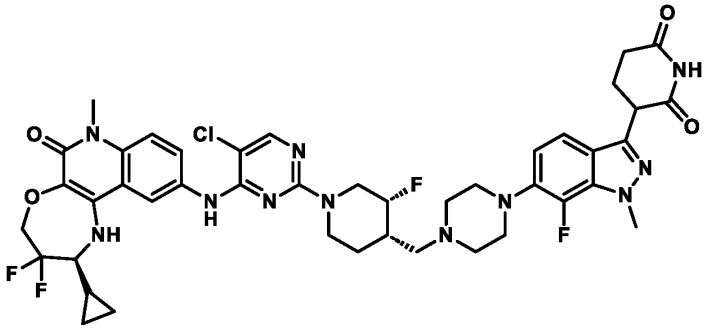
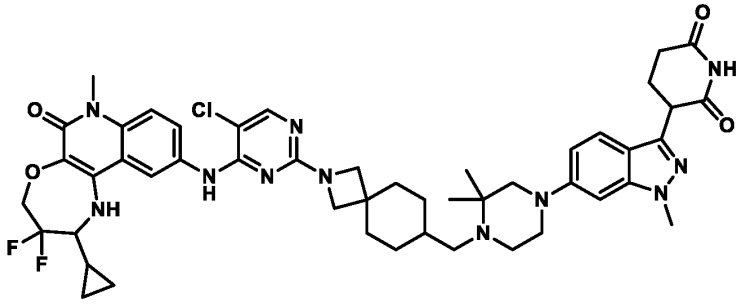
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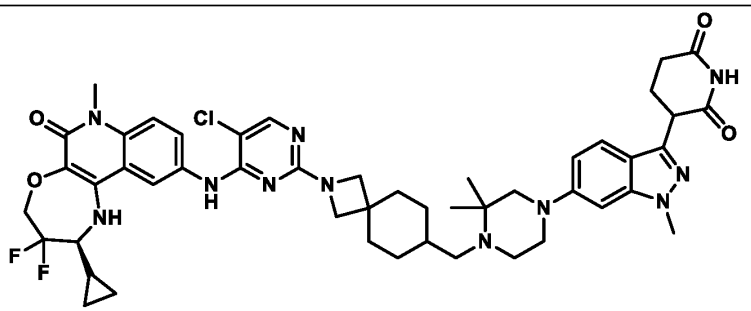
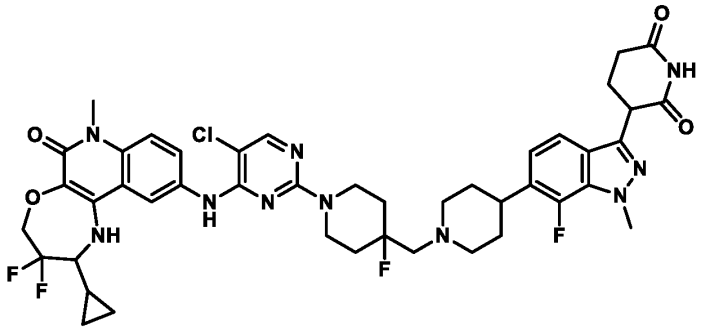
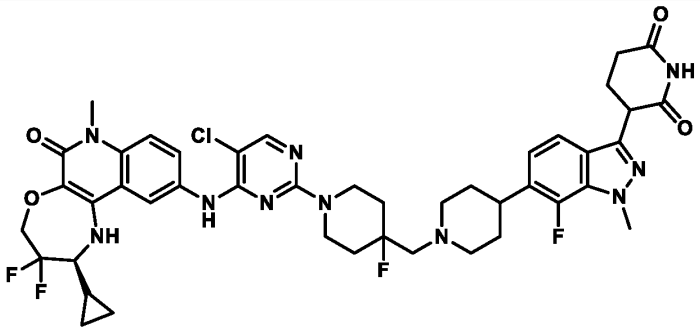
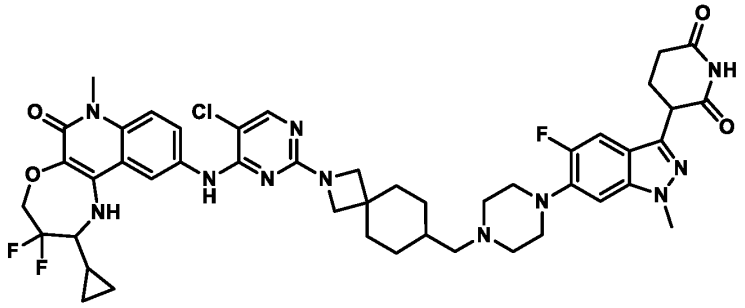
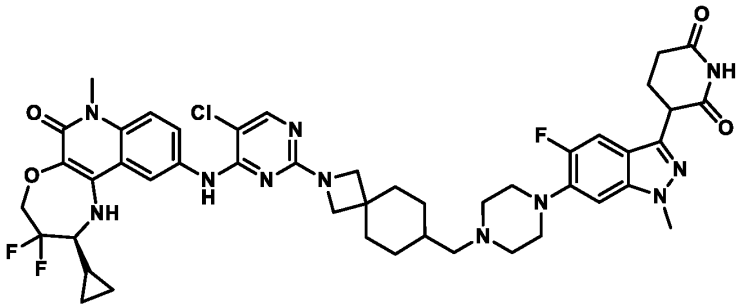
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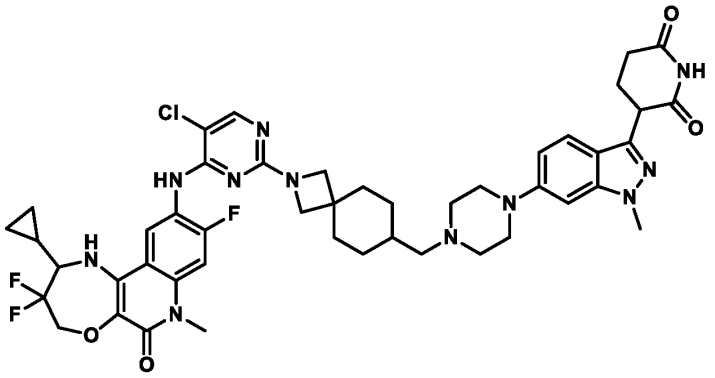
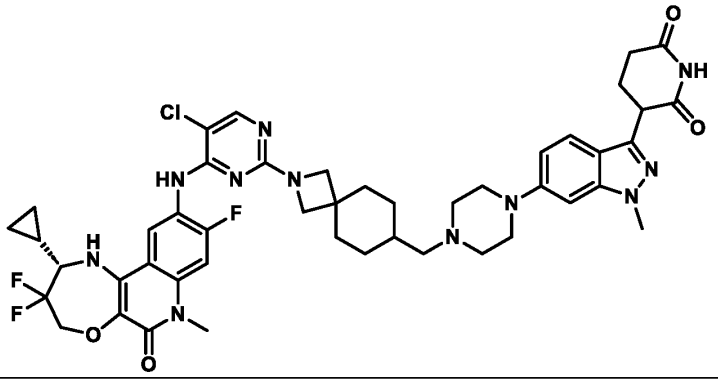
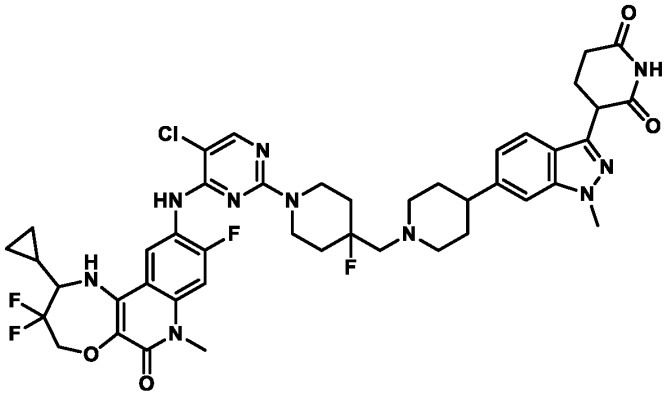
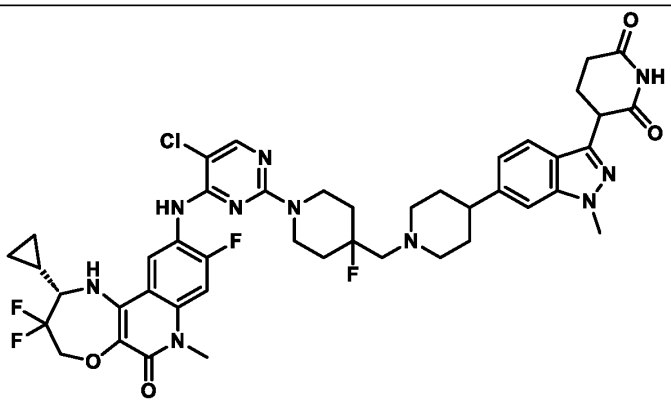
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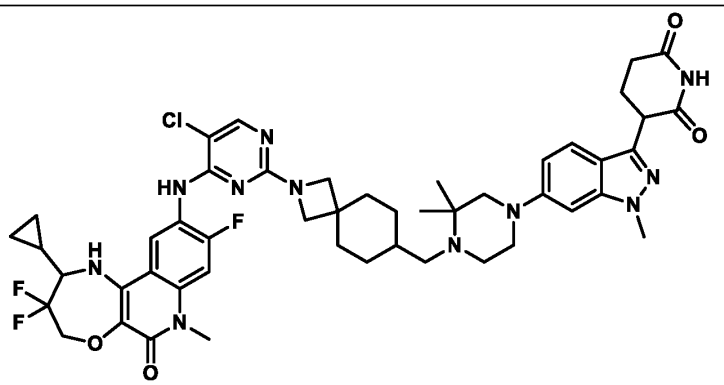
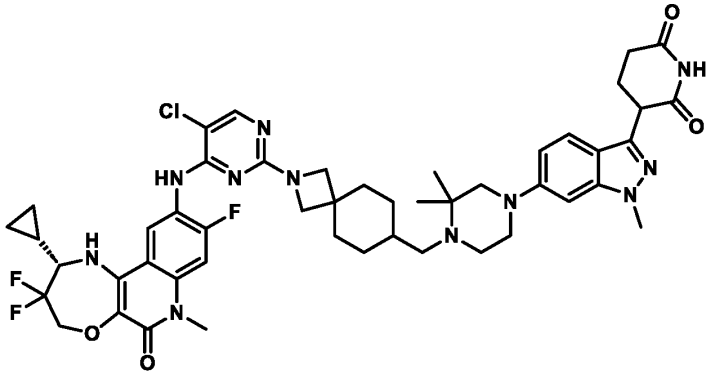
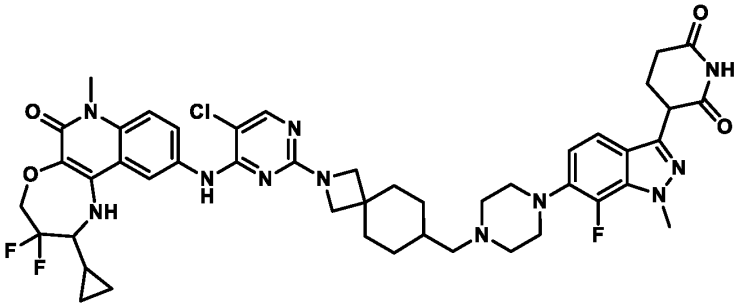
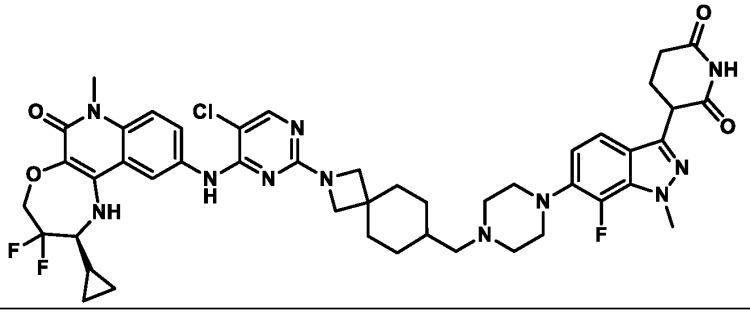
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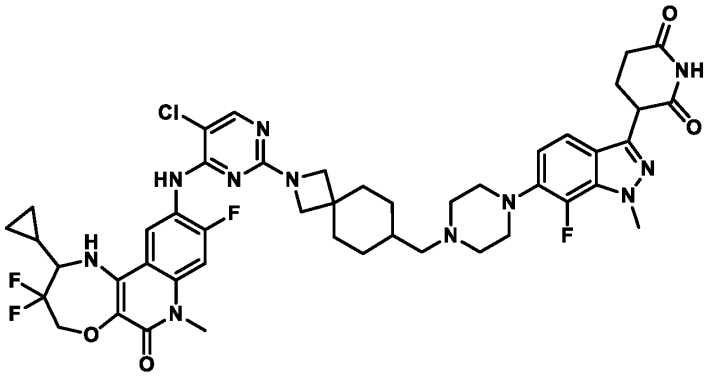
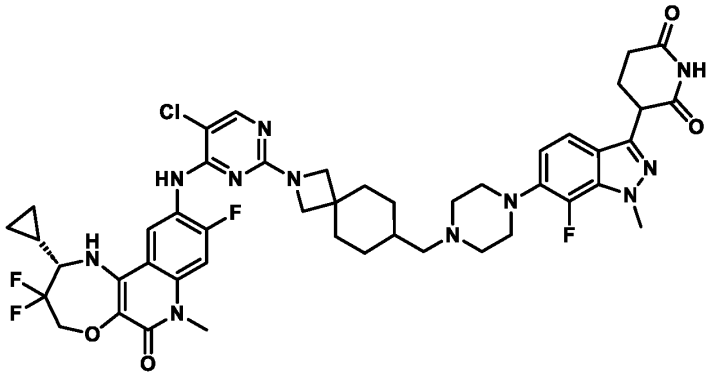
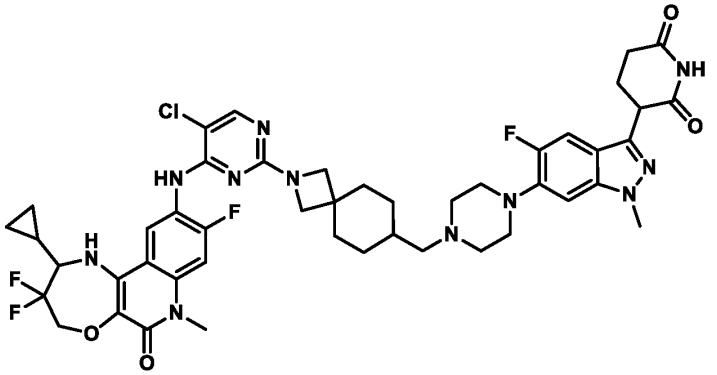
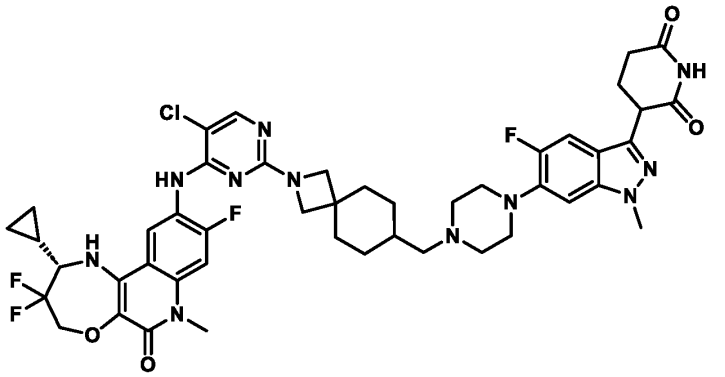
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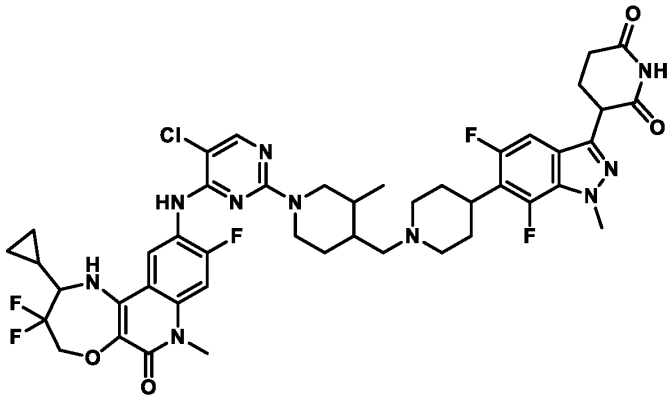
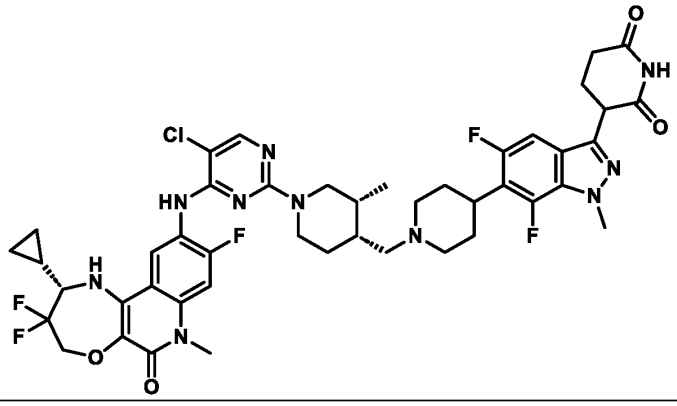
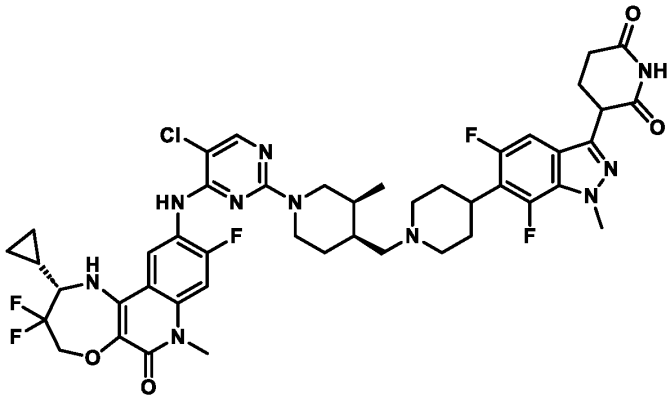
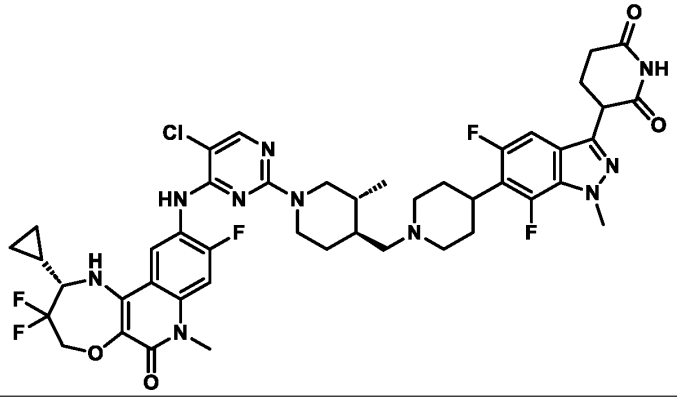
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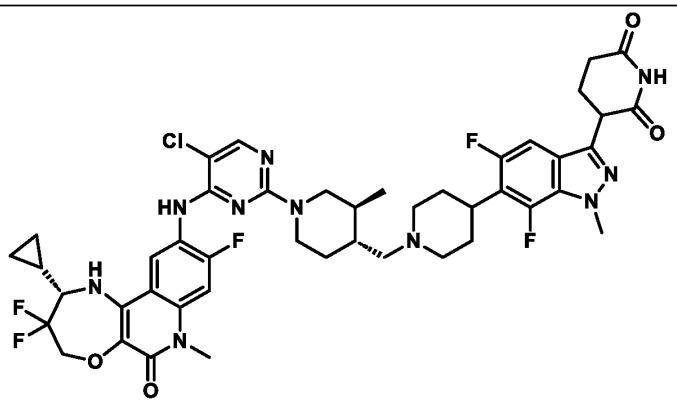
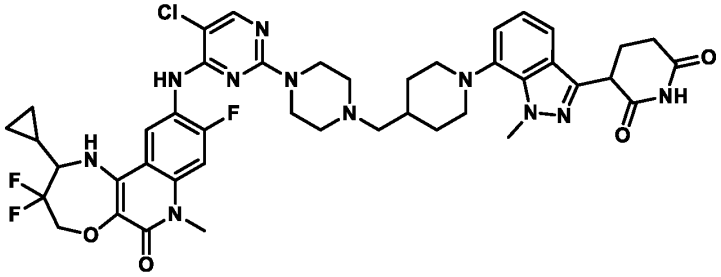
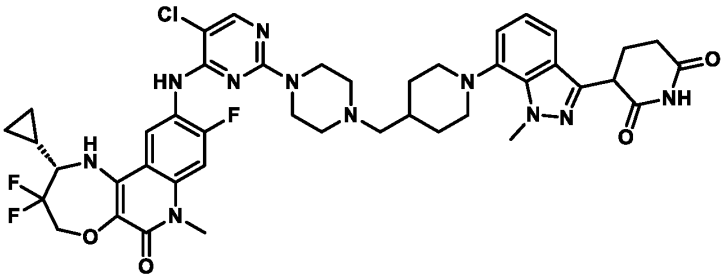
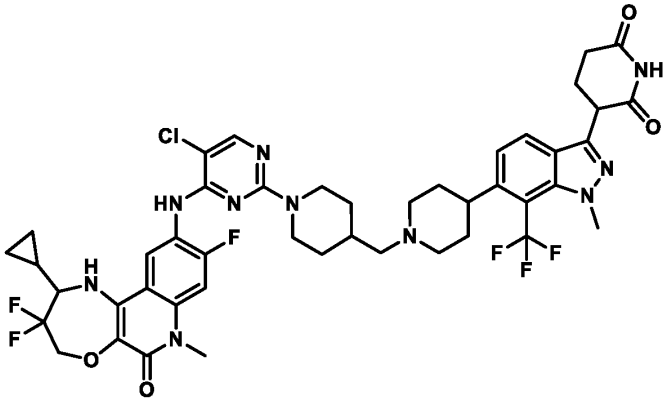
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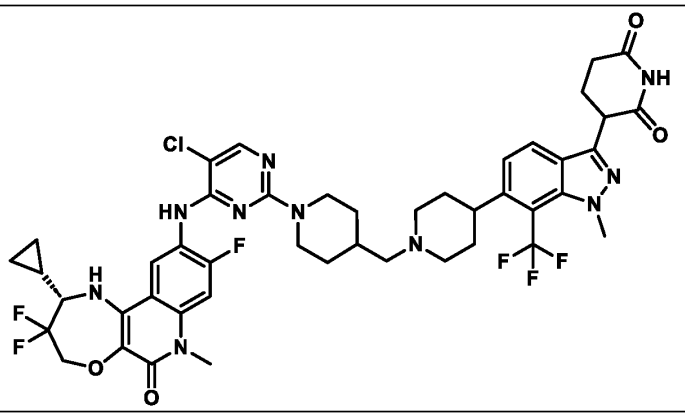
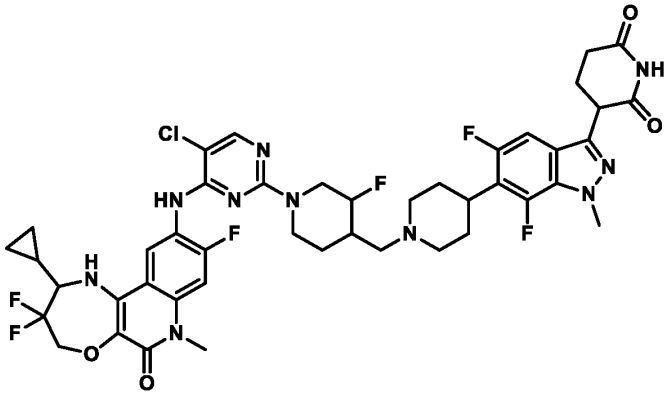
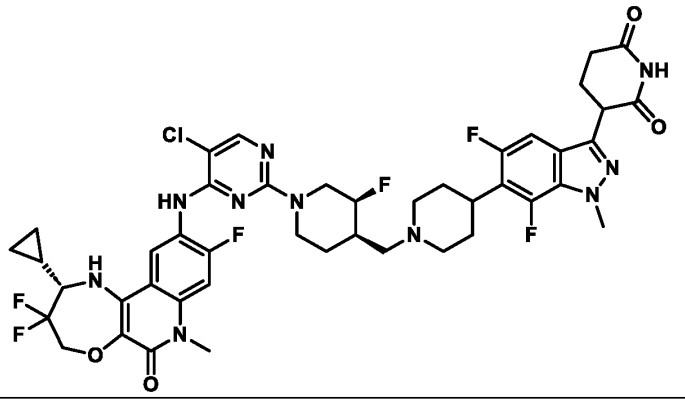
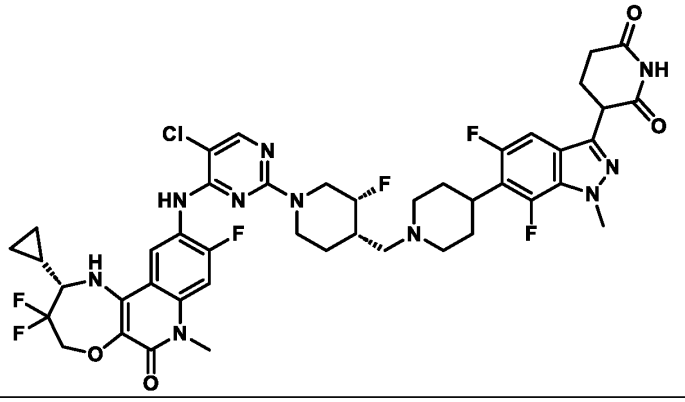
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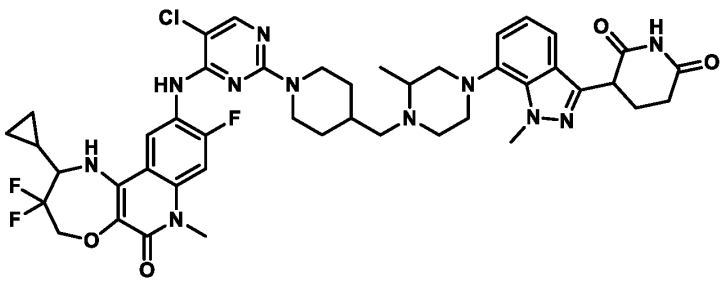
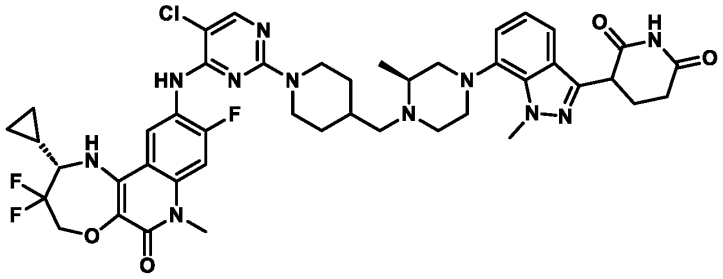
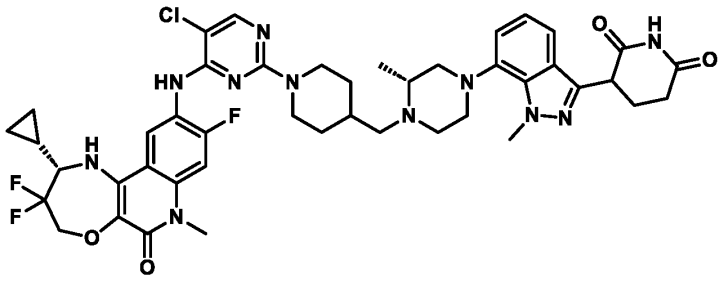
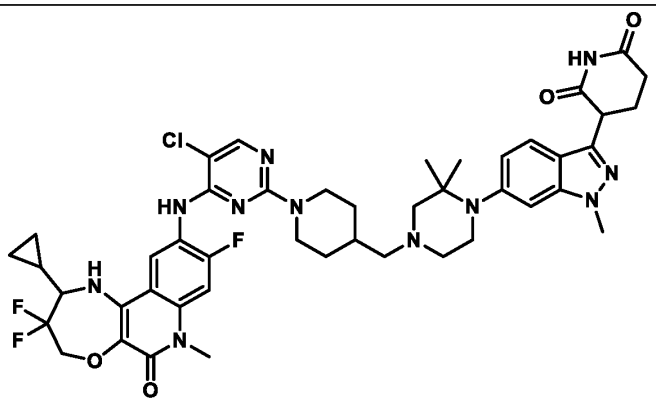
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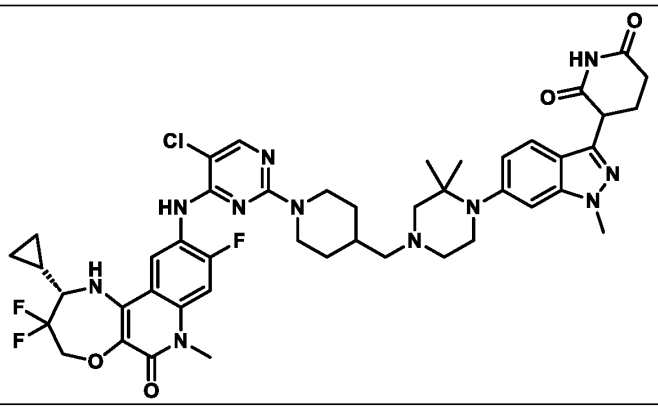
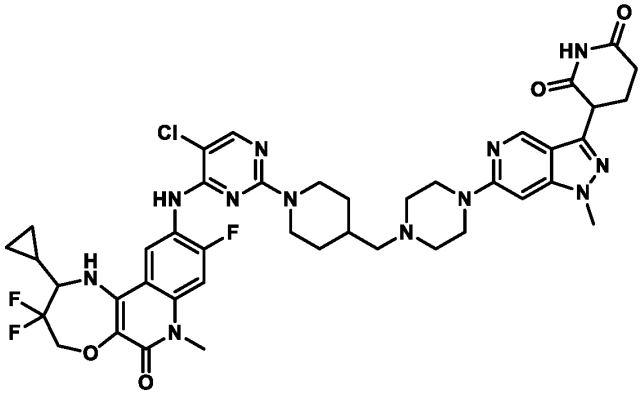
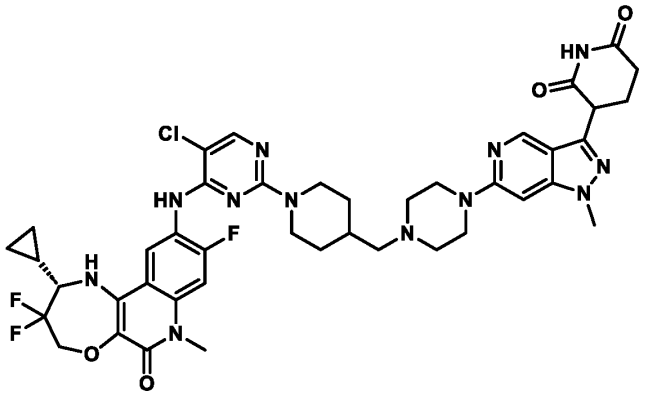
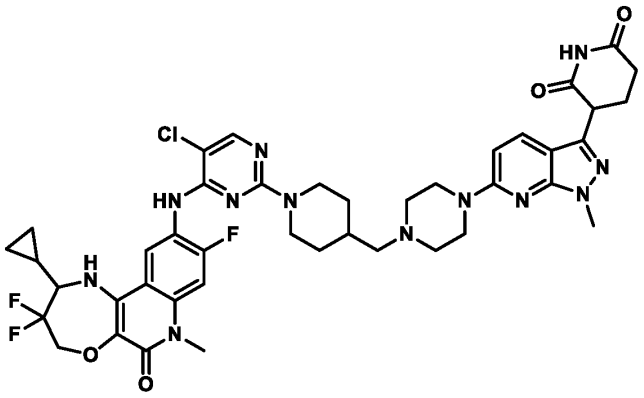
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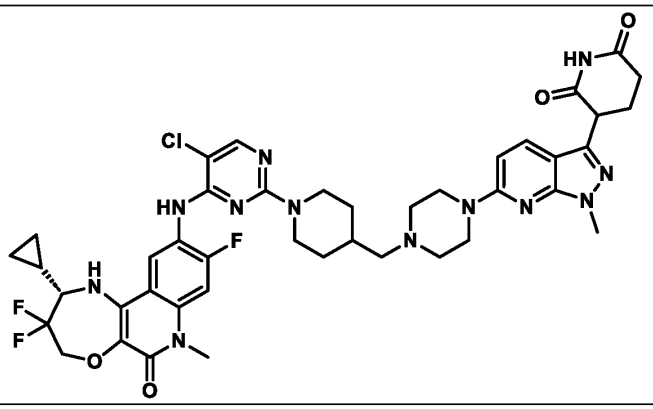
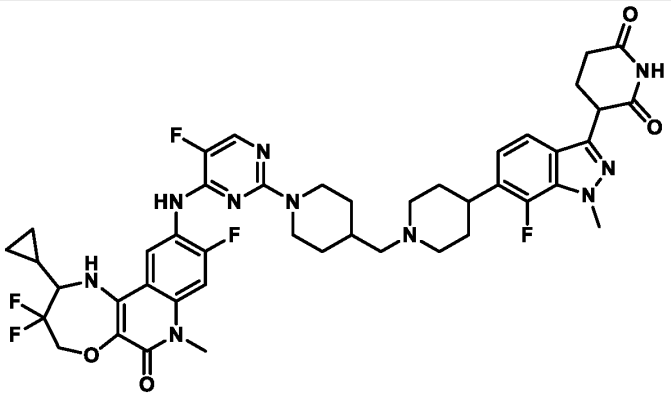
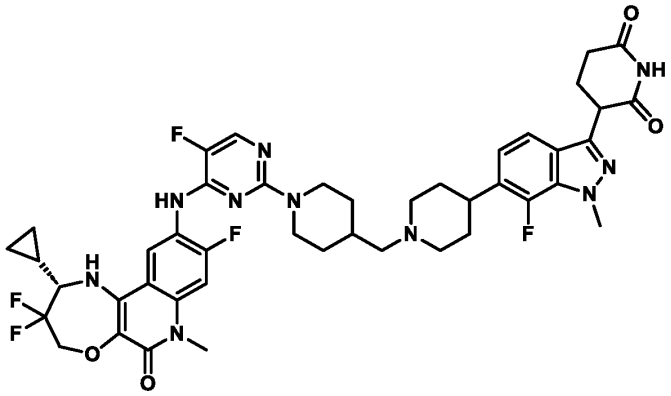
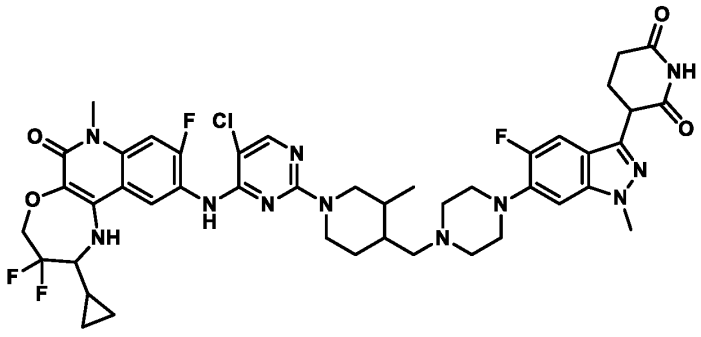
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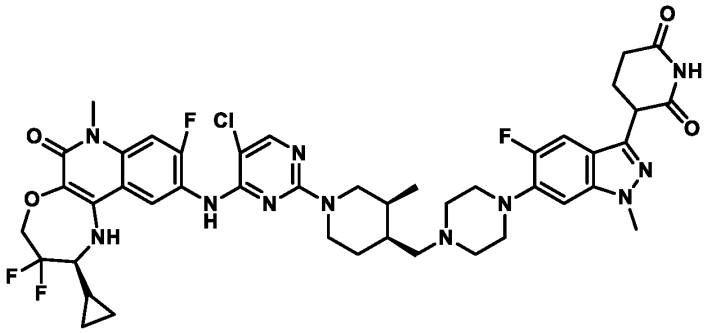
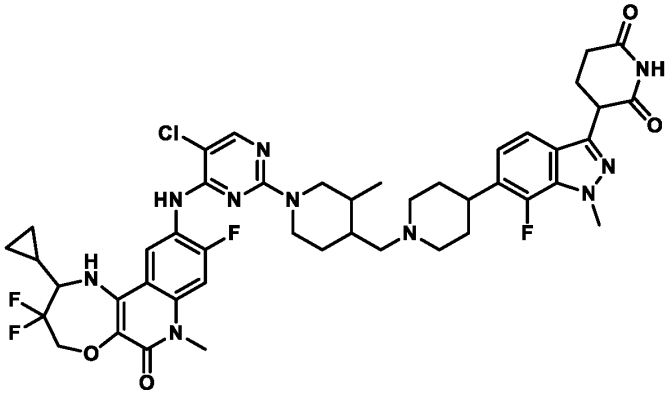
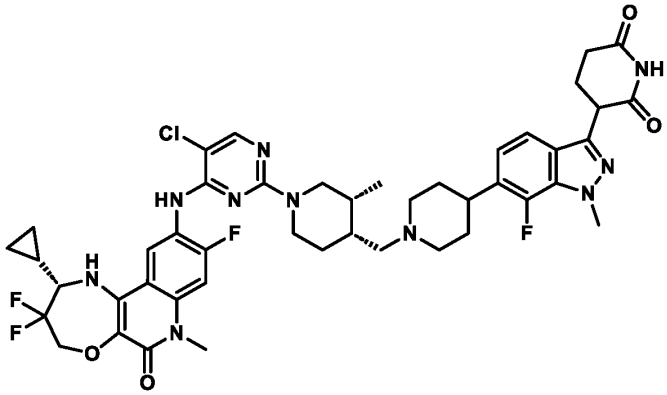
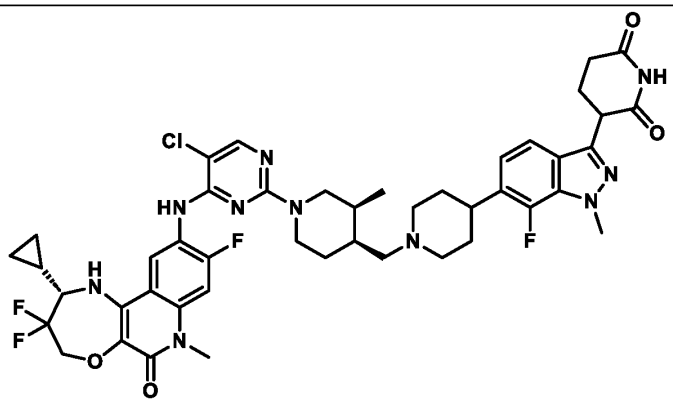
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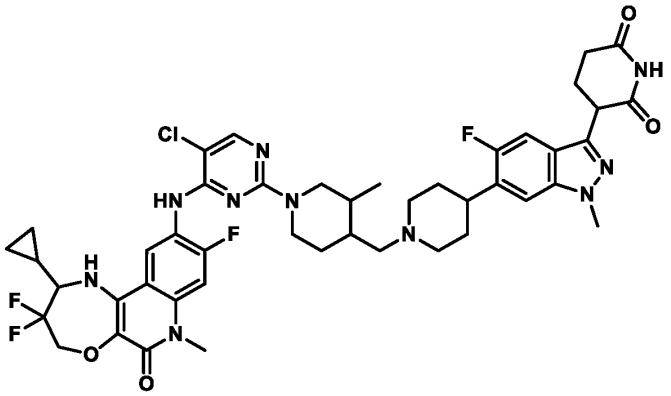
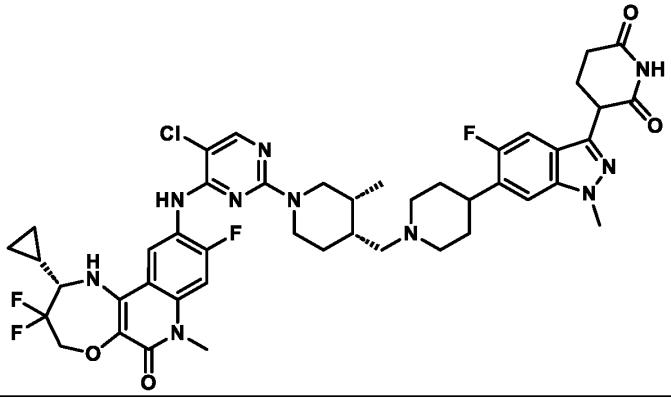
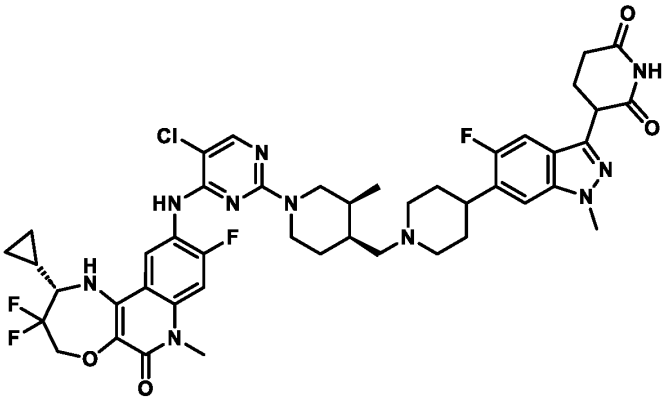
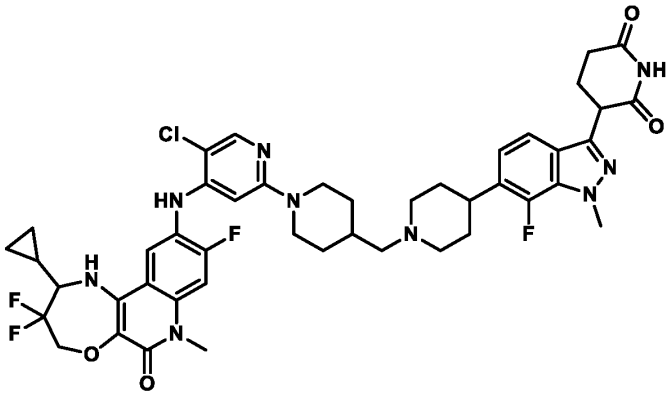
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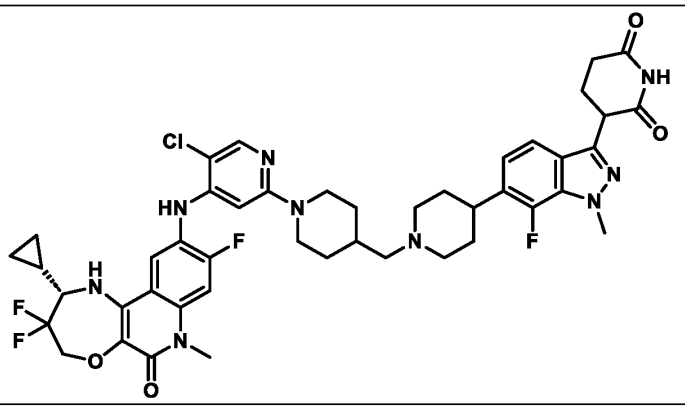
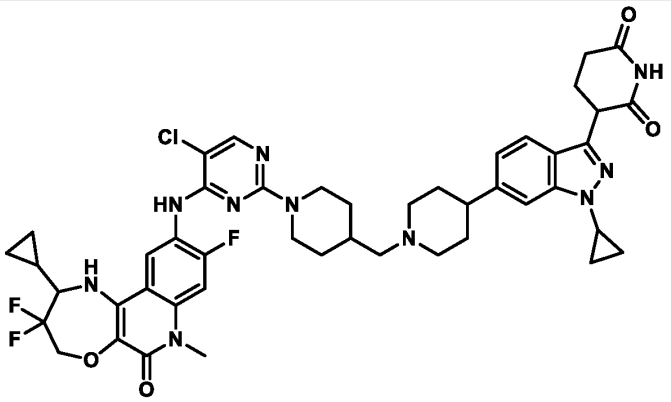
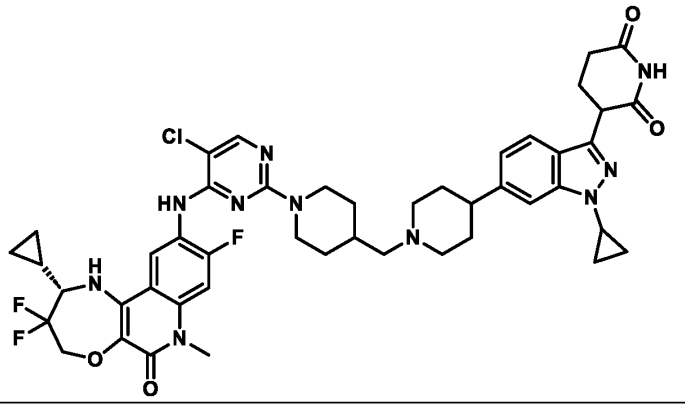
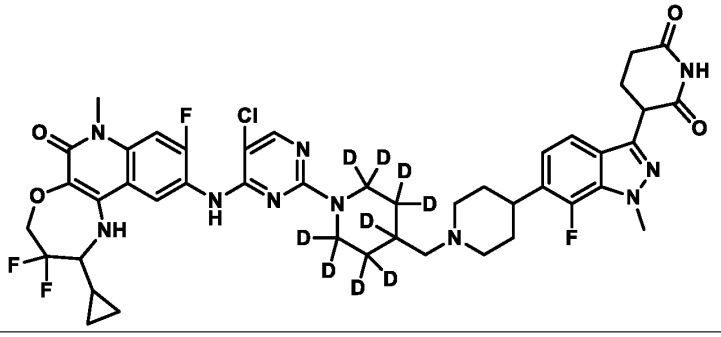
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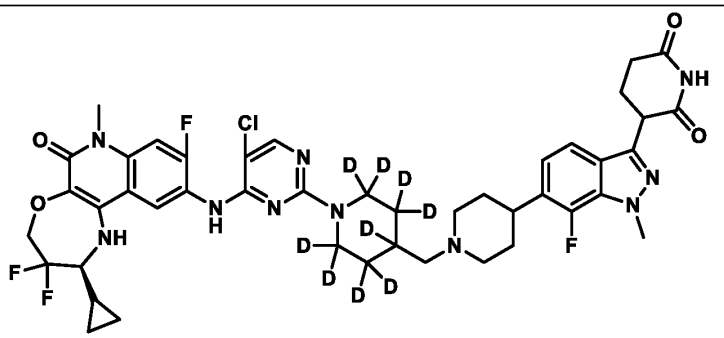
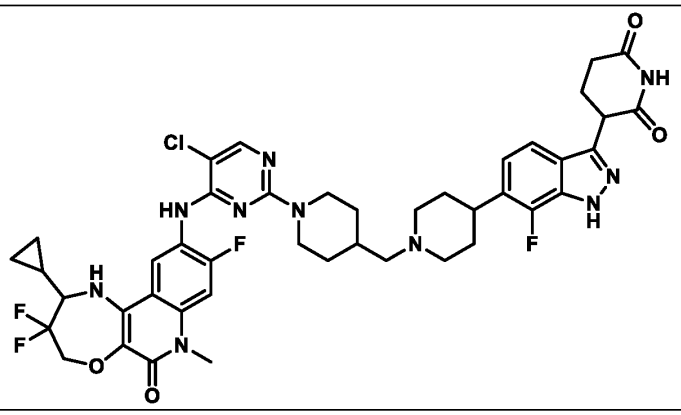
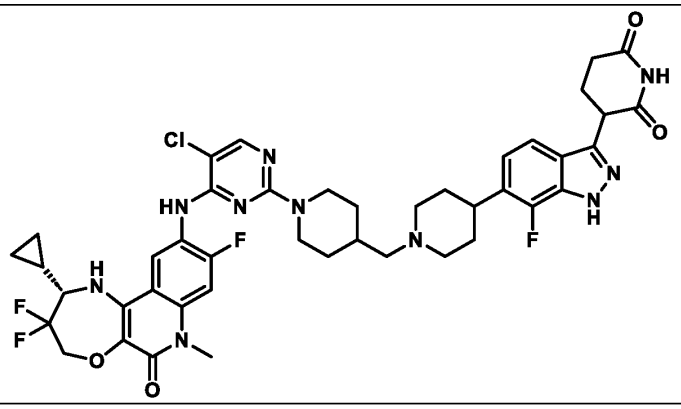
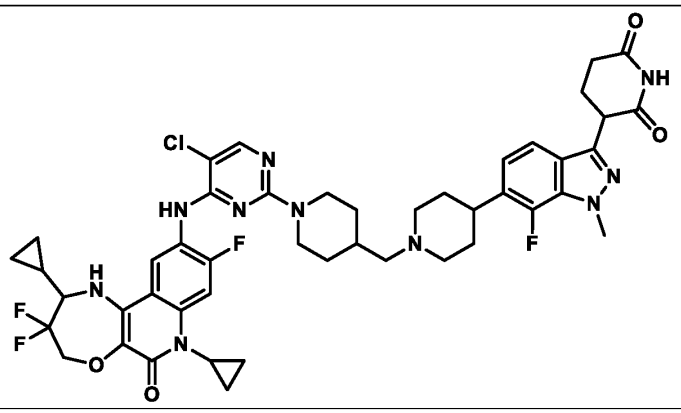
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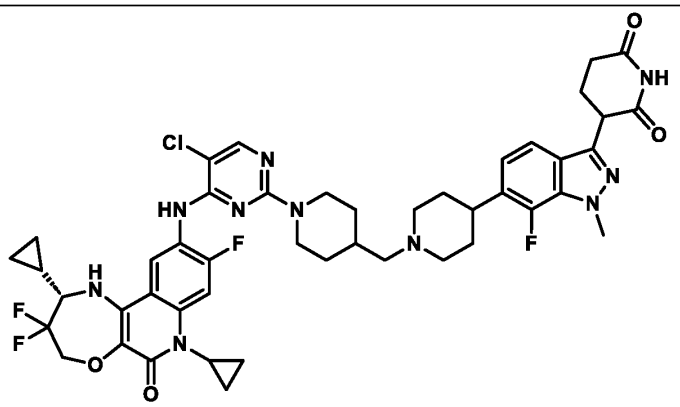
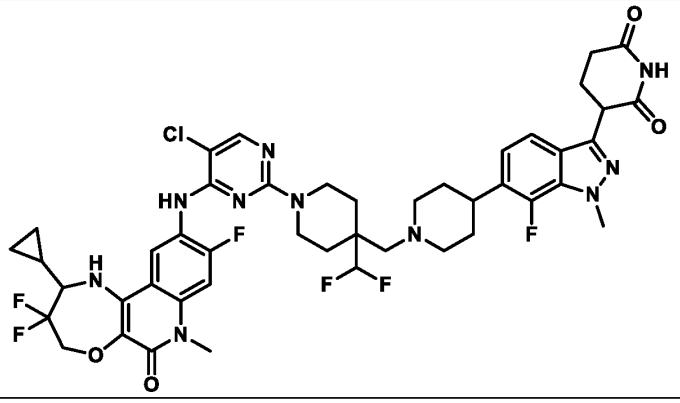
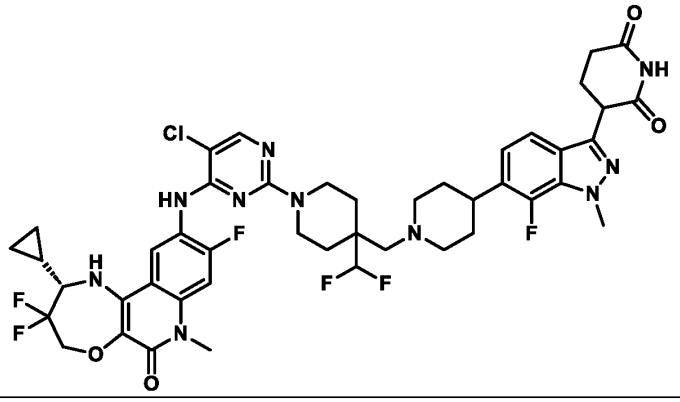
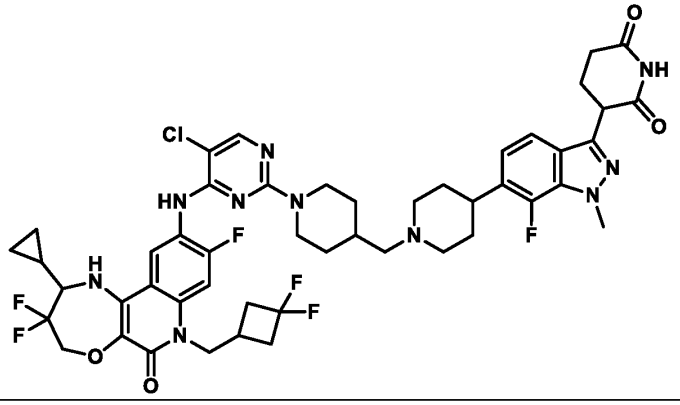
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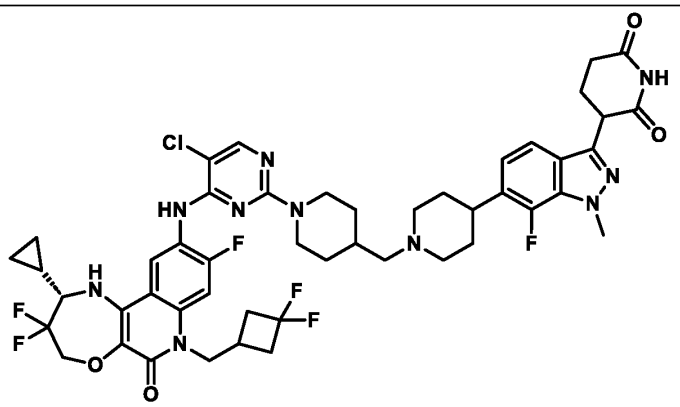
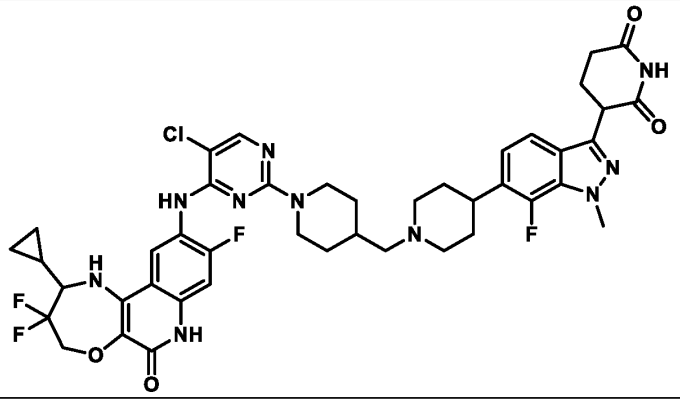
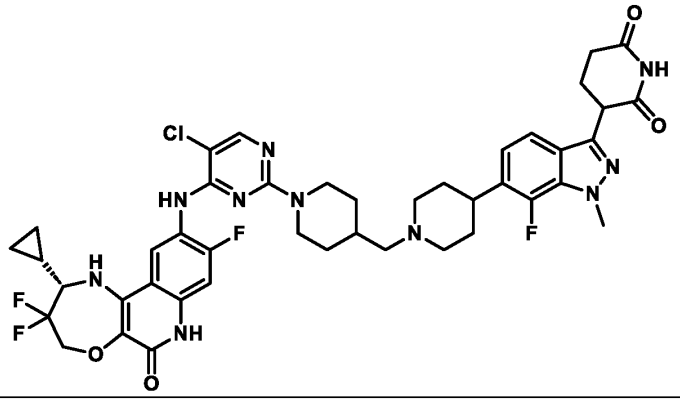
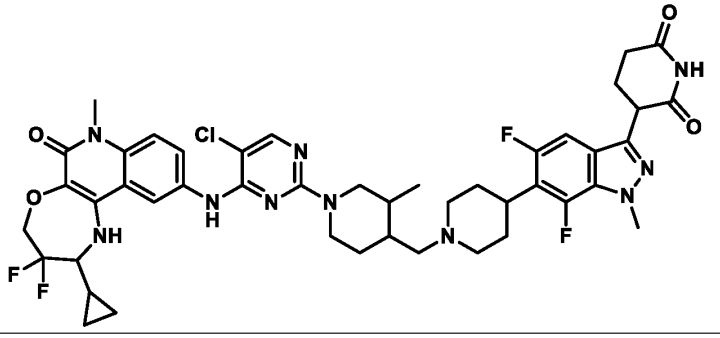
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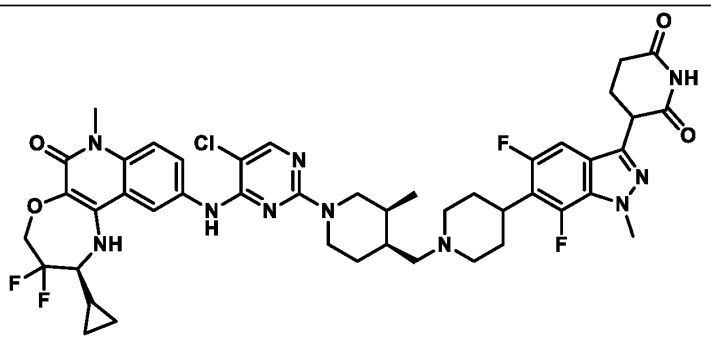
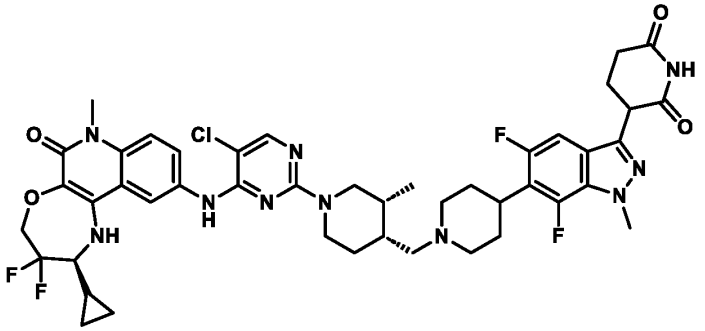
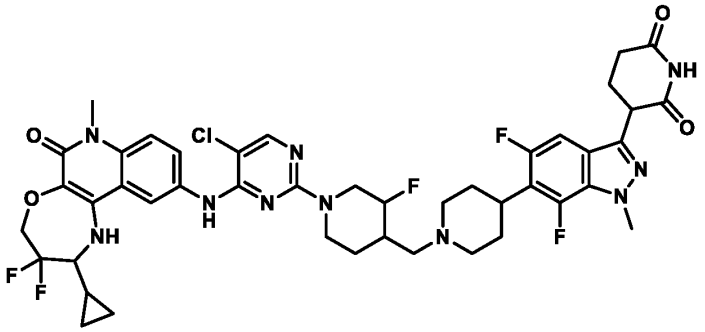
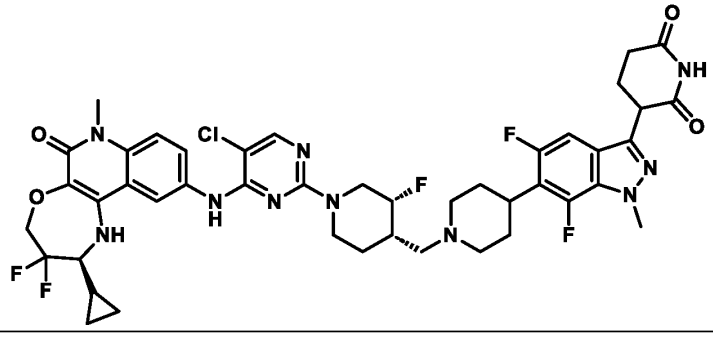
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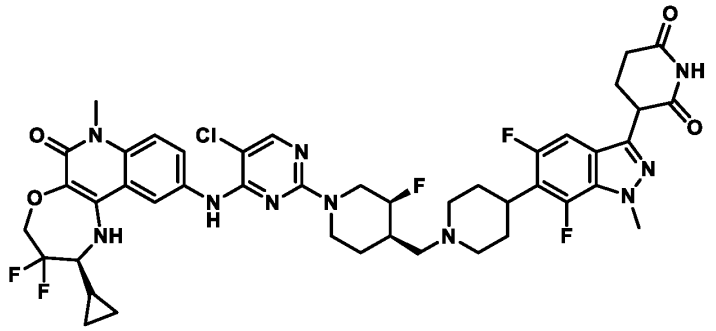
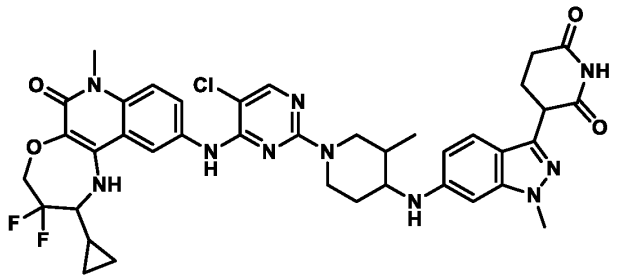
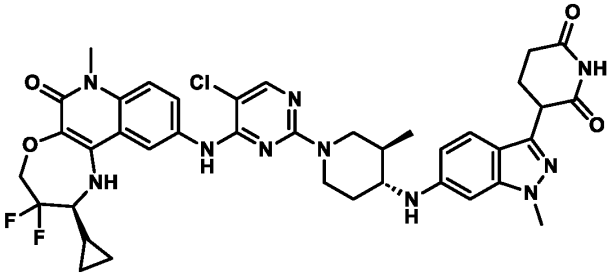
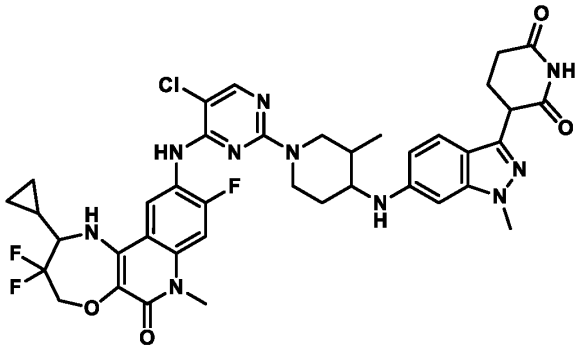
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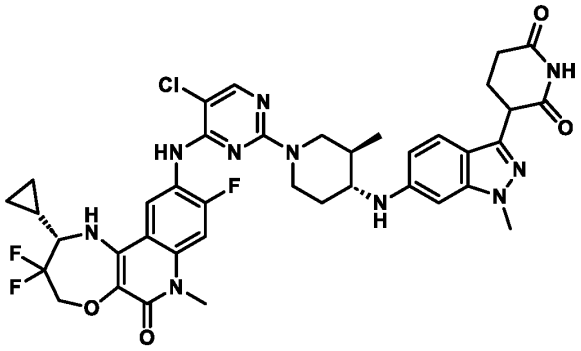
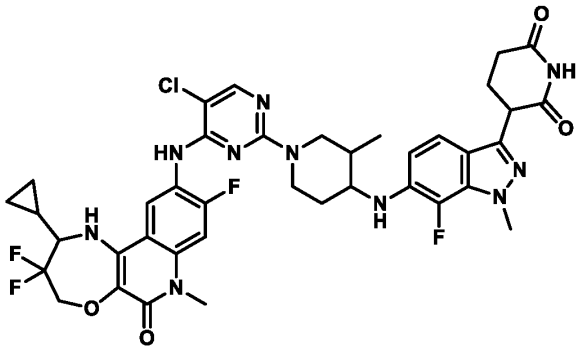
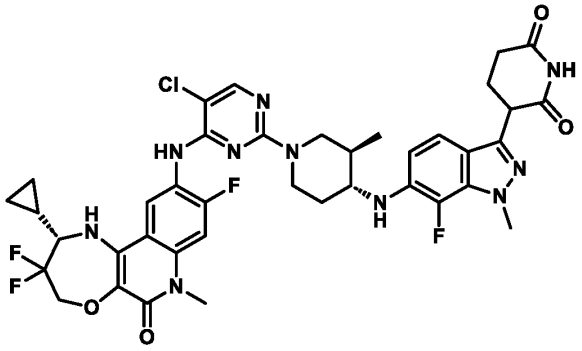
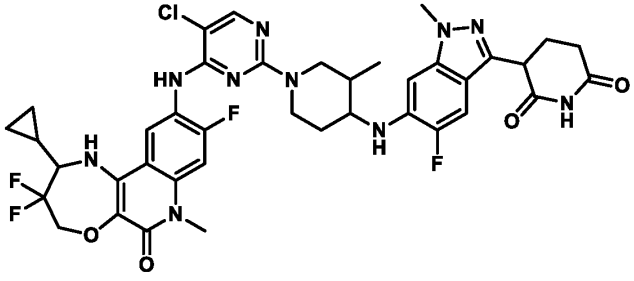
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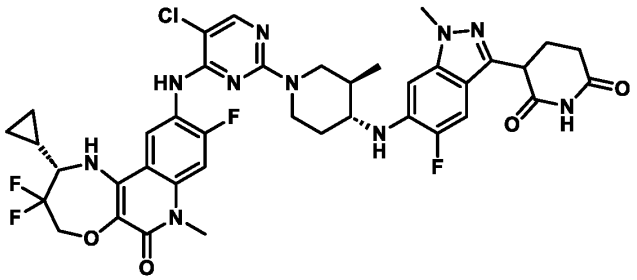
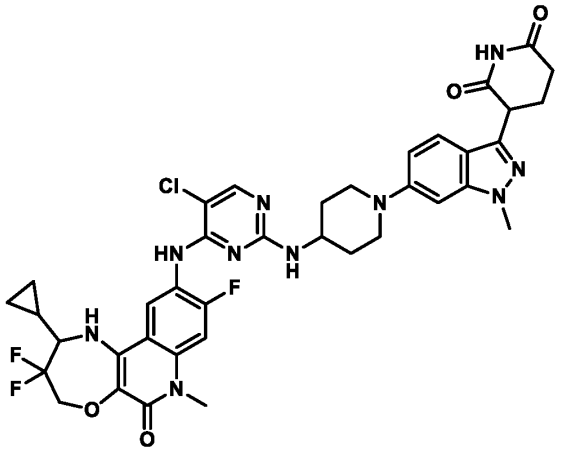
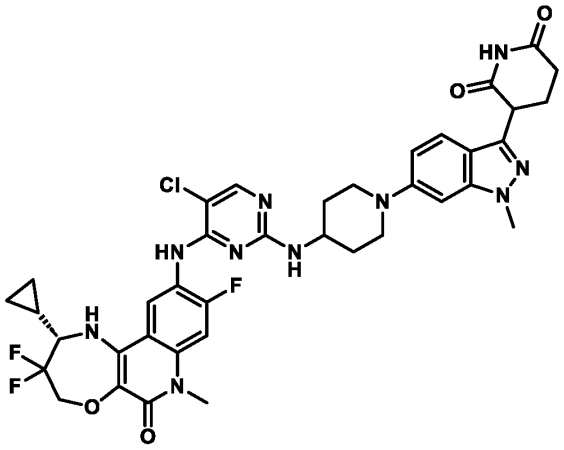
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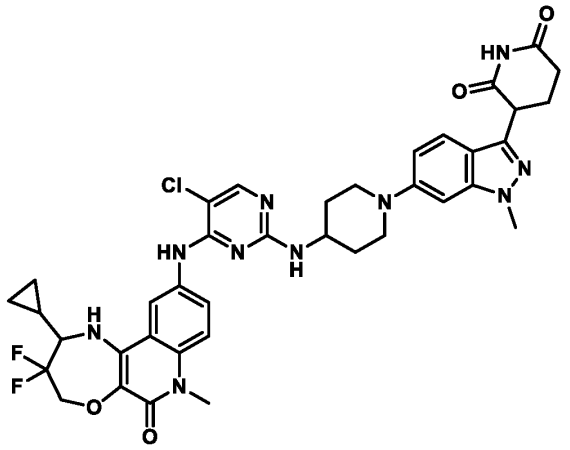
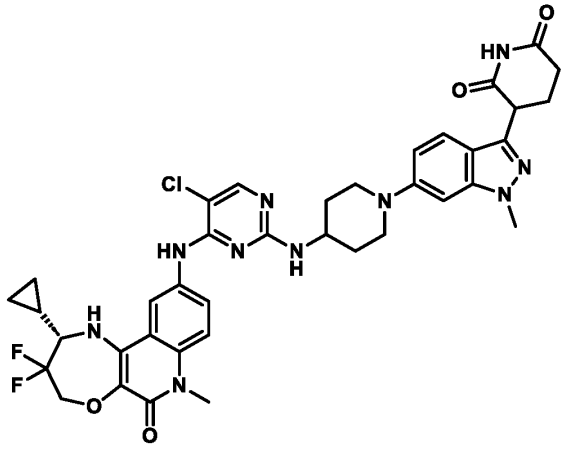
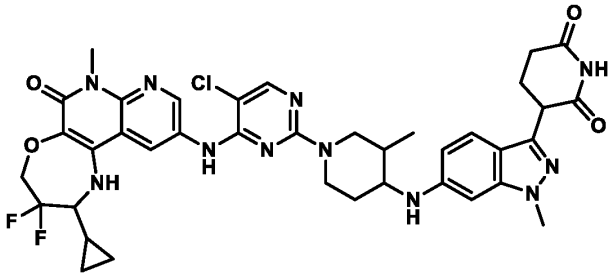
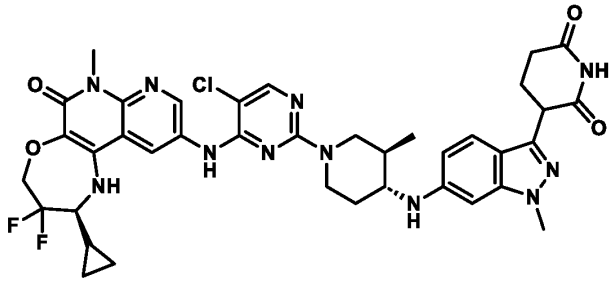
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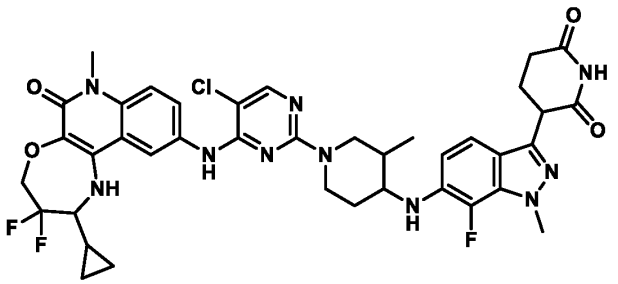
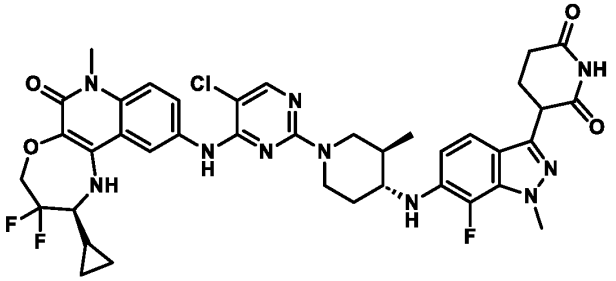
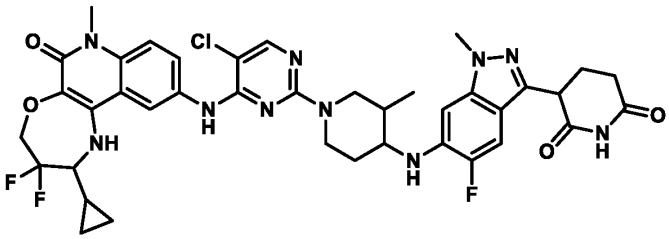
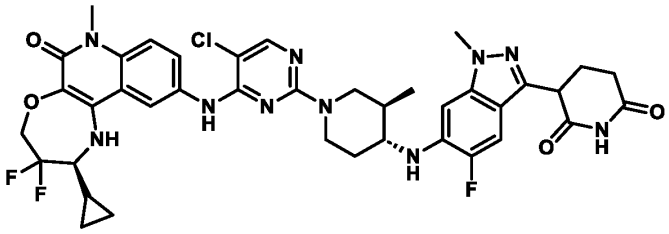
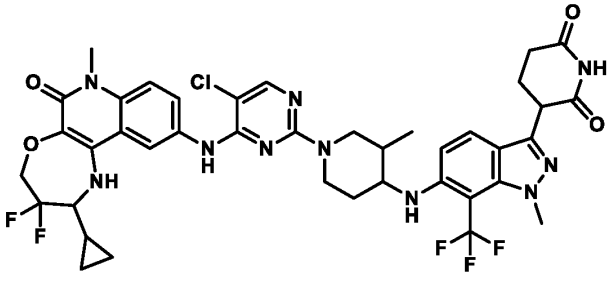
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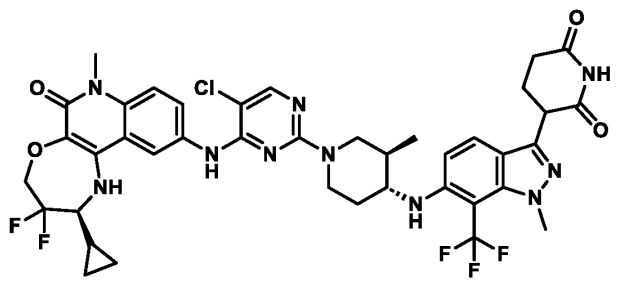
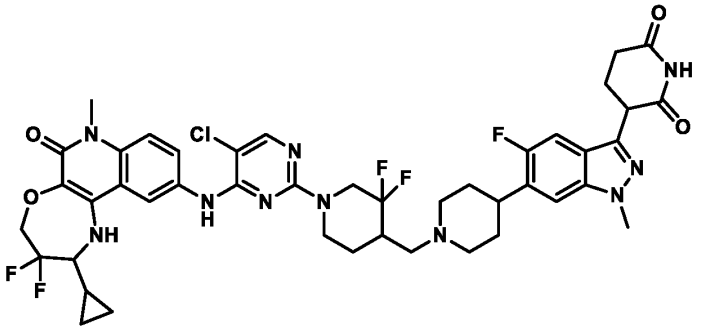
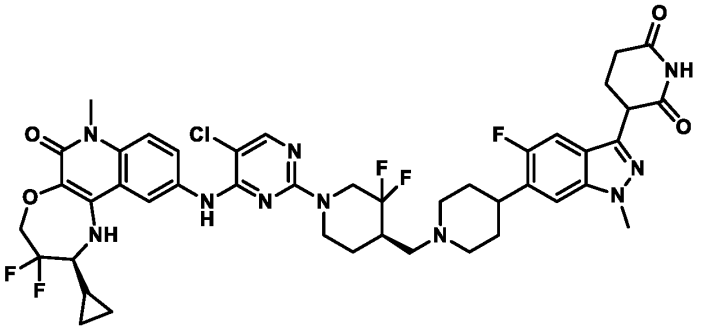
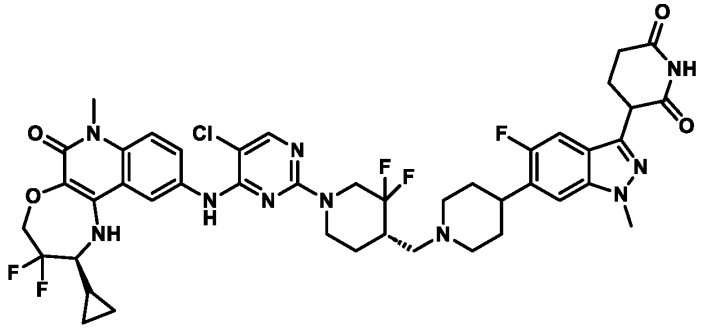
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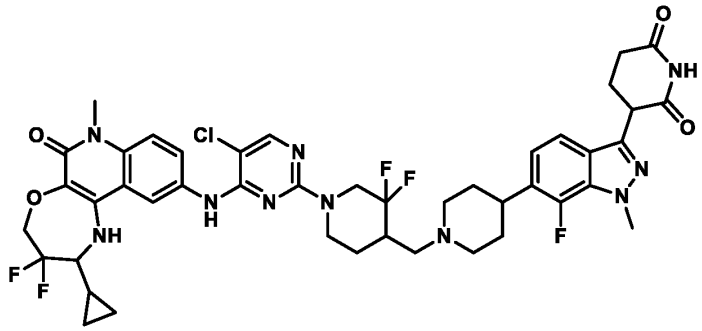
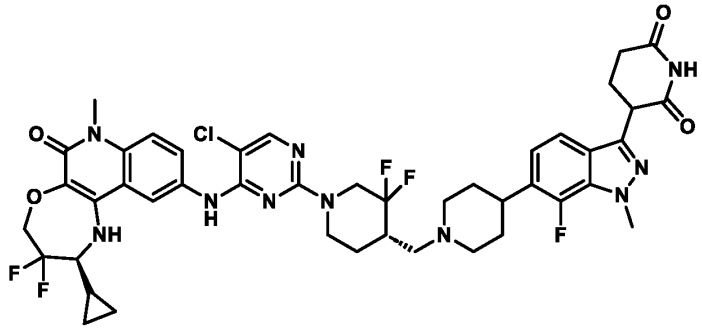
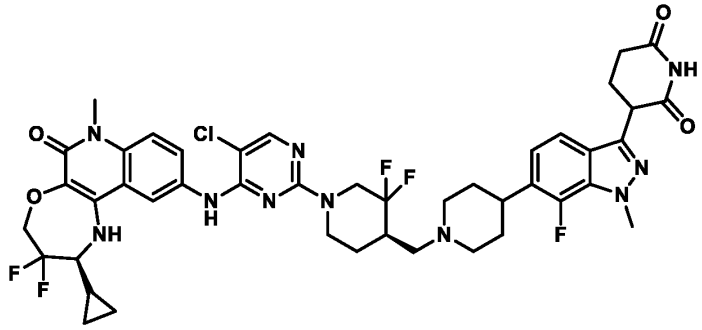
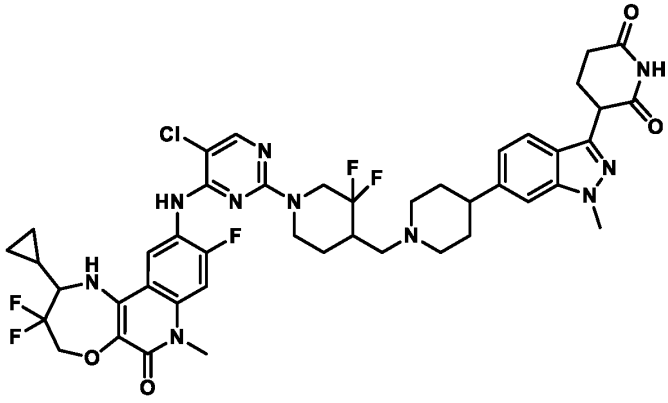
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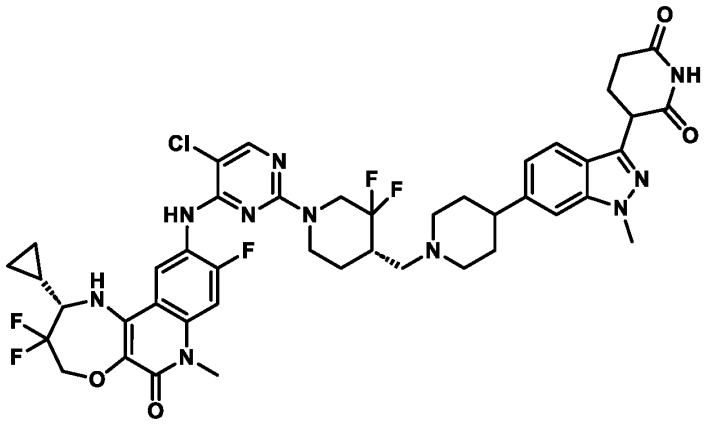
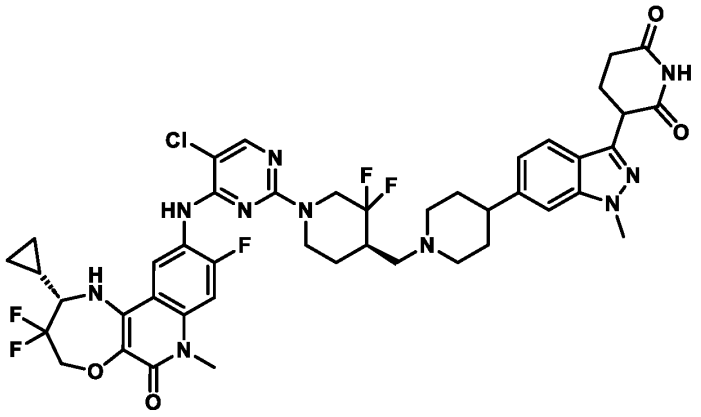
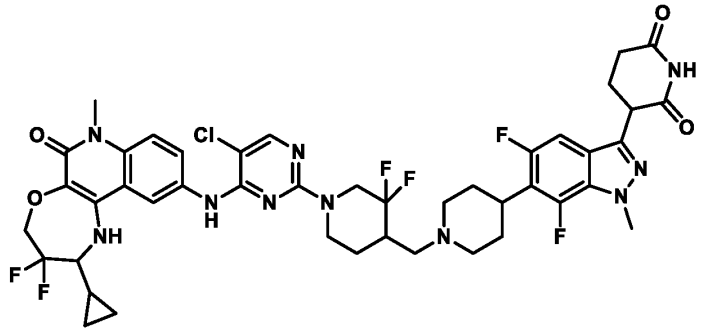
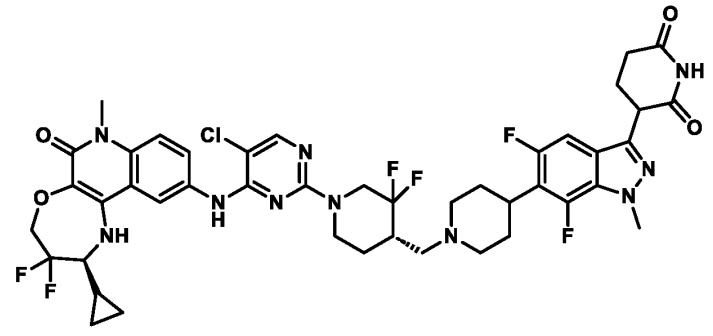
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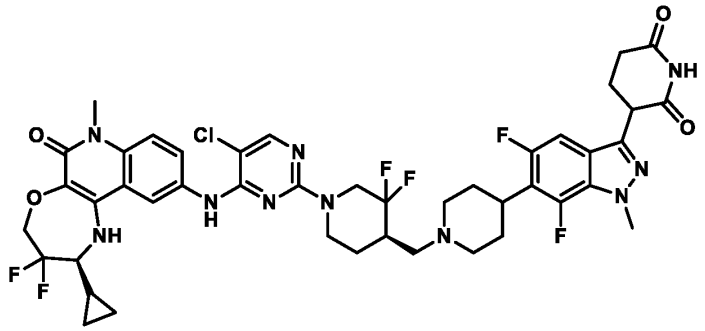
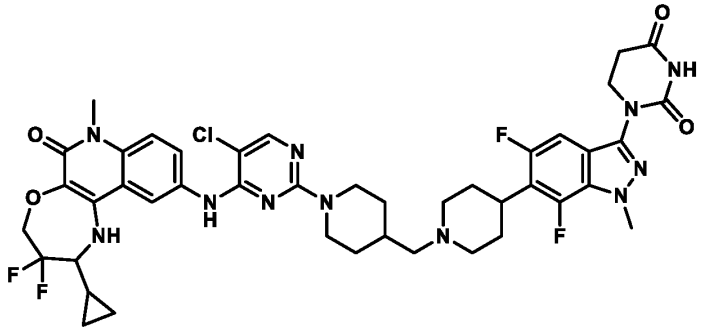
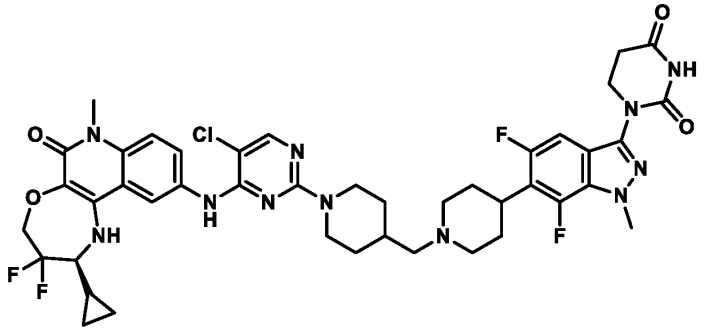
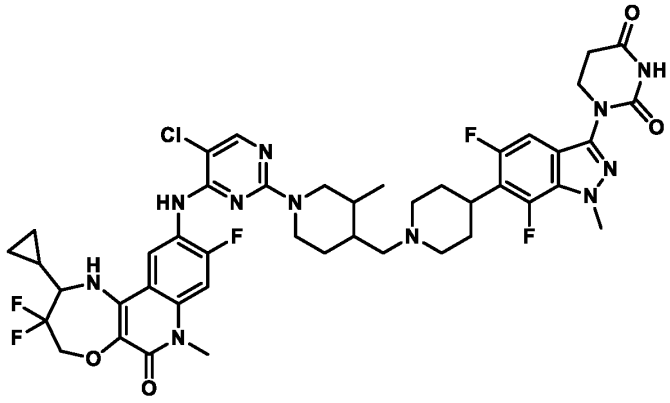
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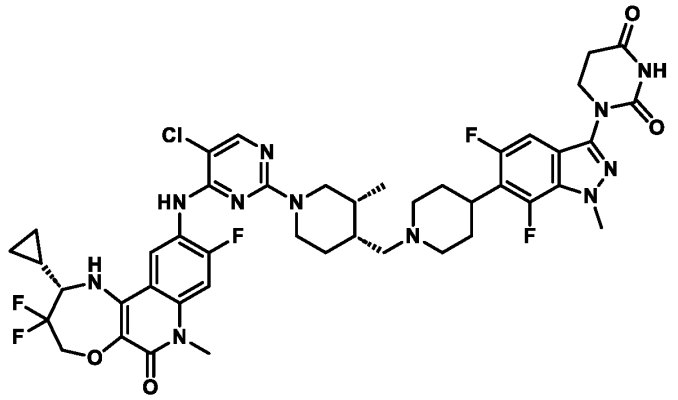
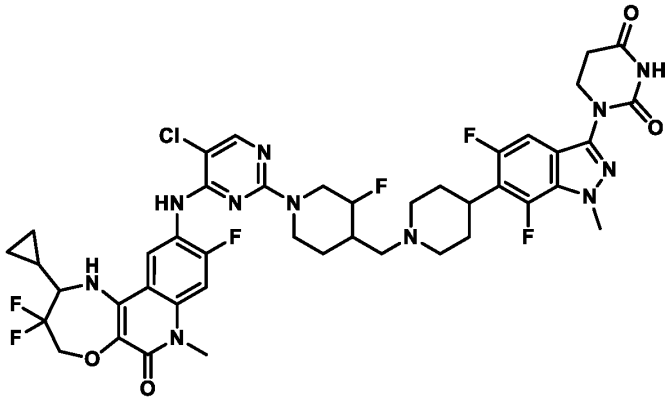
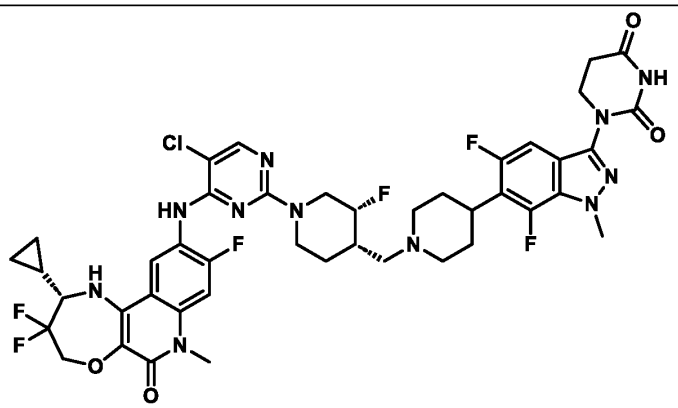
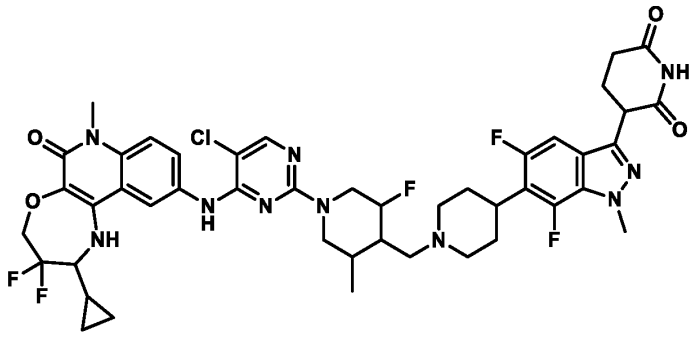
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228a	
229	
229a	
230	

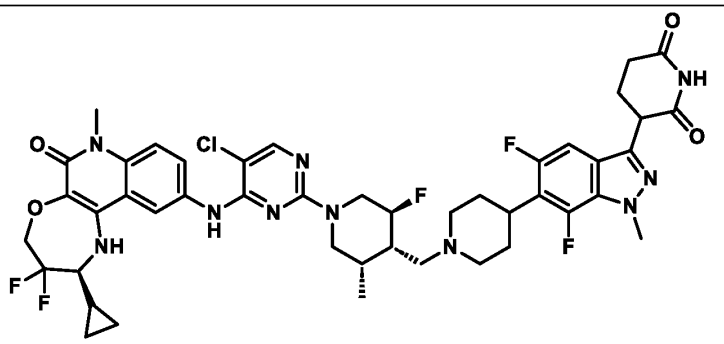
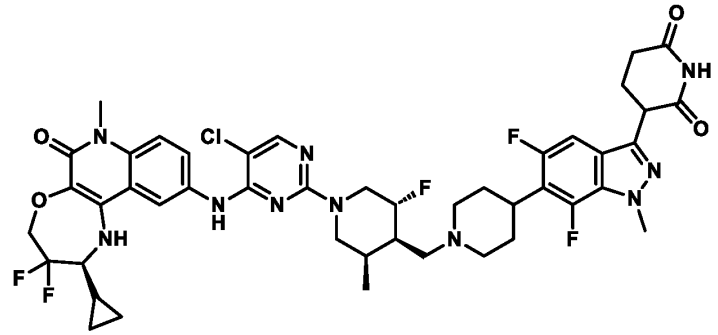
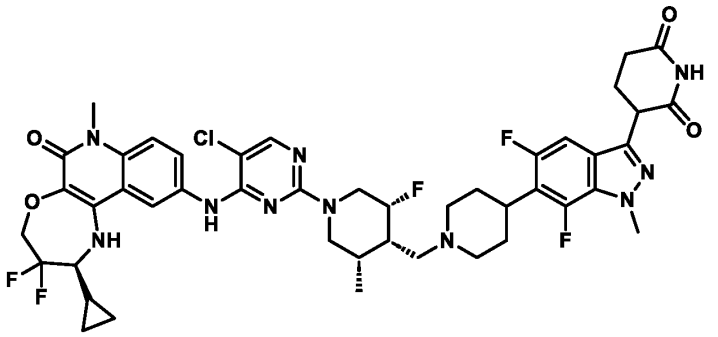
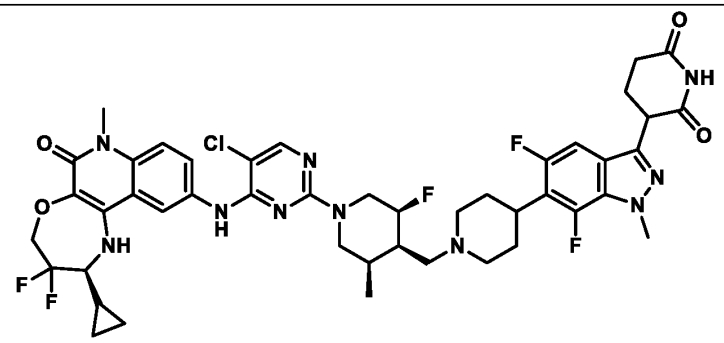
230a	
231	
231a	
231b	

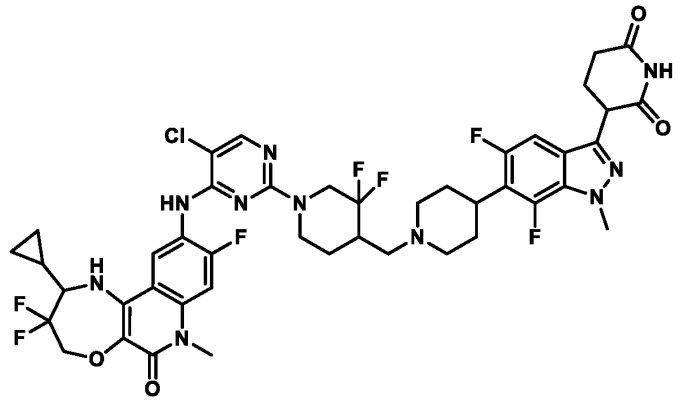
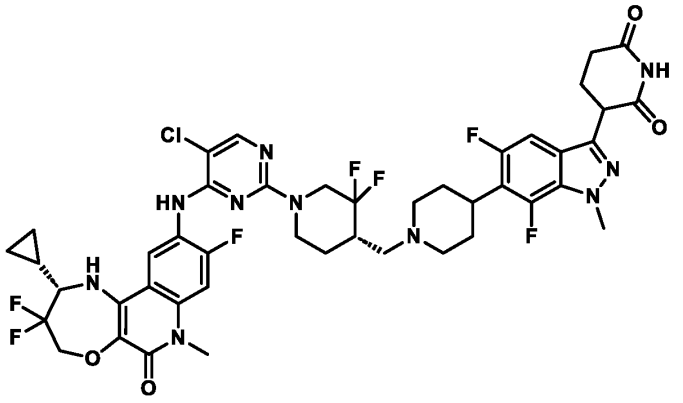
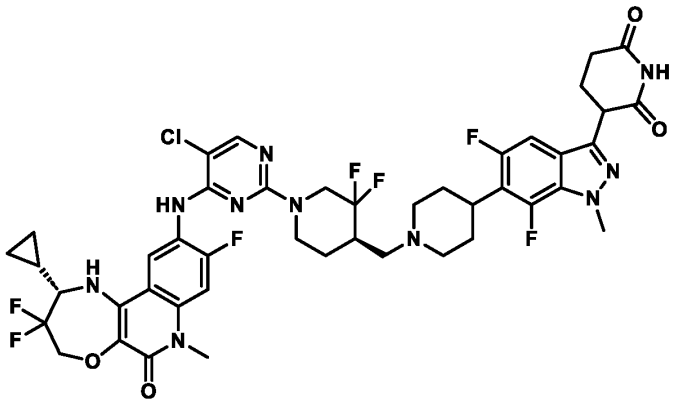
232	
232a	
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233a	
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237a	
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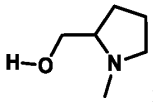
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238b	
238c	
238d	

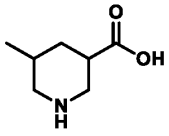
239	
239a	
239b	

Note:

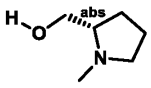
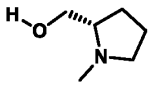
In certain compounds of **Table C1**, **Table C2**, **Table R1**, or **Table R2**, one or more stereogenic centers are denoted with the "V3000 enhanced stereochemical notation" (*see*: support.collaborativedrug.com/hc/en-us/articles/360020872171-Advanced-Stereochemistry-Registration-Atropisomers-Mixtures-Unknowns-and-Non-Tetrahedral-Chirality, accessed on December 23, 2022 and Accelrys Chemical Representation Guide, Accelrys Software Inc., 2014, each of which is incorporated by reference herein in its entirety). Using this

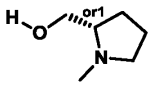
stereochemical notation, certain stereogenic centers are denoted with "*abs*", "*&x*", or "*orx*", wherein x is an integer (e.g., 1 or 2). For avoidance of doubt, the stereochemical notations in **Table C1**, **Table C2**, **Table R1**, or **Table R2** have the following meaning:

(1) When a stereogenic center (e.g., a stereogenic carbon) is depicted with "flat" bonds (i.e., none of the chemical bonds at the stereogenic center is depicted with wedges or dashes) in a structural formula, each of the stereogenic centers can independently adopt the **(*R*)-** or **(*S*)-** configurations. For example, the structure  represents (***S***)-(1-methylpyrrolidin-2-yl)methanol, (***R***)-(1-methylpyrrolidin-2-yl)methanol, or a mixture thereof.

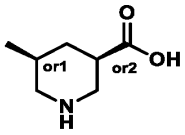
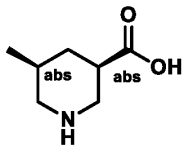
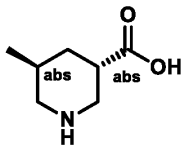
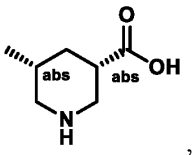
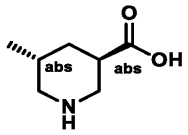
As another non-limiting example, the structure  represents: (***3S,5S***)-5-methylpiperidine-3-carboxylic acid; (***3R,5S***)-5-methylpiperidine-3-carboxylic acid; (***3S,5R***)-5-methylpiperidine-3-carboxylic acid; (***3R,5R***)-5-methylpiperidine-3-carboxylic acid; or a mixture thereof.

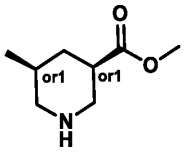
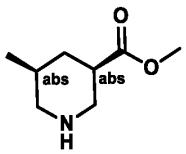
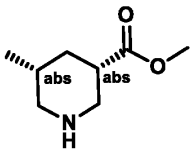
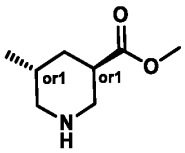
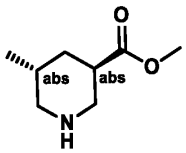
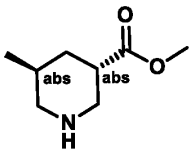
When a stereogenic center or a plurality of stereogenic centers is depicted with wedges and dashes, the following notations are used:

(2) When a stereogenic center is denoted with "*abs*" or when a stereogenic center is not denoted with an enhanced stereochemical notation (e.g., "*abs*", "*&x*", or "*orx*"), the stereogenic center has the absolute configuration as depicted by the structural formula. For example, both of the structures  and  refer to (***S***)-(1-methylpyrrolidin-2-yl)methanol.

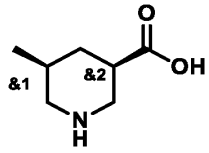
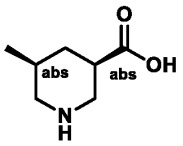
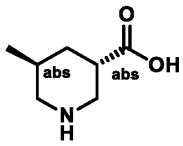
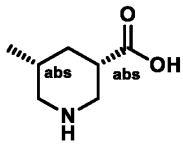
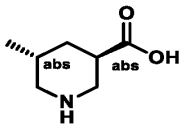
(3) When a stereogenic center is denoted with "*orx*" in a structural formula, the stereogenic center has been resolved but the configuration at the stereogenic center has not been determined. For example, the structure  refers to one stereoisomer selected from the group consisting of (***S***)-(1-methylpyrrolidin-2-yl)methanol and (***R***)-(1-methylpyrrolidin-2-yl)methanol.

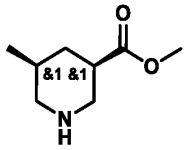
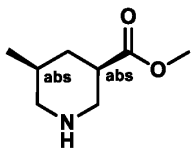
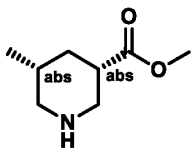
(4) When two or more stereogenic centers are denoted with "*orx*" in a structural formula, each of these stereogenic centers has been resolved but the configurations at the stereogenic centers have not been determined. Specifically:

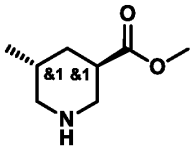
a. For any pair of stereogenic centers denoted with "*orx*" in a structural formula, when the numerical parts in the notation are different (e.g., two stereogenic centers denoted with *"or1"* and *"or2"* respectively), each stereogenic center is independently defined according to **(3)** (*vide supra*). For example, the structure  refers to one stereoisomer selected from the group consisting of: , , , and .

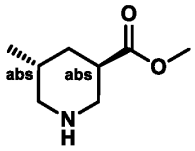
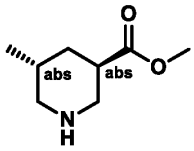
b. For any pair of stereogenic centers denoted with "*orx*" in a structural formula, when the numerical part in the notation is identical (e.g., two stereogenic centers each denoted with *"or1"*), the structural formula refers to one stereoisomer having the relative stereochemistry at these stereogenic centers as depicted in the structural formula, but the absolute configurations of these stereogenic centers have not been determined. For example, the structure  refers to one of the two *"syn"* stereoisomers:  or . As another example, the structure  refers to one of the *"anti"* stereoisomers:  or .

(5) When two or more stereogenic centers are denoted with *"&x"* in a structural formula, the structural formula refers to a mixture of stereoisomers that differ in the configuration at the stereogenic centers. Specifically:

a. For any pair of stereogenic centers denoted with "*&x*" in a structural formula, when the numerical parts in the notation are different (e.g., two stereogenic centers denoted with *"&1"* and *"&2"* respectively), the structural formula refers to a mixture of stereoisomers at these two stereogenic centers, wherein the configuration at each stereogenic center can vary independently of one another. For example, the structure  refers to a mixture of four stereoisomers: , , , and .

b. For any pair of stereogenic centers denoted with "*&x*" in a structural formula, when the numerical part in the notation is identical (e.g., two stereogenic centers each denoted with *"&1"*), the structural formula refers to a mixture of stereoisomers at these two or more stereogenic centers, wherein the relative configurations are as depicted in the structural formula. For example, the structure  refers to a mixture of *"syn"* stereoisomers:  and . As another example, the

structure  refers to a mixture of *"anti"* stereoisomers:

 and .

In some embodiments, the compounds of Formula (**I**) (e.g., Formula (**I-a**) or (**I-b**)) are selected from the group consisting of:

136a	3-(6-(1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione
163a	3-(6-(1-((1-(5-Chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione
171a	3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione
175a	3-(6-(1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione
175b	3-(6-(1-((1-(5-chloro-4-(((*R*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione
212a	3-(6-(1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-1-cyclopropyl-1*H*-indazol-3-yl)piperidine-2,6-dione
213a	3-(6-(1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl-2,2,3,3,4,5,5,6,6-d9)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione
215a	3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2,7-dicyclopropyl-3,3,9-trifluoro-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-4-piperidyl]-7-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione

217a	3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-7-[(3,3-difluorocyclobutyl)methyl]-3,3,9-trifluoro-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-4-piperidyl]-7-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione
132a	3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione
135a	3-[6-[1-[(1*S*)-1-[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]ethyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione
135b	3-[6-[1-[(1*R*)-1-[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]ethyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione
219a	3-[6-[1-[[(3*S*,4*S*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione
219b	3-[6-[1-[[(3*R*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione
220a	3-[6-[1-[[(3*R*,4*S*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione
220b	3-[6-[1-[[(3*S*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione
234a	3-(6-(1-(((*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-5,7-difluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione
105a	3-(6-(1-(((3*R*,4*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione
105b	3-(6-(1-(((3*S*,4*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione
199a	3-[6-[1-[[(3*R*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione

199b	3-[6-[1-[[(3*S*,4*S*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione
209a	3-[6-[1-[[(3*R*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]methyl]-4-piperidyl]-7-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione
209b	3-[7-fluoro-1-methyl-6-[1-[[(3*S*,4*S*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione
210a	3-[5-fluoro-1-methyl-6-[1-[[(3*R*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione
210b	3-[5-fluoro-1-methyl-6-[1-[[(3*S*,4*S*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione
234b	3-(6-(1-(((*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-5,7-difluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione
238d	3-(6-(1-(((3*S*,4*R*,5*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoro-5-methylpiperidin-4-yl)methyl)piperidin-4-yl)-5,7-difluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione
238c	3-(6-(1-(((3*R*,4*S*,5*S*)-1-(5-chloro-4-(((S)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoro-5-methylpiperidin-4-yl)methyl)piperidin-4-yl)-5,7-difluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione
238b	3-(6-(1-(((3*R*,4*R*,5*R*)-1-(5-chloro-4-(((S)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoro-5-methylpiperidin-4-yl)methyl)piperidin-4-yl)-5,7-difluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione
238a	3-(6-(1-(((3*S*,4*S*,5*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoro-5-methylpiperidin-4-yl)methyl)piperidin-4-yl)-5,7-difluoro-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione
118a	3-(6-(1-(((3*R*,4*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

118b	3-[6-[1-[[(3*S*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione
151a	3-[6-[1-[[(3*R*,4*S*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-5-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione
151b	3-[6-[1-[[(3*S*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-5-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione
169a	3-[6-[1-[[(3*R*,4*S*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-7-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione
169b	3-[6-[1-[[(3*S*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-7-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione
202a	3-[6-[1-[[(3*S*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione
202b	3-(6-(1-(((3*R*,4*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-5,7-difluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione
233a	3-(6-(1-(((*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione
233b	3-(6-(1-(((*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione
239a	3-(6-(1-(((*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-5,7-difluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione
239b	3-(6-(1-(((*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-5,7-difluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

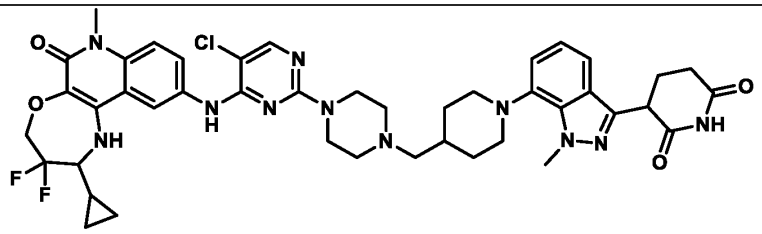
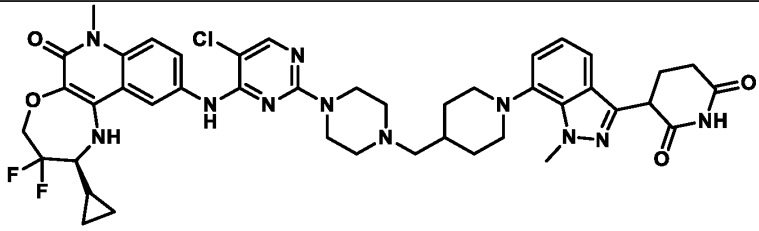
or pharmaceutically acceptable salts thereof.

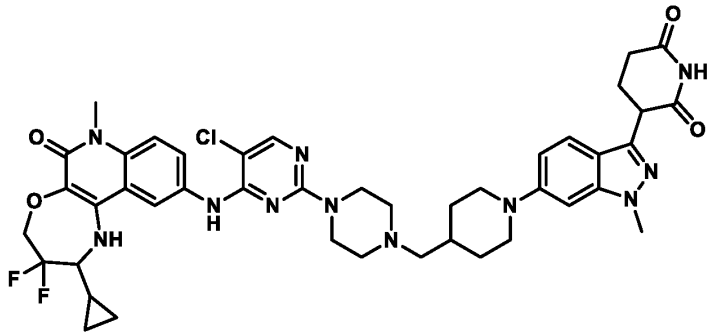
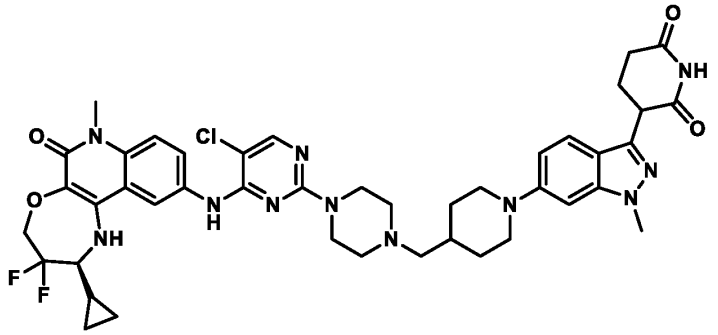
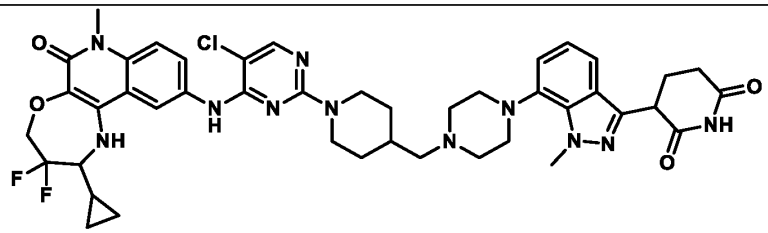
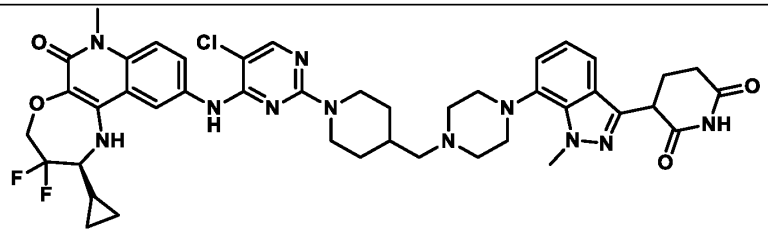
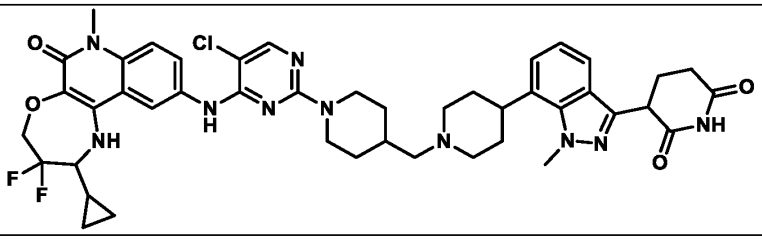
In some embodiments, the compounds of Formula (**I**), or pharmaceutically acceptable salts thereof, are selected from the group consisting of the compounds depicted in **Table C1** of U.S. Provisional Application Serial No. 63/580,207, filed September 1, 2023; **Table C1** of U.S. Provisional Application Serial No. 63/607,009, filed December 6, 2023; **Table C1** of U.S. Provisional Application Serial No. 63/572,811, filed April 1, 2024; and **Table C1** of U.S. Provisional Application Serial No. 63/665,613, filed June 28, 2024; each **Table C1** is hereby incorporated by reference in its entirety.

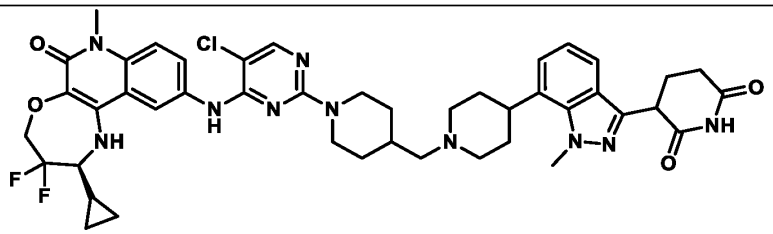
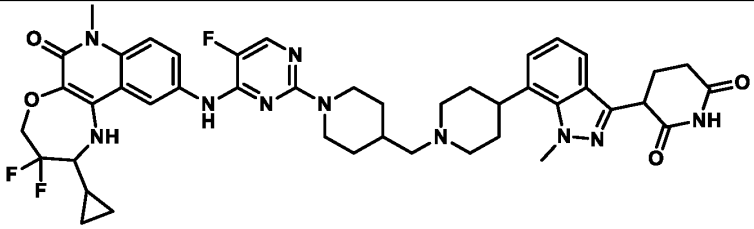
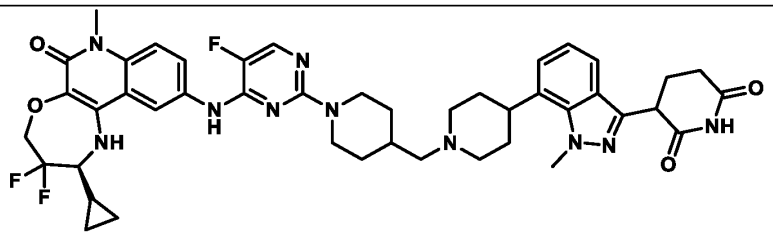
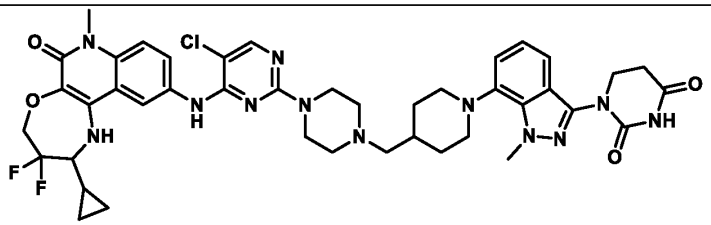
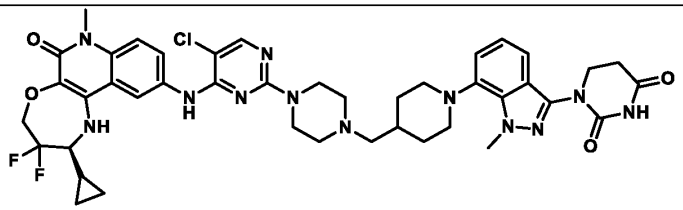
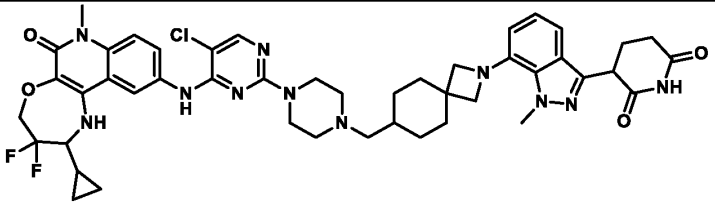
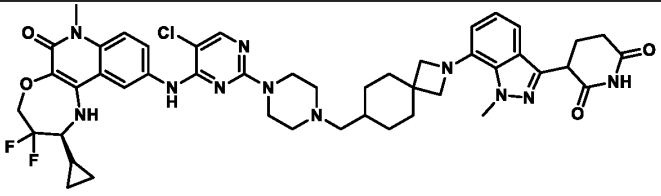
In some embodiments, compounds of Formula (**I**), or pharmaceutically acceptable salts thereof, are other than the compounds in **Table C1** of International Patent Application No. PCT/US/23/67927 (published as WO 2023/240038), filed June 5, 2023, or pharmaceutically acceptable salts thereof, wherein the **Table C1** of International Patent Application No. PCT/US/23/67927 is incorporated herein by reference in its entirety.

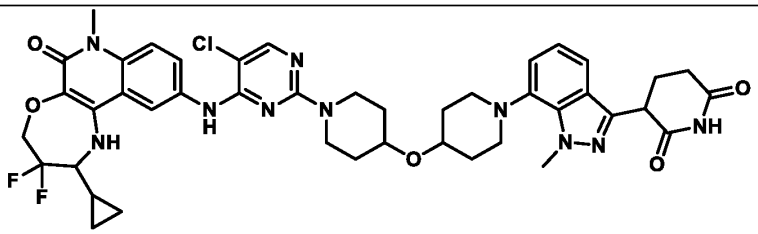
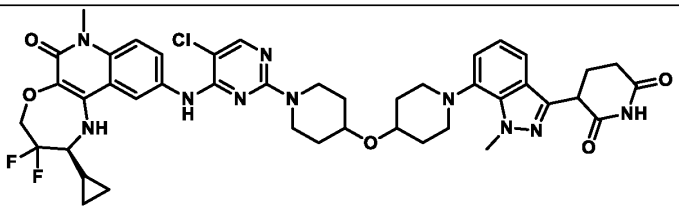
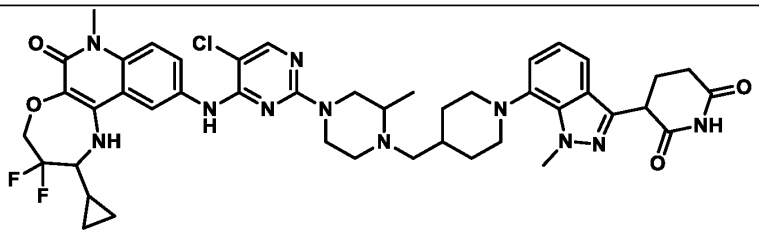
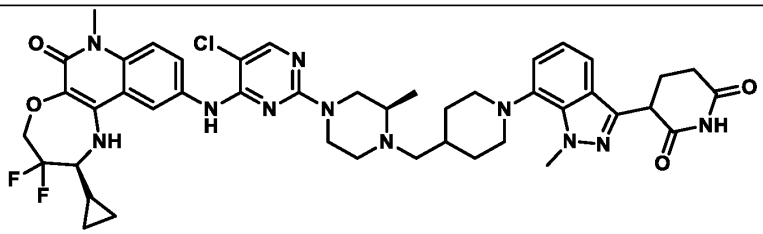
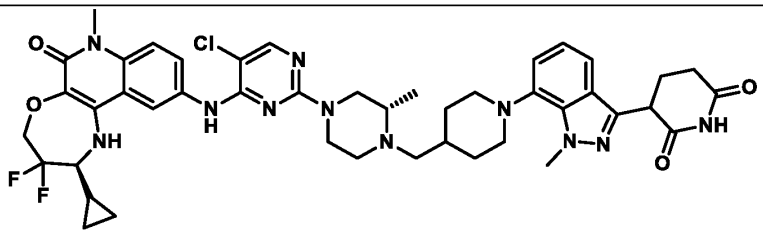
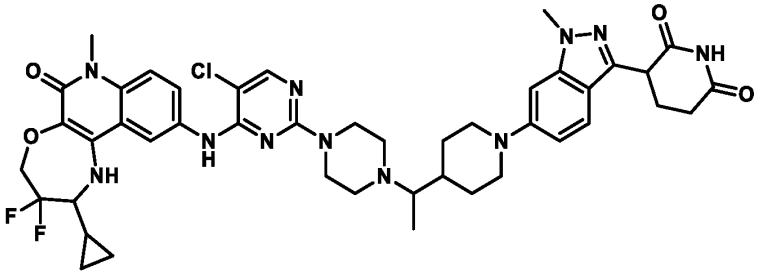
In some embodiments, the compounds of Formula (**I**), or pharmaceutically acceptable salts thereof, are other than the compounds depicted in **Table R1**, or pharmaceutically acceptable salts thereof.

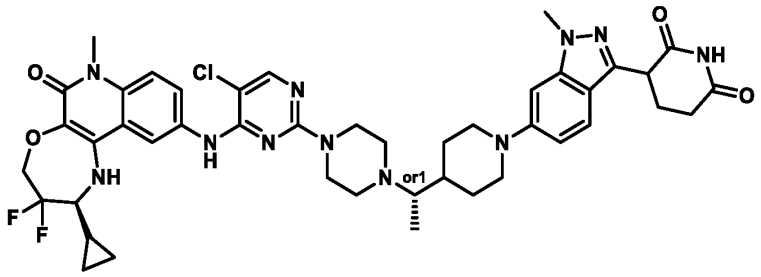
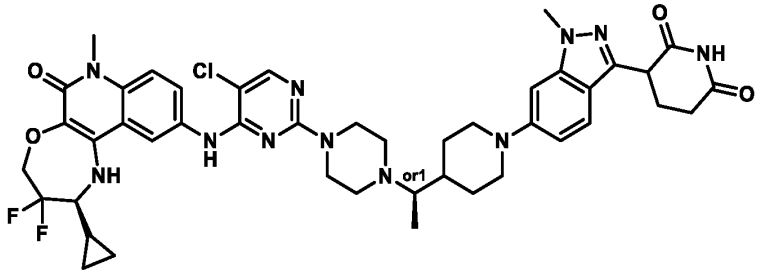
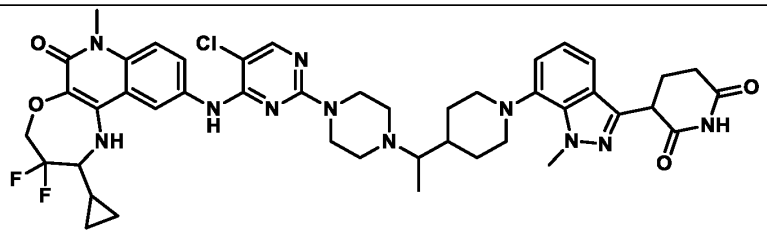
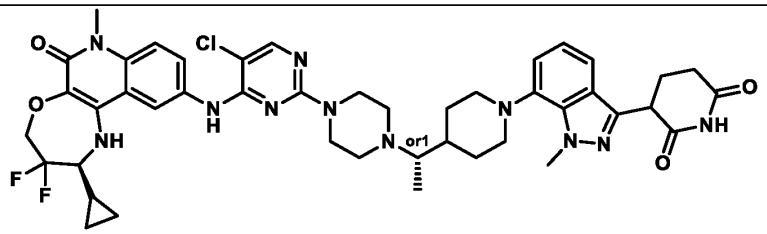
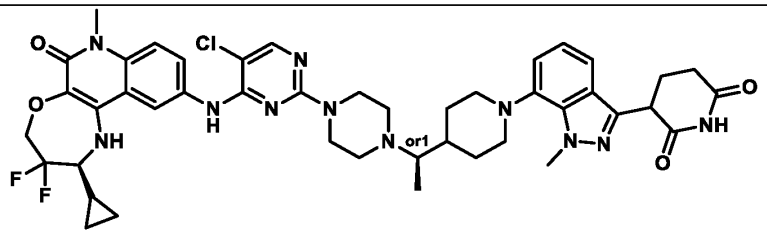
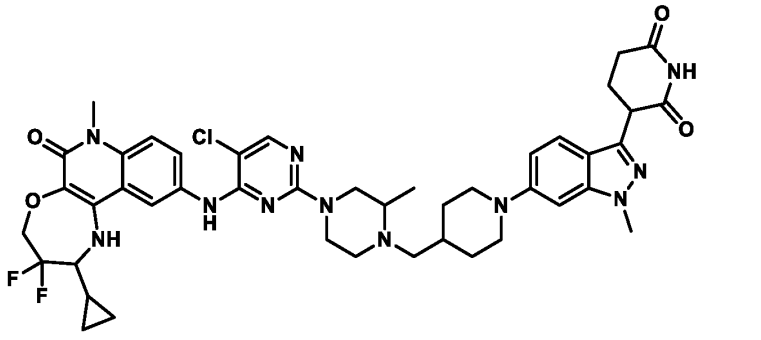
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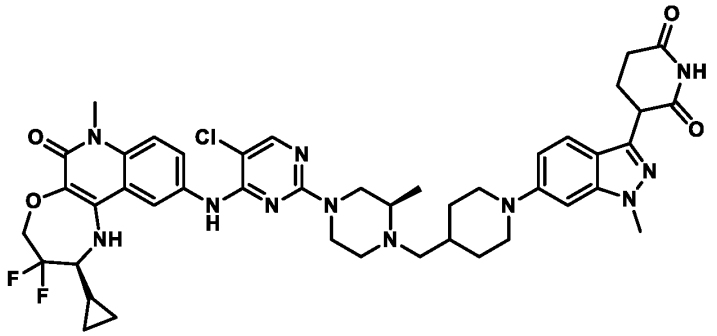
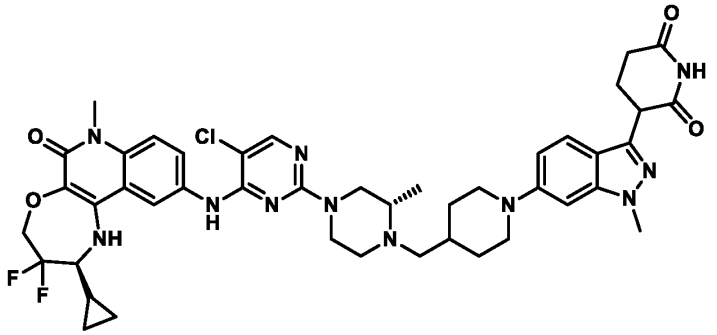
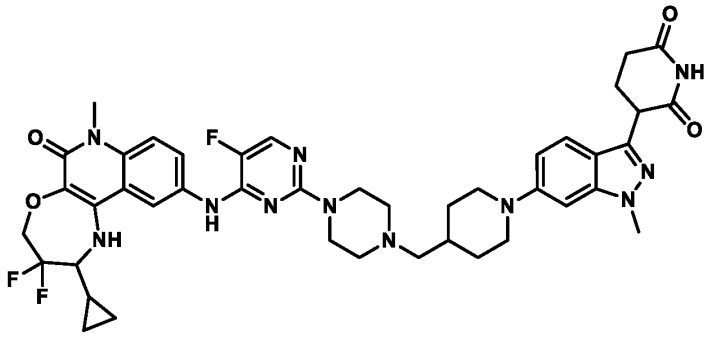
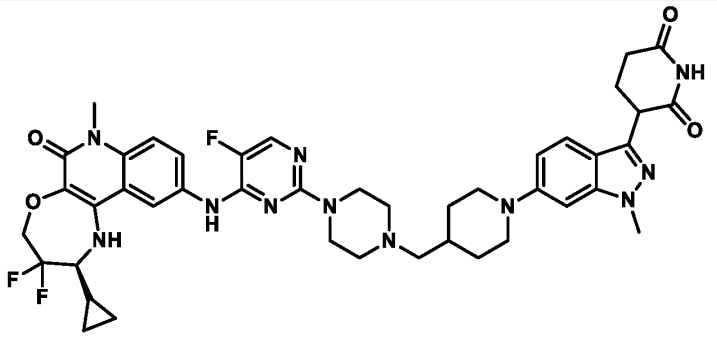
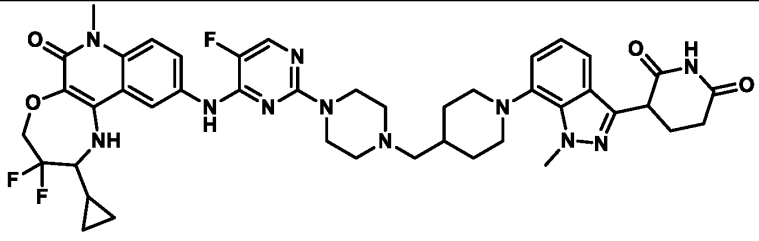
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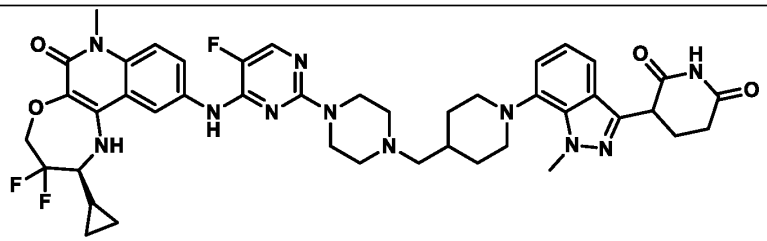
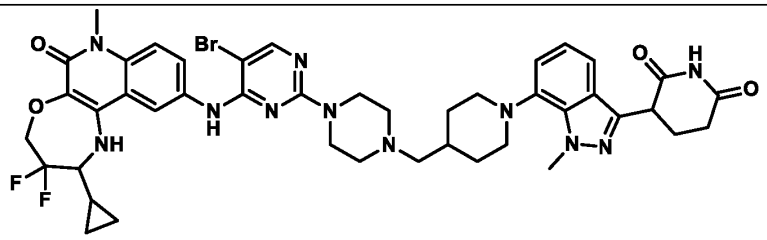
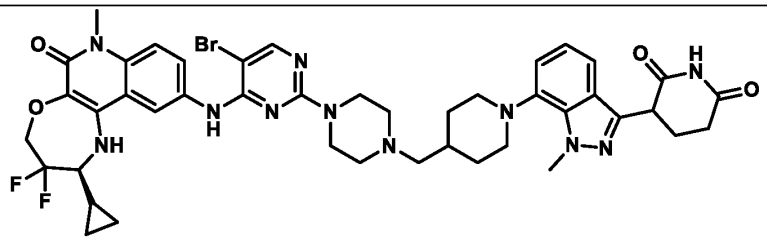
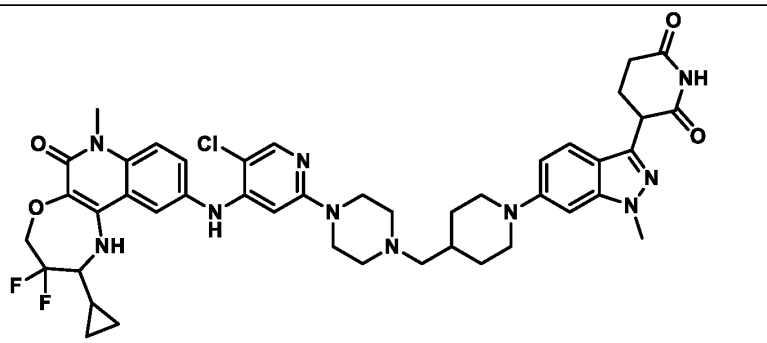
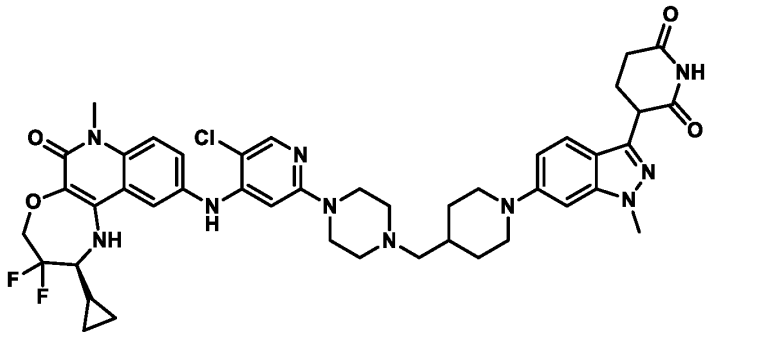
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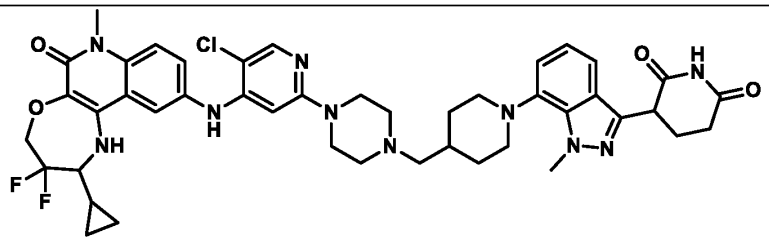
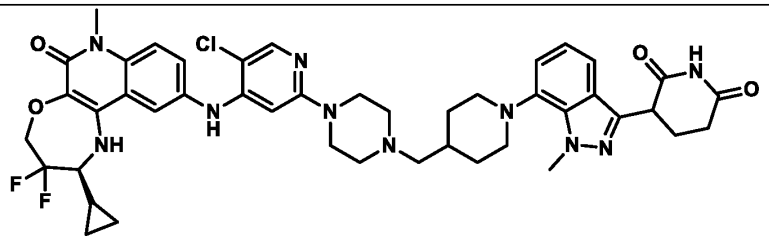
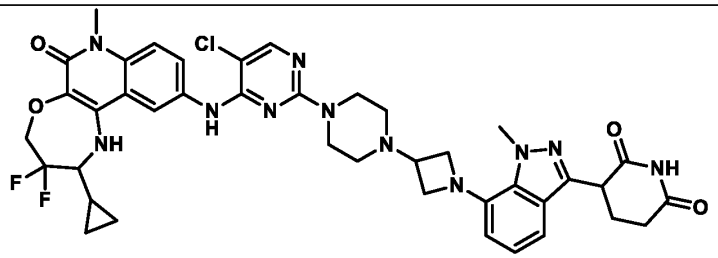
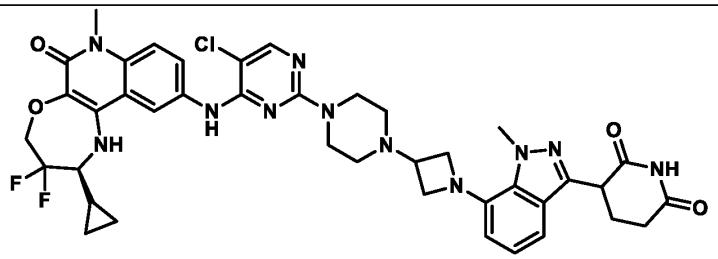
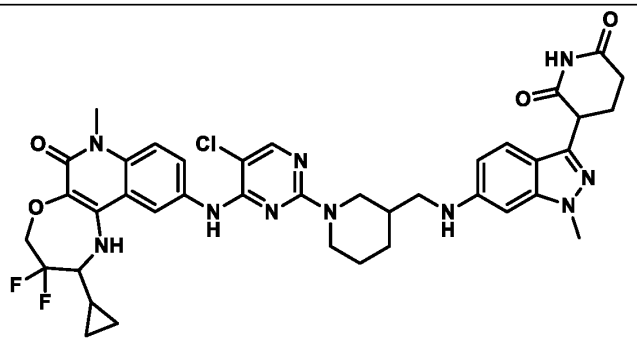
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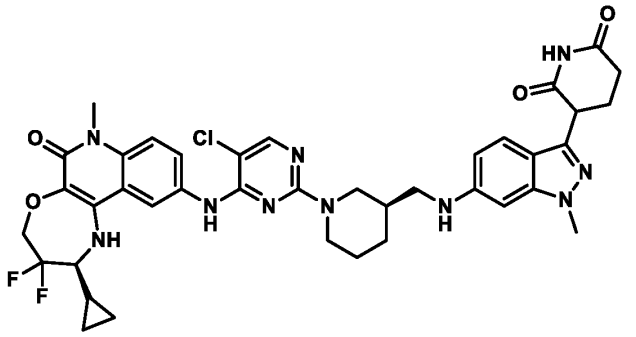
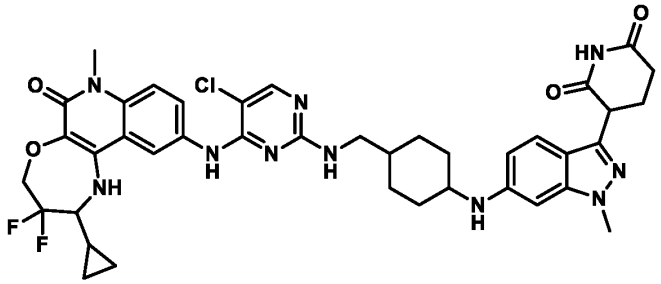
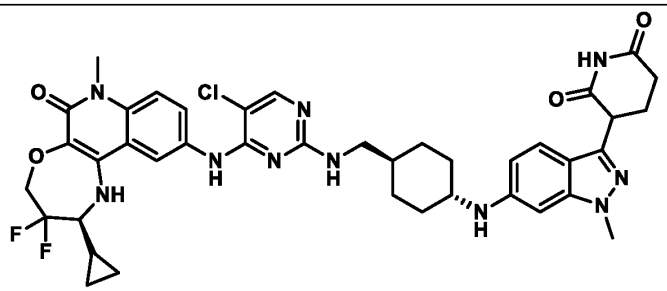
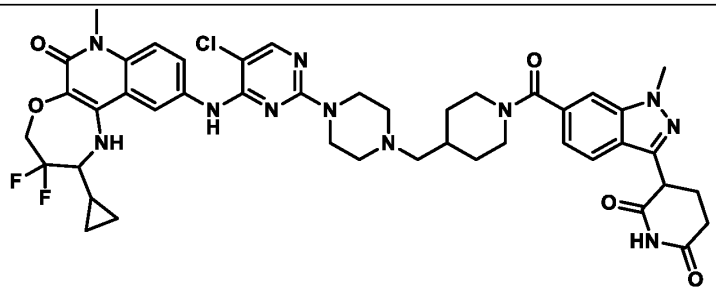
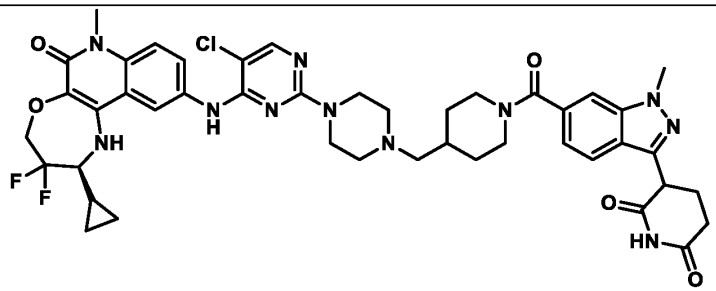
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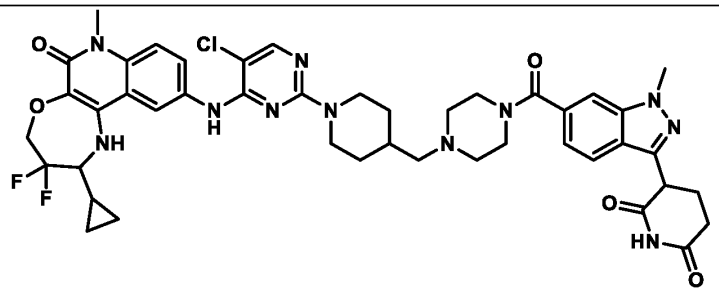
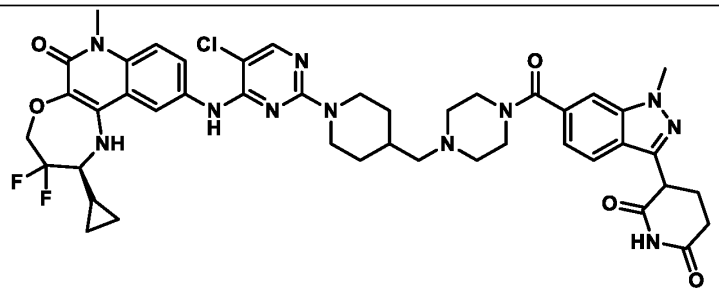
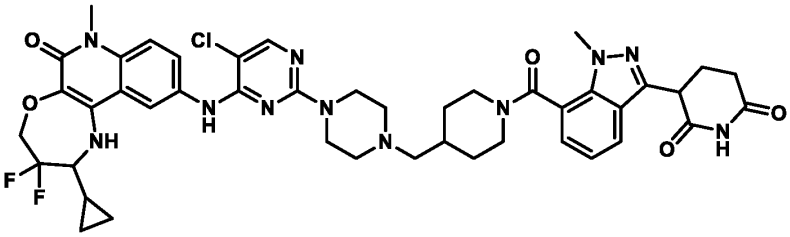
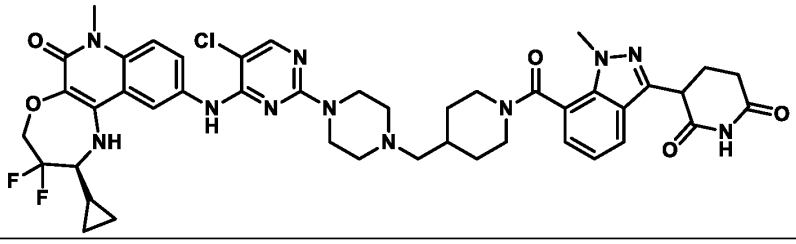
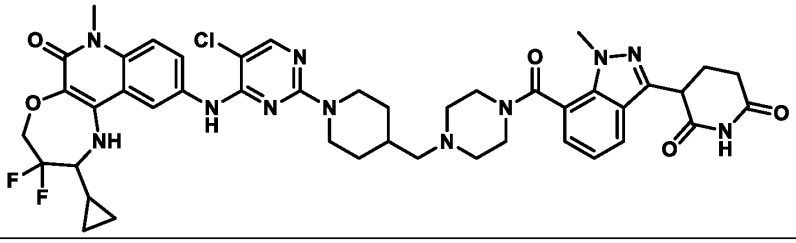
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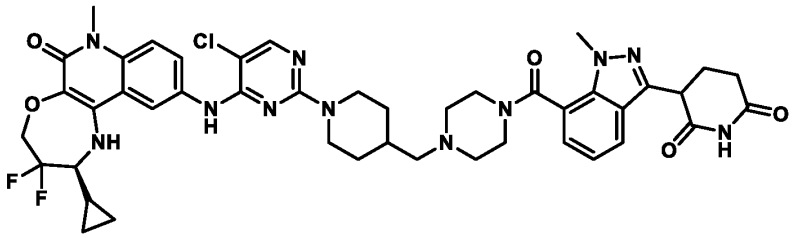
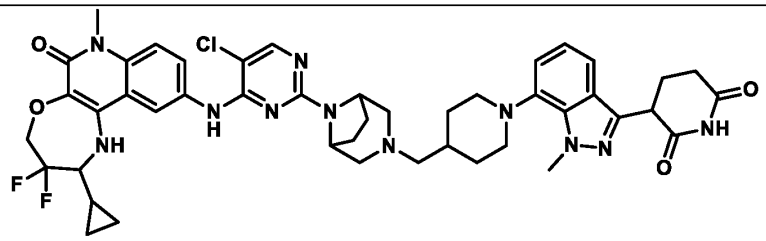
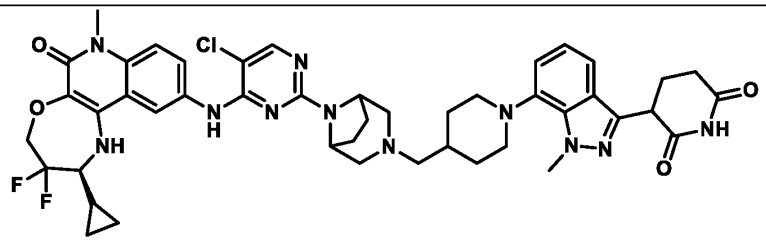
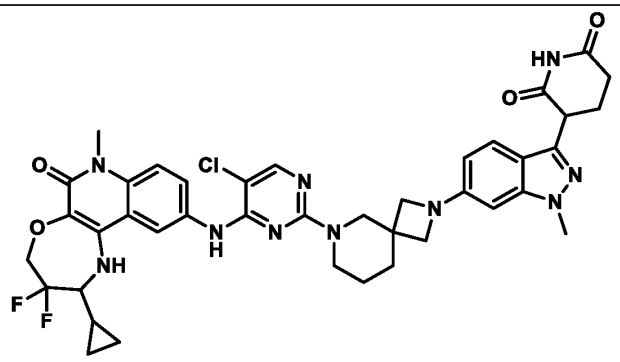
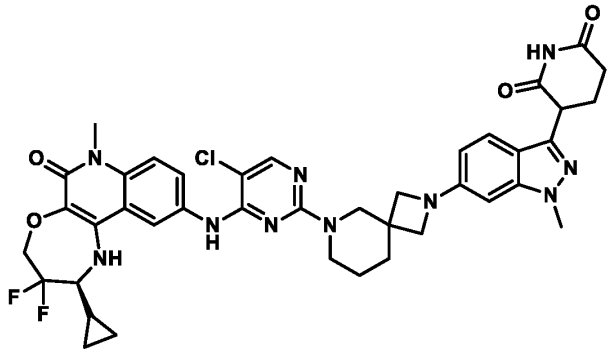
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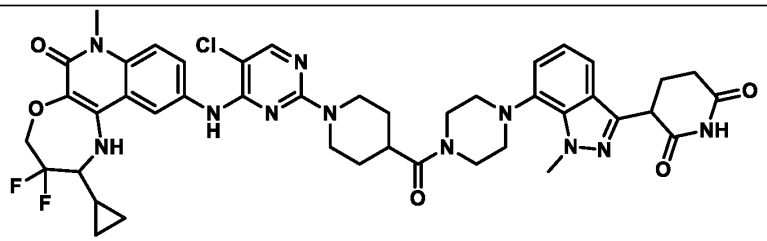
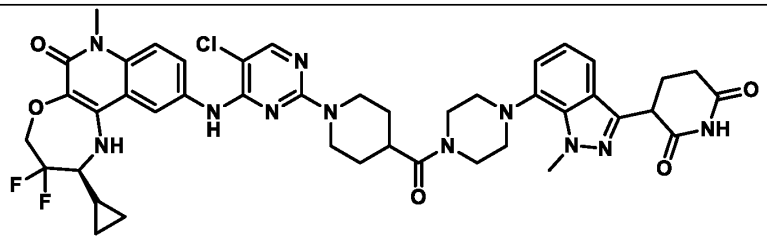
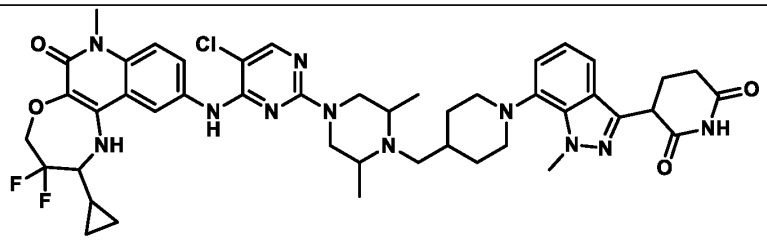
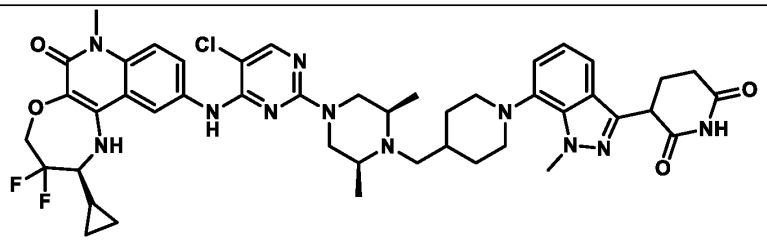
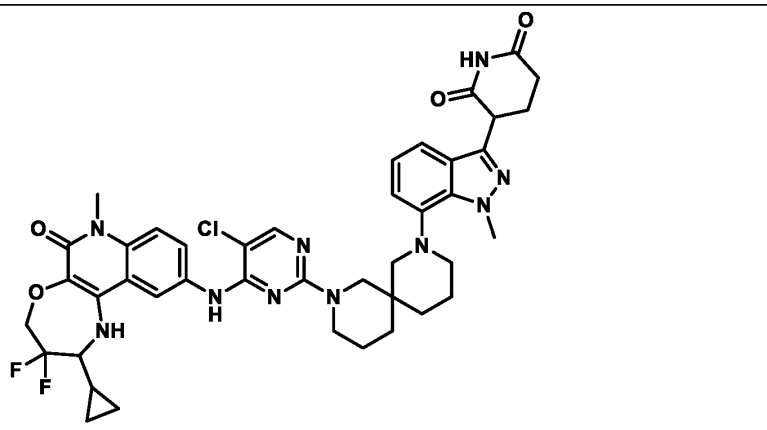
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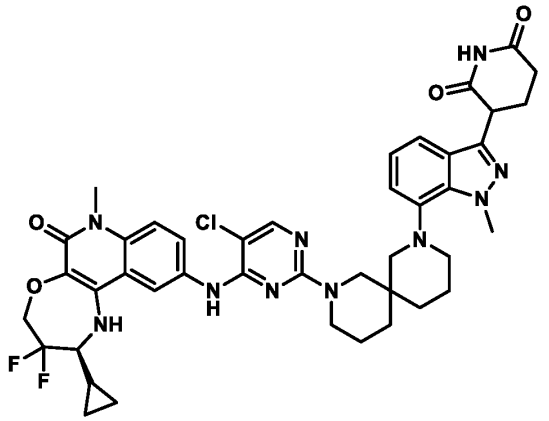
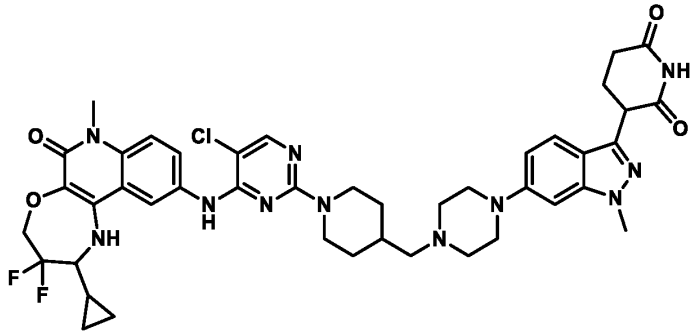
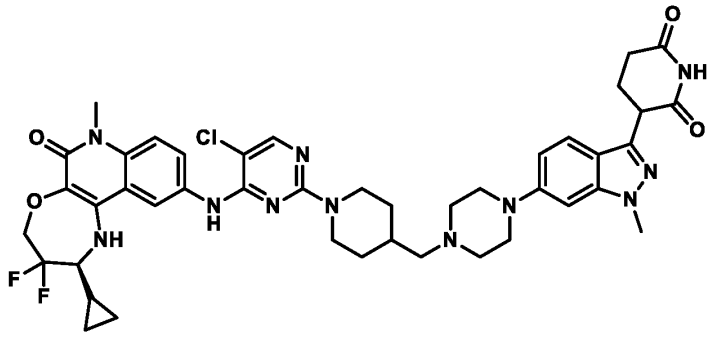
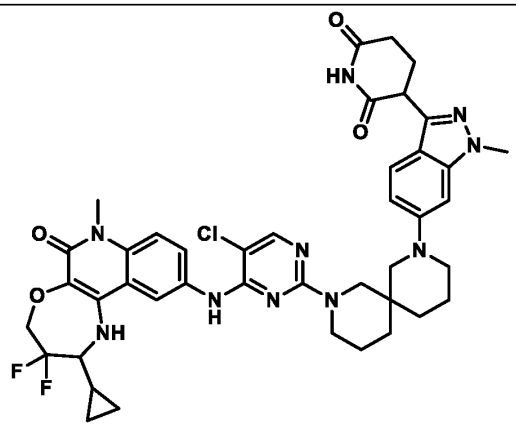
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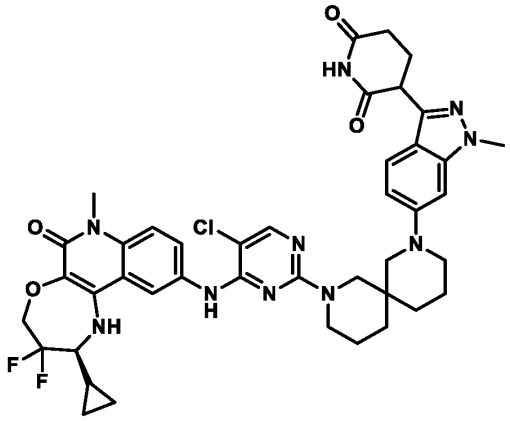
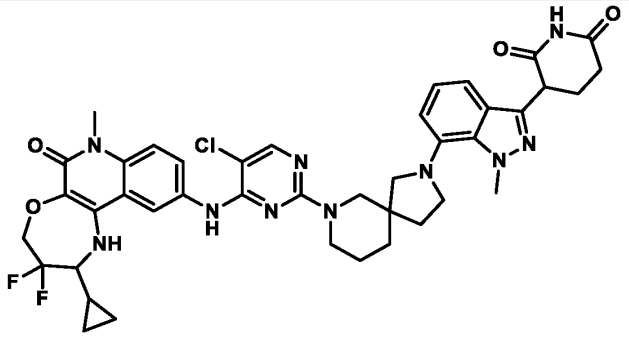
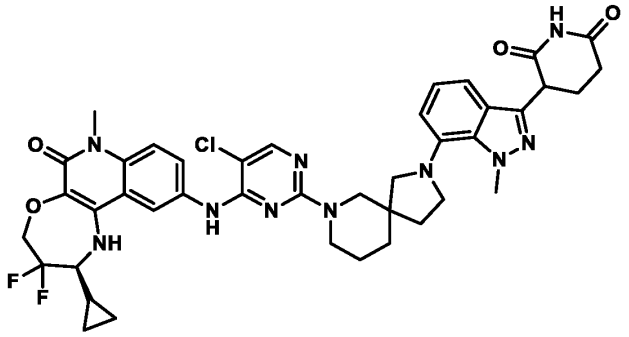
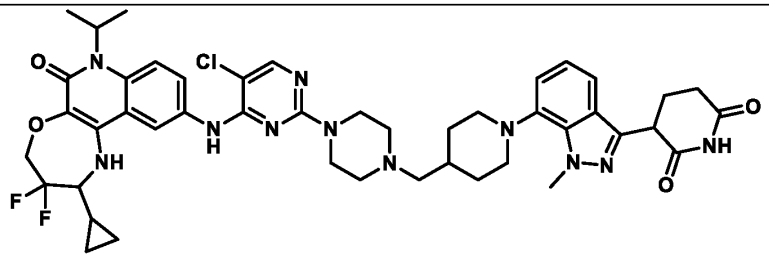
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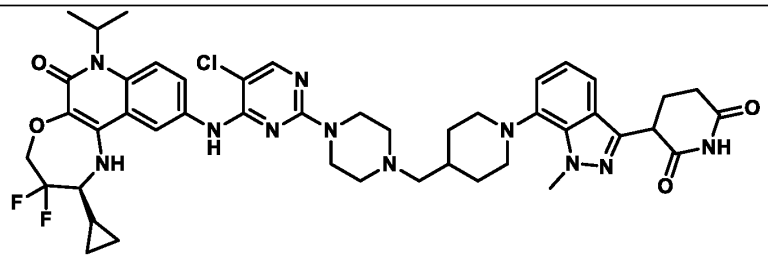
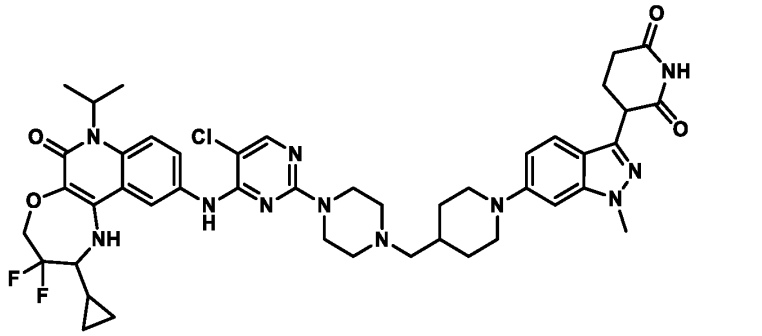
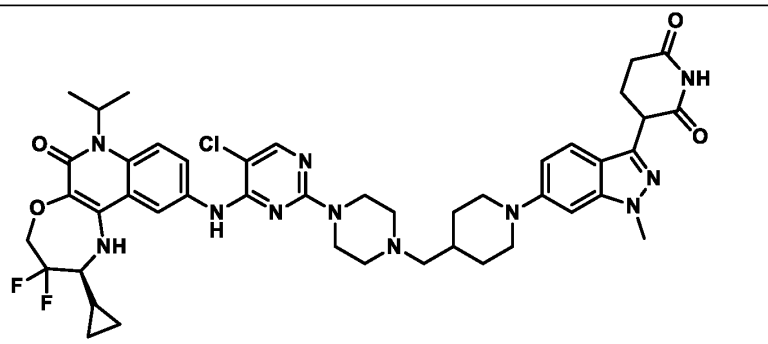
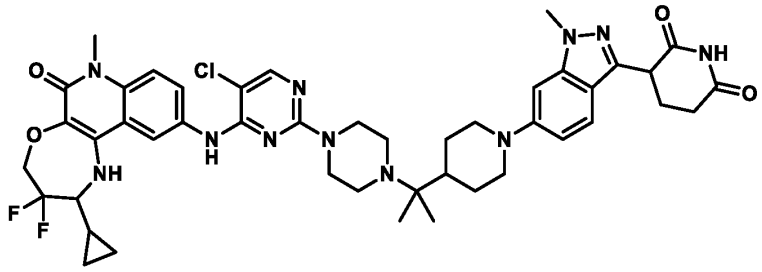
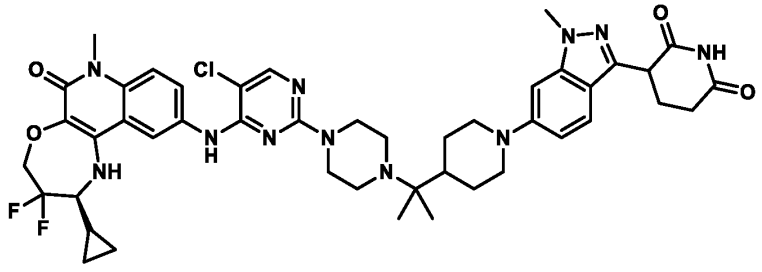
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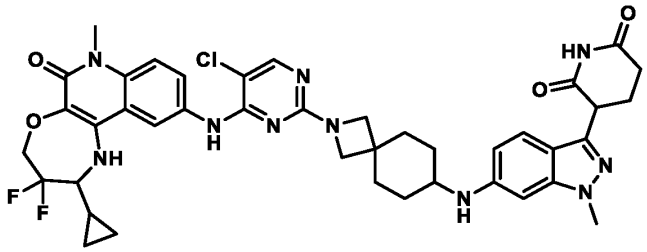
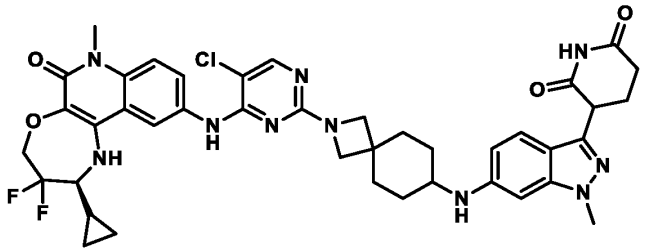
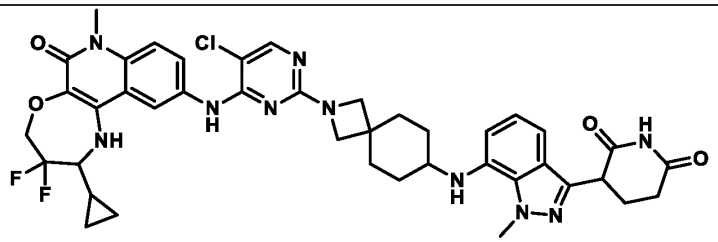
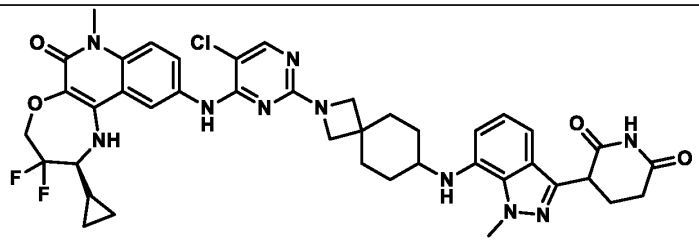
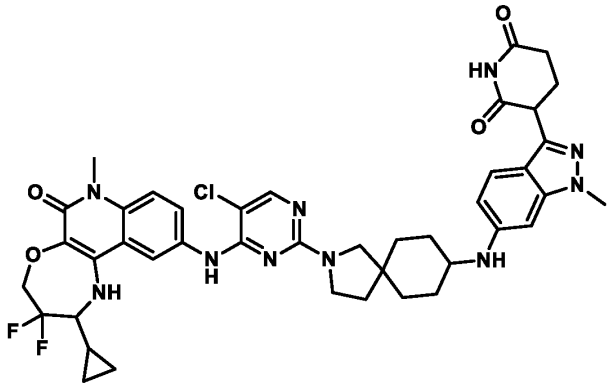
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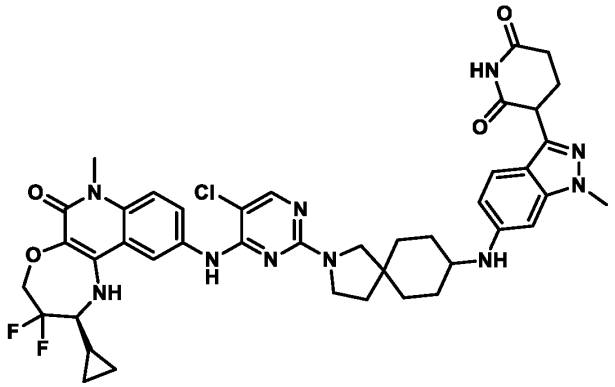
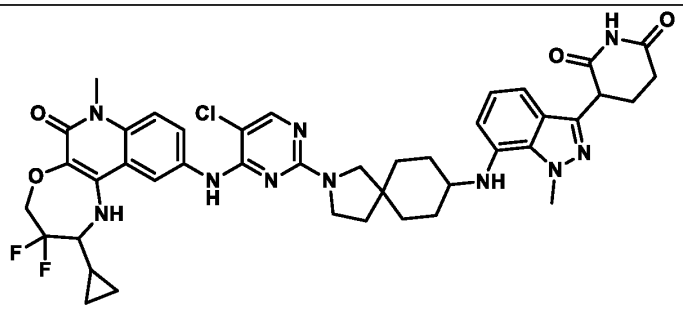
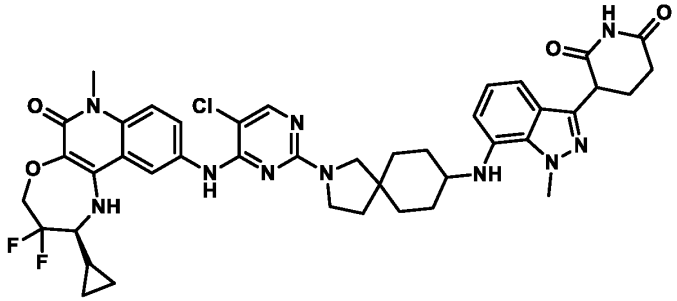
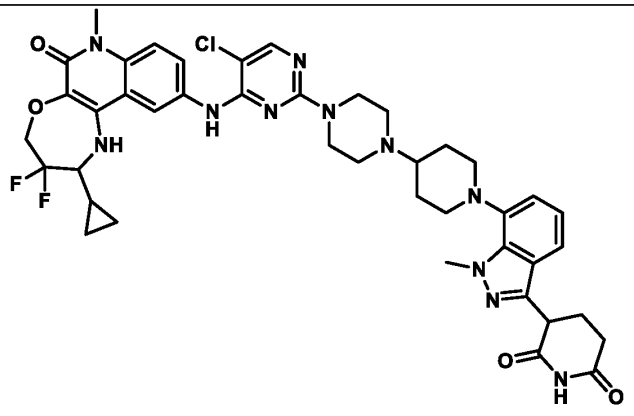
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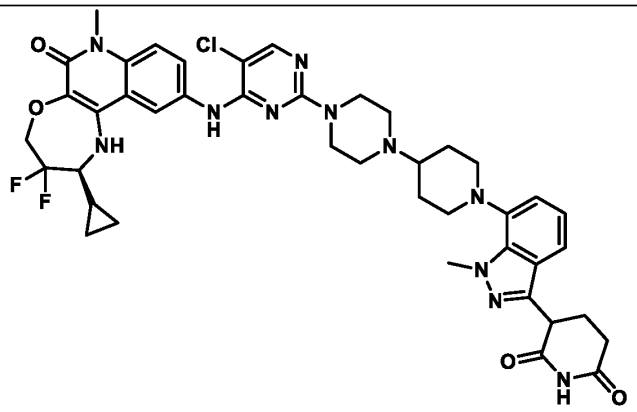
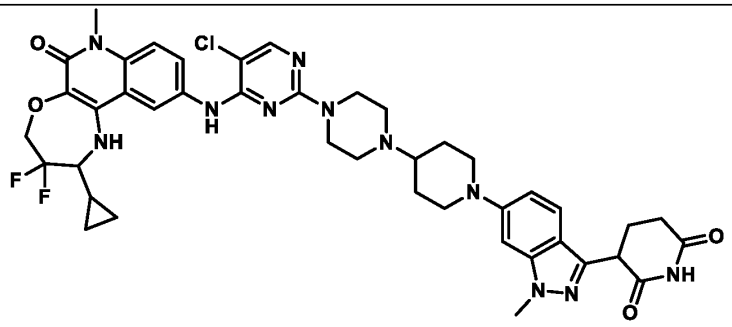
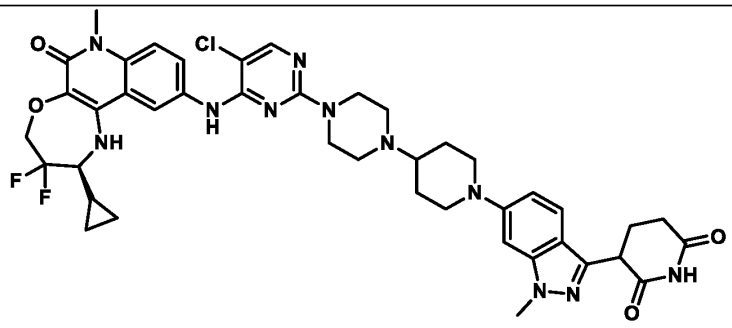
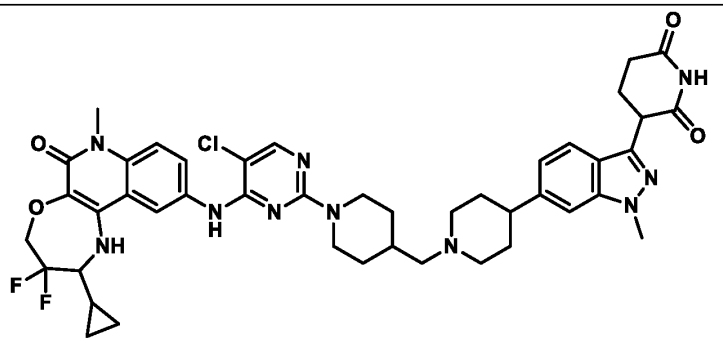
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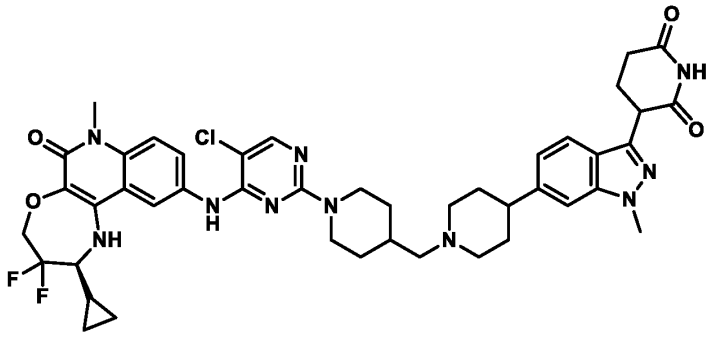
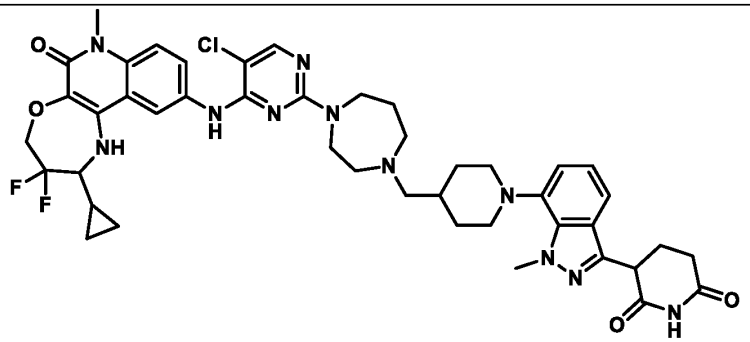
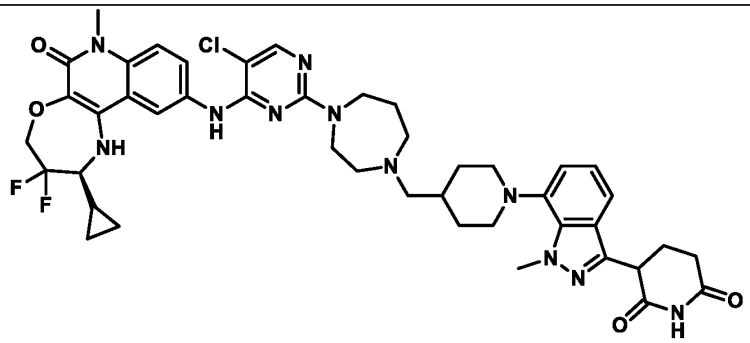
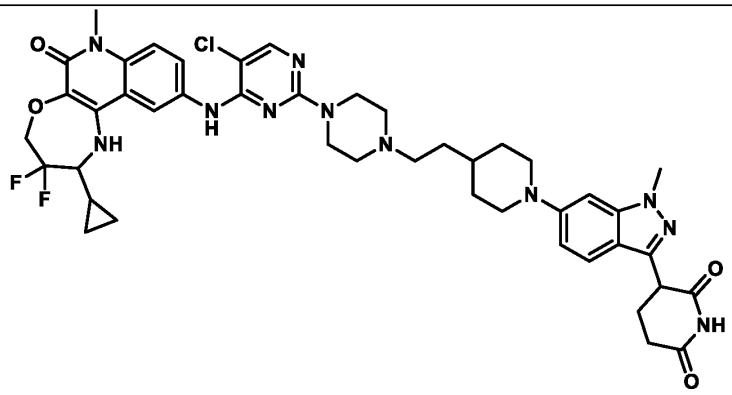
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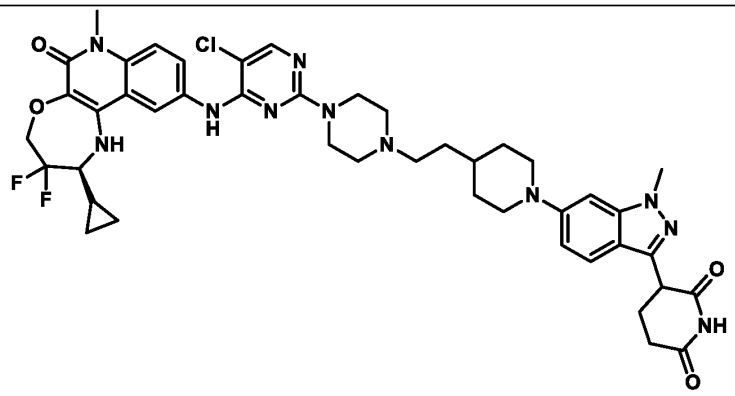
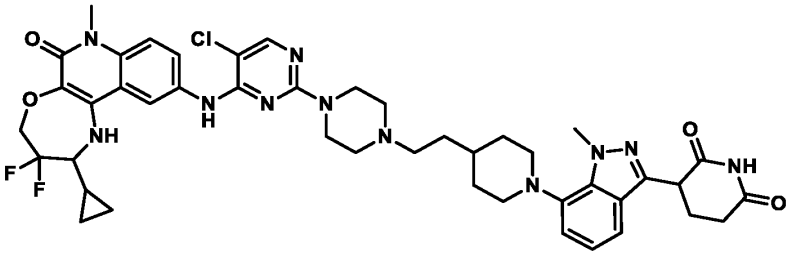
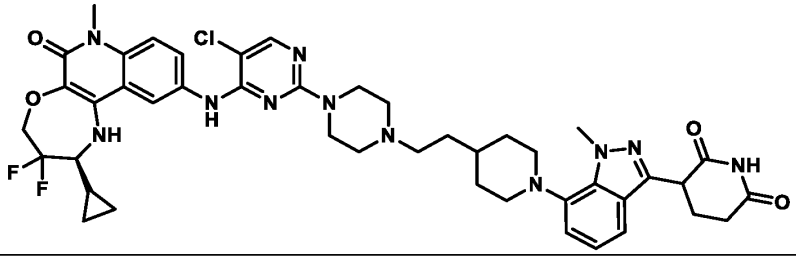
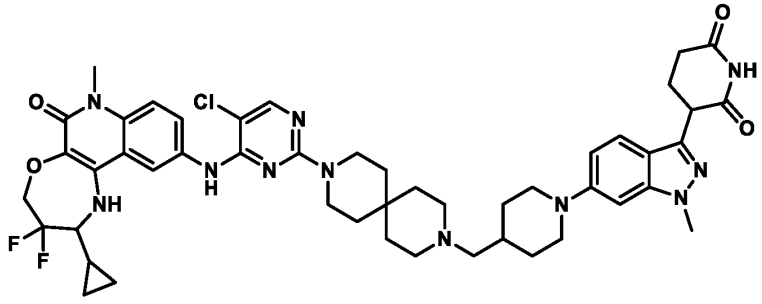
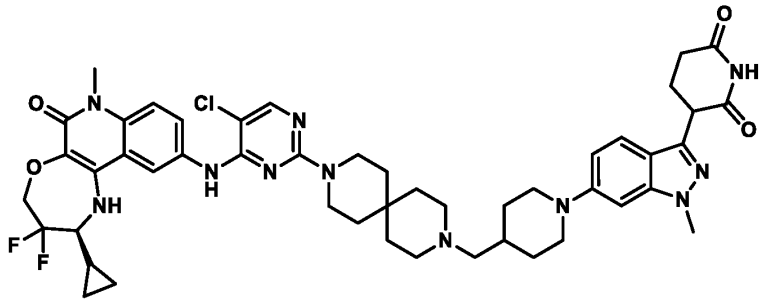
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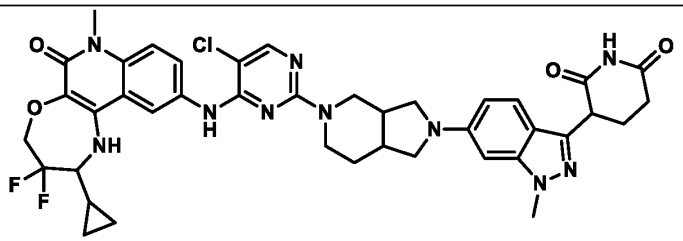
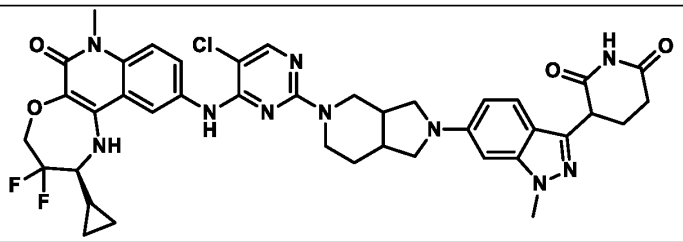
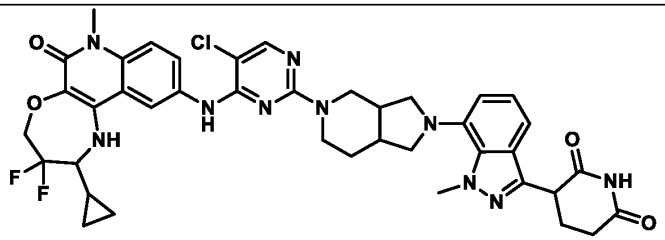
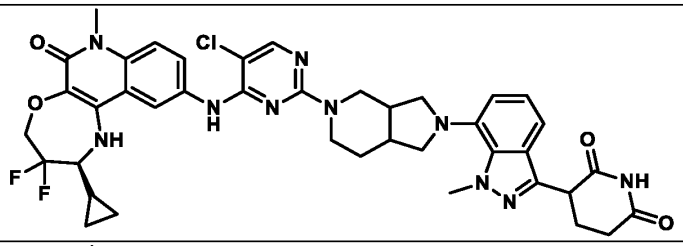
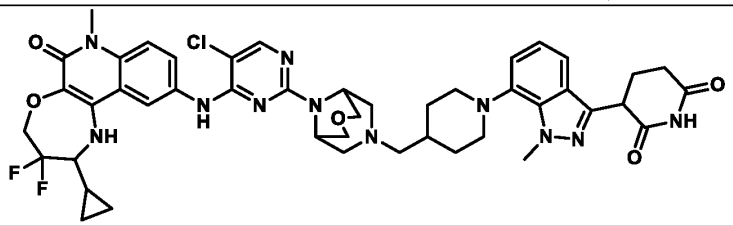
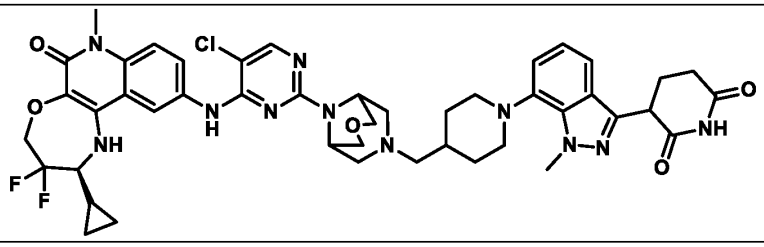
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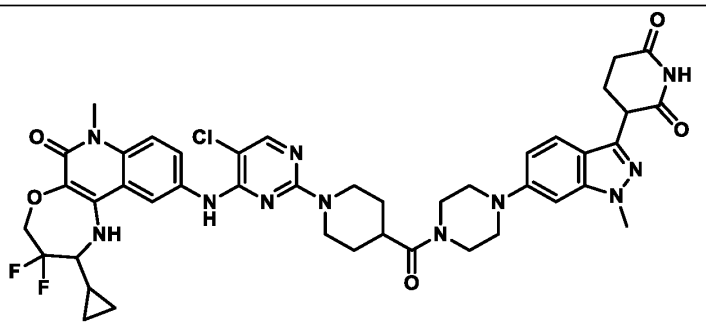
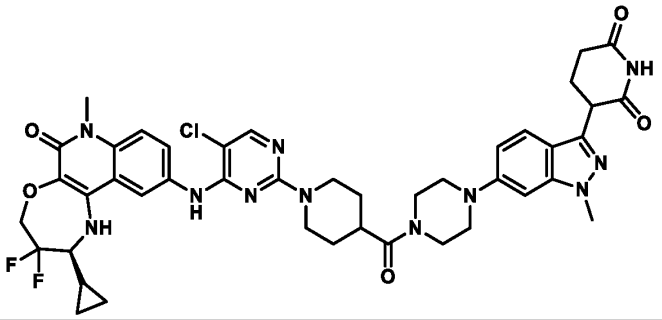
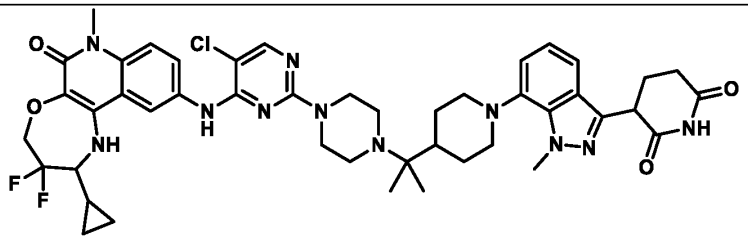
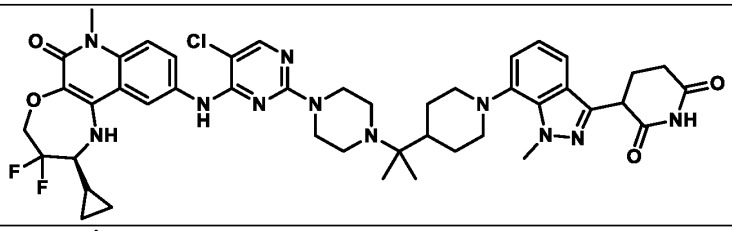
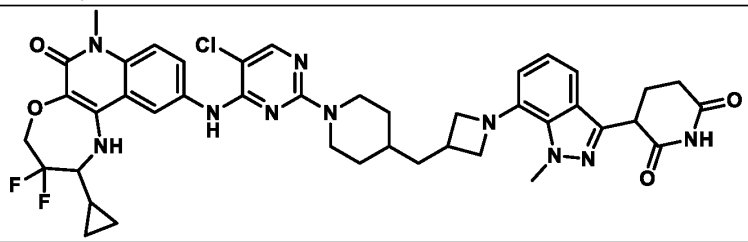
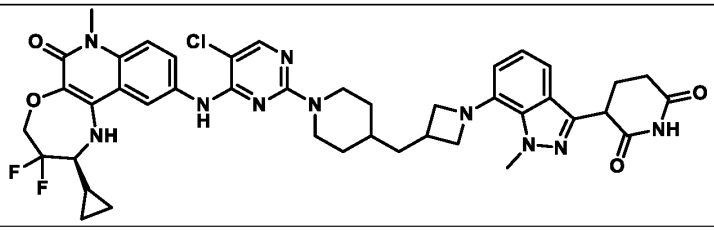
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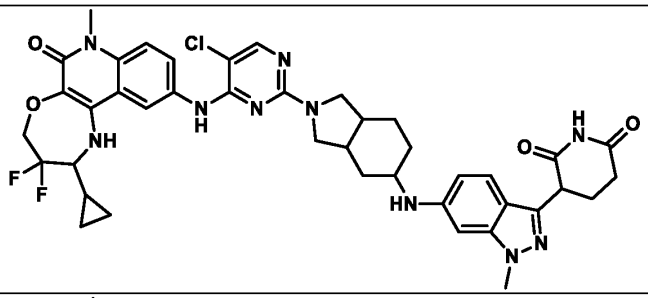
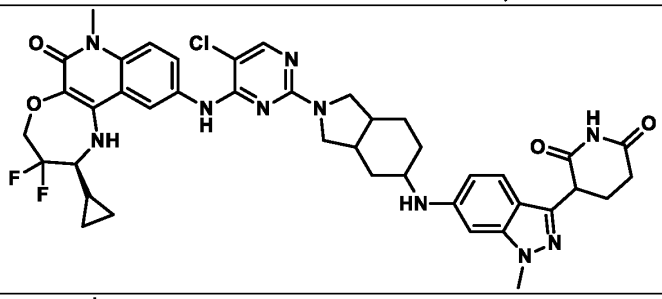
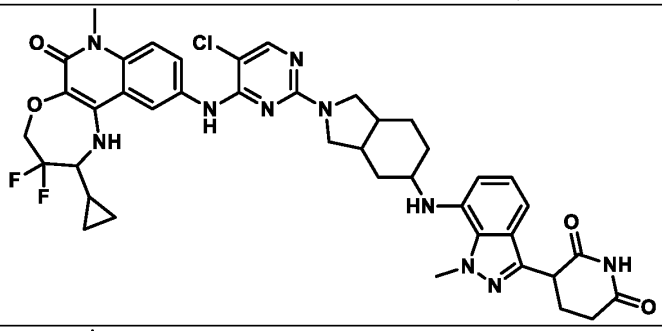
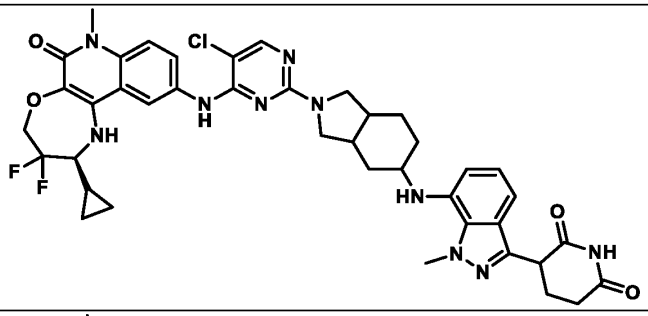
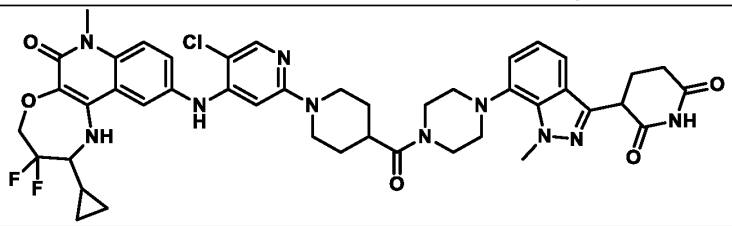
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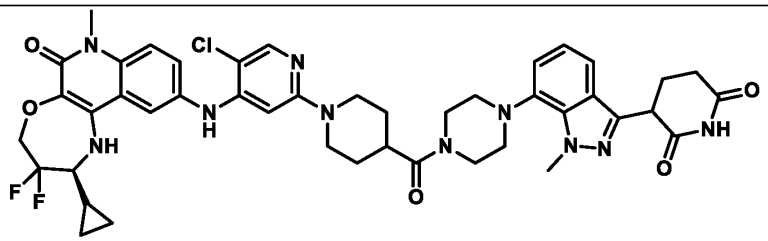
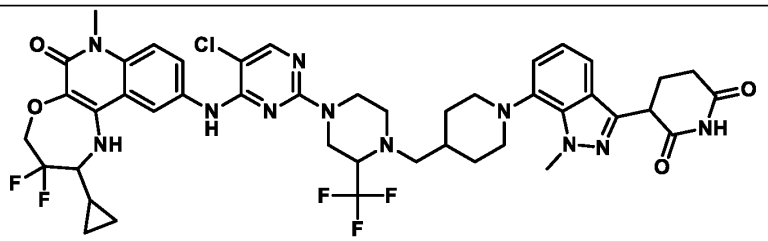
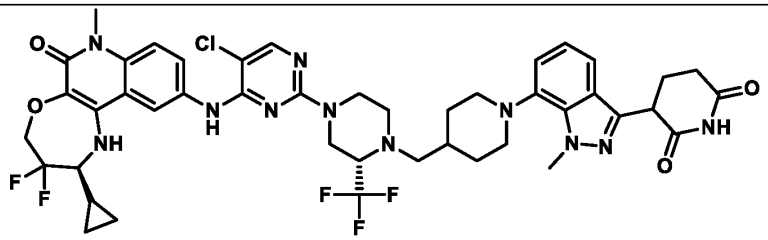
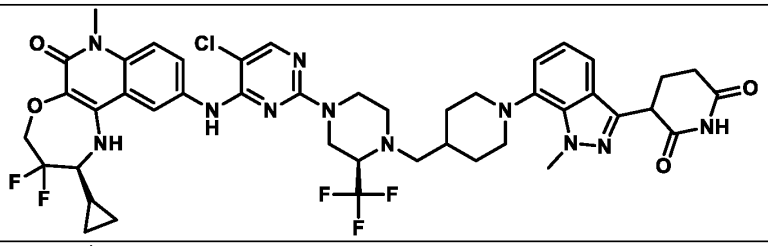
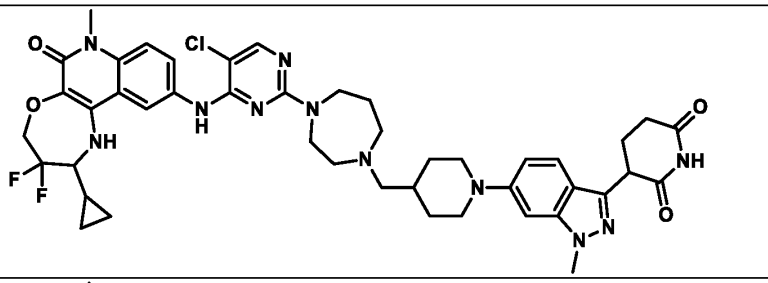
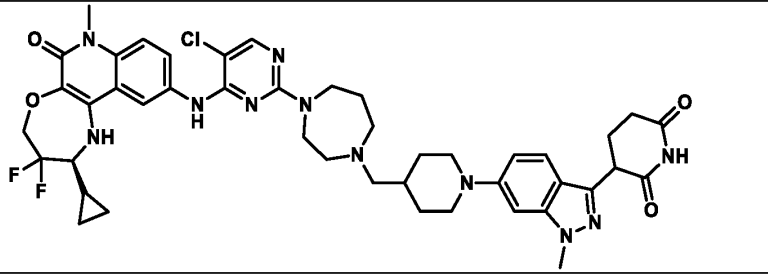
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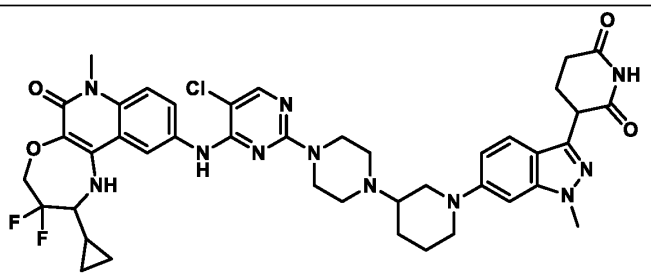
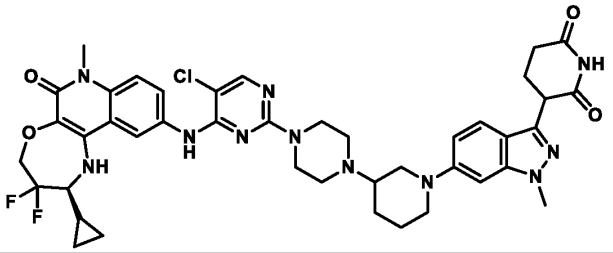
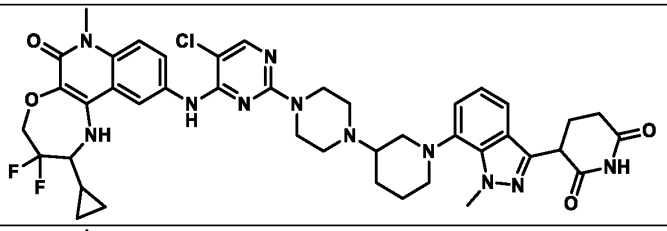
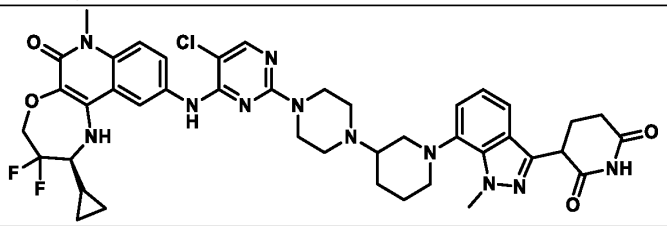
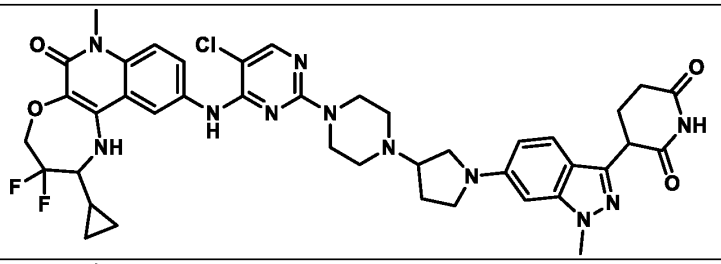
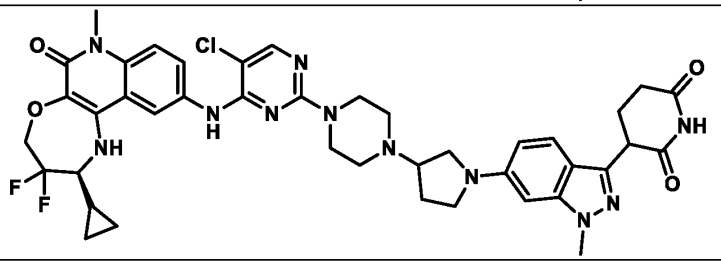
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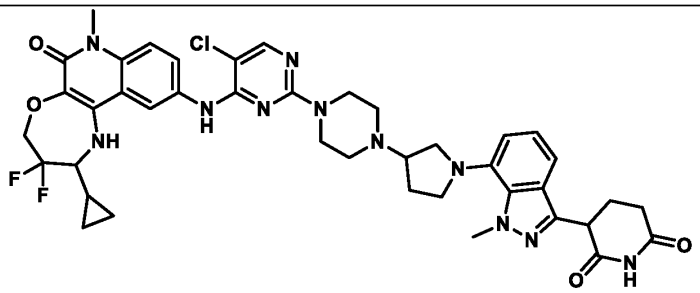
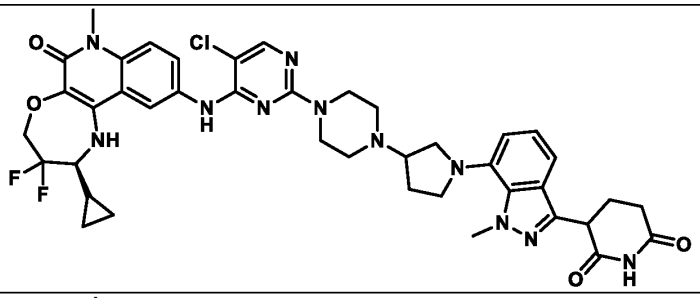
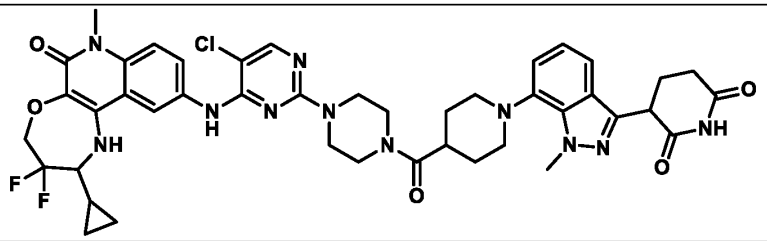
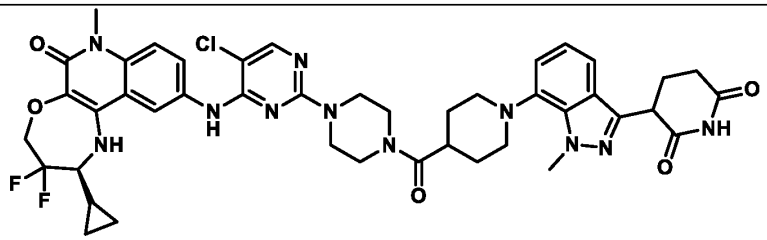
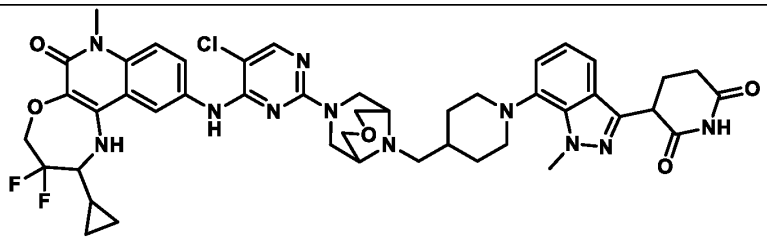
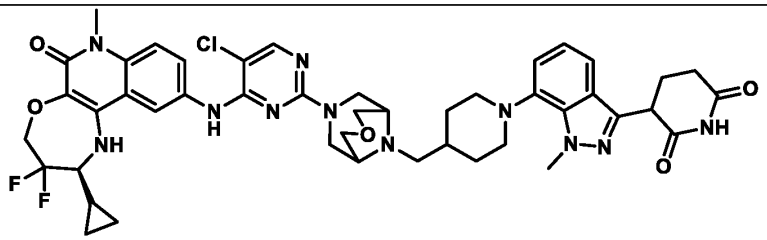
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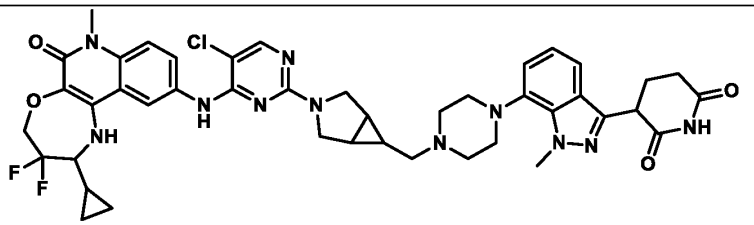
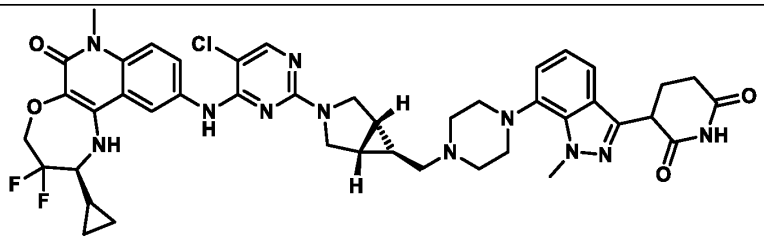
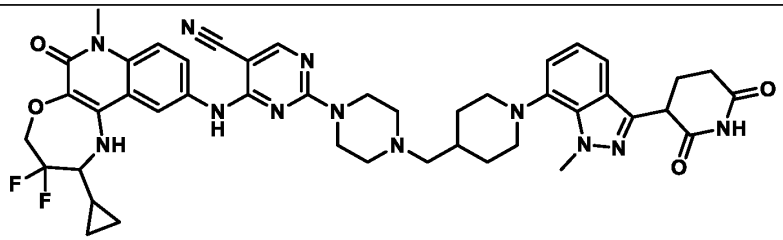
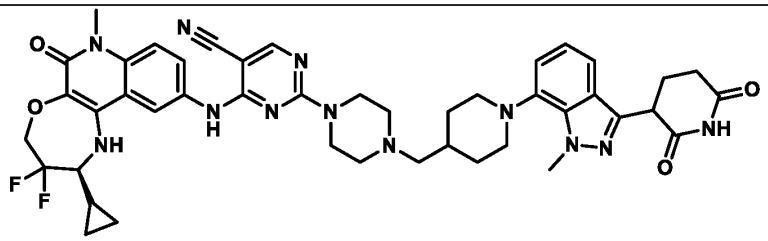
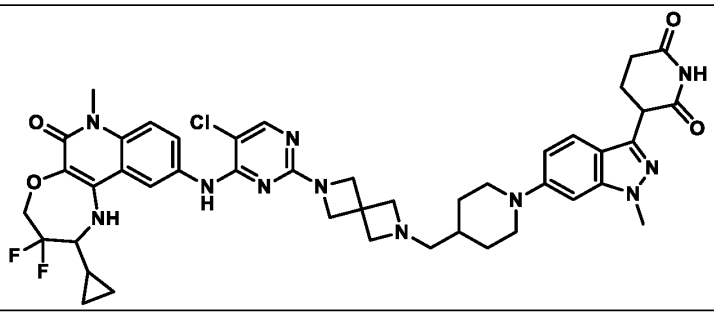
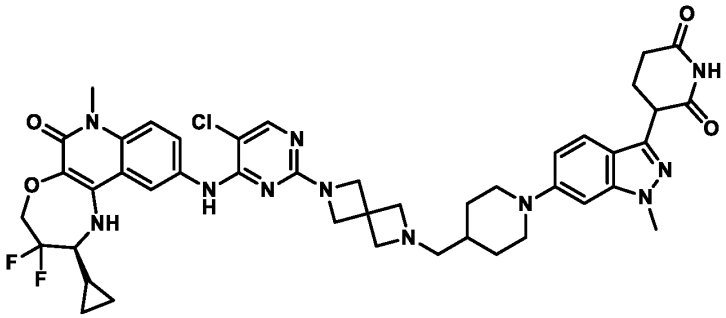
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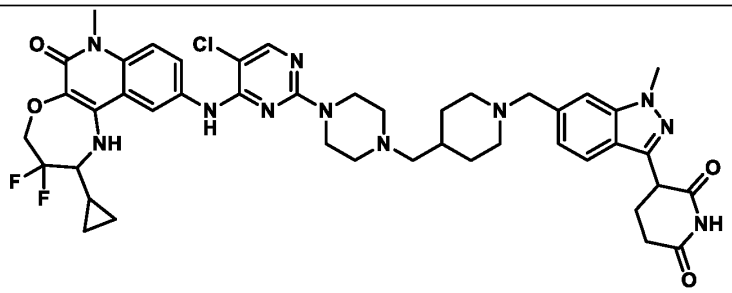
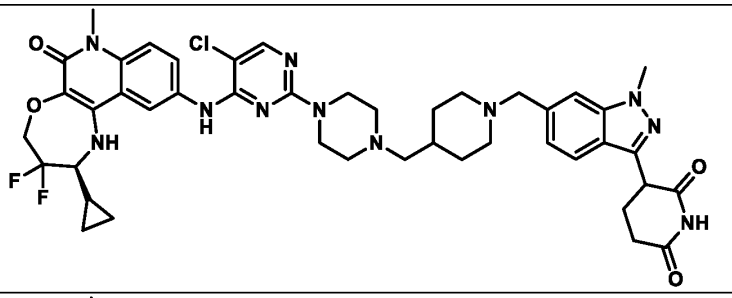
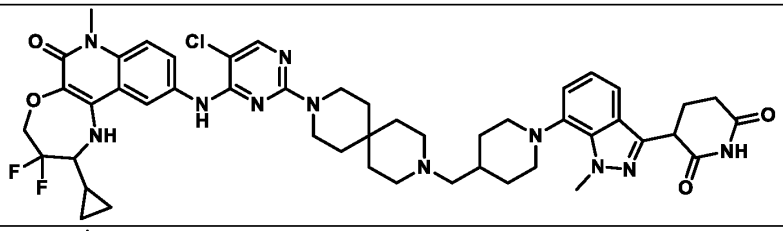
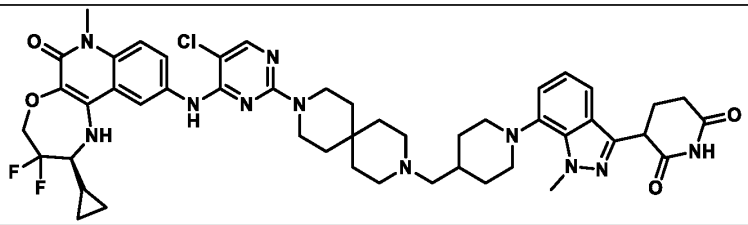
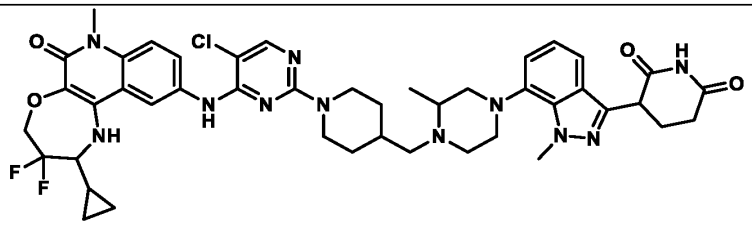
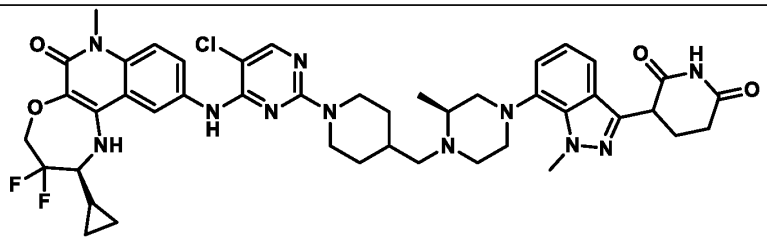
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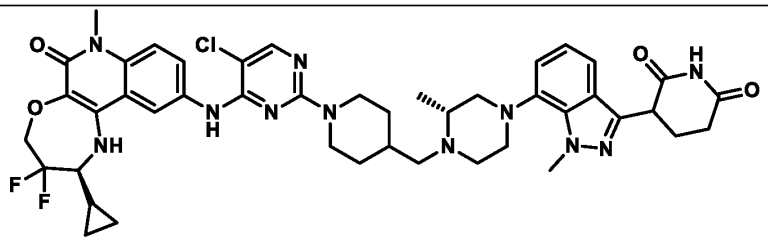
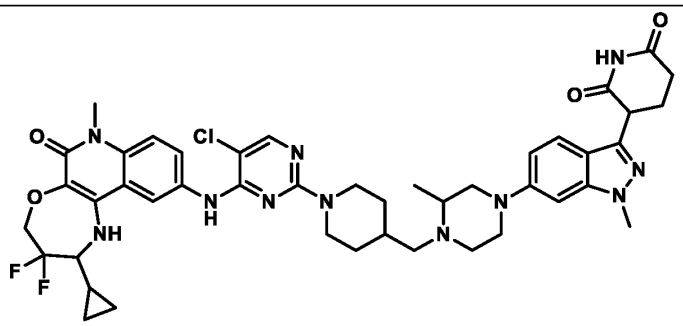
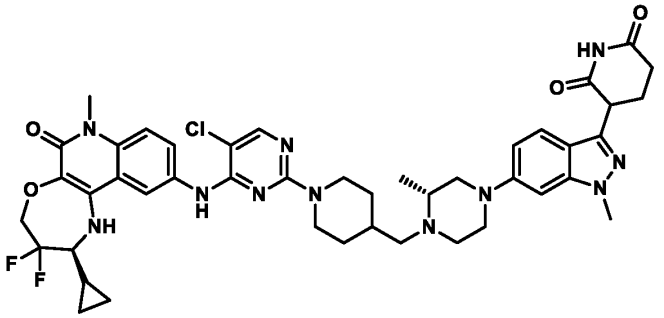
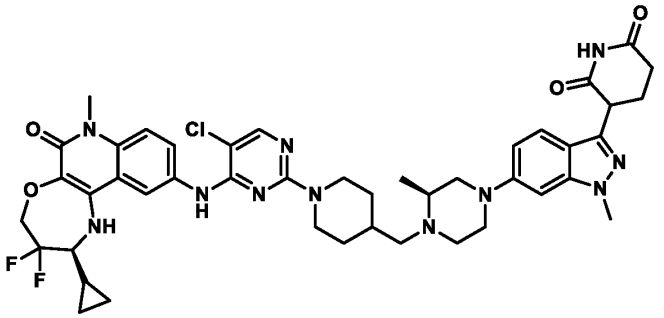
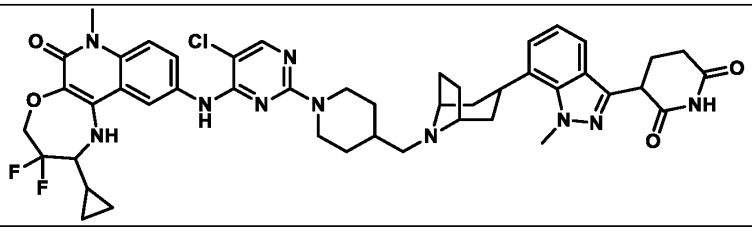
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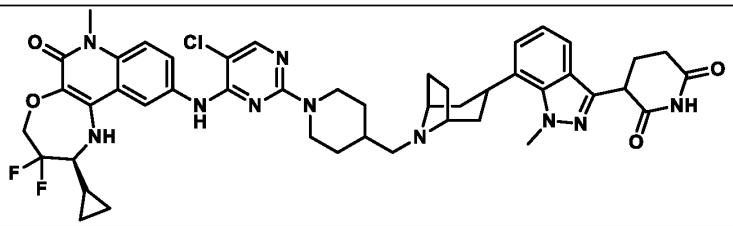
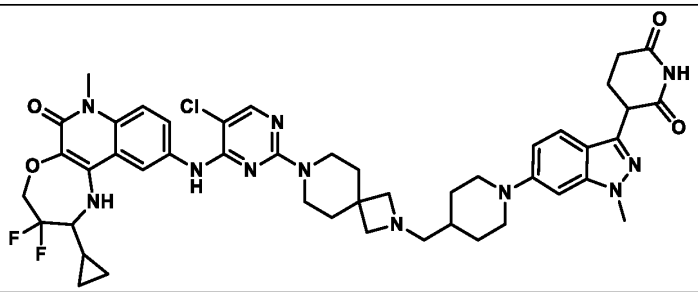
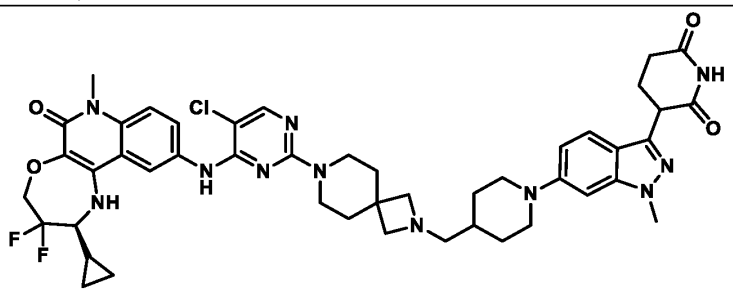
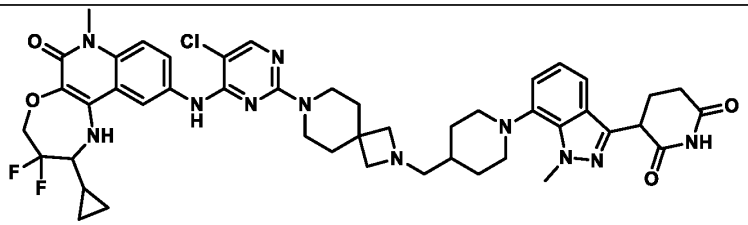
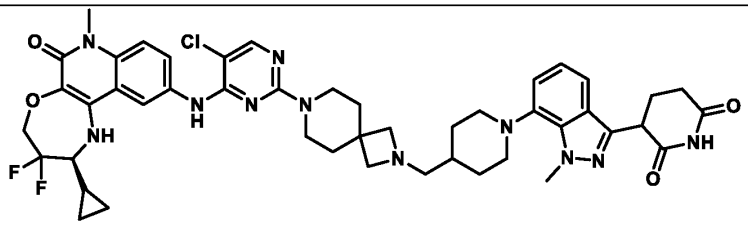
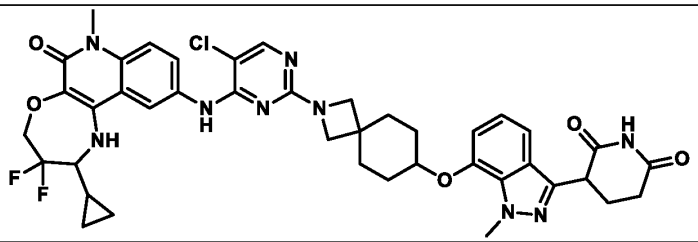
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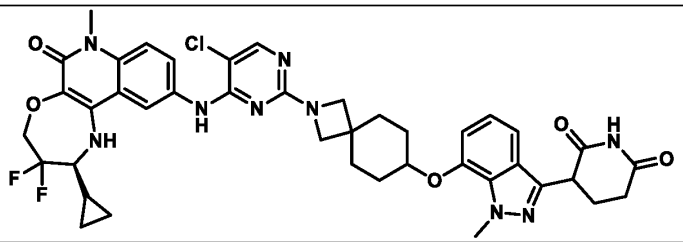
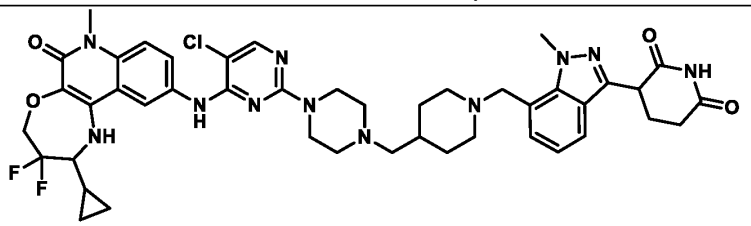
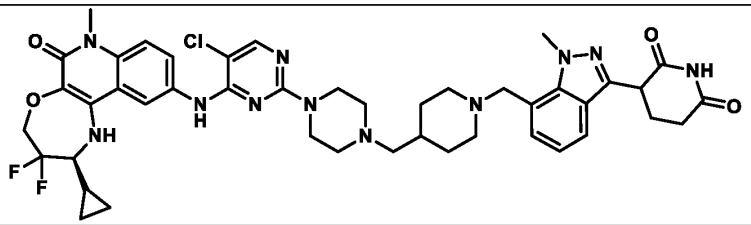
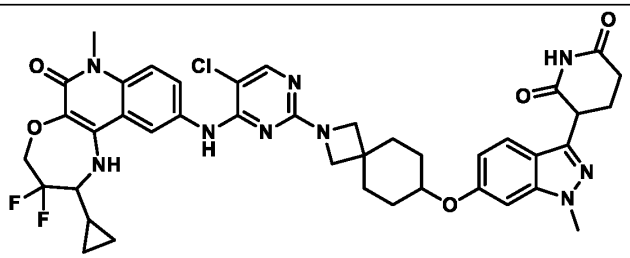
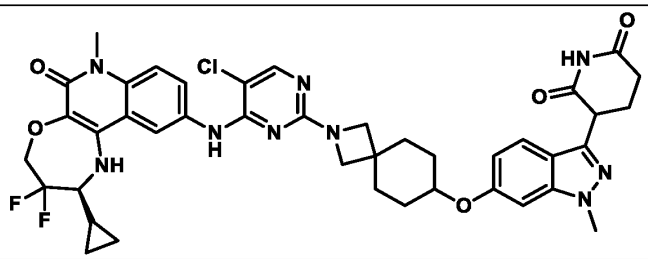
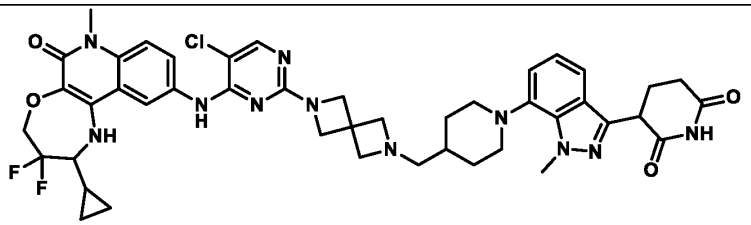
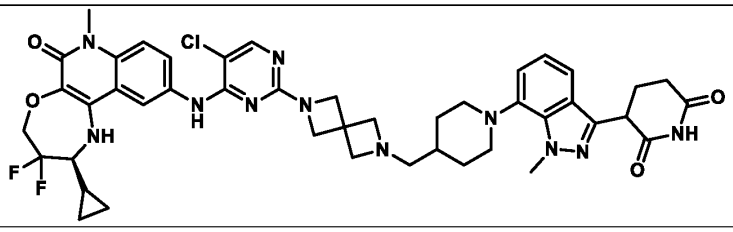
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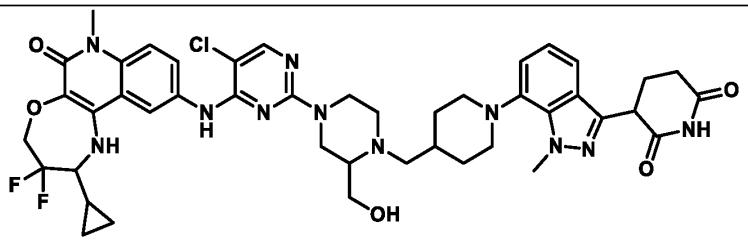
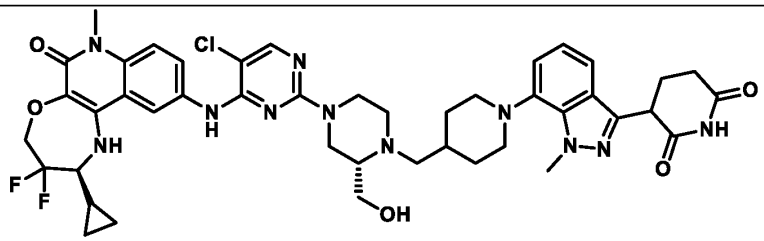
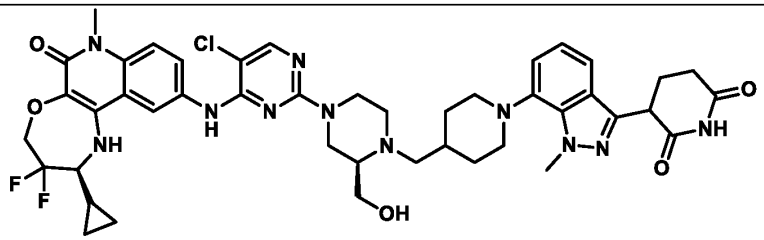
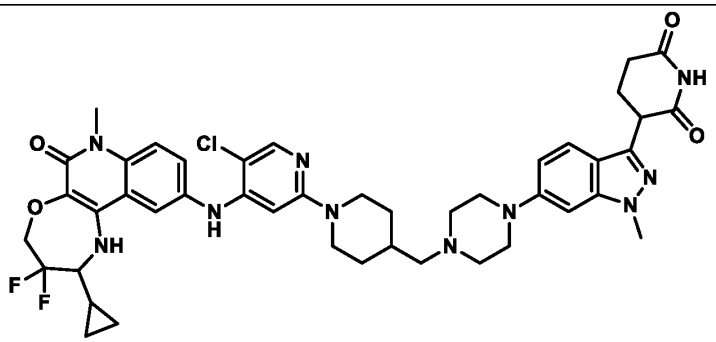
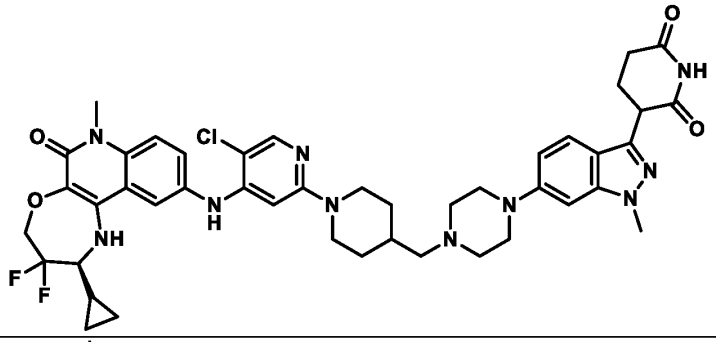
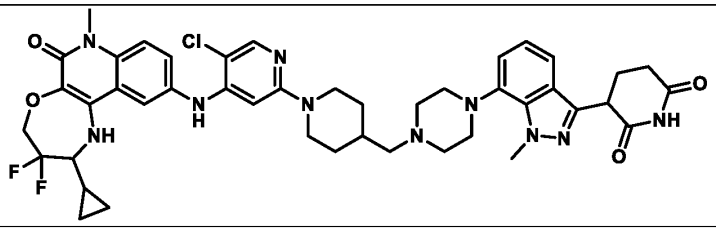
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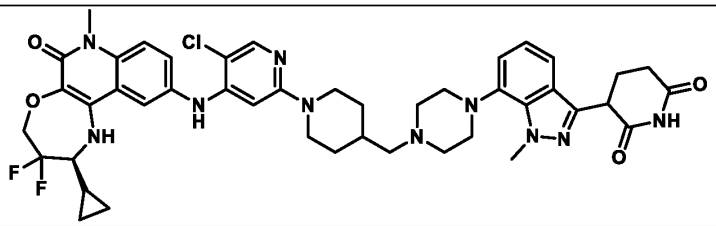
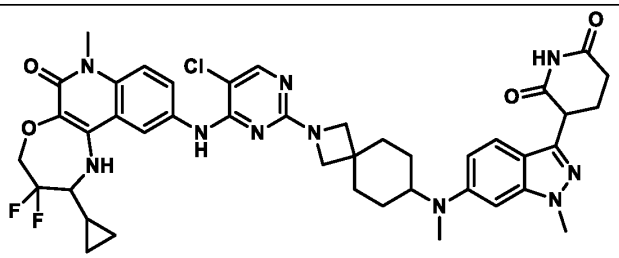
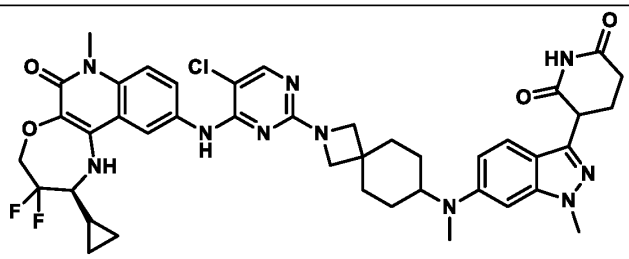
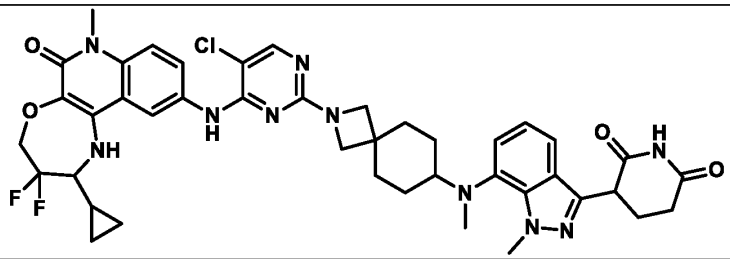
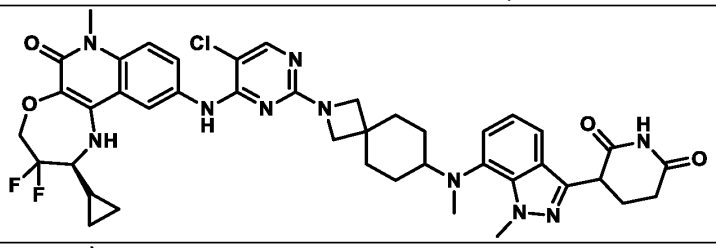
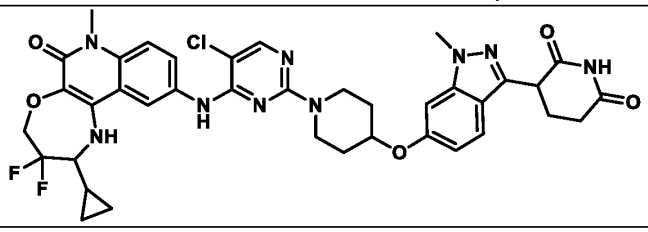
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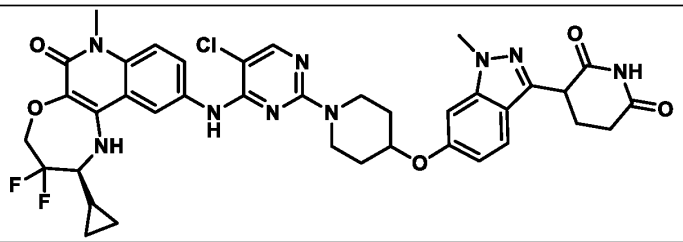
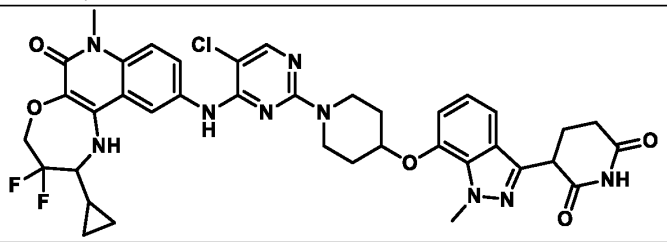
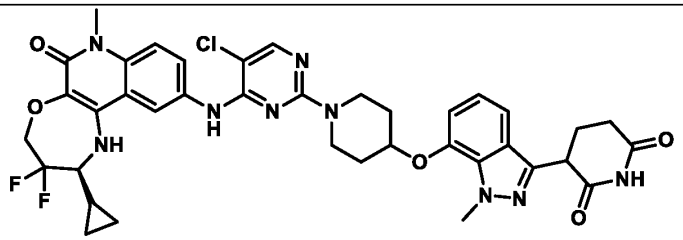
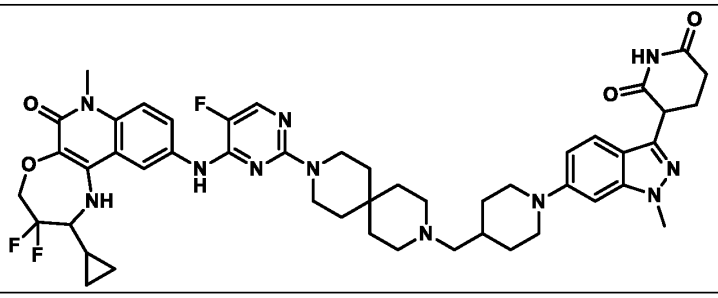
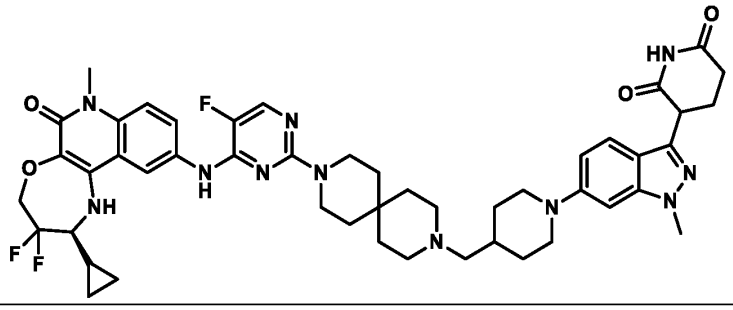
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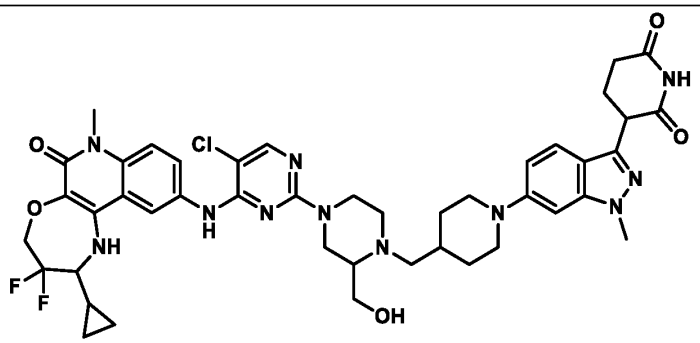
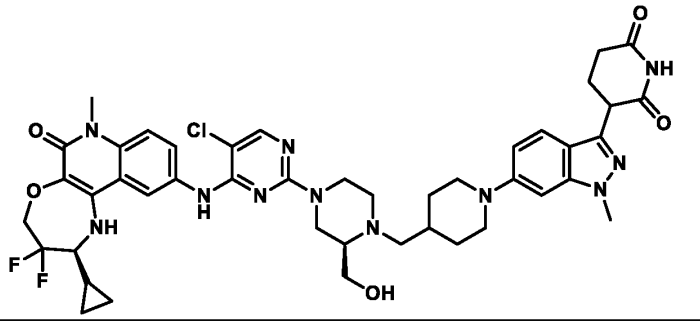
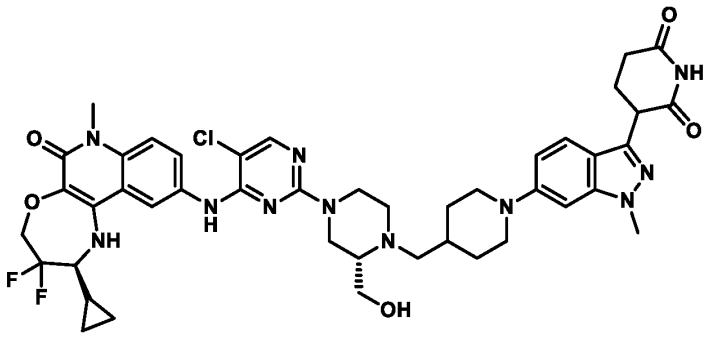
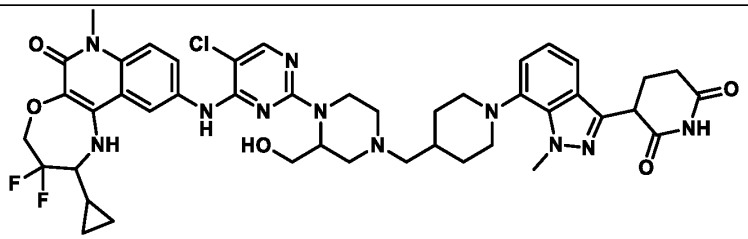
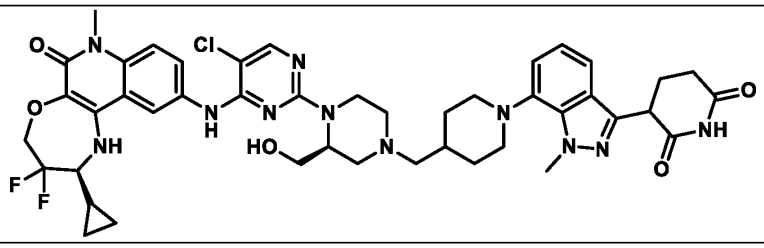
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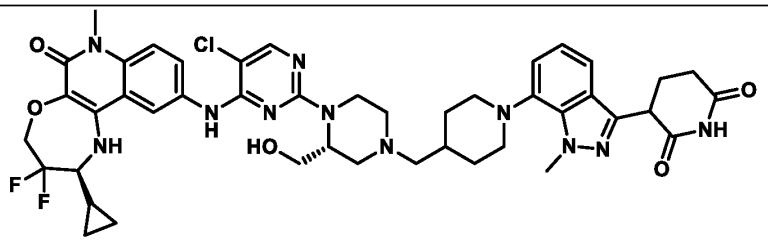
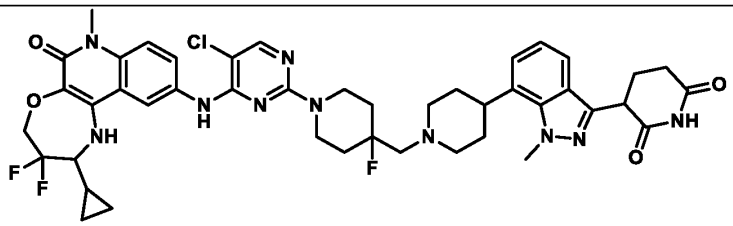
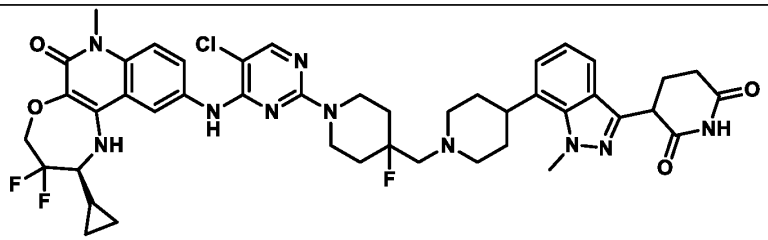
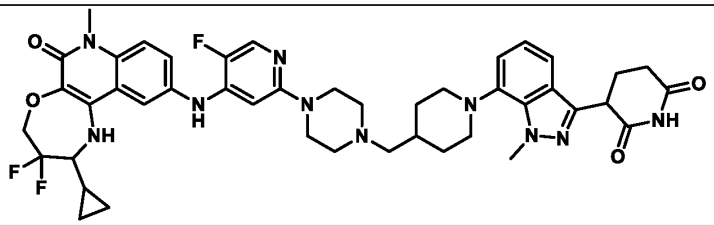
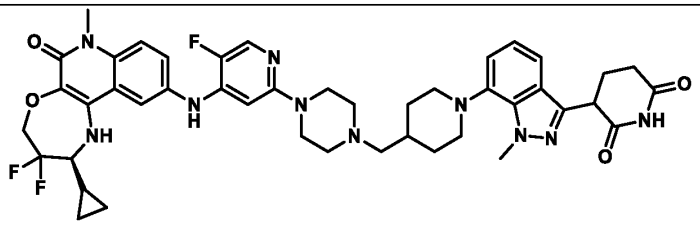
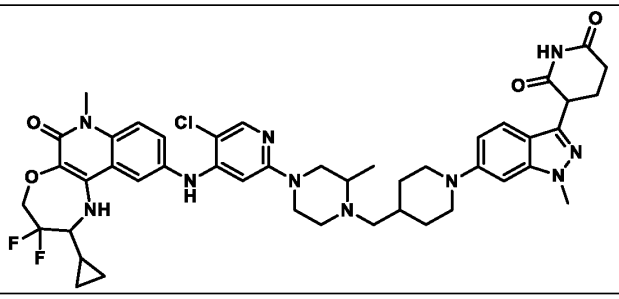
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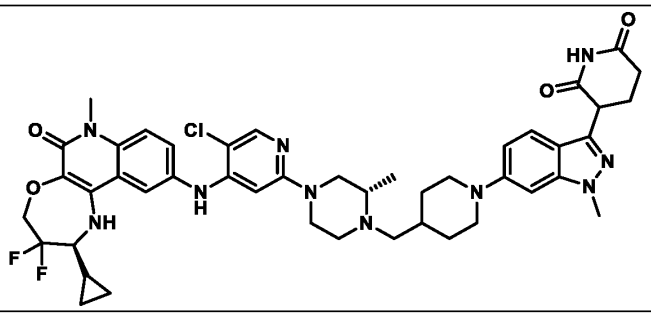
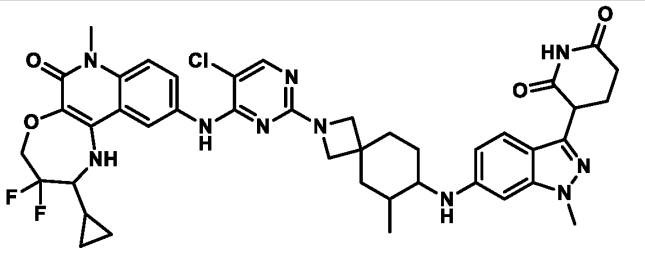
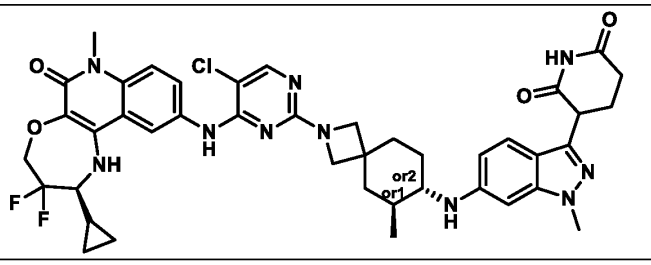
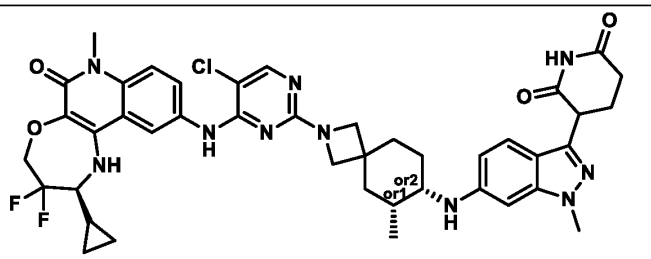
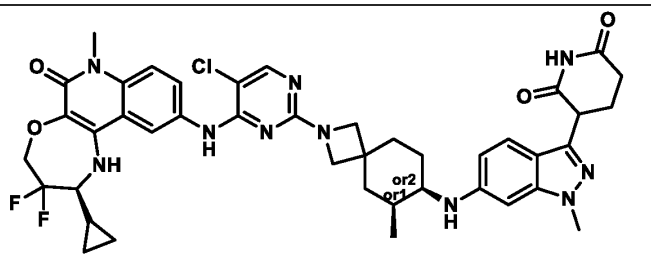
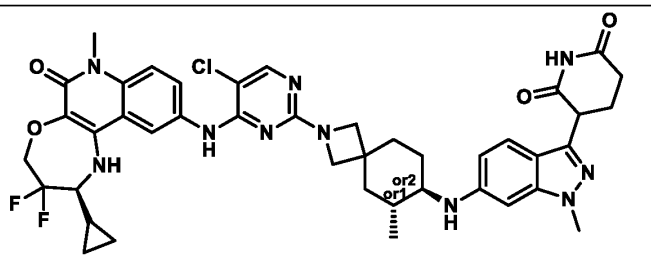
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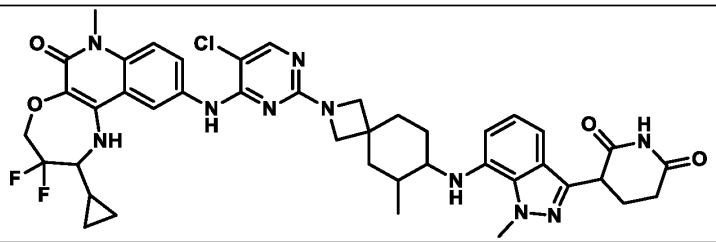
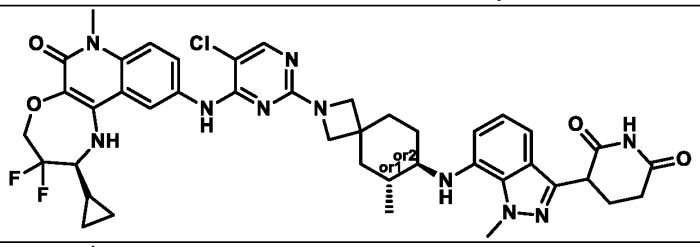
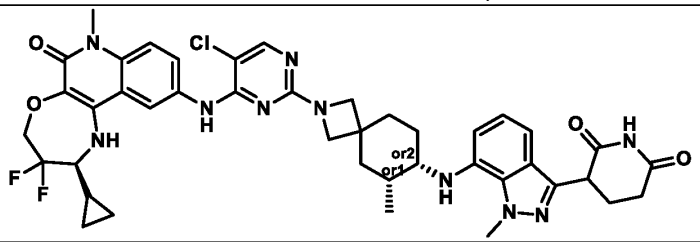
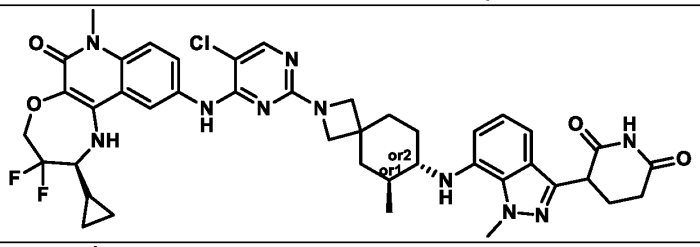
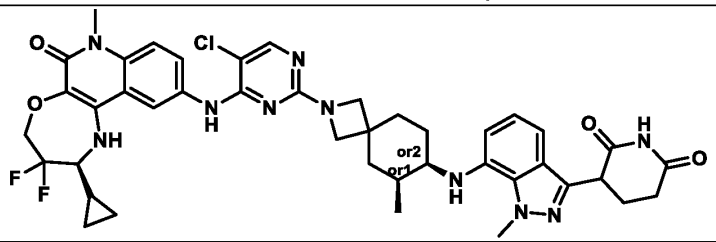
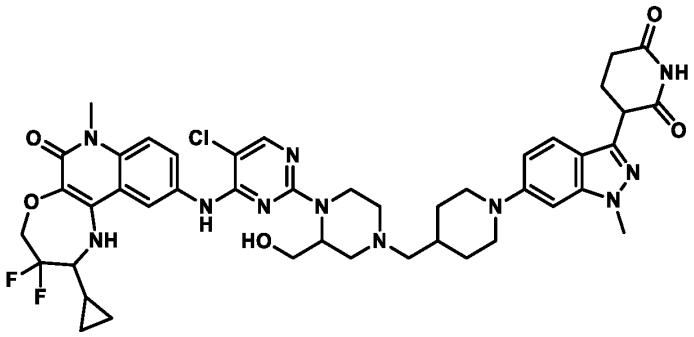
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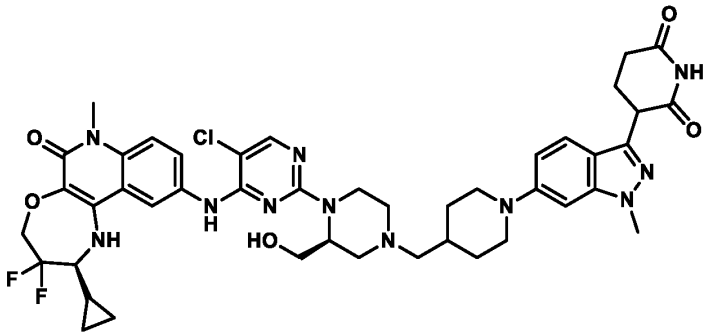
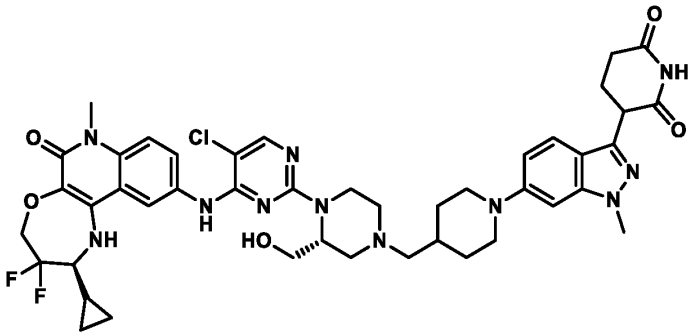
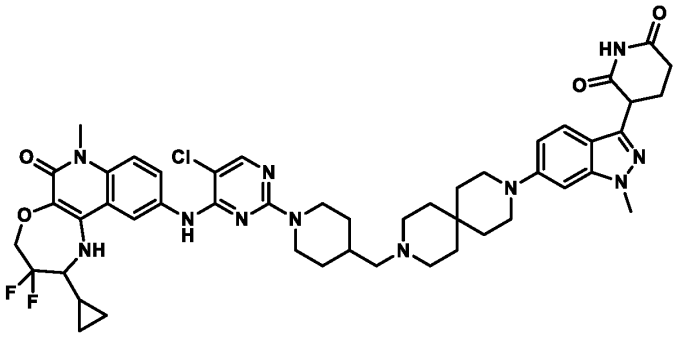
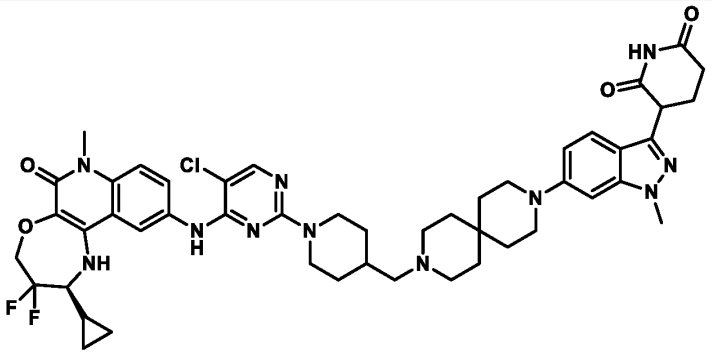
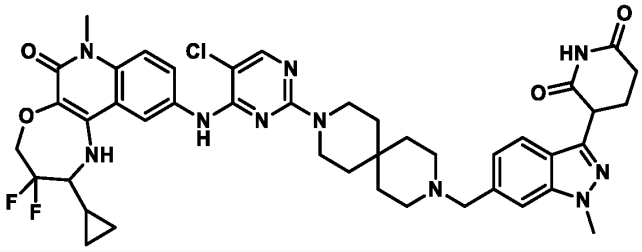
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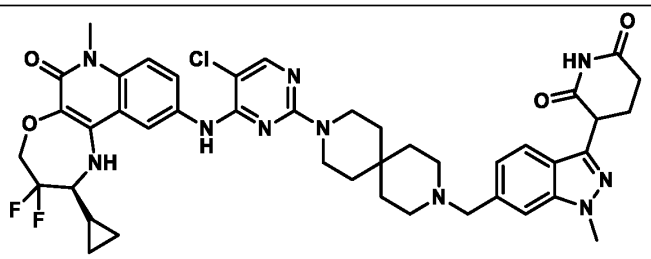
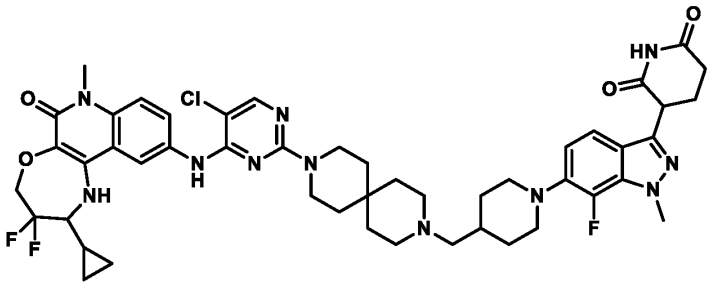
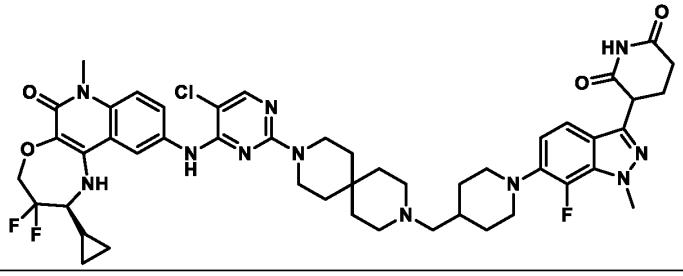
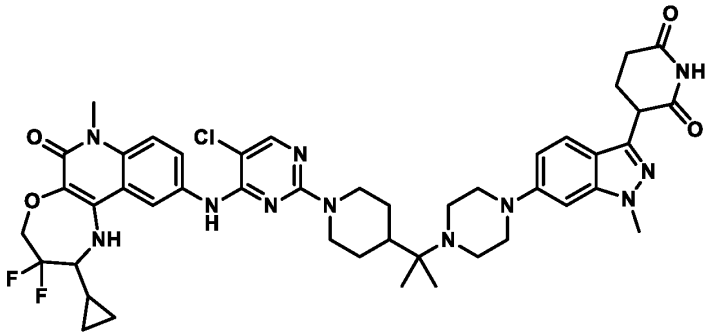
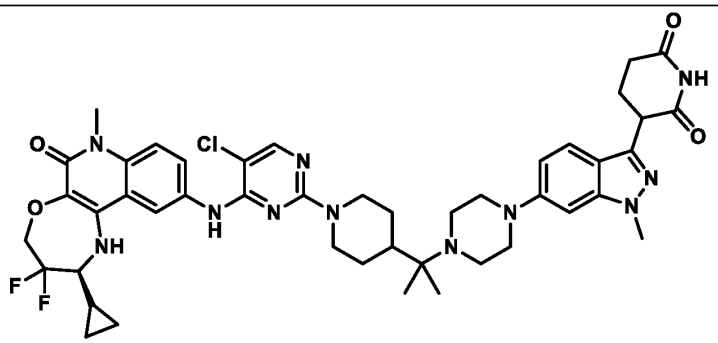
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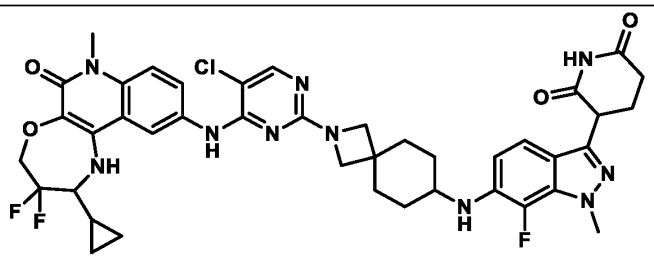
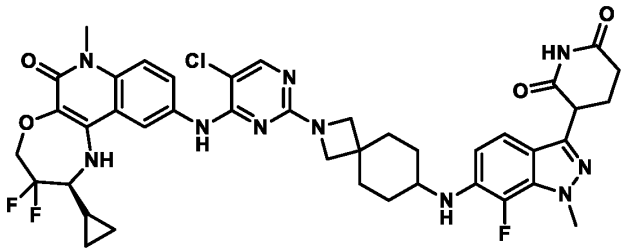
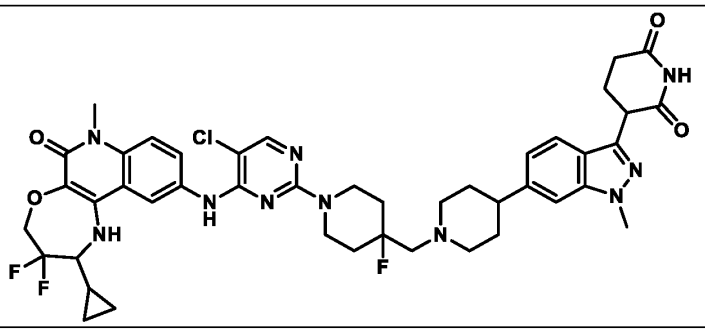
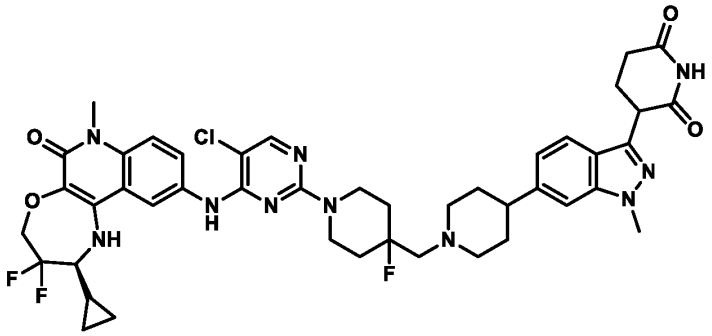
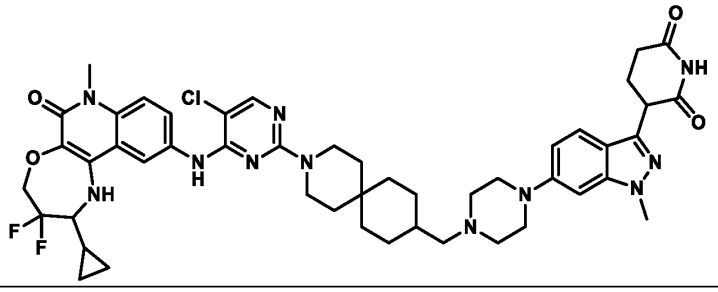
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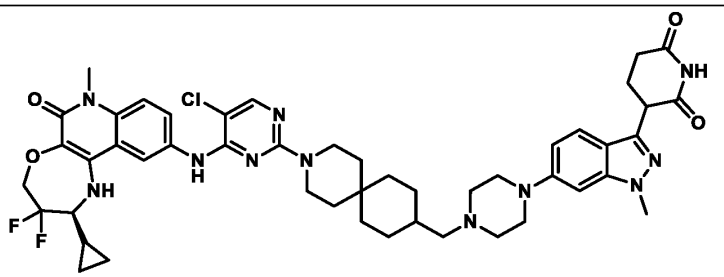
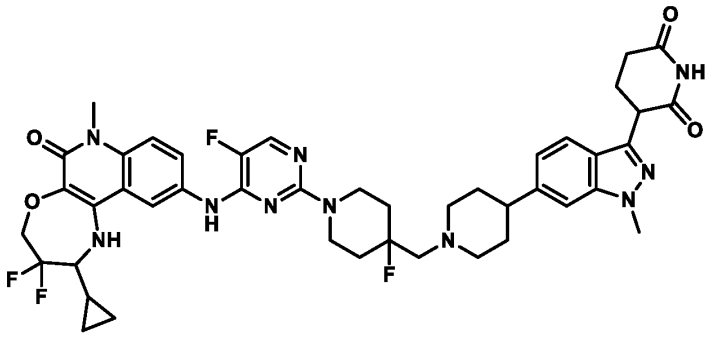
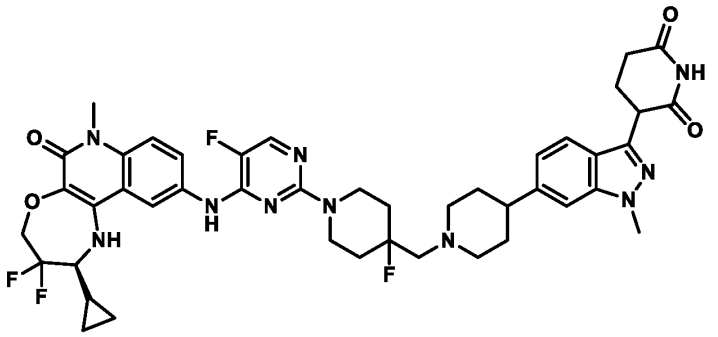
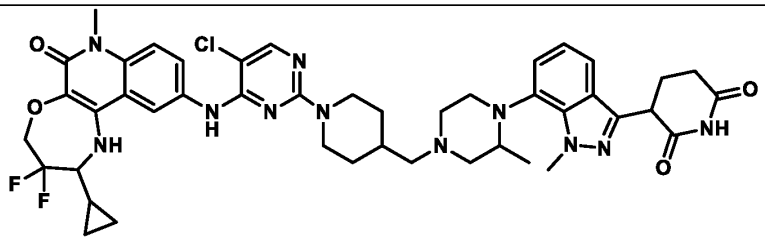
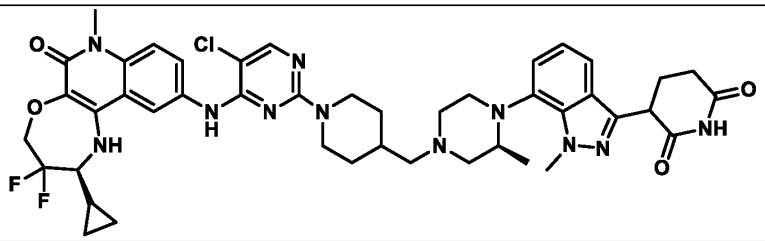
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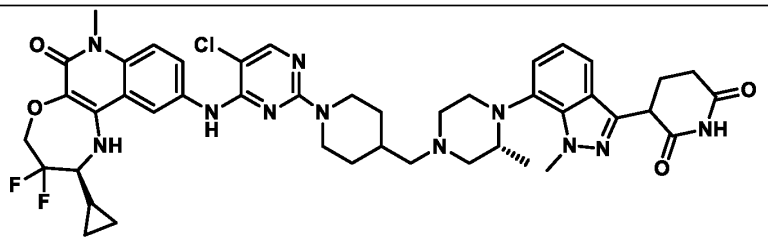
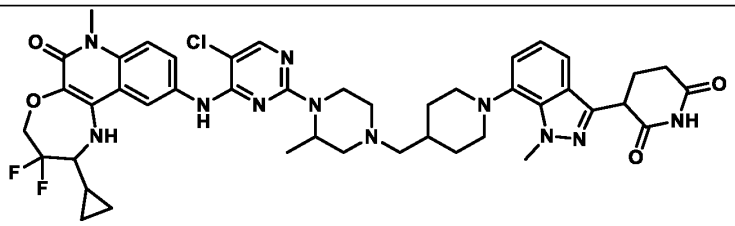
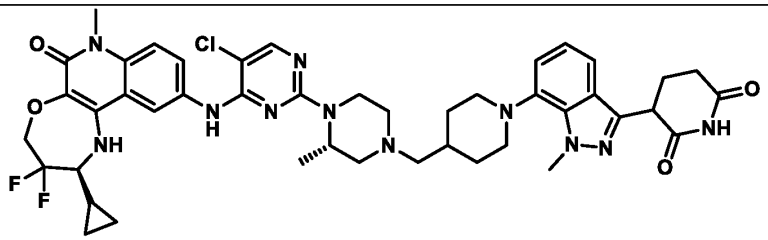
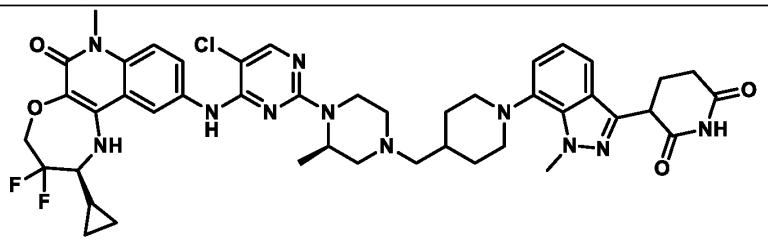
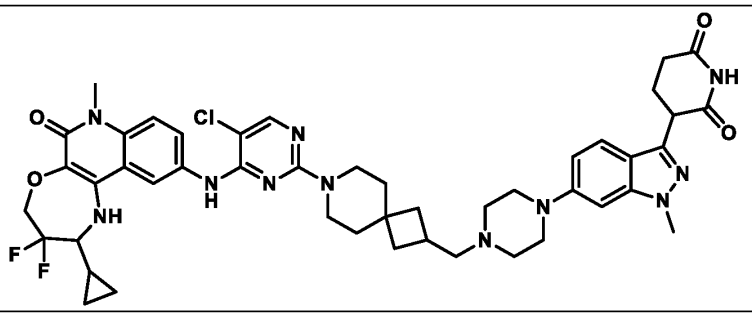
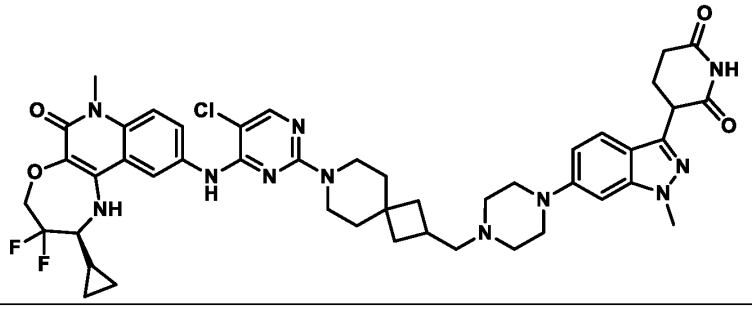
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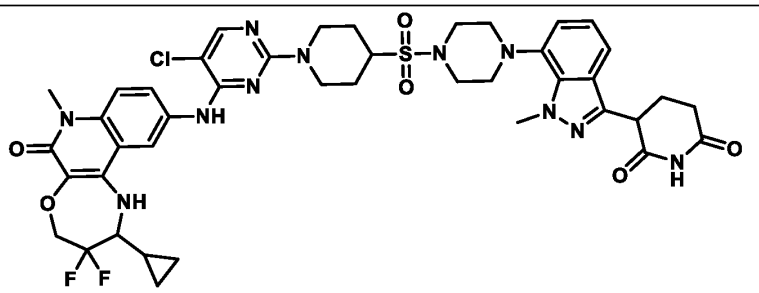
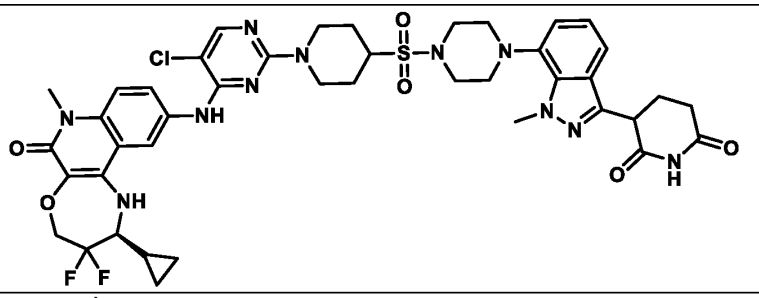
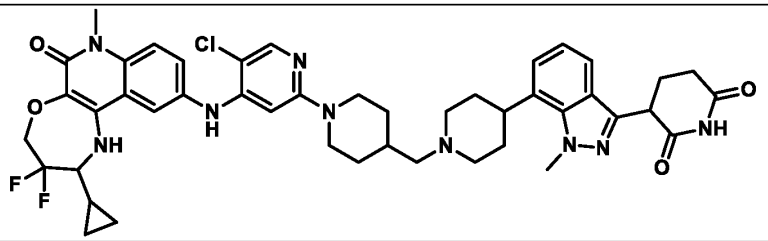
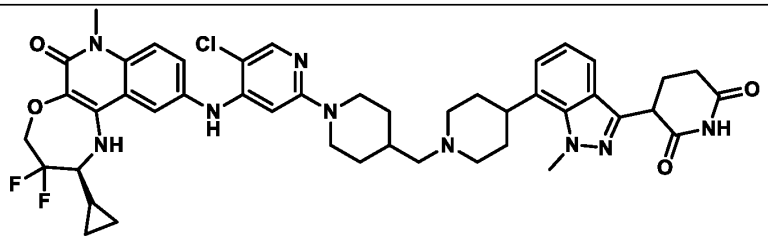
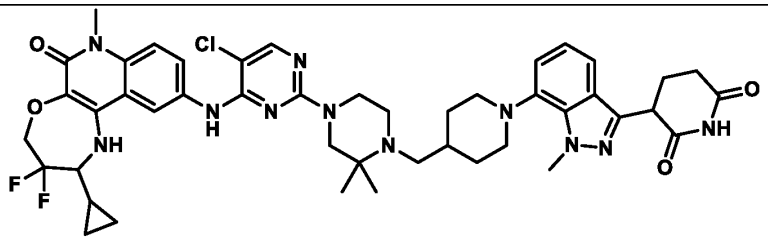
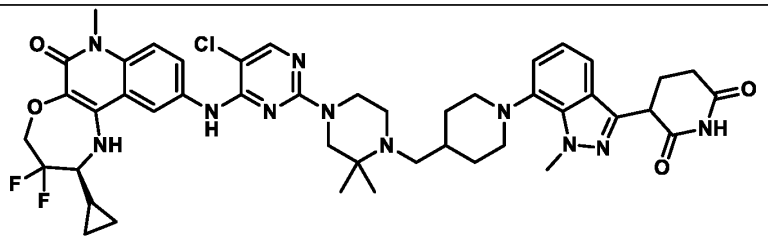
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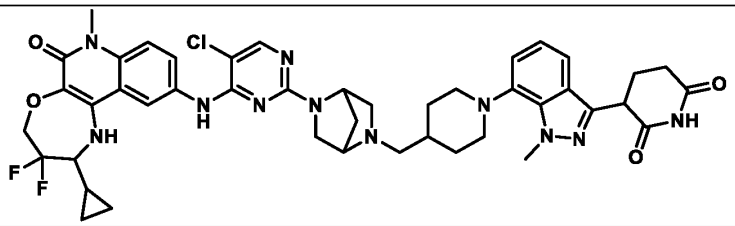
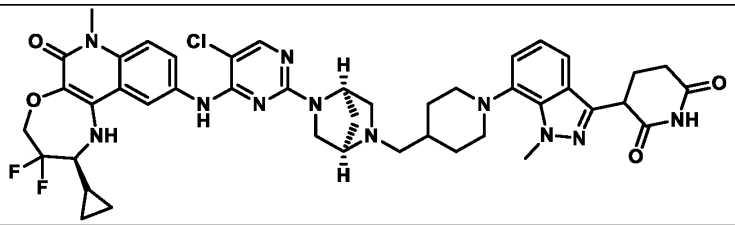
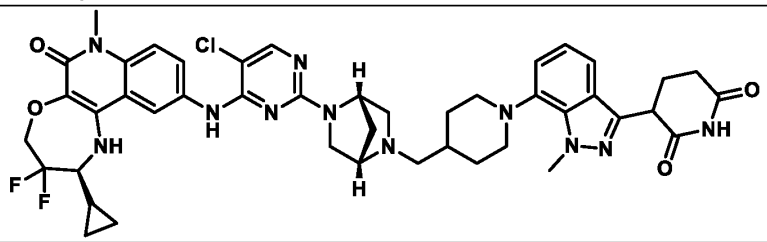
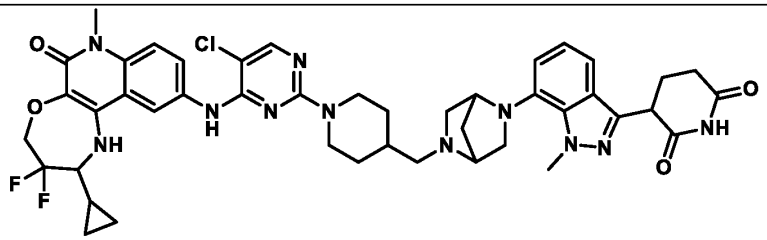
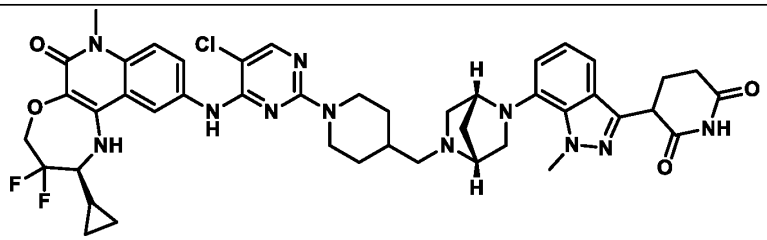
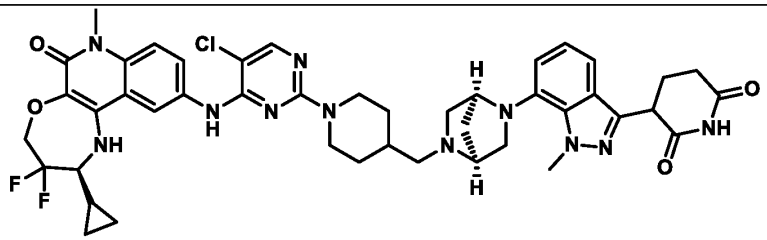
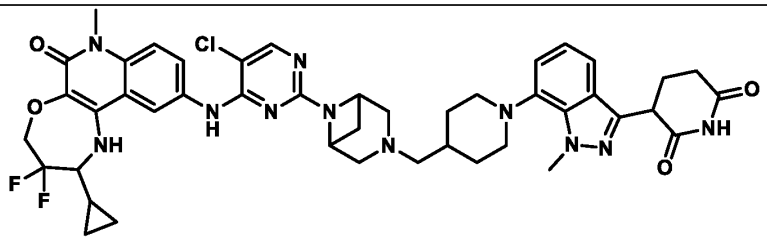
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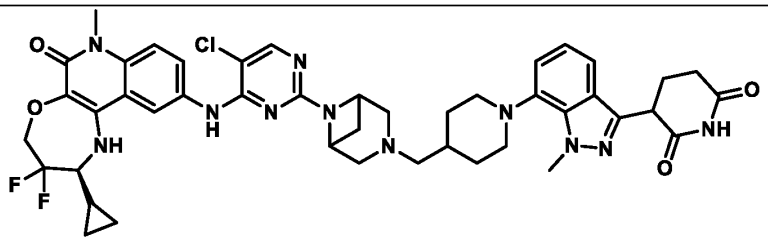
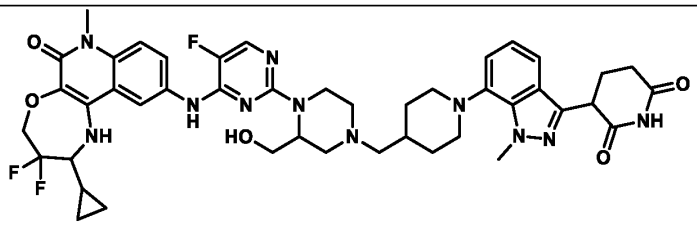
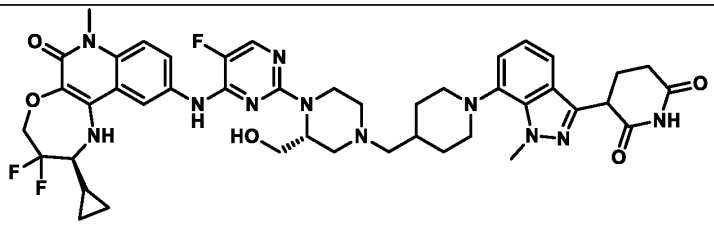
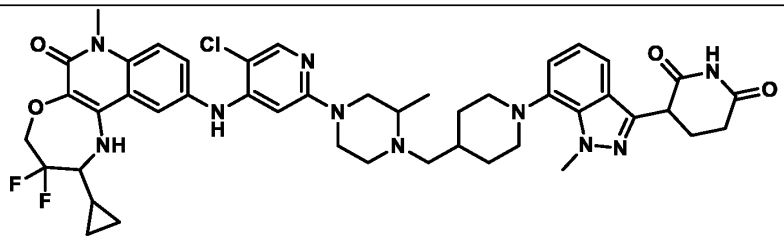
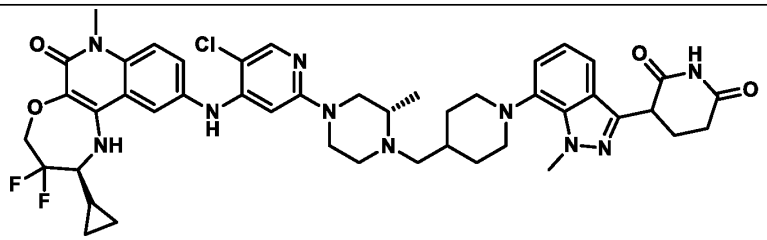
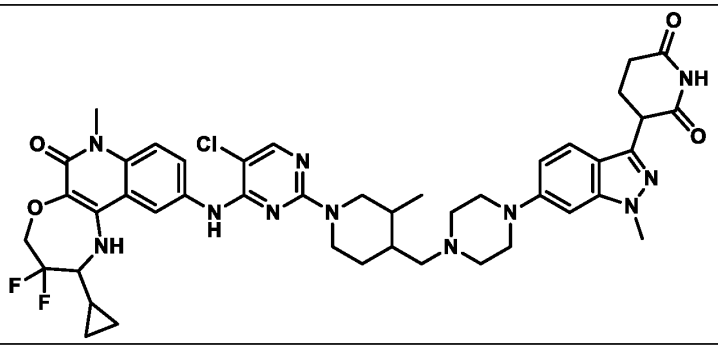
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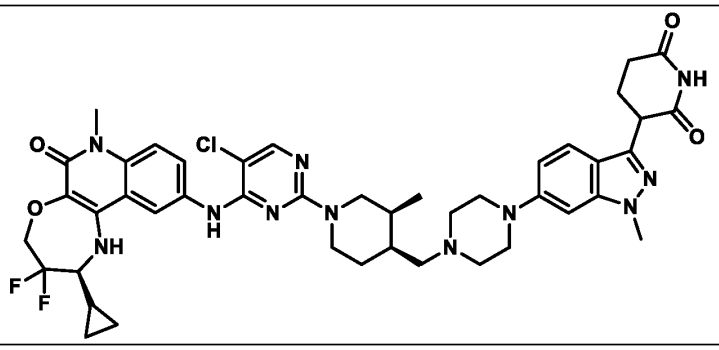
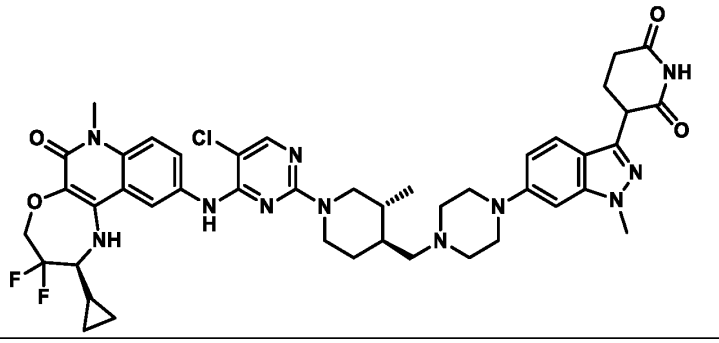
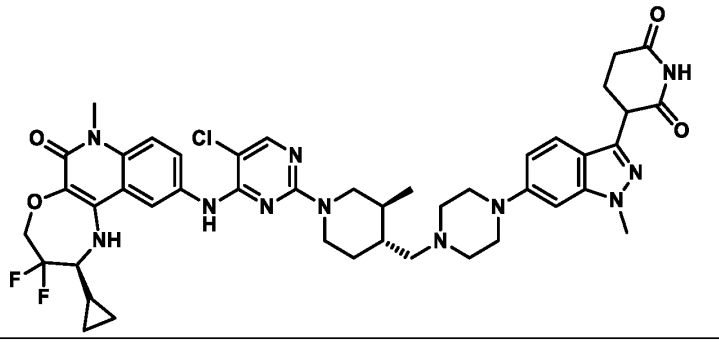
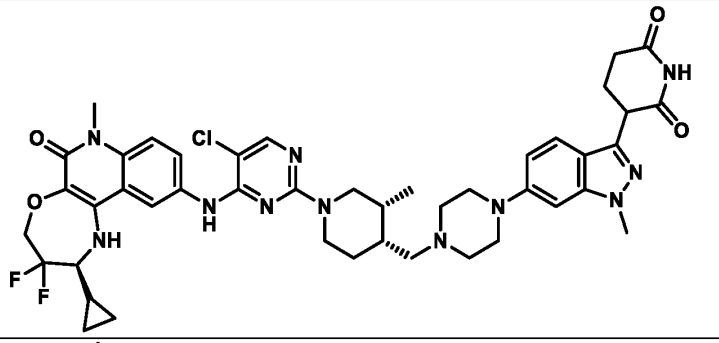
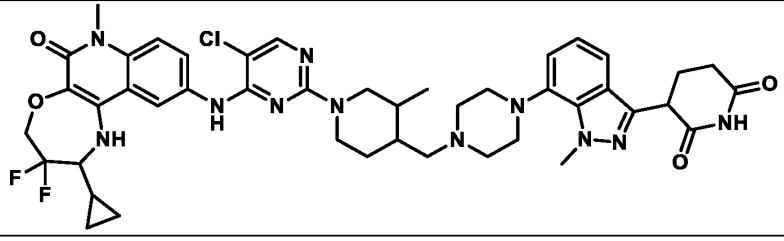
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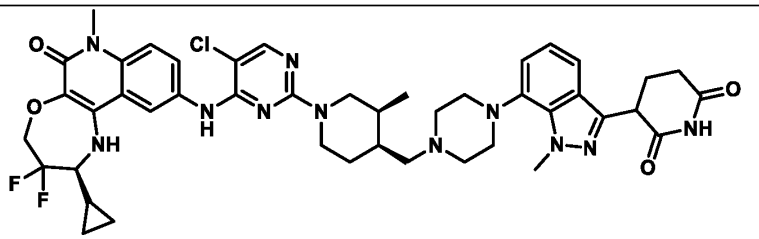
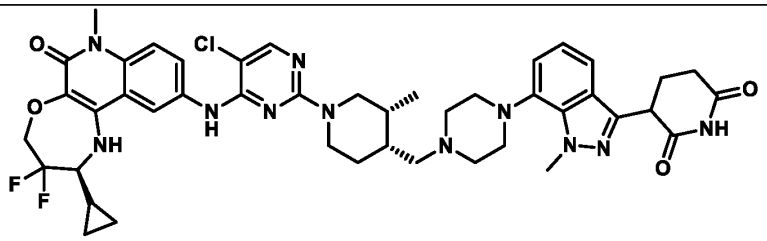
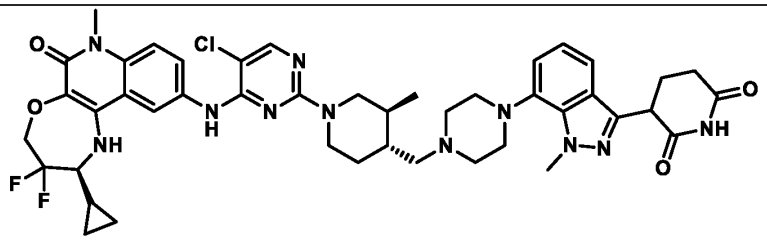
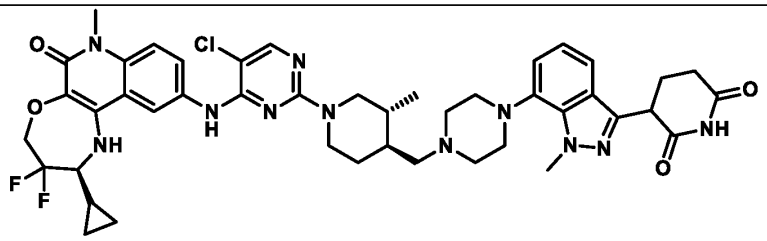
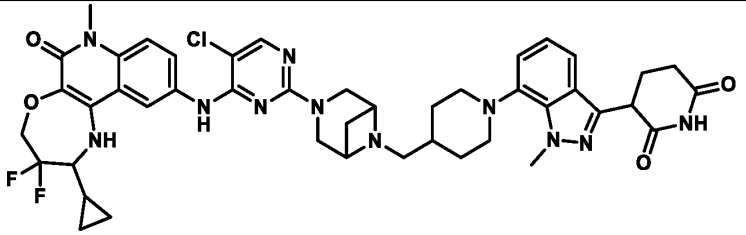
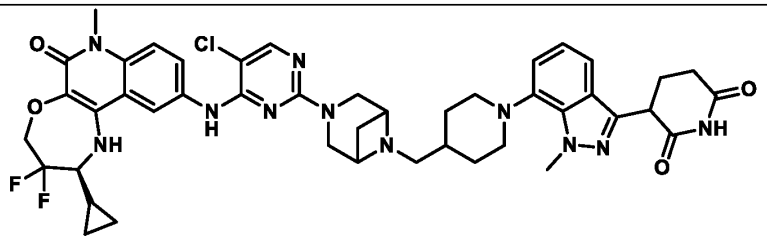
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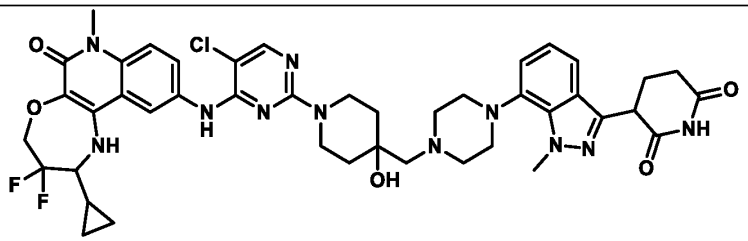
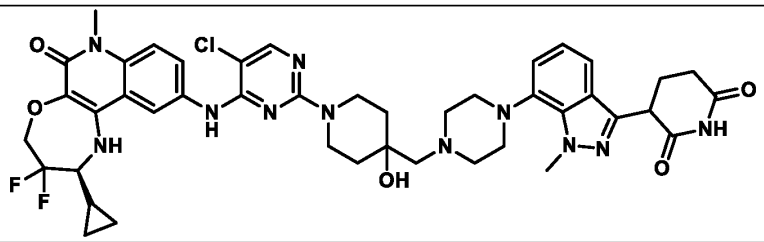
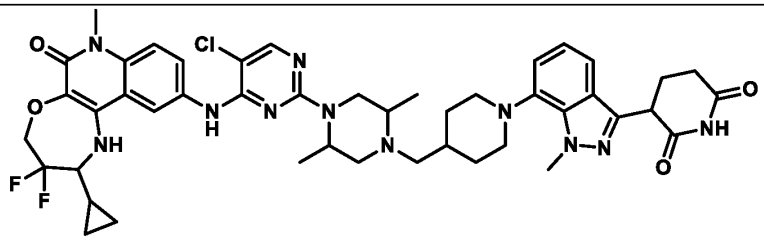
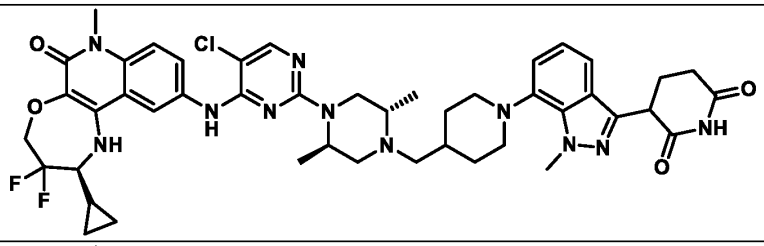
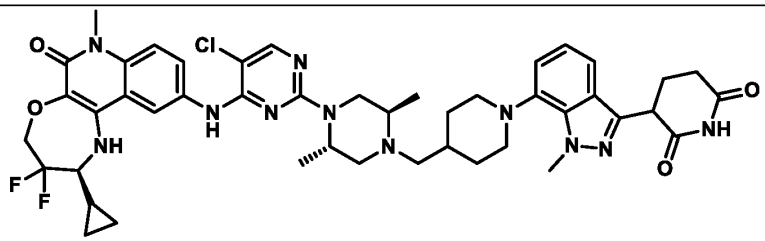
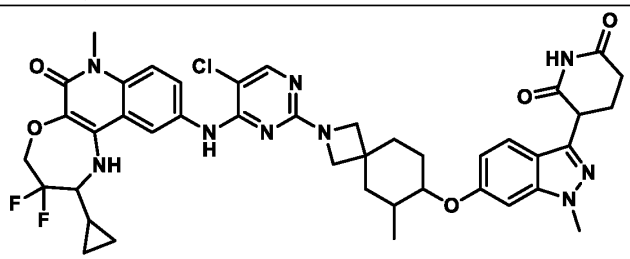
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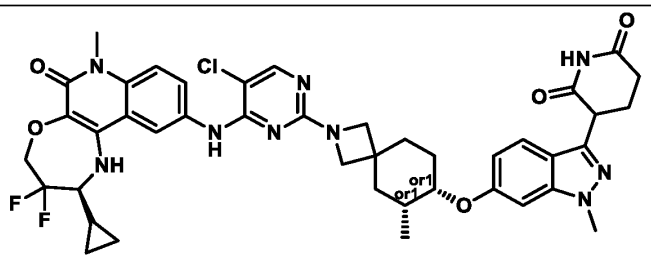
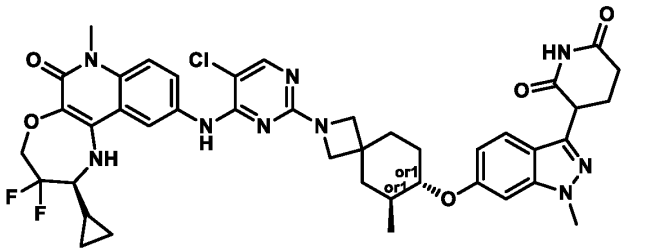
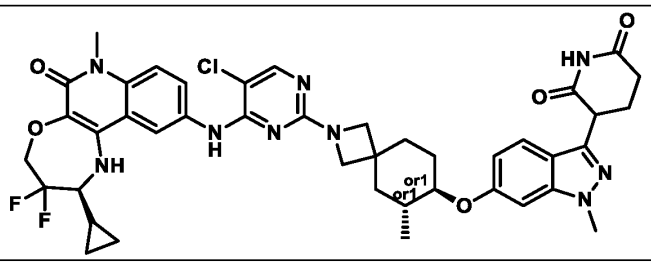
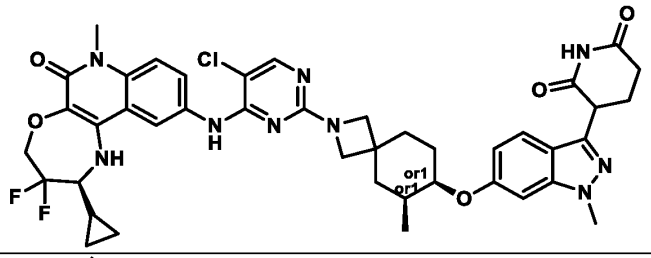
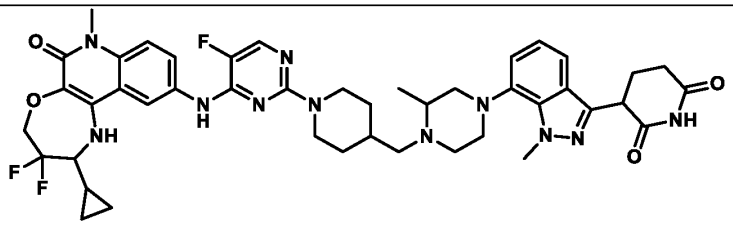
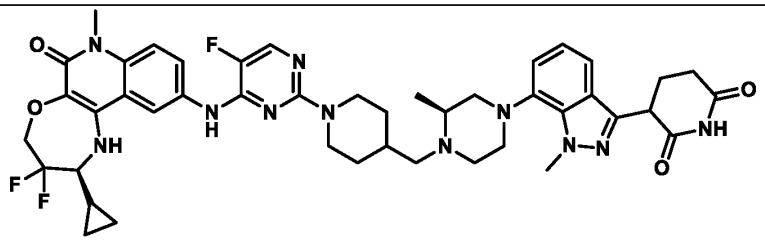
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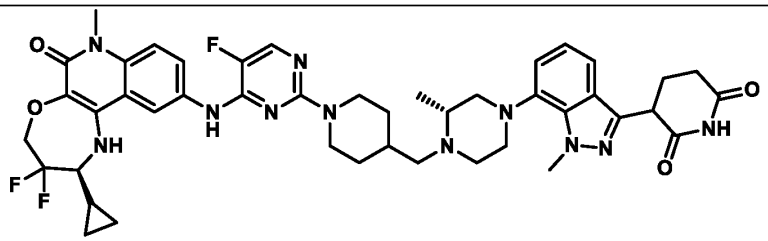
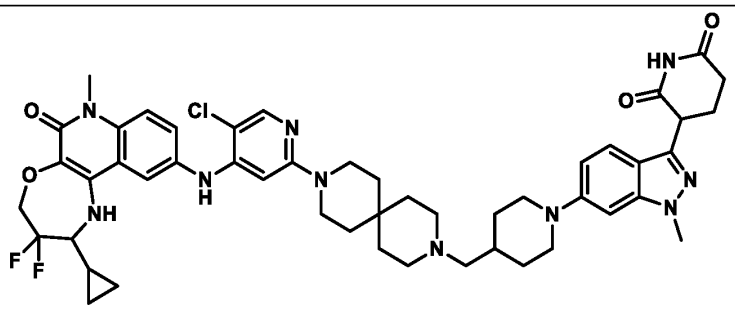
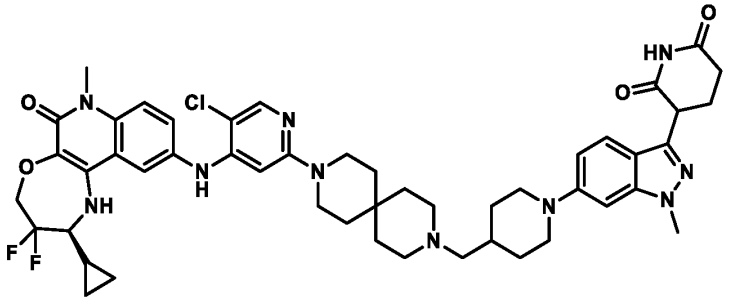
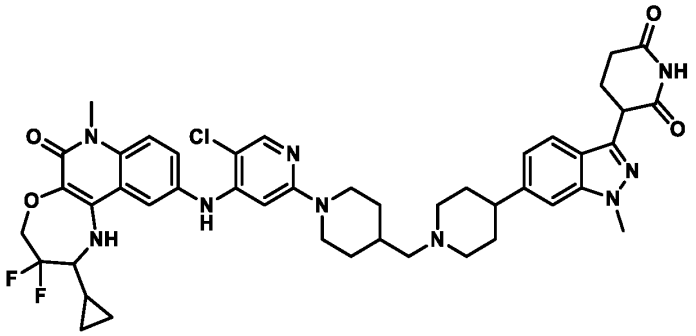
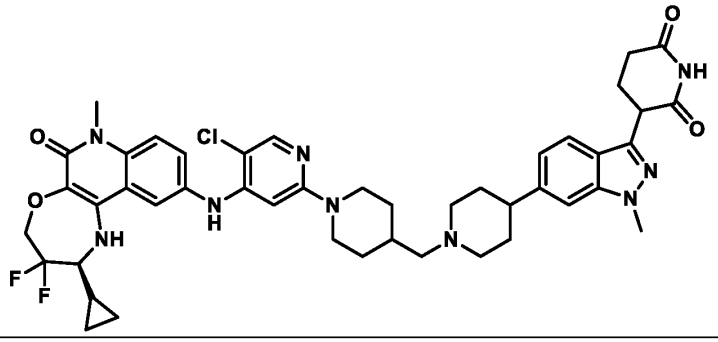
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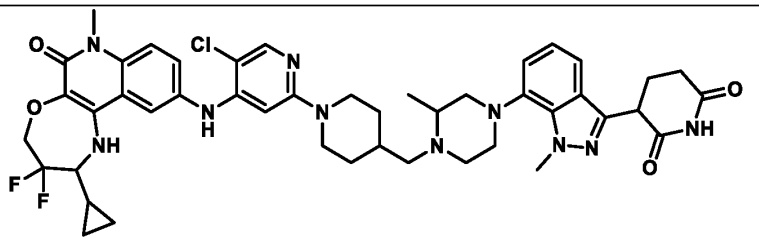
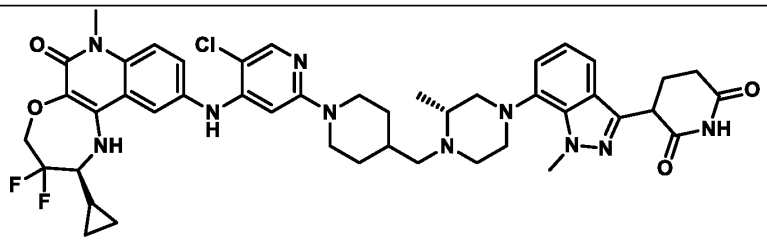
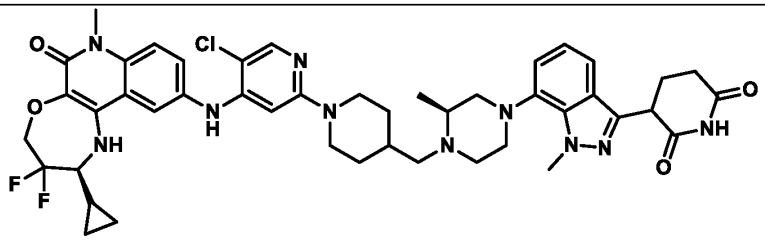
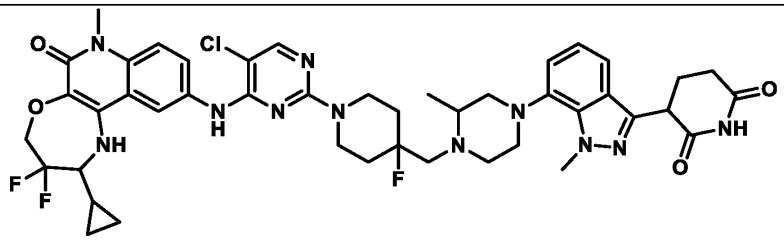
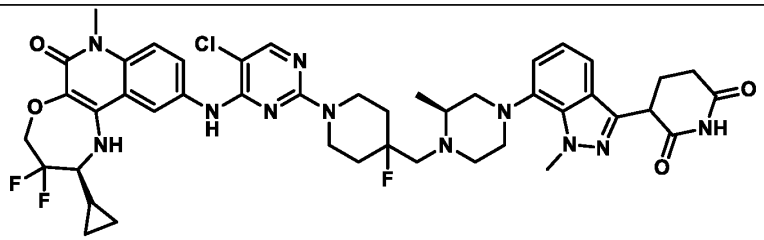
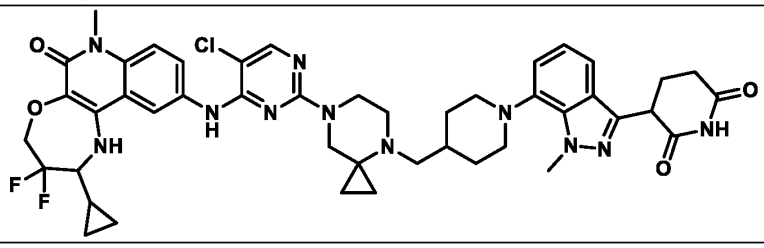
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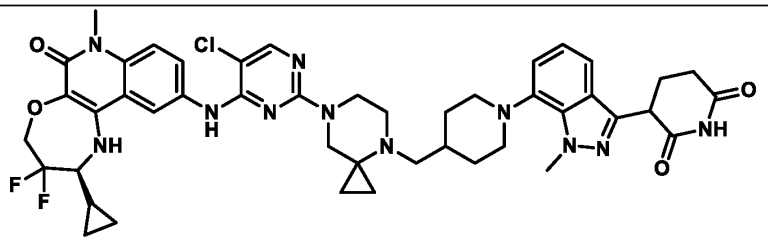
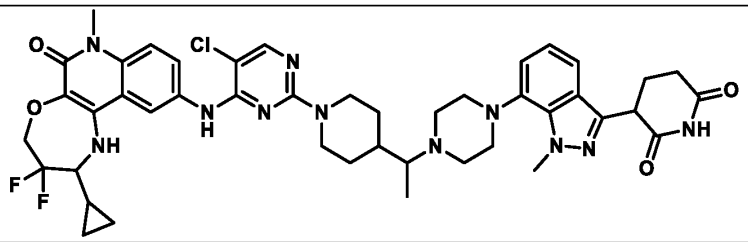
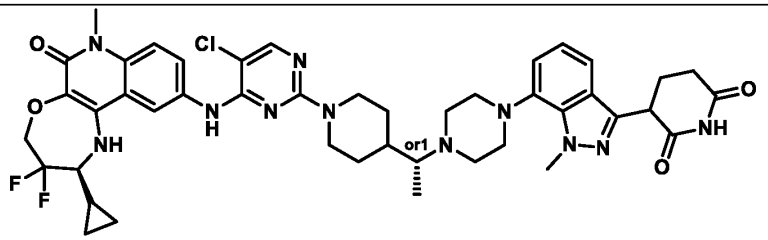
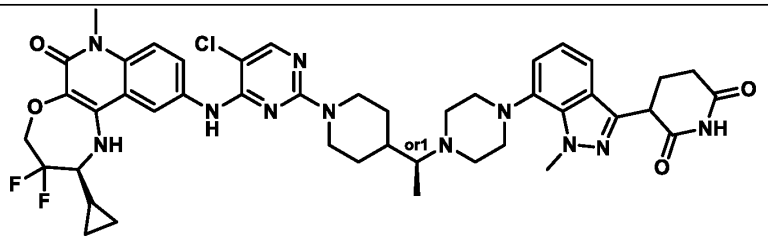
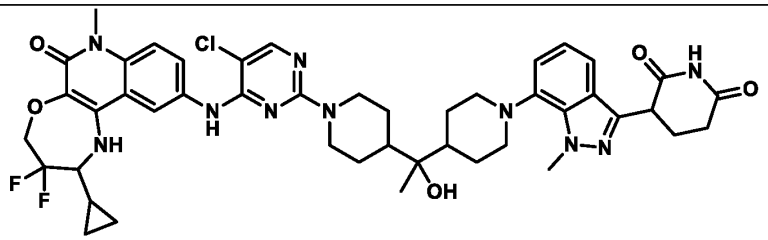
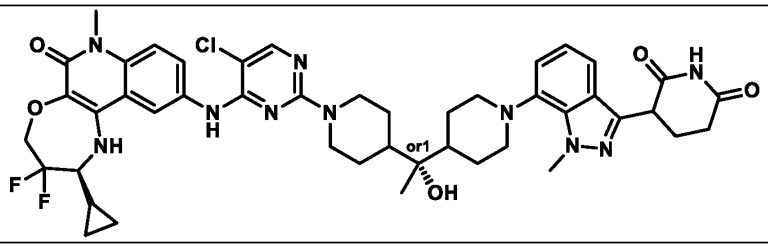
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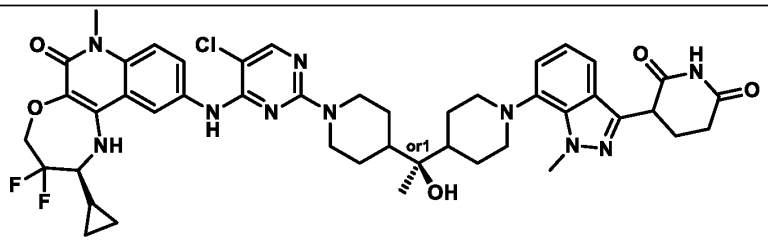
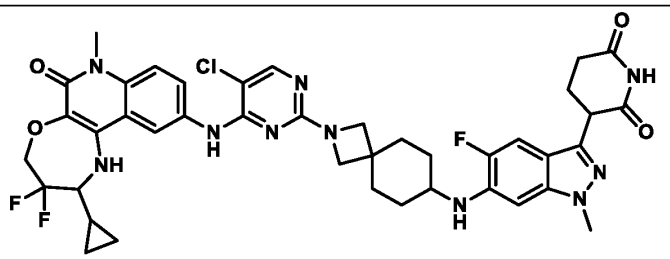
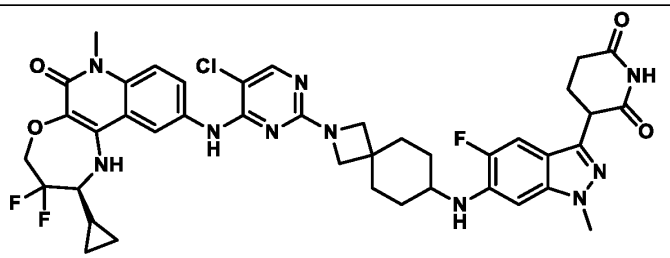
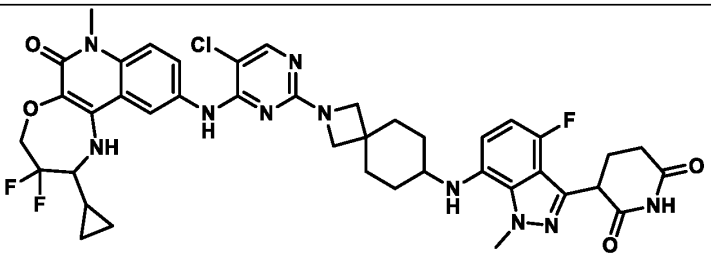
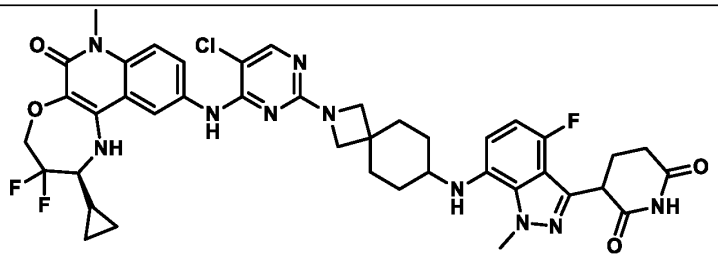
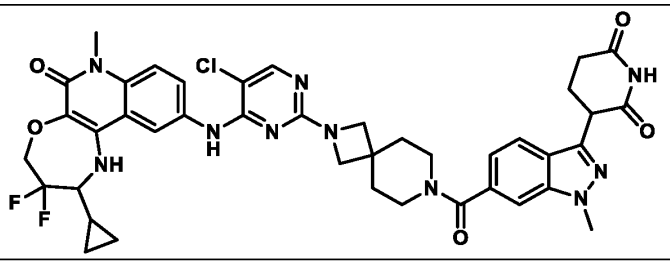
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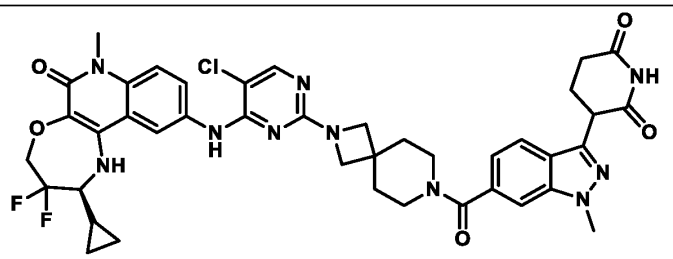
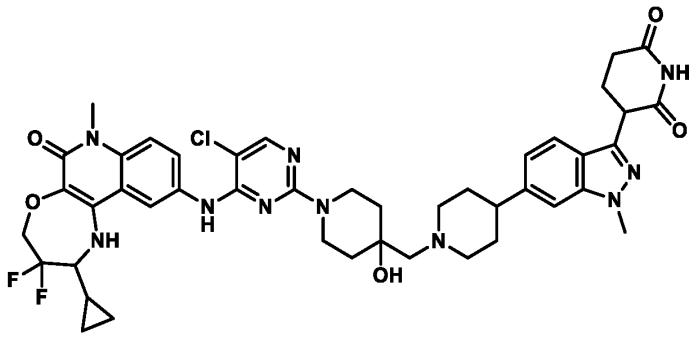
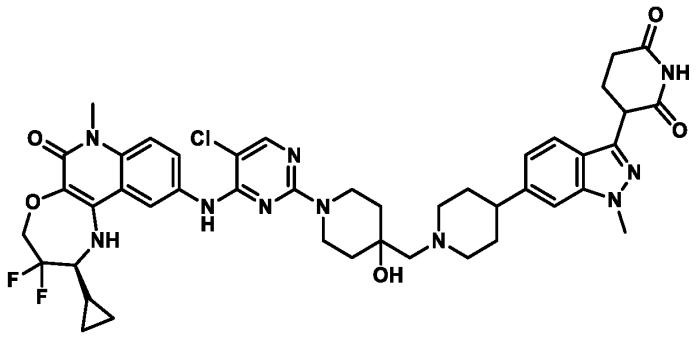
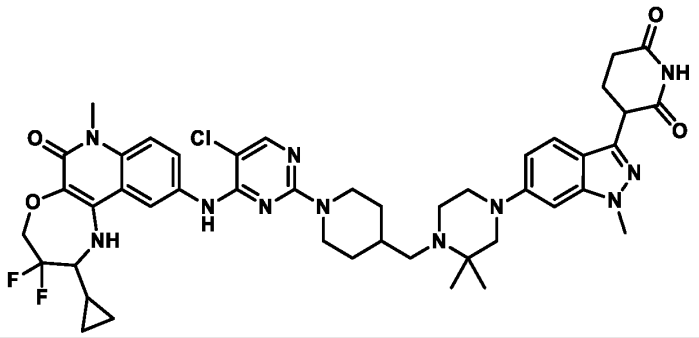
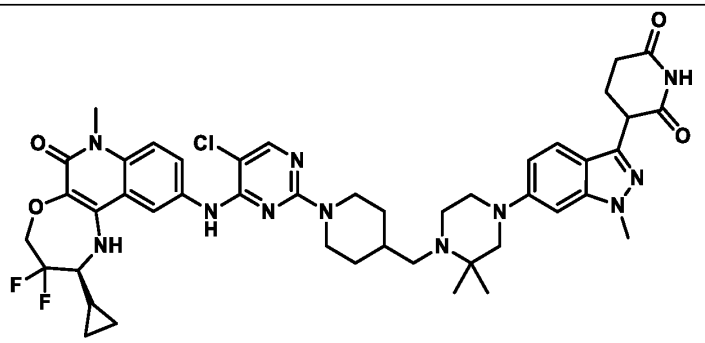
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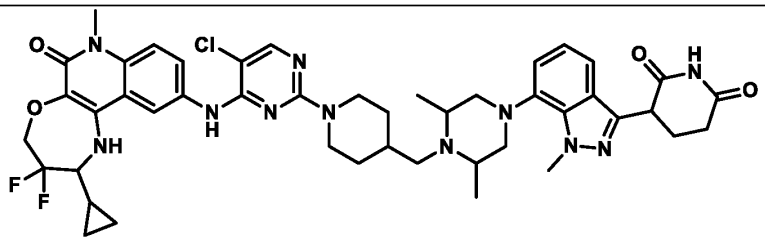
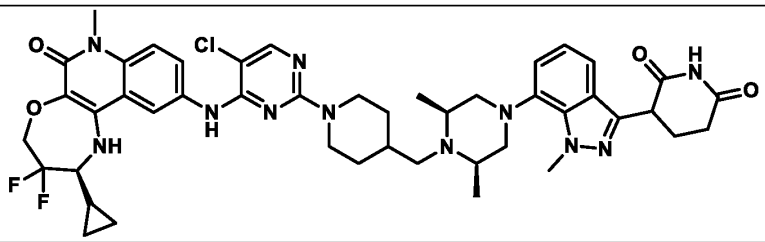
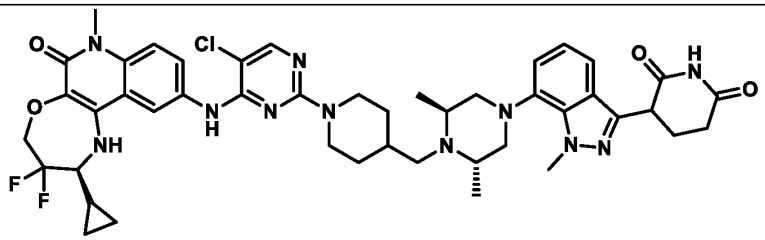
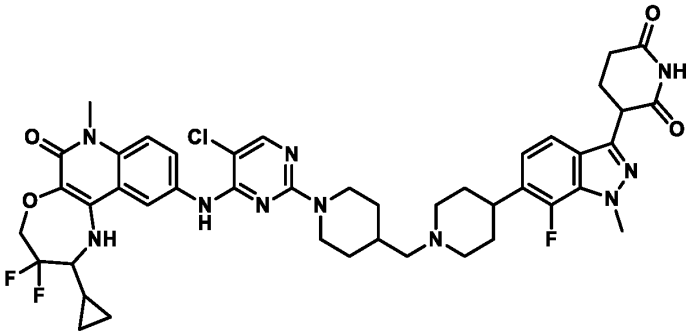
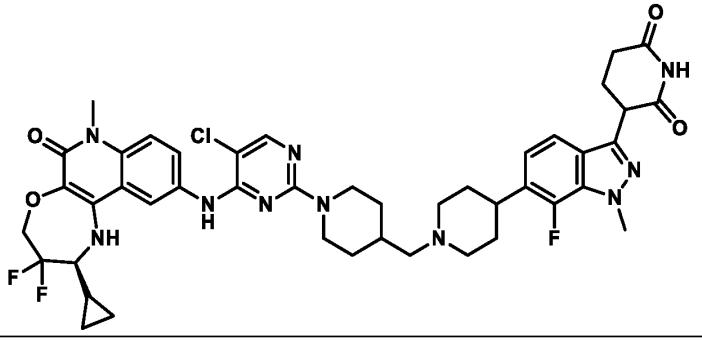
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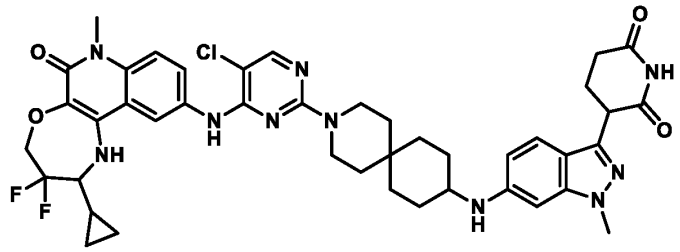
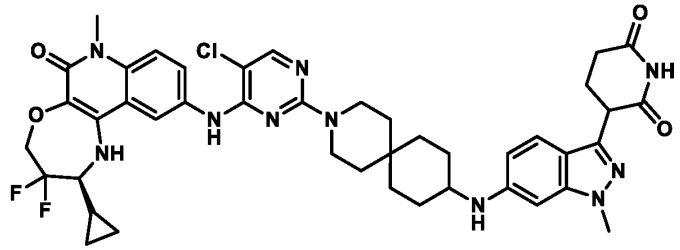
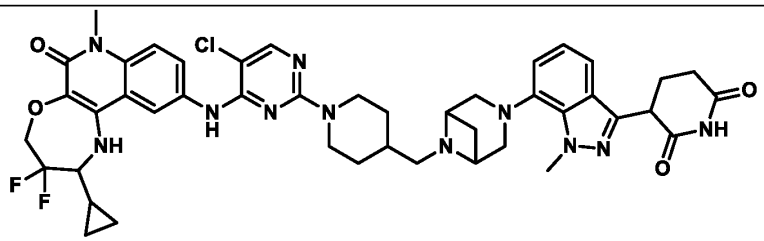
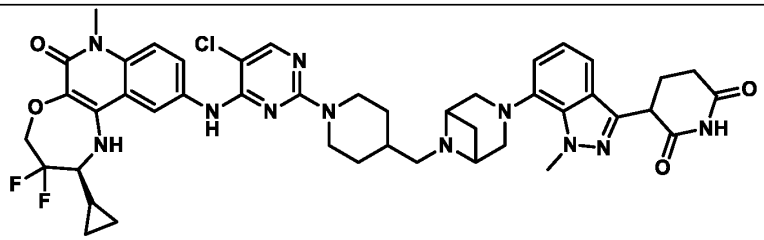
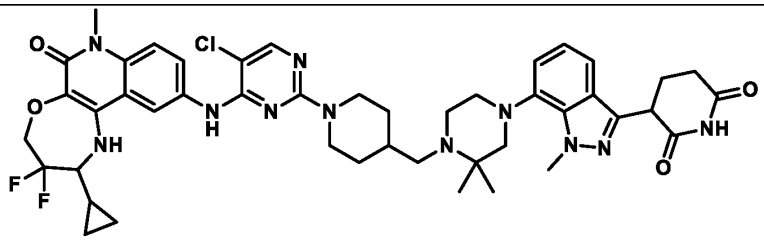
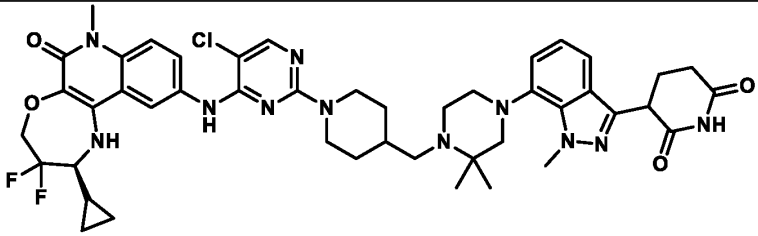
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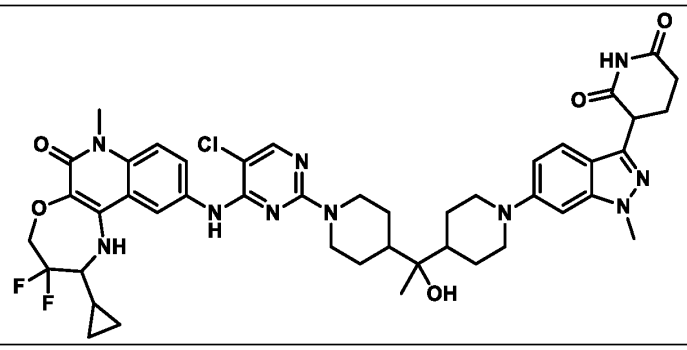
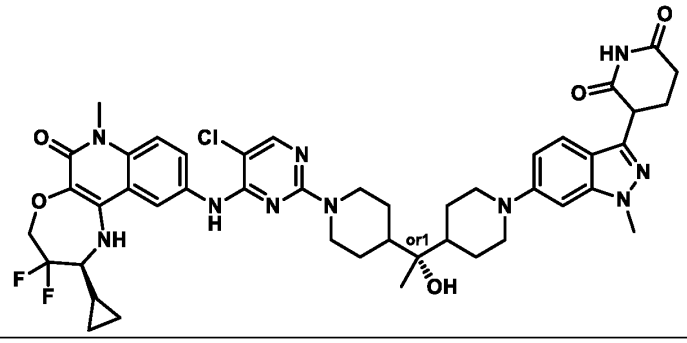
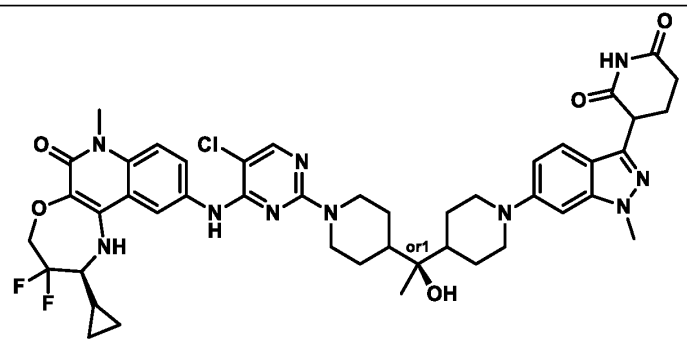
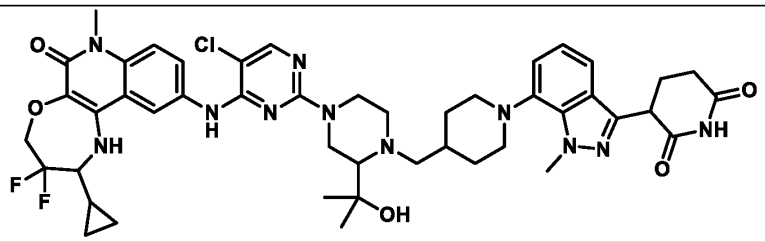
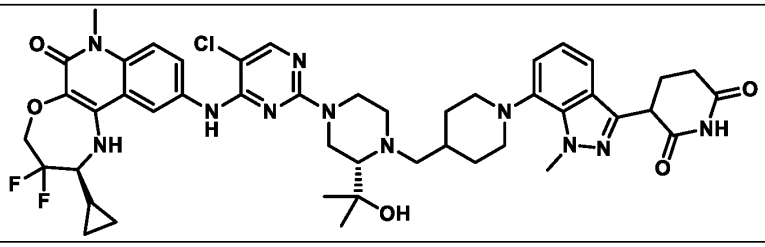
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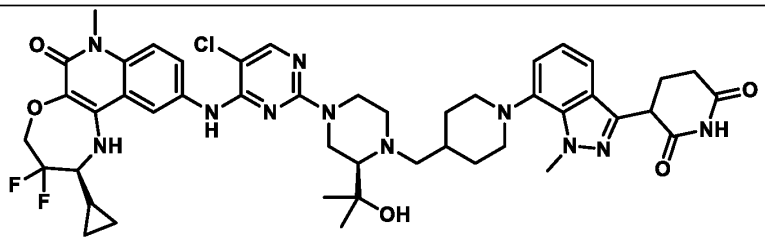
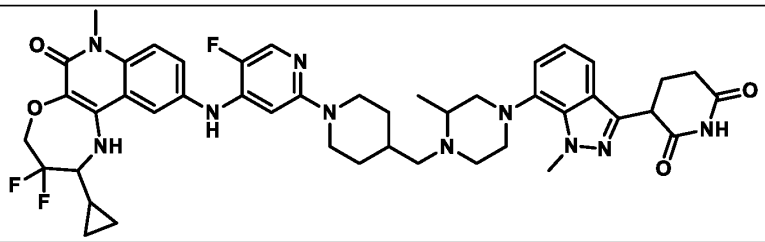
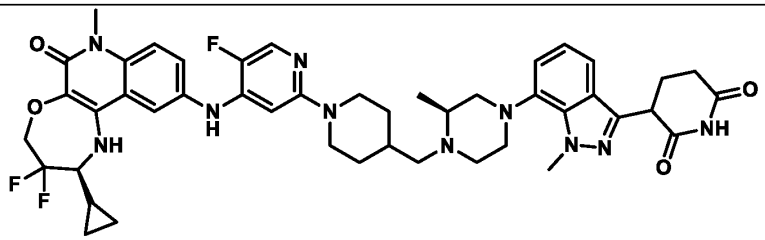
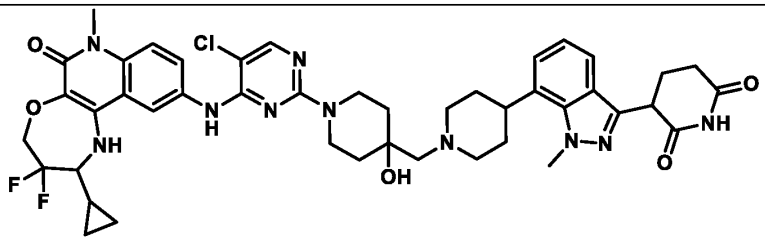
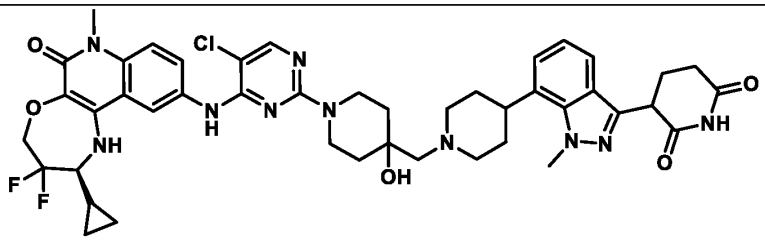
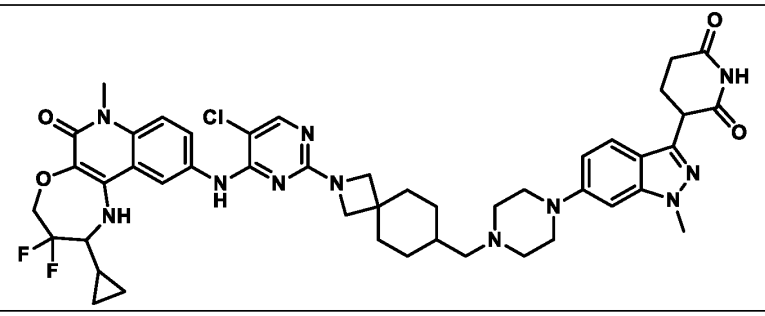
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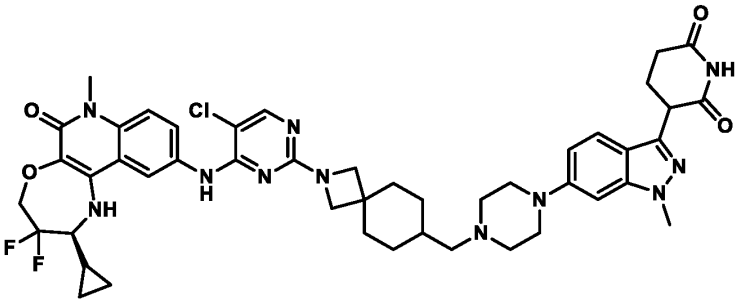
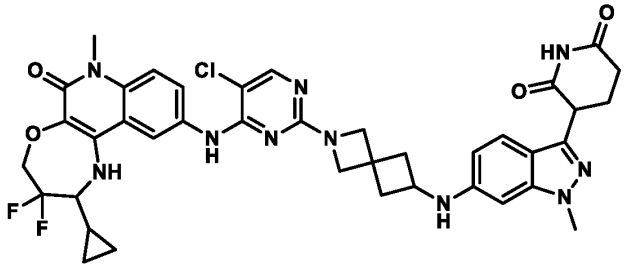
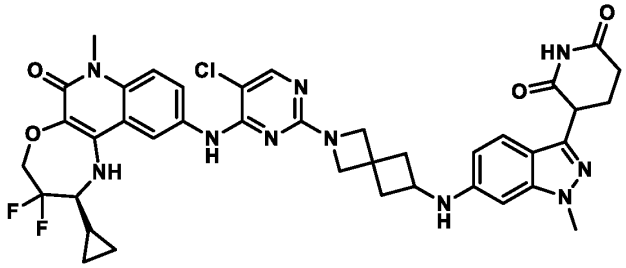
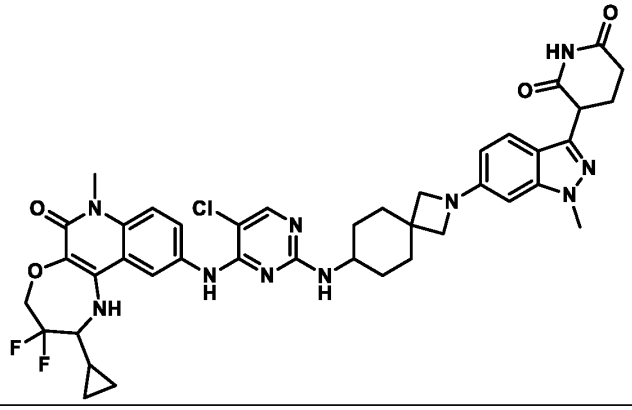
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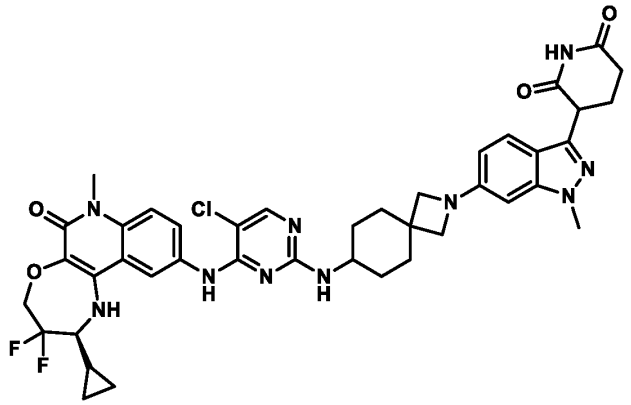
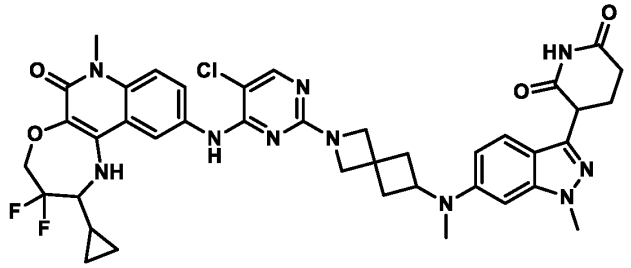
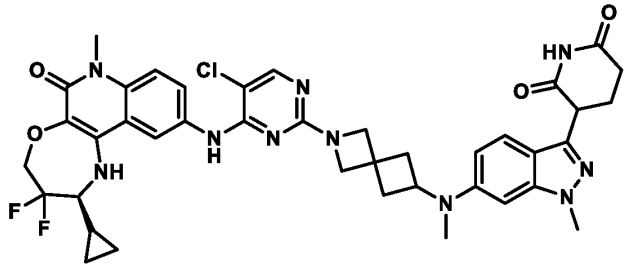
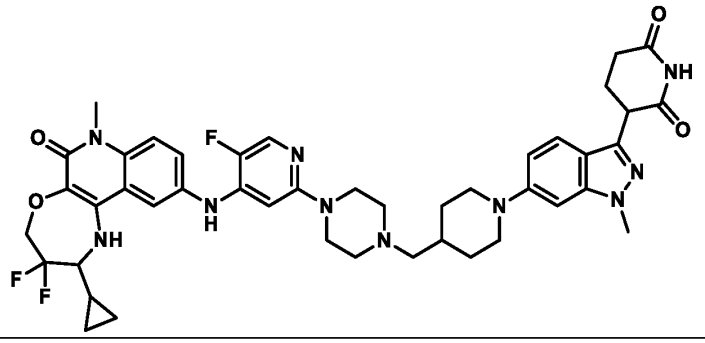
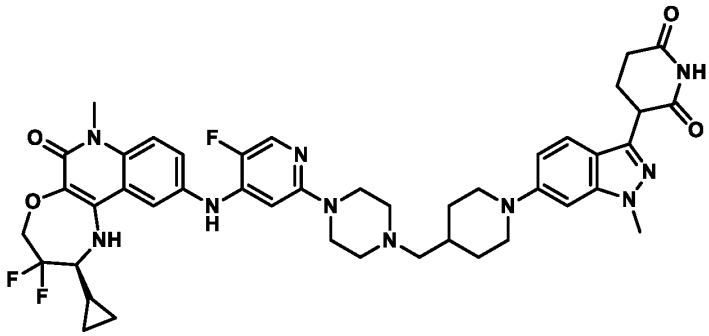
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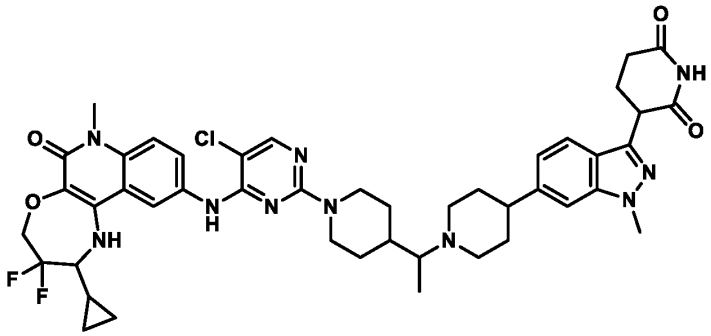
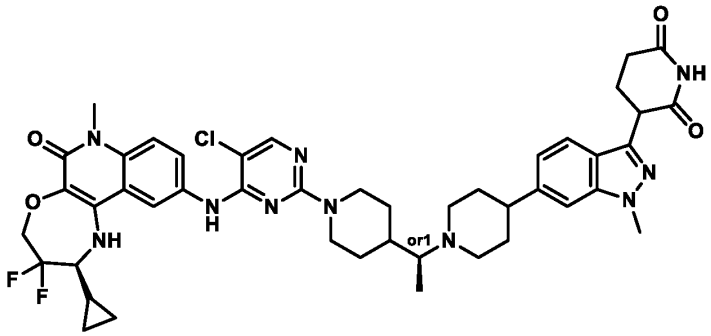
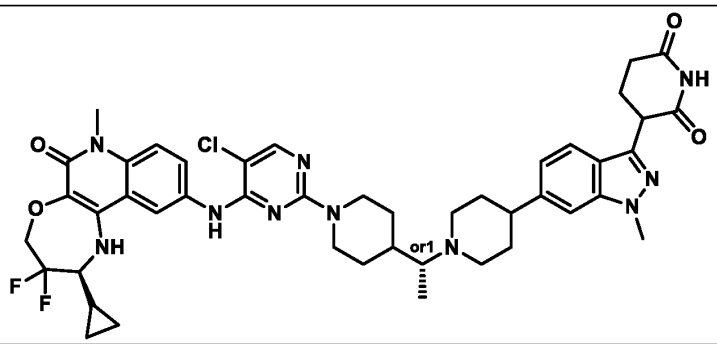
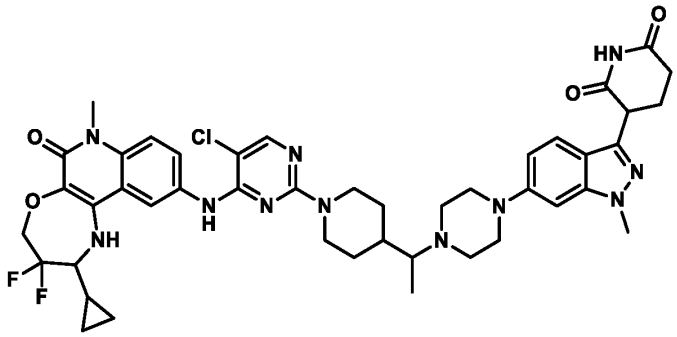
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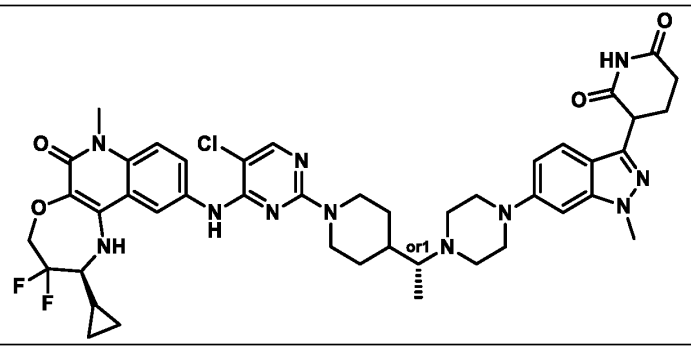
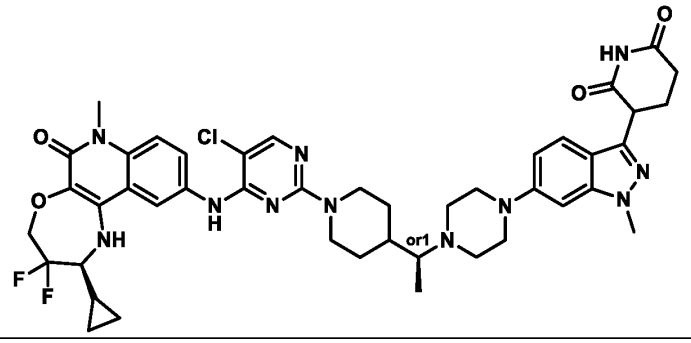
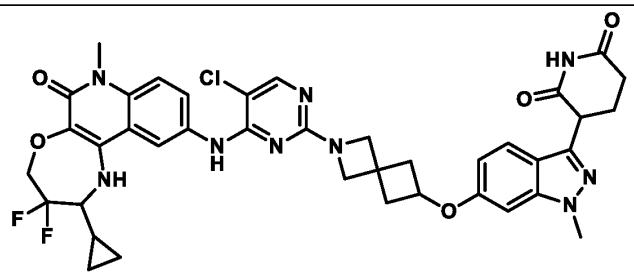
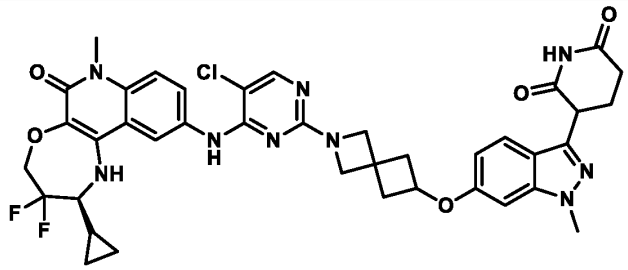
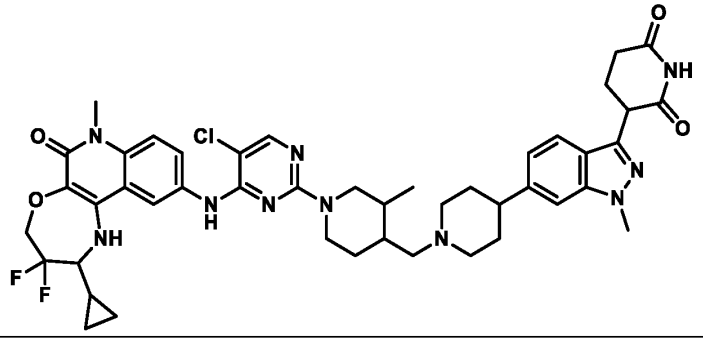
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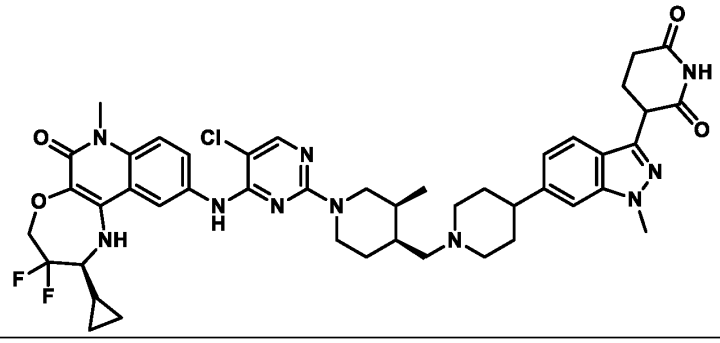
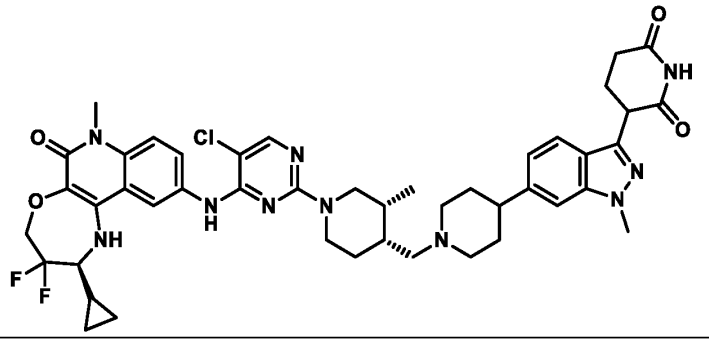
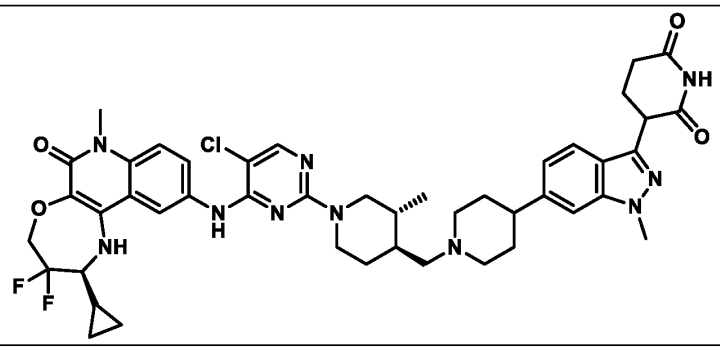
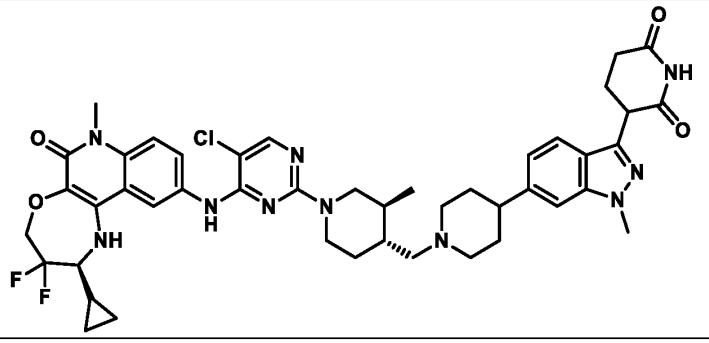
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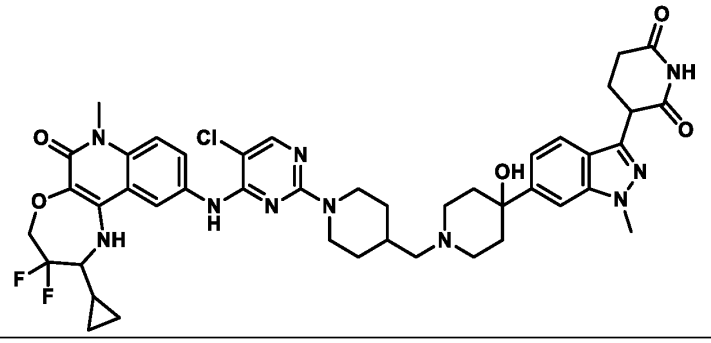
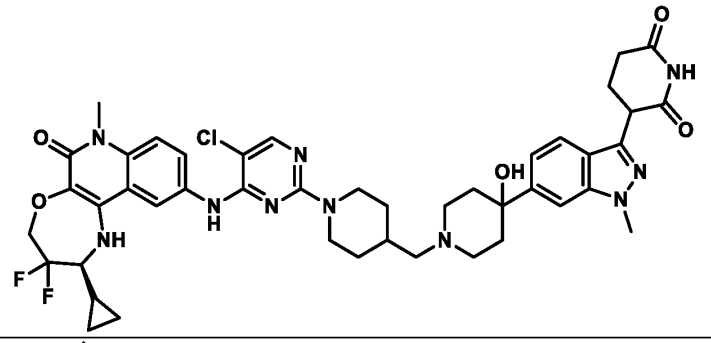
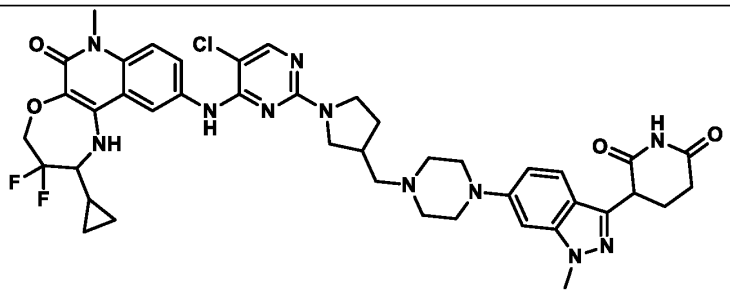
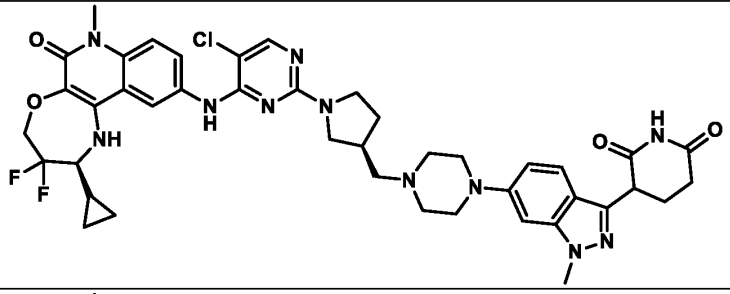
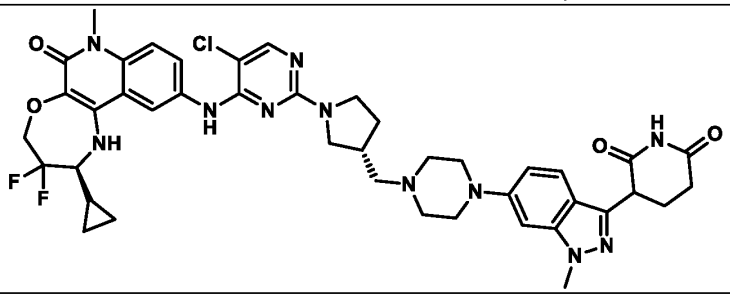
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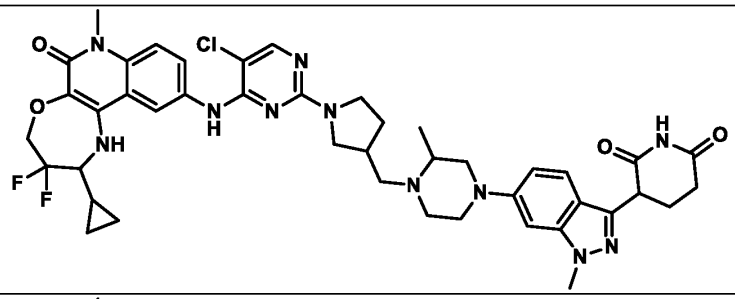
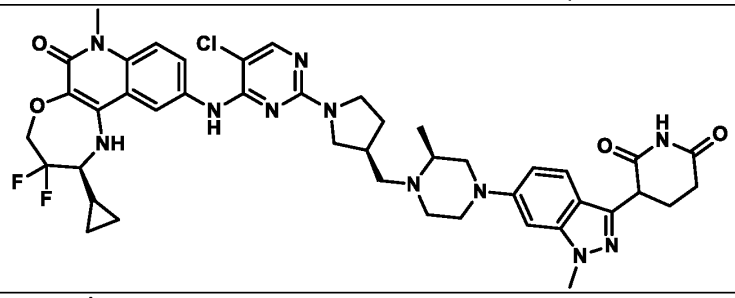
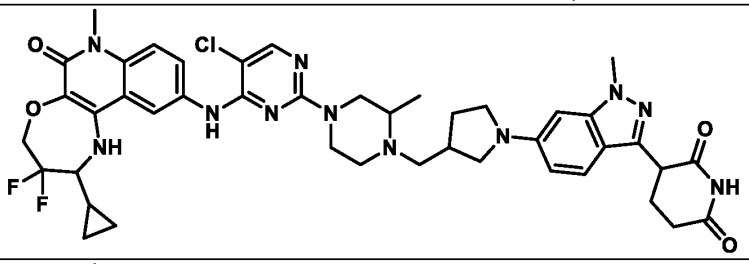
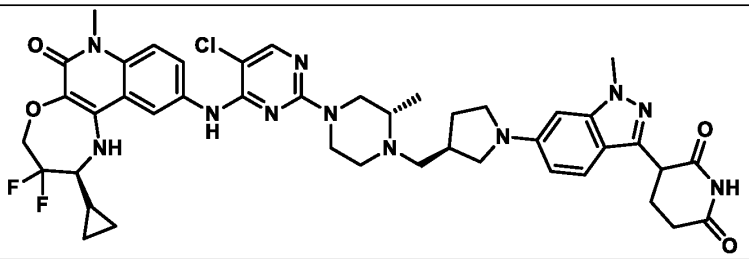
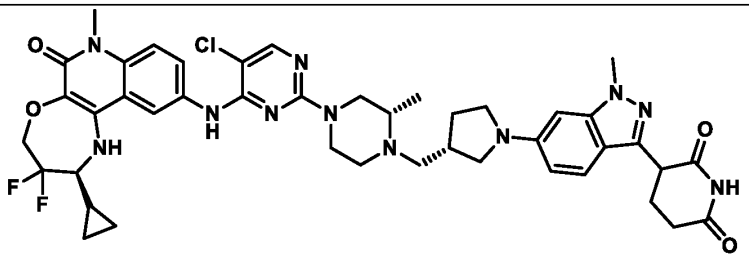
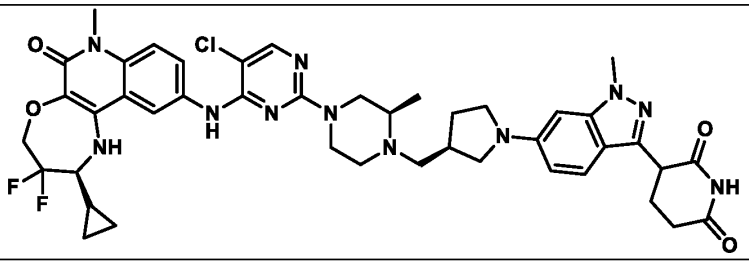
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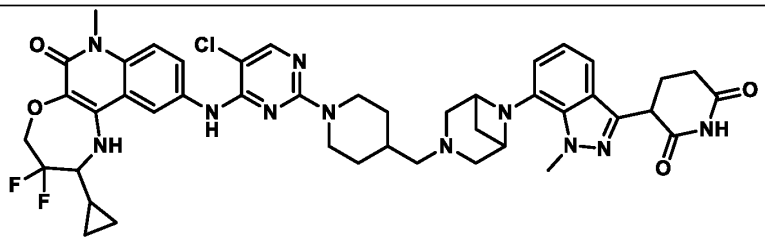
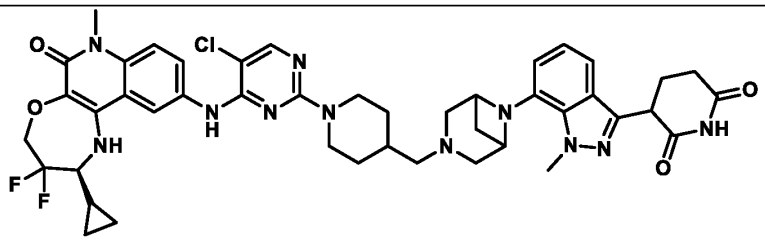
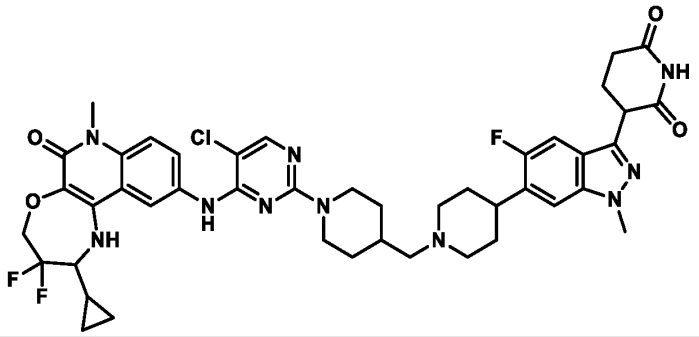
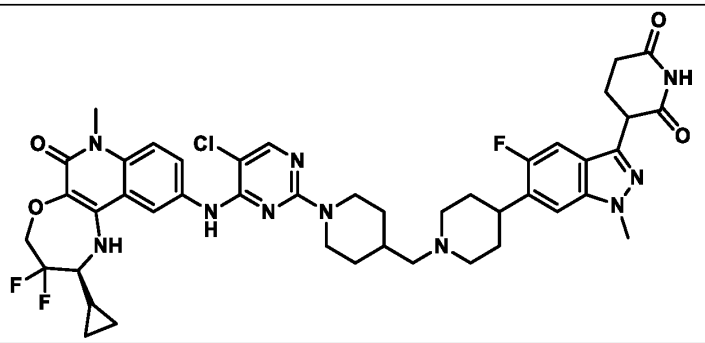
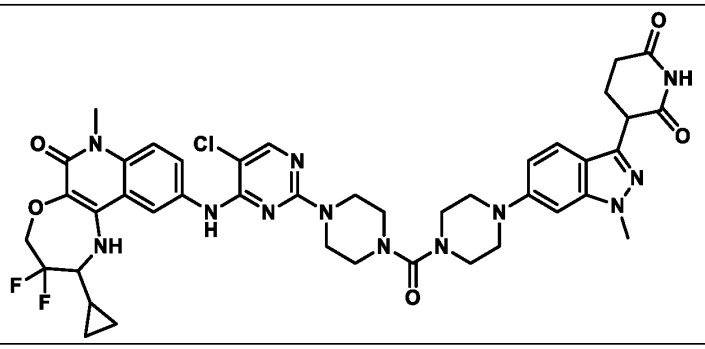
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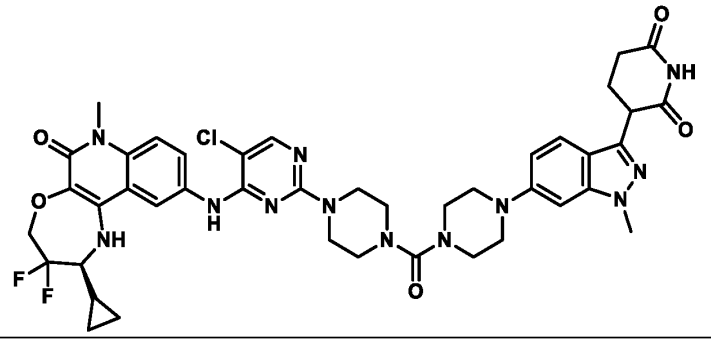
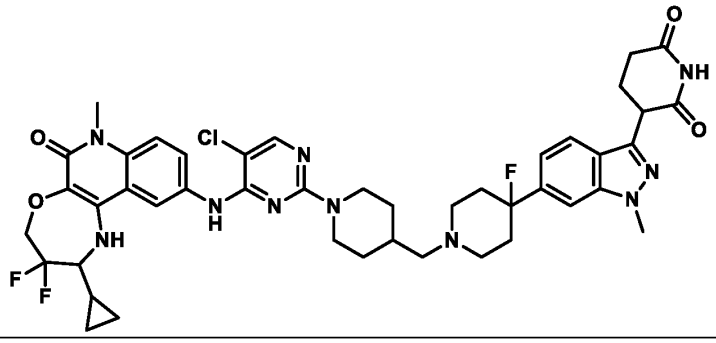
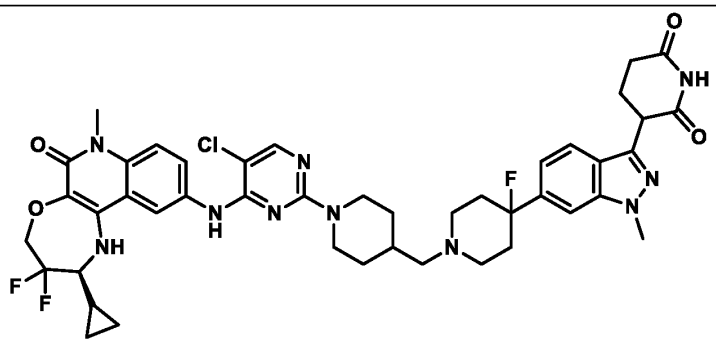
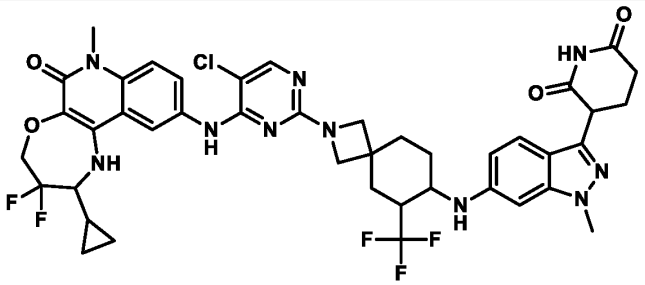
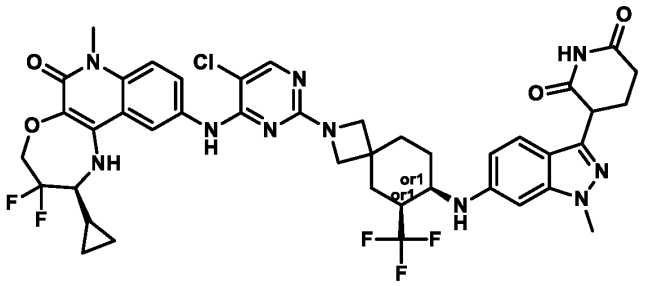
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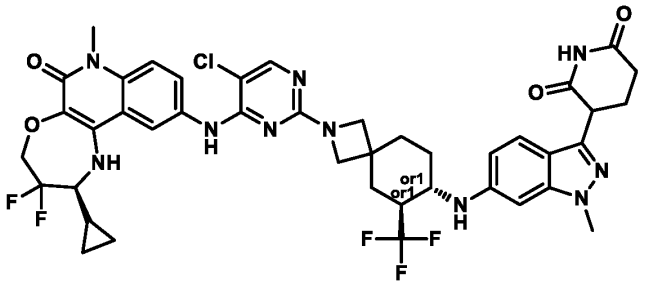
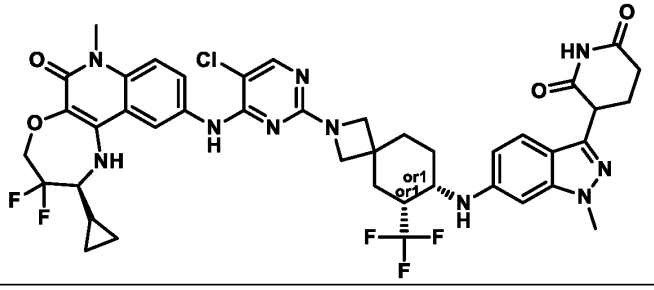
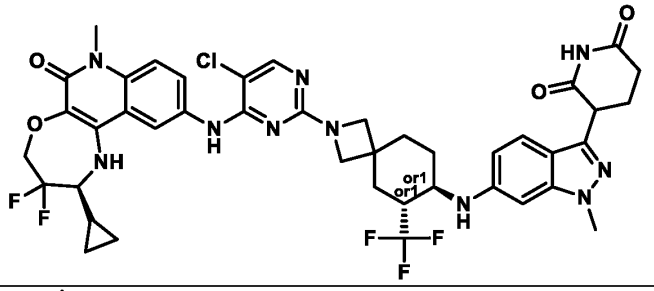
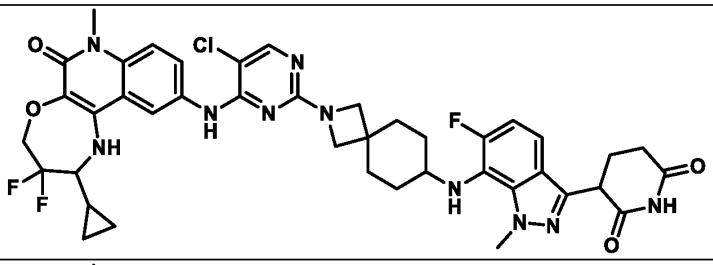
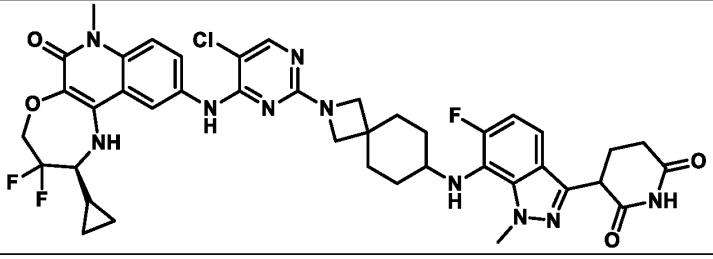
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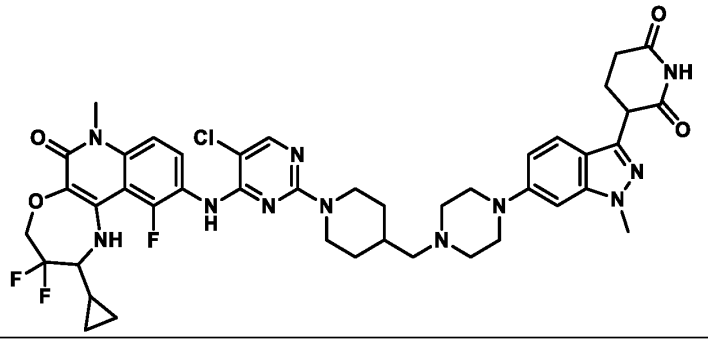
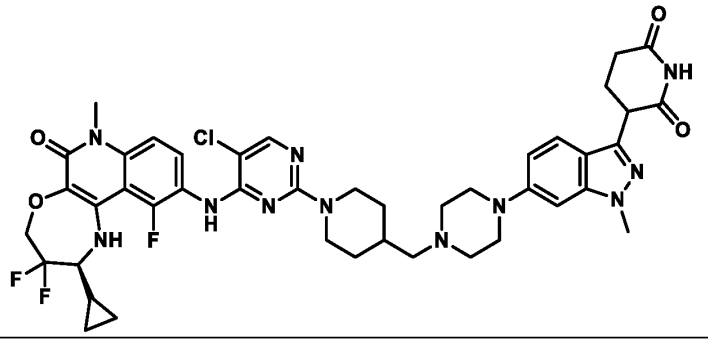
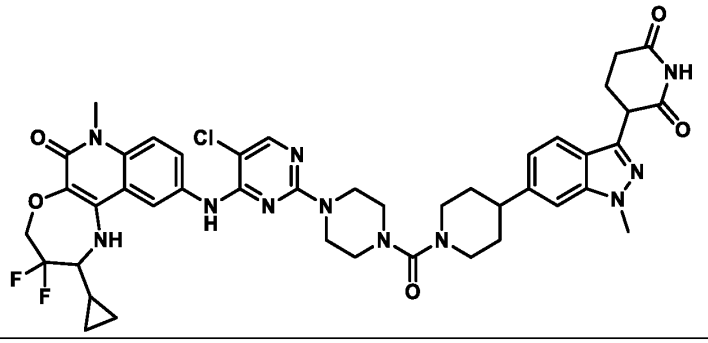
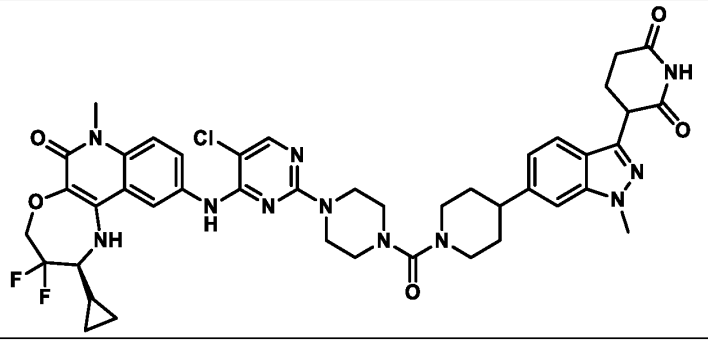
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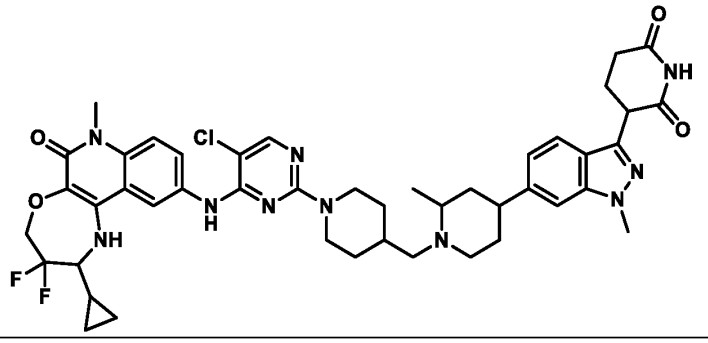
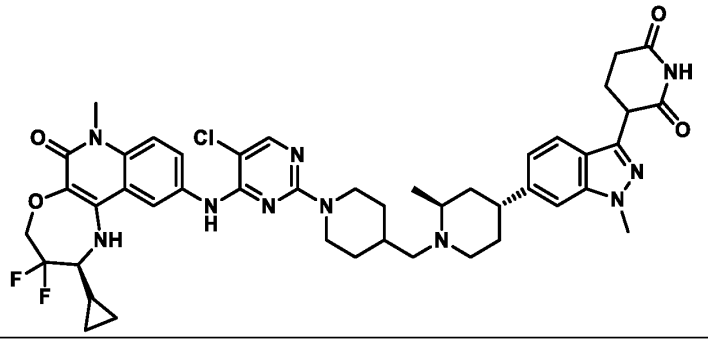
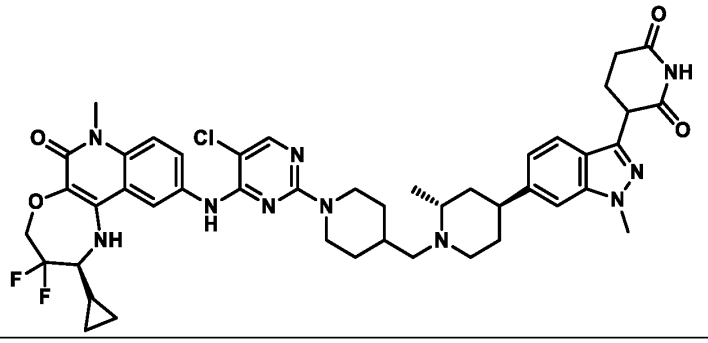
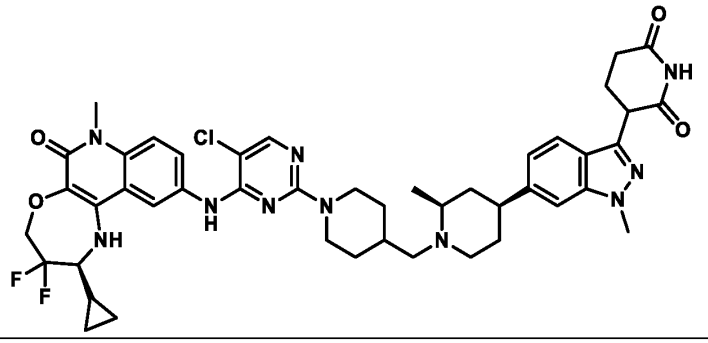
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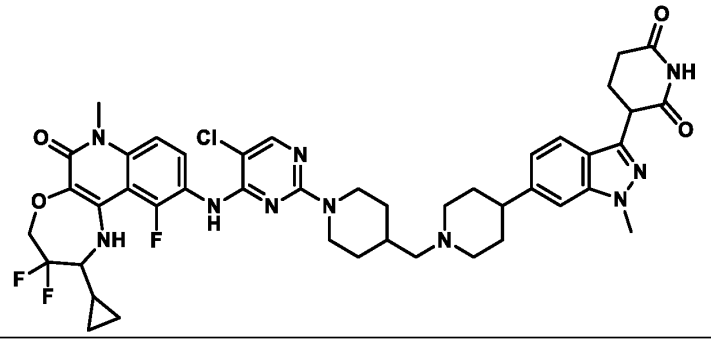
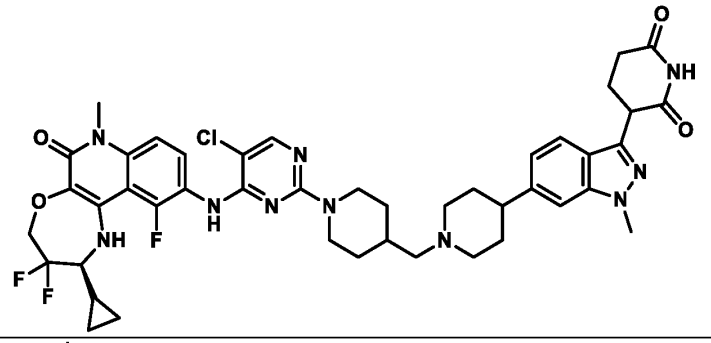
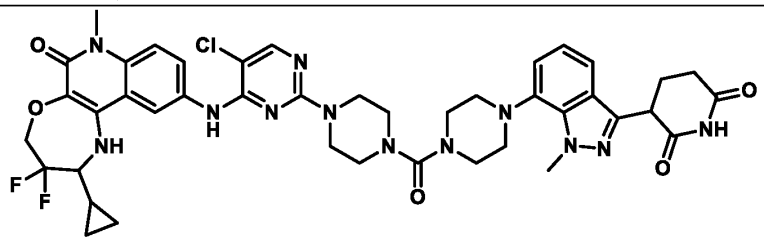
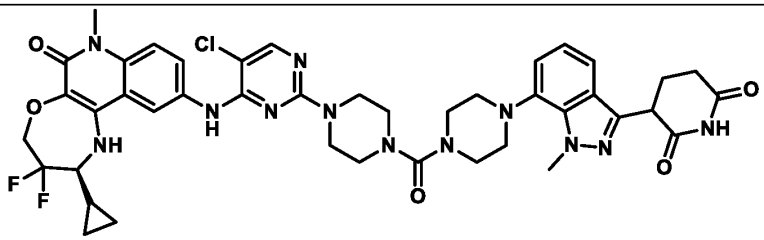
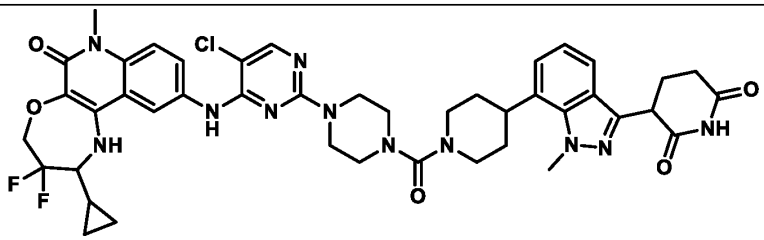
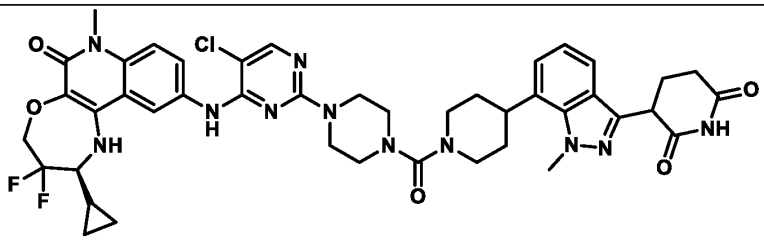
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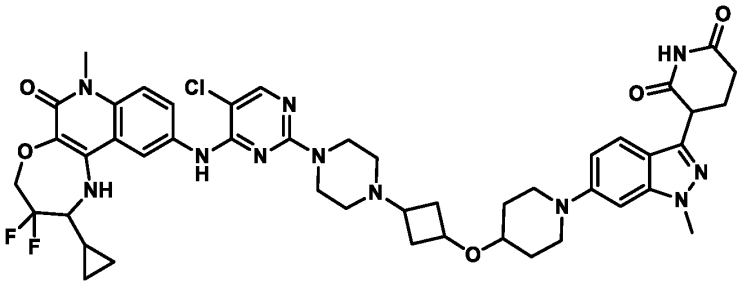
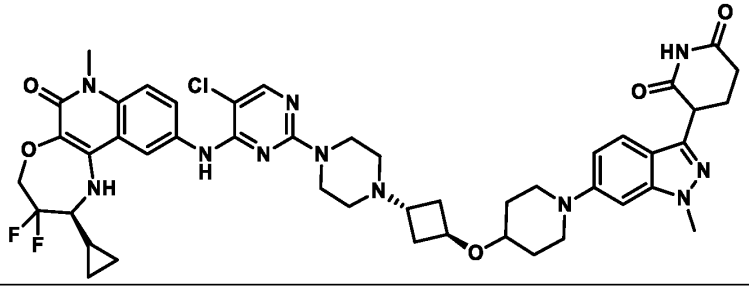
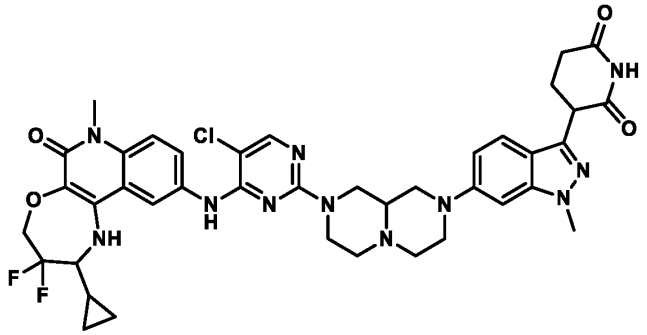
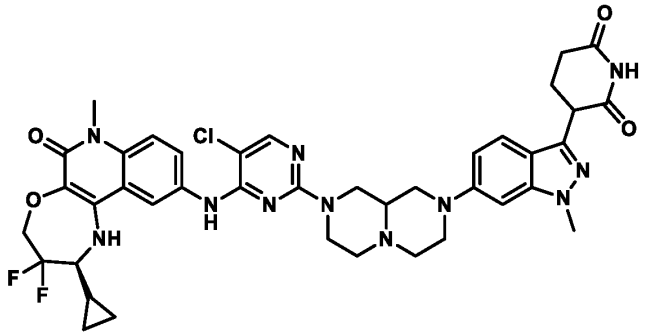
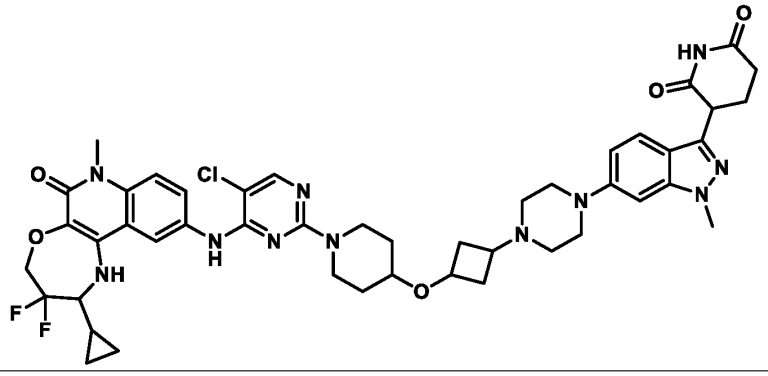
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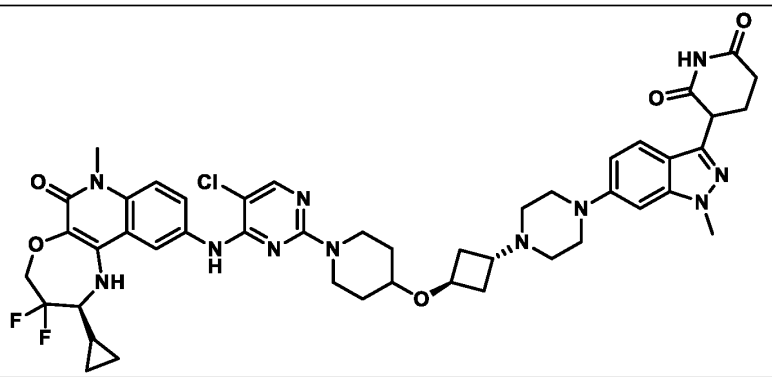
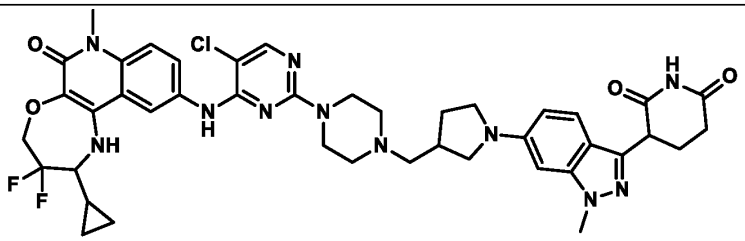
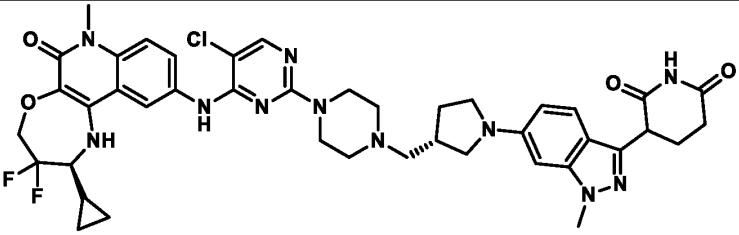
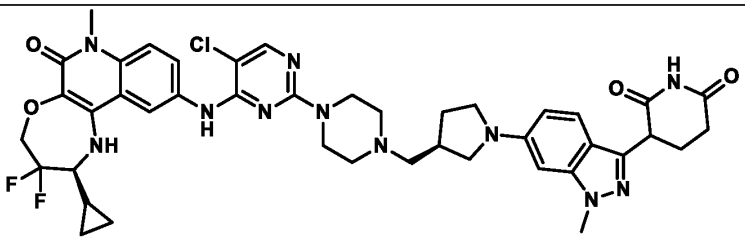
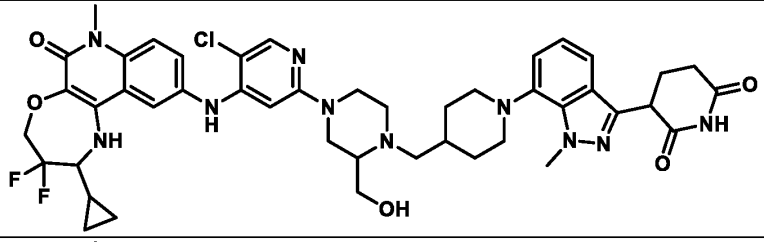
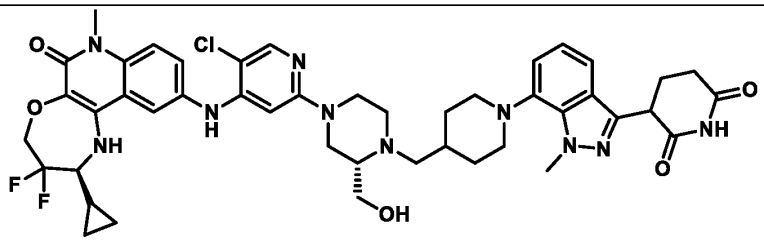
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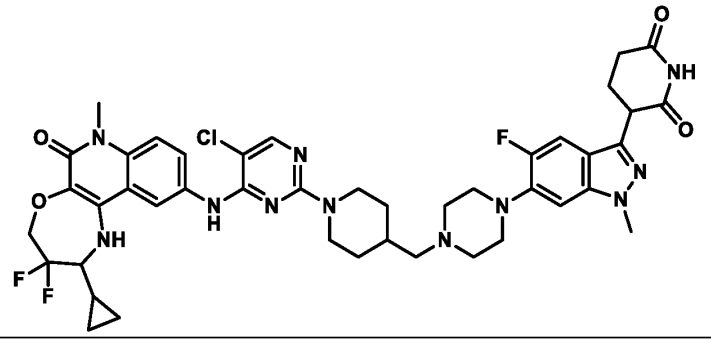
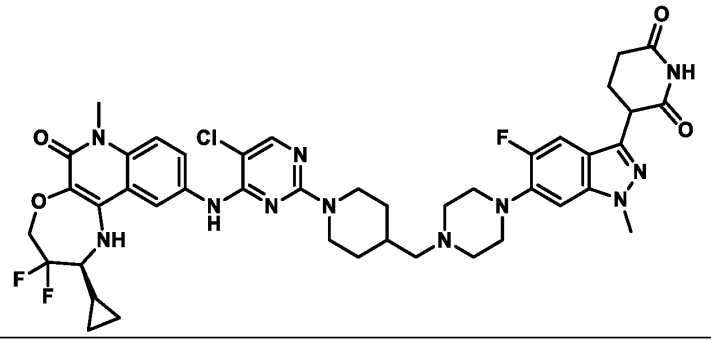
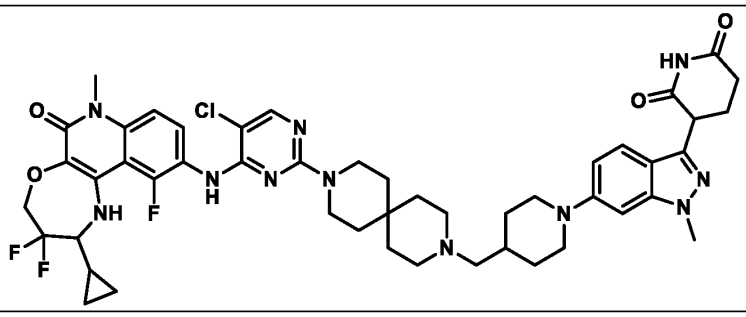
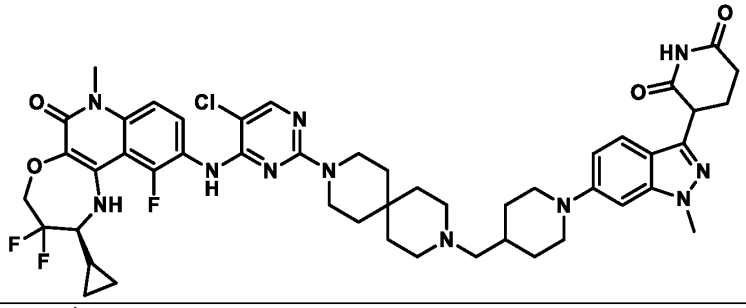
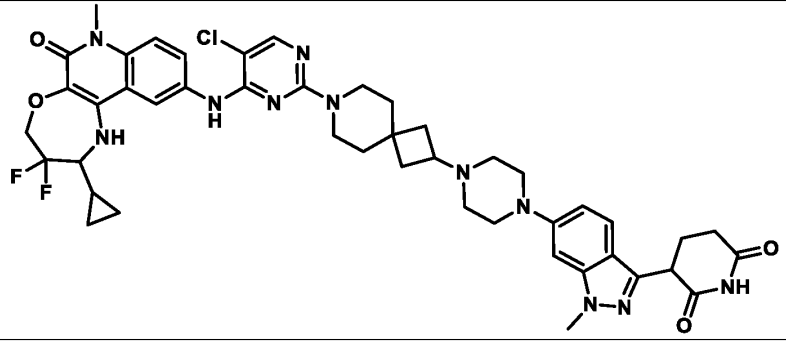
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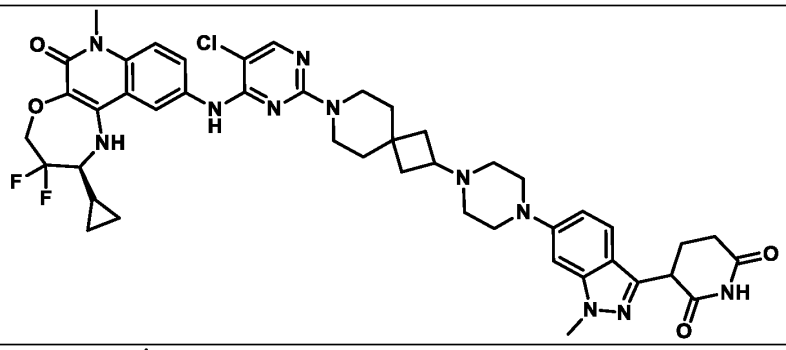
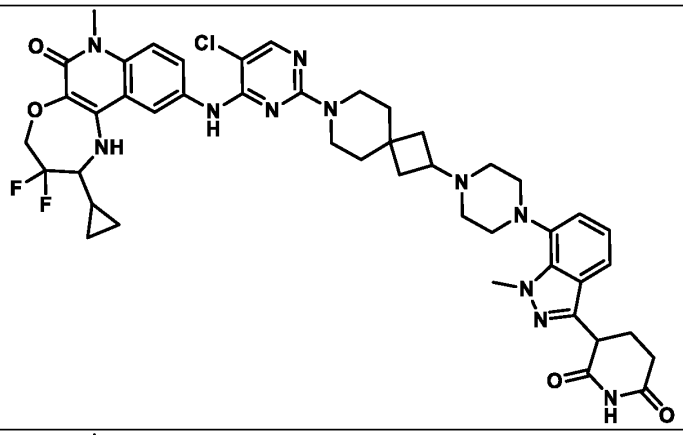
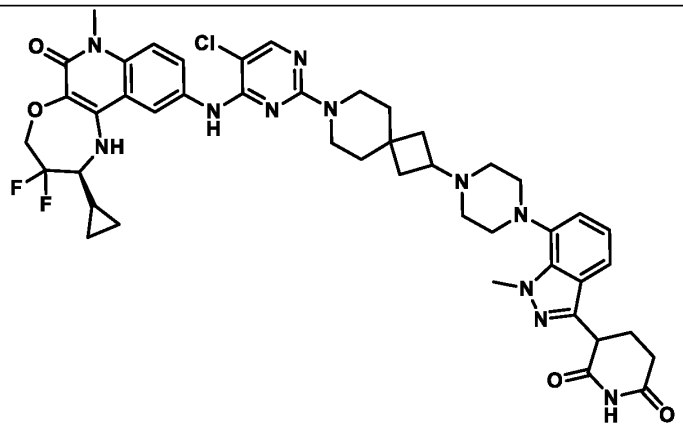
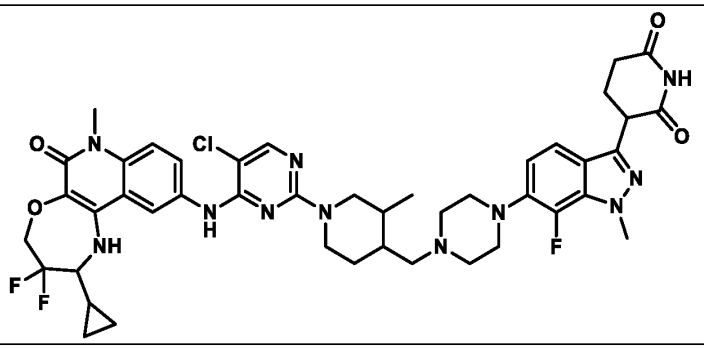
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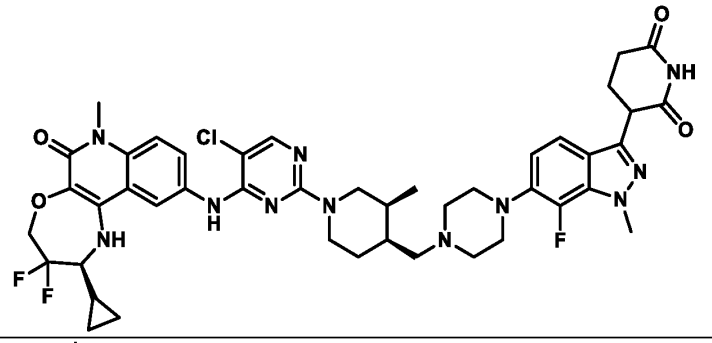
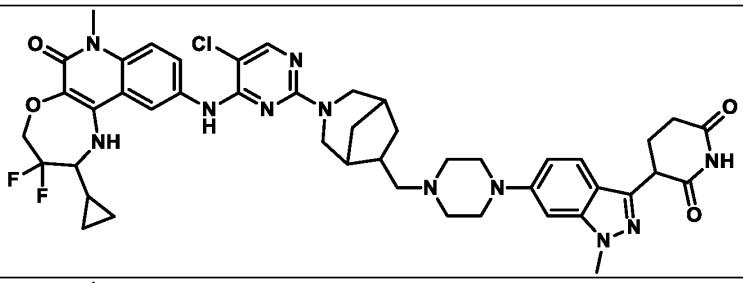
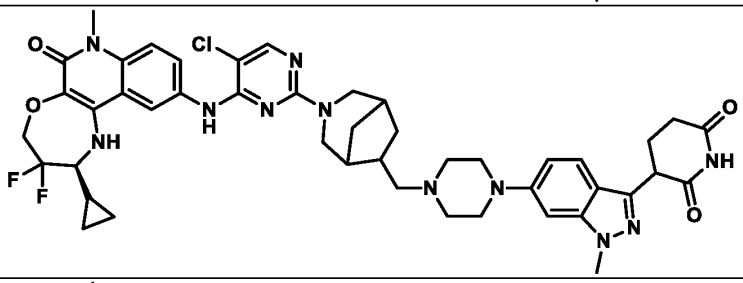
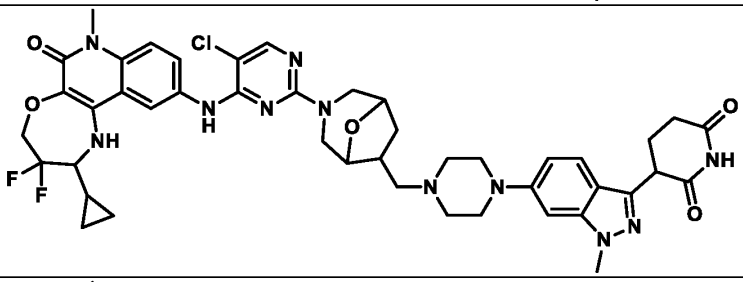
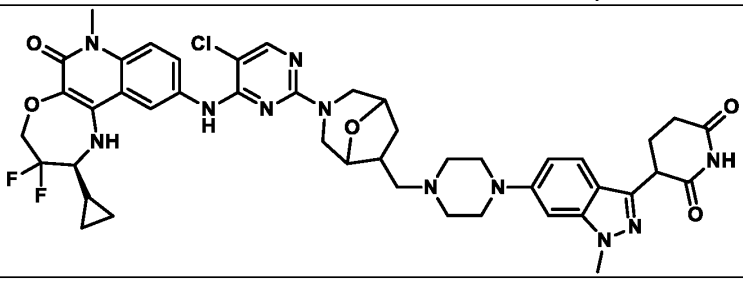
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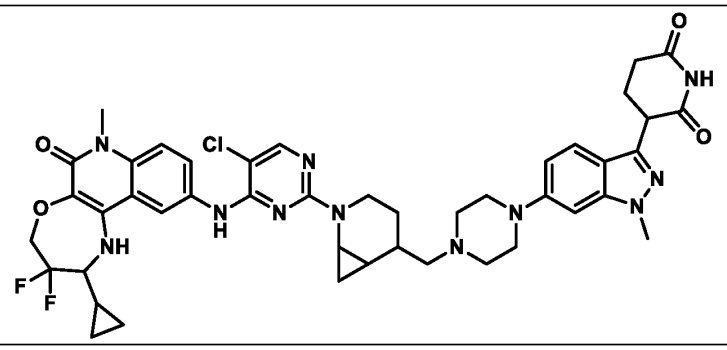
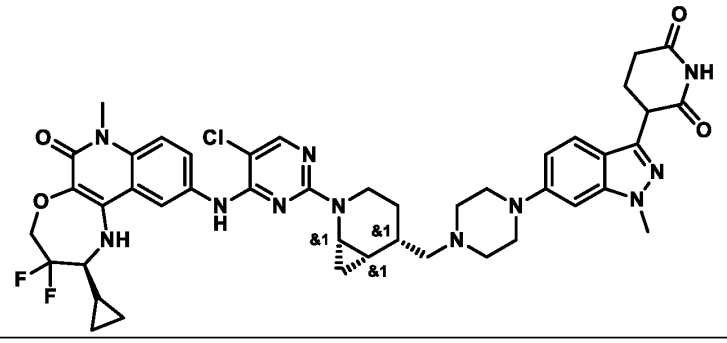
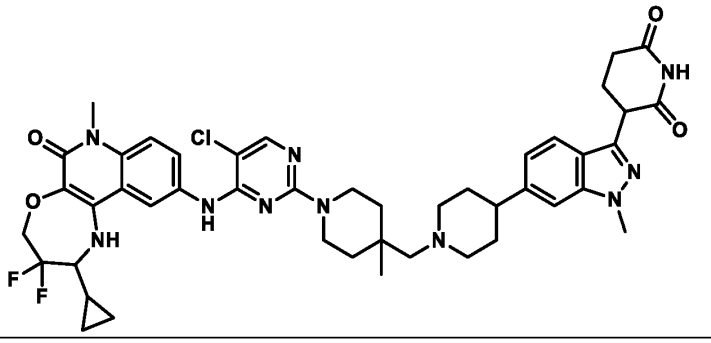
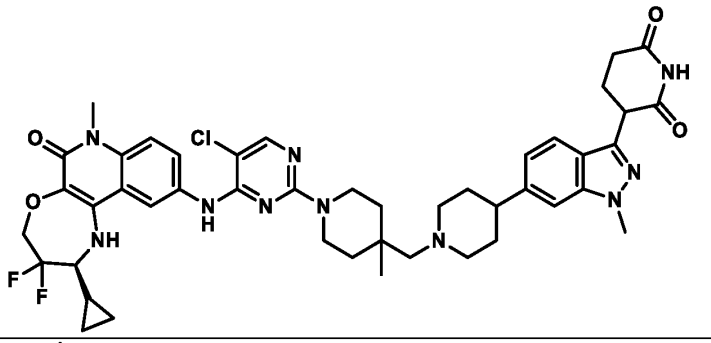
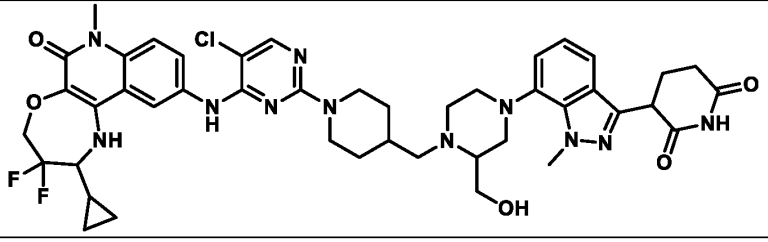
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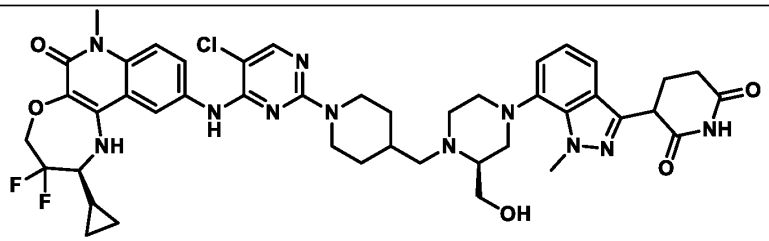
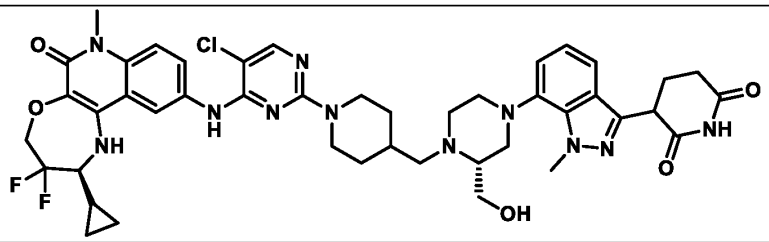
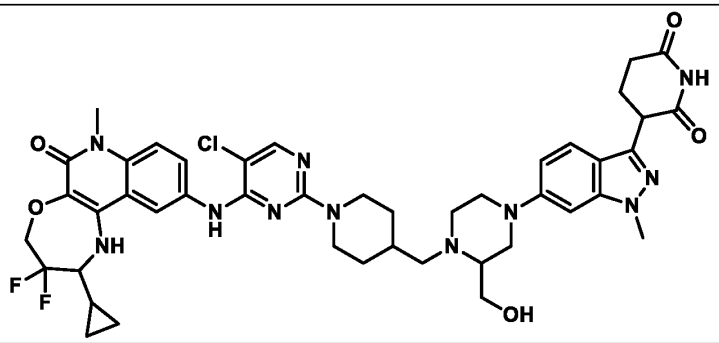
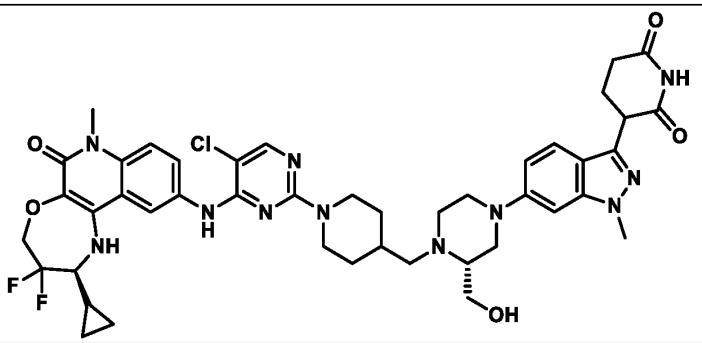
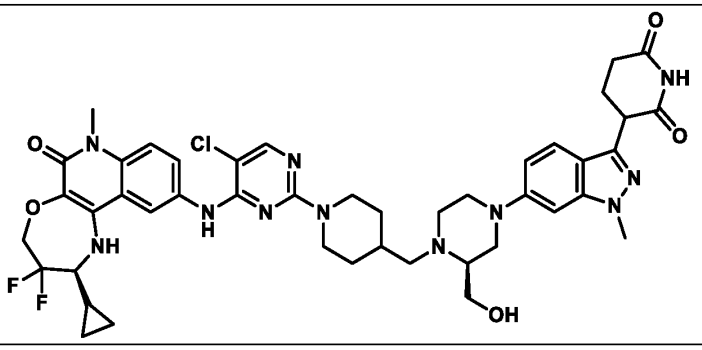
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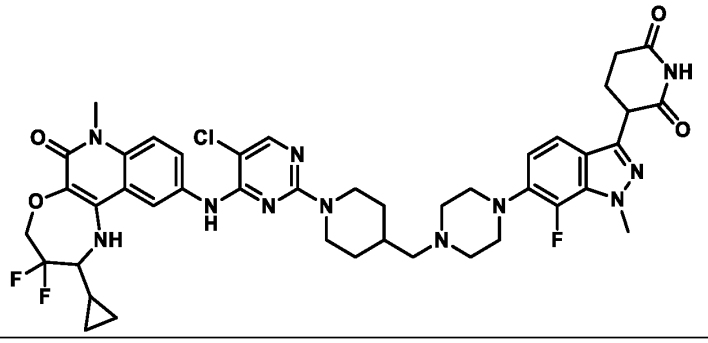
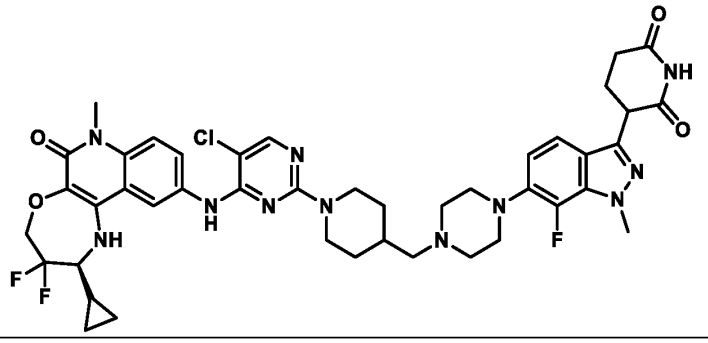
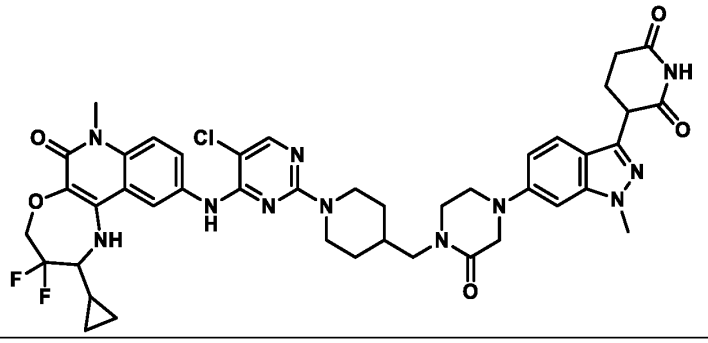
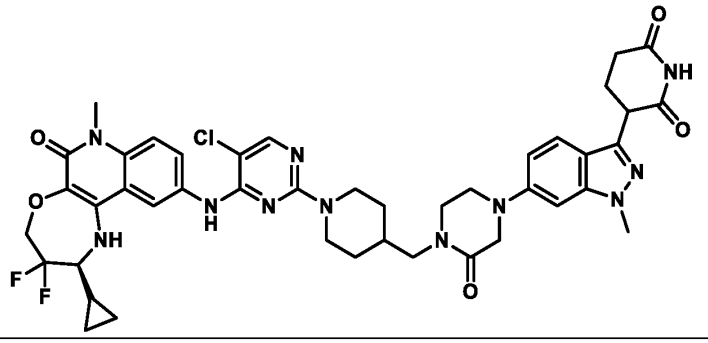
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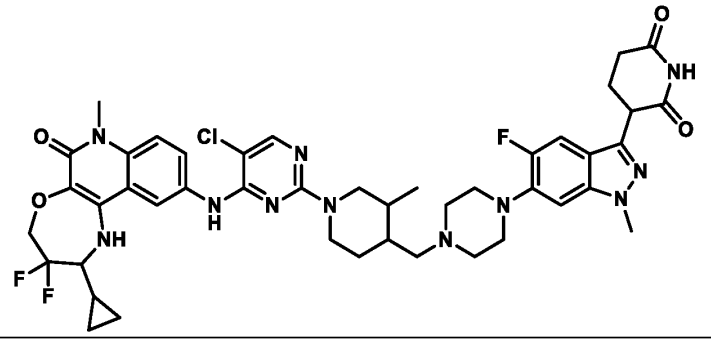
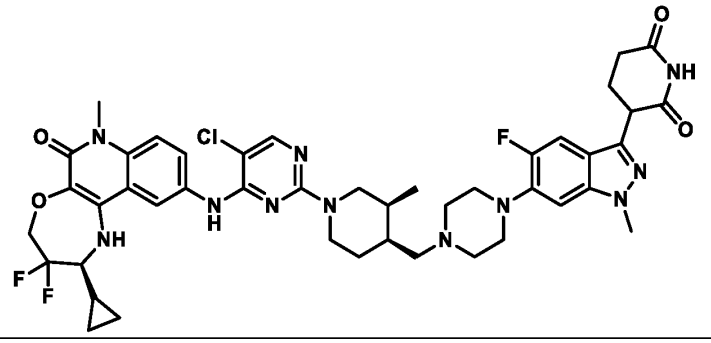
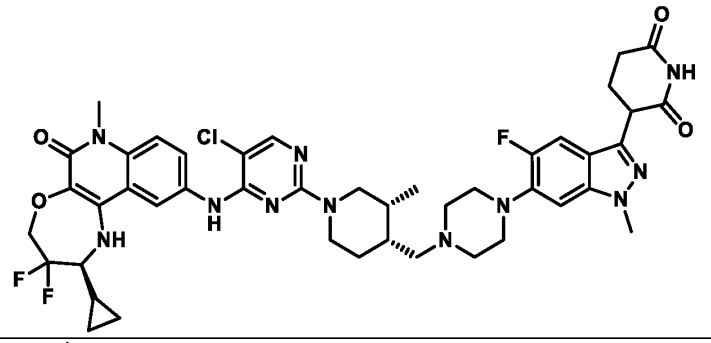
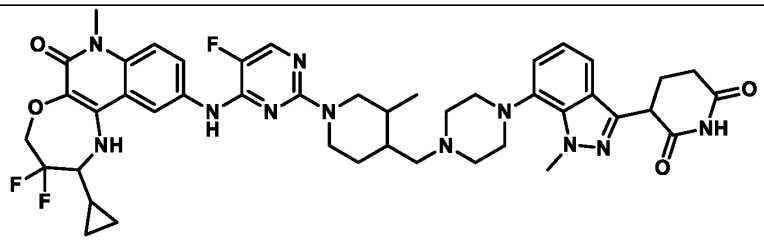
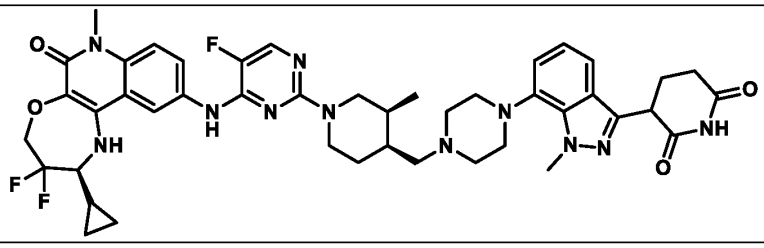
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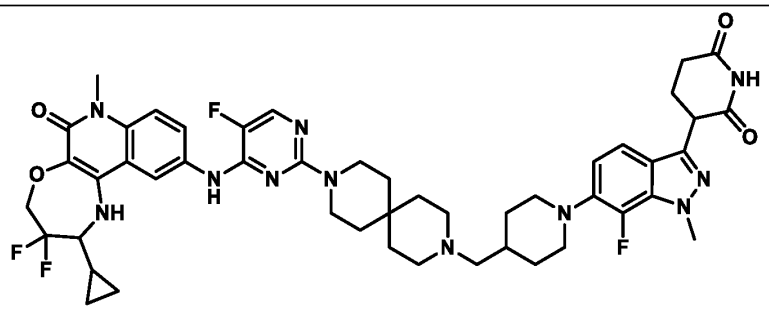
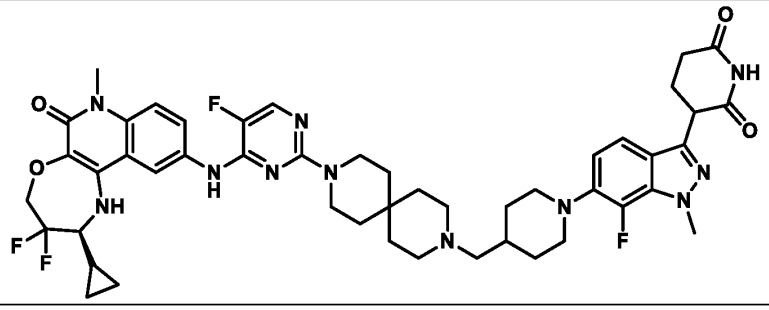
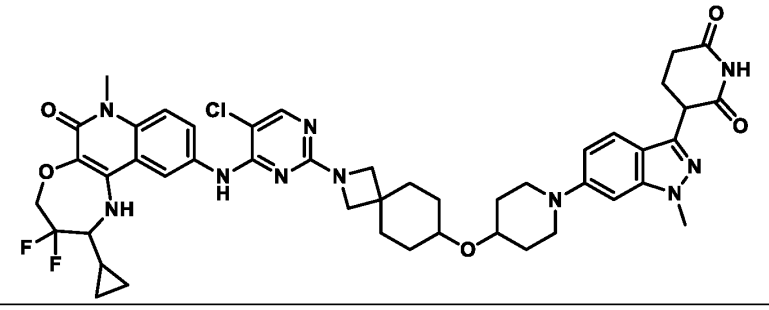
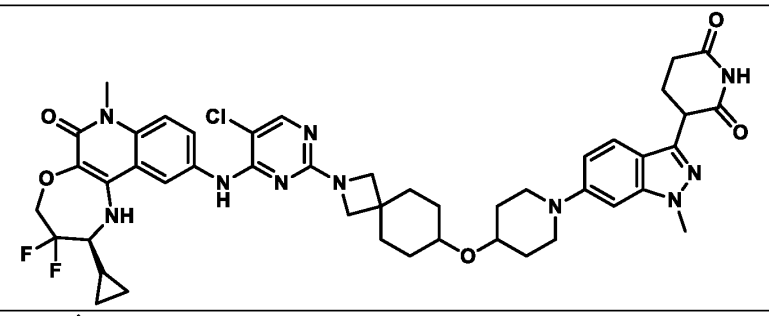
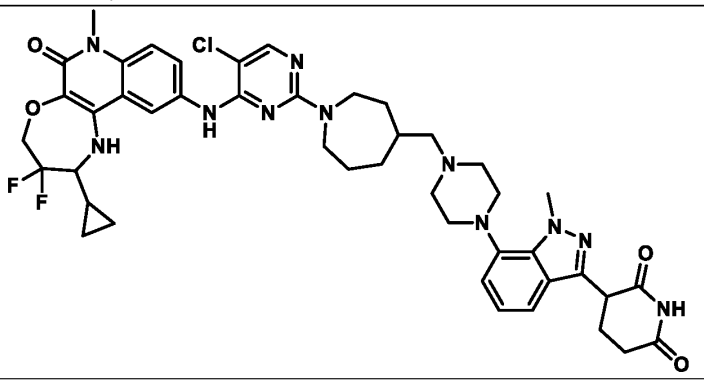
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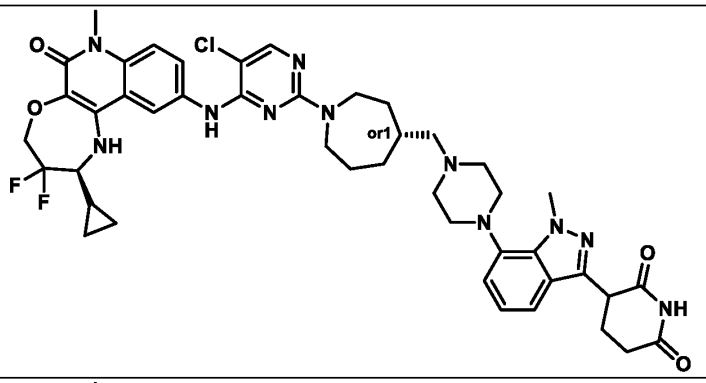
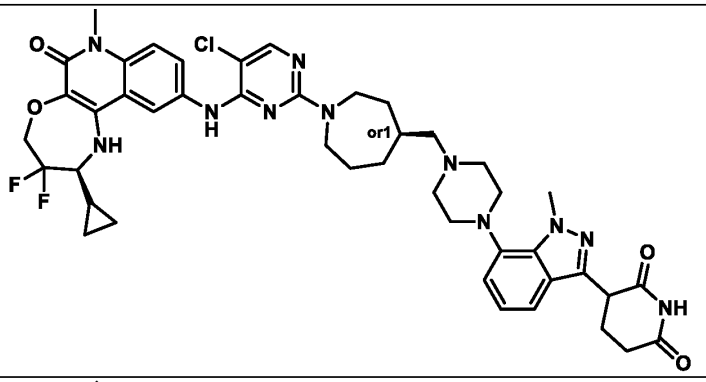
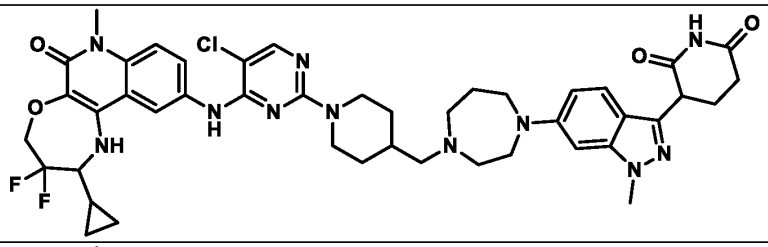
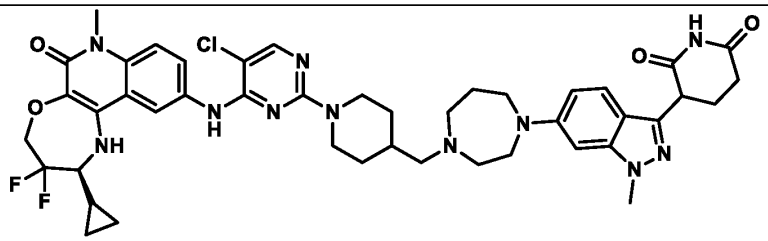
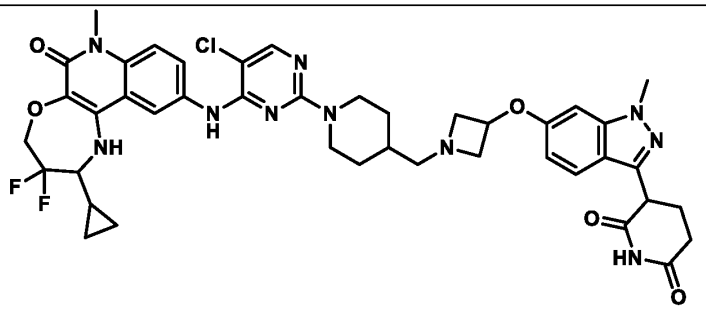
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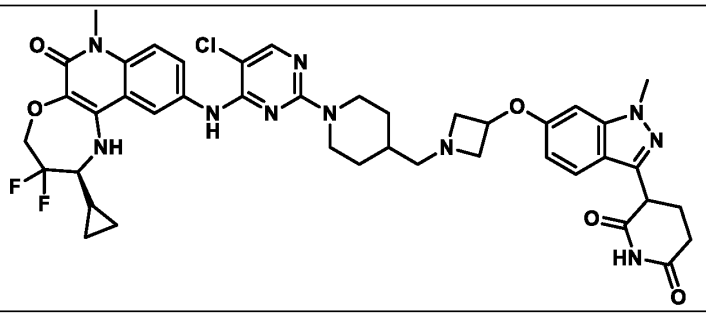
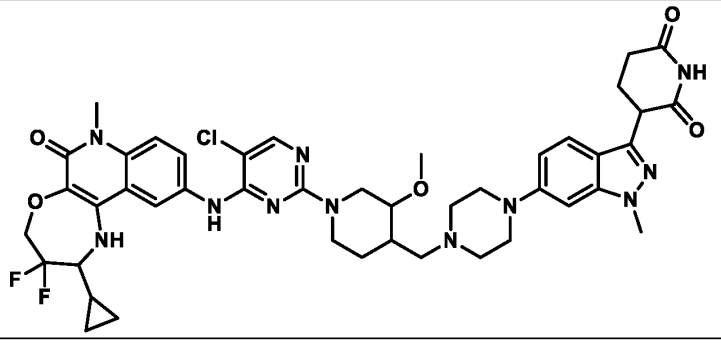
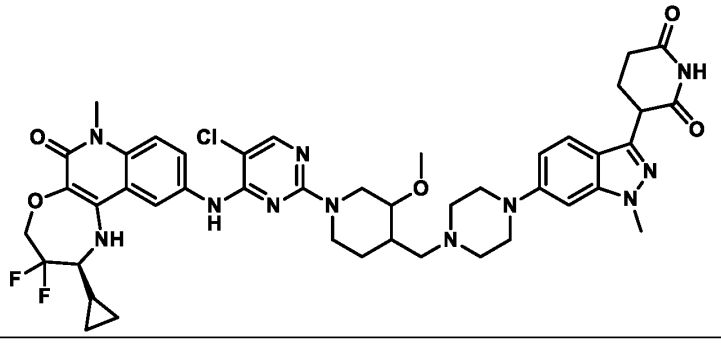
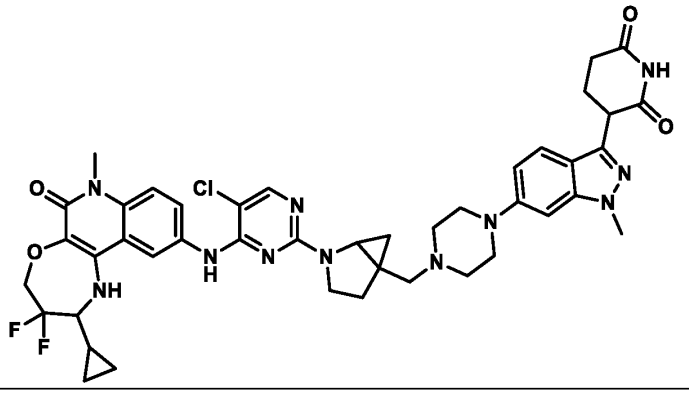
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R560b	

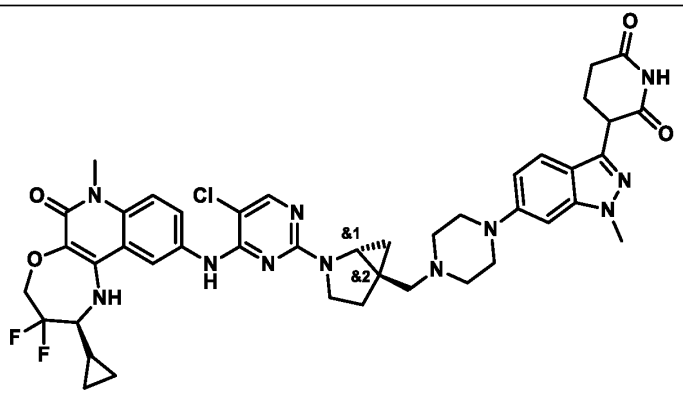
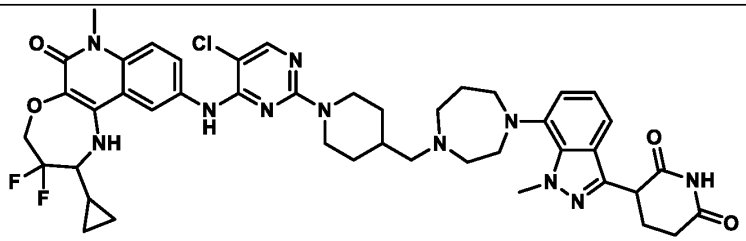
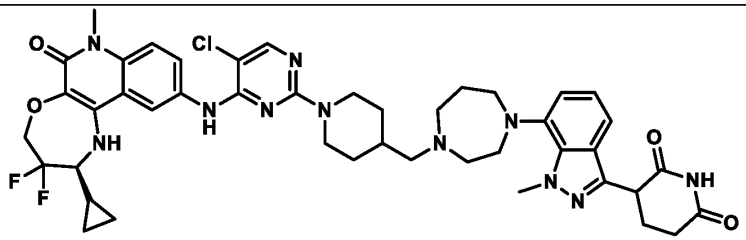
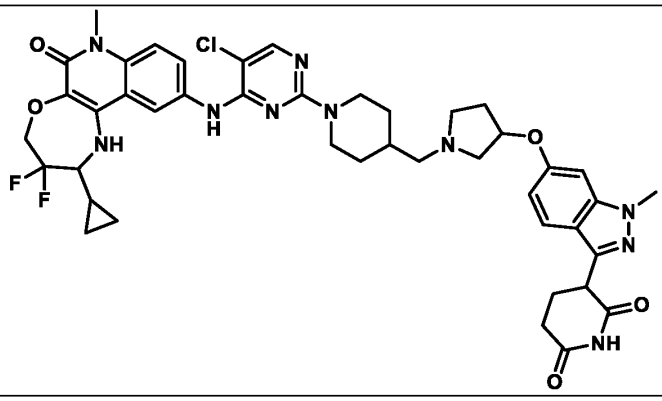
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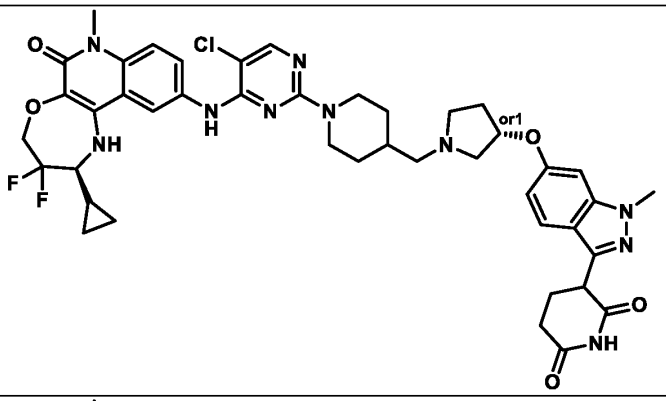
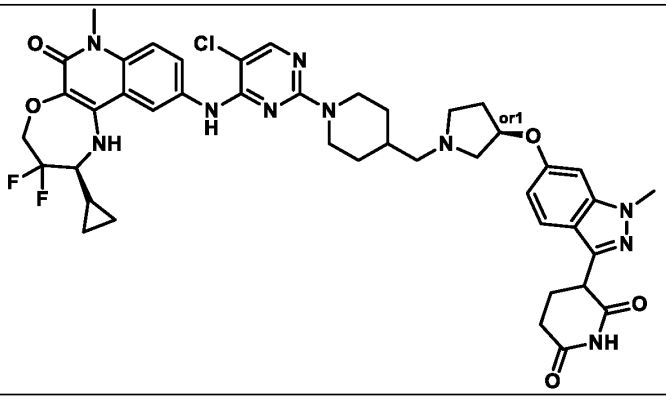
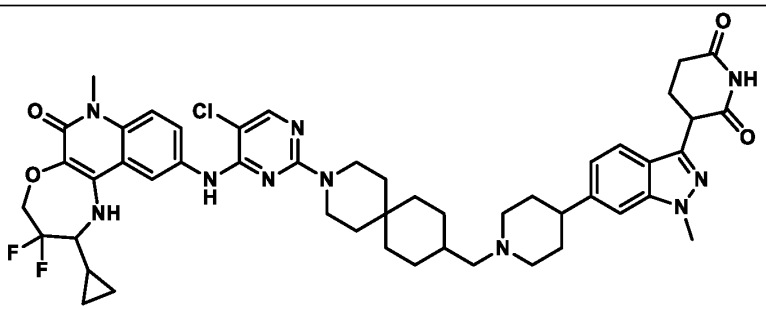
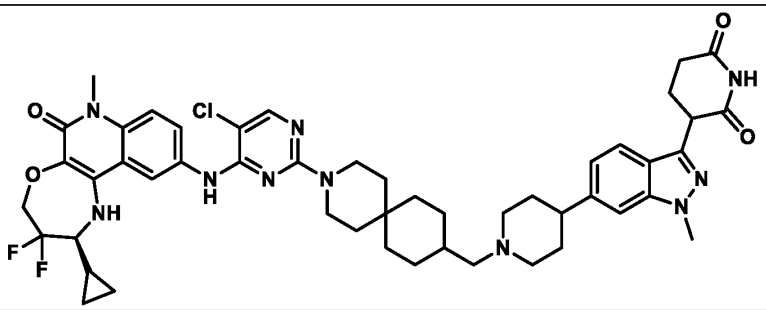
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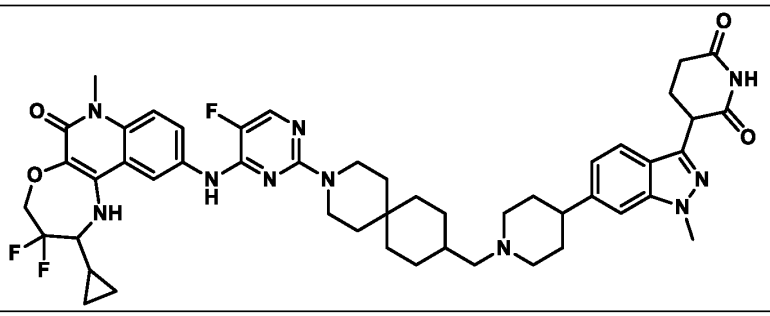
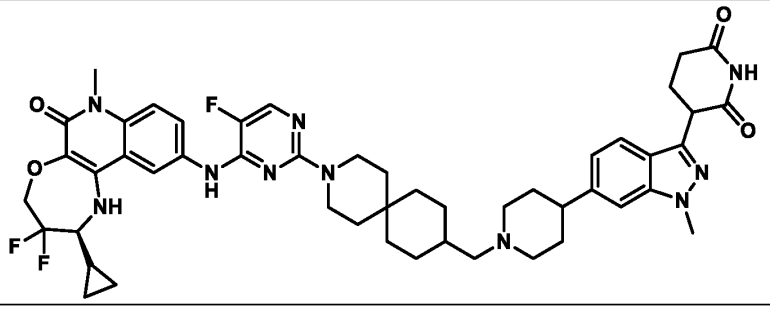
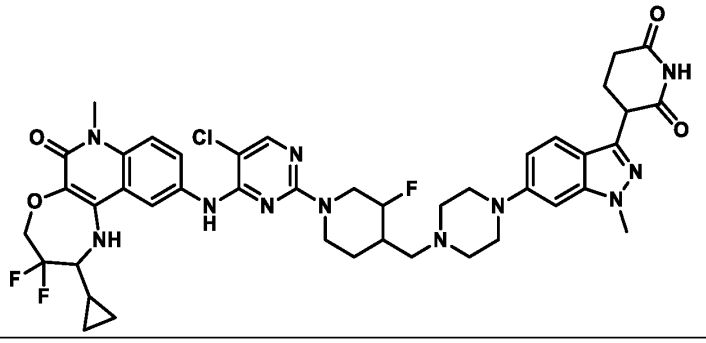
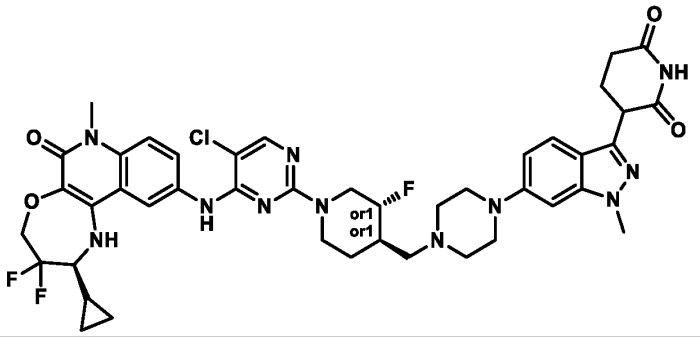
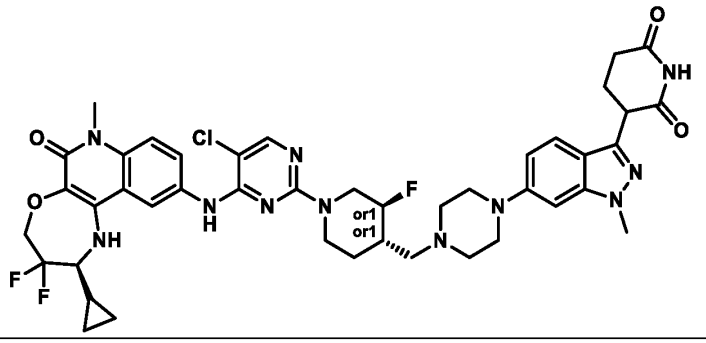
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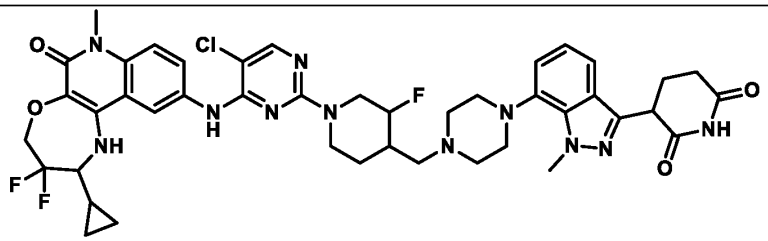
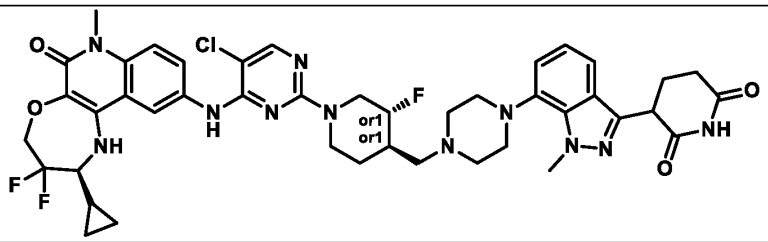
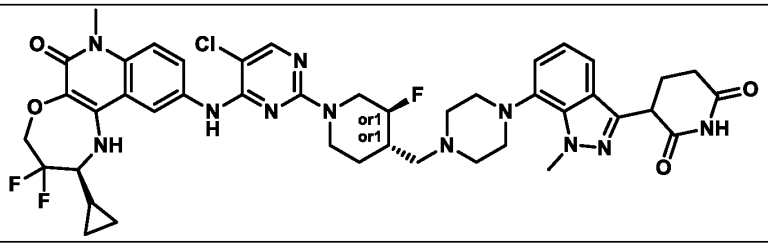
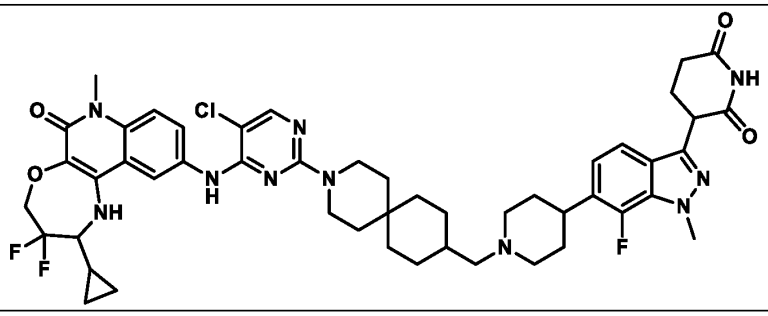
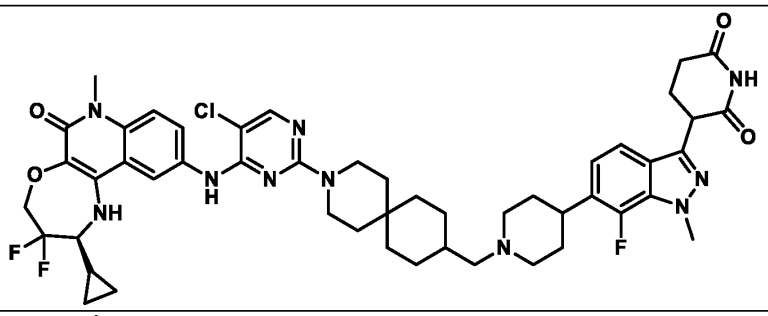
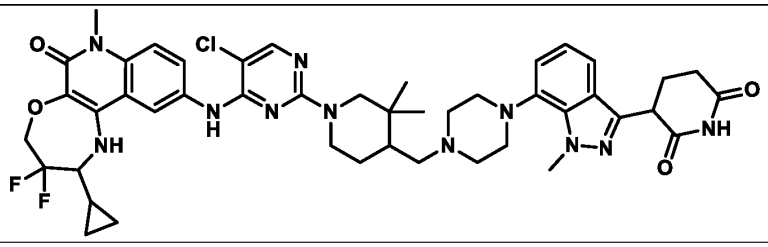
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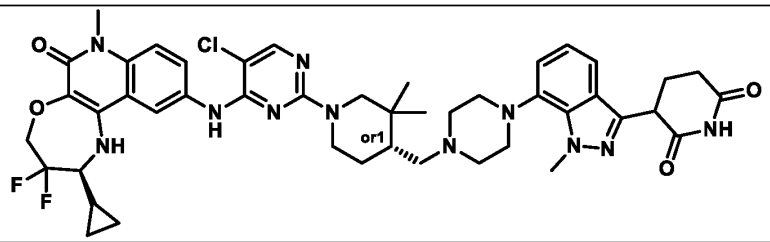
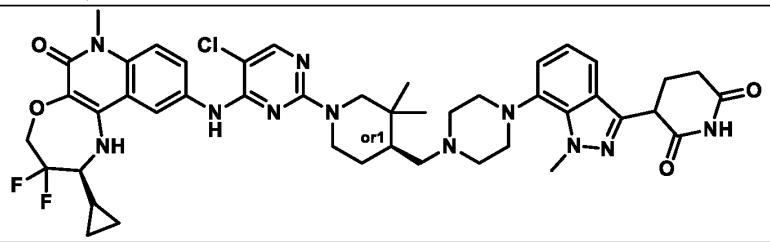
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R573	

R573a	
R574	
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R575	

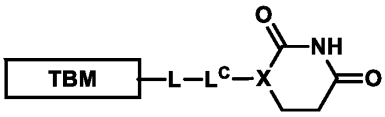
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R576	
R576a	

R577	
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R578	
R578a	
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R581a	
R582	

R582a	
R582b	

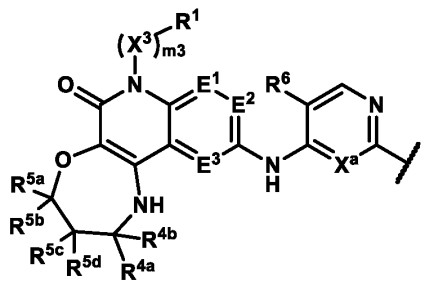
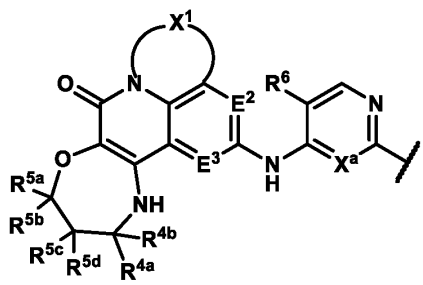
Also provided herein are compounds of Formula (**II**):



Formula (**II**)

or pharmaceutically acceptable salts thereof, wherein:

TBM is selected from the group consisting of (**T1**) and (**T2**):

 (**T1**)	 (**T2**)

wherein:

E^1 is CR^{2a} or N;

E^2 is CR^{2b} or N;

E^3 is CR^{2c} or N;

R^{2a}, R^{2b}, and R^{2c} are independently selected from the group consisting of: H, halo, cyano, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, and C_{1-3} haloalkoxy;

R^{4a} and R^{4b} are independently selected from the group consisting of: H, R^{b1}, -(C_{1-3} alkylene)-R^{b1}, and C_{1-3} alkyl optionally substituted with 1-3 R^c; or

$\mathbf{R^{4a}}$ and $\mathbf{R^{4b}}$ taken together with the ring carbon to which each is attached form a C_{3-6} cycloalkyl ring or a 4-6 membered heterocyclyl ring, each of which is optionally substituted with 1-3 $\mathbf{R^g}$;

$\mathbf{R^{5a}}$ and $\mathbf{R^{5b}}$ are each independently selected from the group consisting of: H and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$;

$\mathbf{R^{5c}}$ and $\mathbf{R^{5d}}$ are each independently selected from the group consisting of: H, F, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$;

$\mathbf{X^1}$ is C_{2-6} alkylene optionally substituted with 1-3 $\mathbf{R^c}$, wherein one CH_2 group of the C_{2-6} alkylene is optionally replaced with $\mathbf{X^2}$, wherein $\mathbf{X^2}$ is selected from the group consisting of: O, N($\mathbf{R^d}$), and $S(O)_{0-2}$;

m3 is 0 or 1;

$\mathbf{X^3}$ is C_{1-3} alkylene optionally substituted with 1-3 $\mathbf{R^c}$;

$\mathbf{R^1}$ is selected from the group consisting of: H, halo, and $\mathbf{R^{b1}}$;

$\mathbf{X^a}$ is selected from the group consisting of: N and C$\mathbf{R^{Xa}}$;

$\mathbf{R^6}$ and $\mathbf{R^{Xa}}$ are independently selected from the group consisting of: H, halo, C_{1-2} alkyl, C_{1-2} haloalkyl, C_{1-2} alkoxy, CN, and C≡CH;

L is $-(\mathbf{L^A})_{n1}-$, wherein:

n1 is an integer from 1 to 5; and

each $\mathbf{L^A}$ is independently selected from the group consisting of: $\mathbf{L^{A1}}$, $\mathbf{L^{A3}}$, and $\mathbf{L^{A4}}$, wherein:

0-2 of $\mathbf{L^A}$ is $\mathbf{L^{A1}}$;

0-2 of $\mathbf{L^A}$ is $\mathbf{L^{A3}}$; and

1-3 of $\mathbf{L^A}$ is $\mathbf{L^{A4}}$,

each $\mathbf{L^{A1}}$ is independently selected from the group consisting of: CH_2, CH$\mathbf{R^L}$, and C($\mathbf{R^L}$)$_2$, wherein:

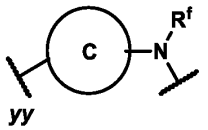
each $\mathbf{R^L}$ is independently selected from the group consisting of: halo, cyano, OH, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -(C_{0-3} alkylene)-(C_{3-5} cycloalkyl), -(C_{0-3} alkylene)-(4-6 membered heterocyclyl), and C_{1-6} alkyl optionally substituted with 1-6 $\mathbf{R^c}$;

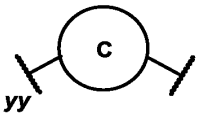
each $\mathbf{L^{A3}}$ is independently selected from the group consisting of: N($\mathbf{R^d}$), N($\mathbf{R^b}$), O, $S(O)_{0-2}$, and C(=O);

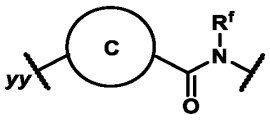
each $\mathbf{L^{A4}}$ is independently selected from the group consisting of:

(a) C_{3-15} cycloalkylene or 4-15 membered heterocyclylene, each of which is optionally substituted with 1-6 substituents independently selected from the group consisting of: $\mathbf{R^a}$ and $\mathbf{R^b}$; and

(b) phenylene or 5-6 membered heteroarylene, each of which is optionally substituted with 1-3 substituents independently selected from the group consisting of: $\mathbf{R^a}$ and $\mathbf{R^b}$;

$\mathbf{L^C}$ is selected from the group consisting of: 

, 

, and 

, wherein *yy* represents the point of attachment to **L**, and

Ring C is selected from the group consisting of: C_{6-10} arylene and 5-15 membered heteroarylene, each of which is optionally substituted with 1-6 substituents independently selected from the group consisting of: $\mathbf{R^a}$ and $\mathbf{R^b}$; and

X is CH or N, wherein:

each $\mathbf{R^a}$ is independently selected from the group consisting of:

(a) halo;

(b) cyano;

(c) OH;

(d) oxo;

(e) C_{1-6} alkoxy optionally substituted with 1-6 $\mathbf{R^c}$;

(f) $N\mathbf{R^d}\mathbf{R^e}$;

(g) $C(=O)C_{1-6}$ alkyl;

(h) $C(=O)OC_{1-6}$ alkyl;

(i) $C(=O)N(\mathbf{R^f})_2$;

(j) $S(O)_{0-2}(C_{1-6}$ alkyl);

(k) $S(O)_{0-2}(C_{1-6}$ haloalkyl); and

(l) C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, each optionally substituted with 1-6 $\mathbf{R^c}$;

each $\mathbf{R^b}$ is independently selected from the group consisting of: $\mathbf{-(L^b)_b-R^{b1}}$ and $\mathbf{R^{b1}}$, wherein:

each **b** is independently 1, 2, or 3;

each $\mathbf{L^b}$ is independently selected from the group consisting of: O, N(H), $N(C_{1-3}$ alkyl), $S(O)_{0-2}$, C(=O), and C_{1-3} alkylene; and

each $\mathbf{R^{b1}}$ is independently selected from the group consisting of: C_{3-6} cycloalkyl and 4-8 membered heterocyclyl, each of which is optionally substituted with 1-3 $\mathbf{R^g}$;

each $\mathbf{R^c}$ is independently selected from the group consisting of: halo, cyano, OH, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $\mathbf{NR^dR^e}$, $C(=O)C_{1-6}$ alkyl, $C(=O)OC_{1-6}$ alkyl, $C(=O)N(\mathbf{R^f})_2$, $S(O)_{0-2}(C_{1-6}$ alkyl), and $S(O)_{0-2}(C_{1-6}$ haloalkyl);

each $\mathbf{R^d}$ and $\mathbf{R^e}$ is independently selected from the group consisting of: H, $C(=O)C_{1-6}$ alkyl, $C(=O)C_{1-6}$ haloalkyl, $C(=O)OC_{1-6}$ alkyl, $C(=O)OC_{1-6}$ haloalkyl, $C(=O)N(\mathbf{R^f})_2$, $S(O)_{1-2}(C_{1-6}$ alkyl), $S(O)_{1-2}(C_{1-6}$ haloalkyl), $S(O)_{1-2}N(\mathbf{R^f})_2$, and C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^h}$;

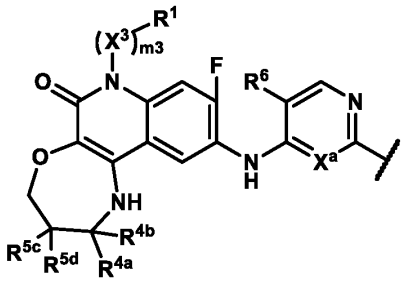
each $\mathbf{R^f}$ is independently selected from the group consisting of: H and C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^h}$;

each $\mathbf{R^g}$ is independently selected from the group consisting of: $\mathbf{R^h}$, oxo, C_{1-3} alkyl, and C_{1-3} haloalkyl; and

each $\mathbf{R^h}$ is independently selected from the group consisting of: halo, cyano, OH, $-(C_{0-3}$ alkylene)-C_{1-6} alkoxy, $-(C_{0-3}$ alkylene)-C_{1-6} haloalkoxy, $-(C_{0-3}$ alkylene)-NH_2, $-(C_{0-3}$ alkylene)-N(H)(C_{1-3} alkyl), and $-(C_{0-3}$ alkylene)-$N(C_{1-3}$ alkyl)$_2$.

In some embodiments of Formula (**II**), **TBM** is (**T1**). In some embodiments of (**T1**), $\mathbf{E^2}$ is $\mathbf{CR^{2b}}$. For example, $\mathbf{E^2}$ can be CF. In some embodiments of (**T1**), $\mathbf{E^1}$ is CH; and $\mathbf{E^3}$ is CH.

In some embodiments of Formula (**II**), **TBM** is (**T1a**):



(**T1a**)

wherein:

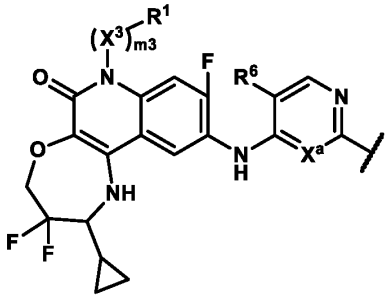
R^{4a} and R^{4b} are independently selected from the group consisting of: H, R^{b1}, -(C_{1-3} alkylene)-R^{b1}, and C_{1-3} alkyl optionally substituted with 1-3 F; and

R^{5c} and R^{5d} are each independently selected from the group consisting of: H, F, and C_{1-3} alkyl optionally substituted with 1-3 F.

In some embodiments of (**T1a**), R^{5c} and R^{5d} are each F.

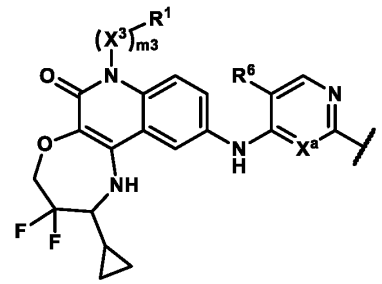
In some embodiments of (**T1a**), R^{4b} is H; and R^{4a} is R^{b1}. For example, R^{4a} can be C_{3-6} cycloalkyl (e.g., cyclopropyl).

In some embodiments of Formula (**II**), **TBM** is (**T1a1**):



(**T1a1**).

In some embodiments of Formula (**II**), **TBM** is (**T1a2**):

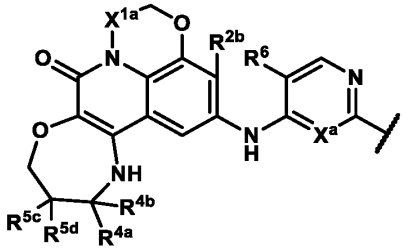


(**T1a2**).

In some embodiments of (**T1**), (**T1a**), (**T1a1**), or (**T1a2**), -$(X^3)_{m3}$-R^1 is C_{1-3} alkyl (e.g., methyl or isopropyl).

In some embodiments of Formula (**II**), **TBM** is (**T2**). In some embodiments of (**T2**), E^2 is CR^{2b}. For example, E^2 can be CF. For example, E^2 can be CH. In some embodiments of (**T2**), E^3 is CH.

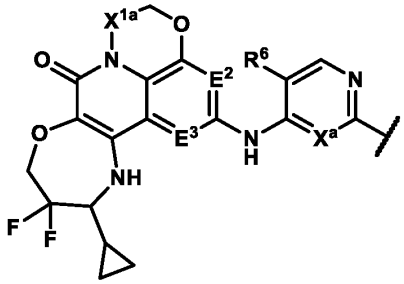
In some embodiments of Formula (**II**), **TBM** is (**T2a**):



(**T2a**)

wherein X^{1a} is a C_{1-3} alkylene optionally substituted with 1-2 R^c. In some embodiments of (**T2a**), R^{2b} is F. In some embodiments of (**T2a**), R^{2b} is H.

In some embodiments of Formula (**II**), **TBM** is (**T2a1**):

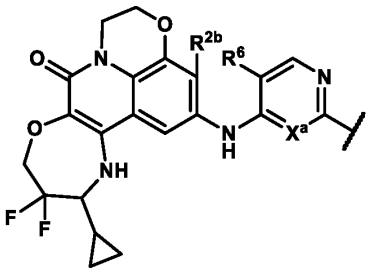
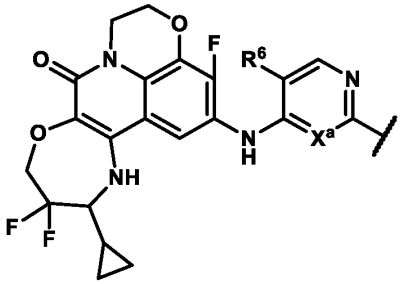
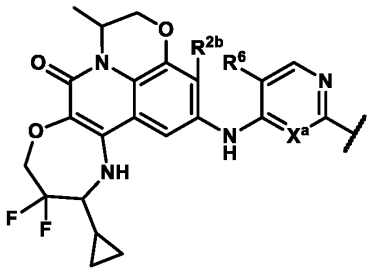
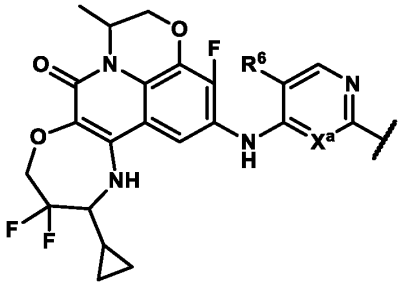


(**T2a1**)

wherein X^{1a} is CH_2 or CH(Me).

In some embodiments of (**T2a1**), E^3 is CH.

In some embodiments of (**T2a1**), E^2 is CR^{2b}; and R^{2b} is F. In some embodiments of (**T2a1**), E^2 is CR^{2b}; and R^{2b} is H.

For example, (**T2a1**) can be  (e.g., ) or  (e.g., ).

In some embodiments of Formula (**II**), X^a is N.

In some embodiments of Formula (**II**), R^6 is F or Cl (e.g., Cl).

In some embodiments of Formula (**II**), **L** is selected from the group consisting of:

$-L^{A4a}-L^{A1}-L^{A4b}-bb$;

$-L^{A4a}-L^{A3}-L^{A4b}-bb$;

$-L^{A4a}-L^{A4b}-bb$;

$-L^{A4a}-L^{A3}-L^{A4c}-L^{A4b}-bb$; and

$-L^{A4a}-L^{A4c}-L^{A3}-L^{A4b}-bb$, wherein:

$\mathbf{L}^{A4a}$, $\mathbf{L}^{A4b}$, and $\mathbf{L}^{A4c}$ are each an independently selected $\mathbf{L}^{A4}$,

$\mathbf{L}^{A3}$ is selected from the group consisting of: O and N($\mathbf{R}^{d}$), and

bb represents the point of attachment to $\mathbf{L}^{C}$.

In some embodiments of Formula (**II**), **L** is selected from the group consisting of:

-$\mathbf{L}^{A4a}$-$\mathbf{L}^{A1}$-$\mathbf{L}^{A4b}$-*bb*;

-$\mathbf{L}^{A4a}$-$\mathbf{L}^{A3}$-$\mathbf{L}^{A4b}$-*bb*;

-$\mathbf{L}^{A4a}$-$\mathbf{L}^{A4b}$-*bb*;

-$\mathbf{L}^{A4a}$-$\mathbf{L}^{A3}$-$\mathbf{L}^{A4c}$- $\mathbf{L}^{A4b}$-*bb*;

-$\mathbf{L}^{A4a}$-$\mathbf{L}^{A4c}$-$\mathbf{L}^{A1}$-$\mathbf{L}^{A4b}$-*bb*;

-$\mathbf{L}^{A4a}$-$\mathbf{L}^{A1}$-$\mathbf{L}^{A4c}$- $\mathbf{L}^{A4b}$-*bb*; and

-$\mathbf{L}^{A4a}$-$\mathbf{L}^{A4c}$-$\mathbf{L}^{A3}$-$\mathbf{L}^{A4b}$-*bb*, wherein:

bb represents the point of attachment to $\mathbf{L}^{C}$;

$\mathbf{L}^{A3}$ is selected from the group consisting of: O and N($\mathbf{R}^{d}$);

$\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ are independently 4-12 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R}^{a}$;

$\mathbf{L}^{A4c}$ is a C_{3-10} cycloalkylene optionally substituted with 1-3 $\mathbf{R}^{a}$; and

each $\mathbf{R}^{L}$ is independently selected from the group consisting of: F, OH, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R}^{c}$ (e.g., C_{1-3} alkyl optionally substituted with 1-3 F). In some embodiments, $\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ each contain 1-2 ring nitrogen atoms and no additional ring heteroatoms. In some embodiments, one of $\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ is a 1,4-piperidinylene; and the other of $\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ is independently selected from the group consisting of: 1,4-piperidinylene and 1,4-piperazinylene, wherein each of the 1,4-piperidinylene or 1,4-piperazinylene is optionally substituted with 1-2 $\mathbf{R}^{a}$. In some embodiments, $\mathbf{L}^{A4c}$ is C_{3-4} cycloalkylene (e.g., C_4 cycloalkylene (e.g., )) optionally substituted with 1-2 $\mathbf{R}^{a}$. In some embodiments, each $\mathbf{R}^{a}$ present on $\mathbf{L}^{A4a}$, $\mathbf{L}^{A4b}$, and/or $\mathbf{L}^{A4c}$ is independently selected from the group consisting of: F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F.

In some embodiments of Formula (**II**), **L** is selected from the group consisting of:

-$\mathbf{L}^{A4a}$-$\mathbf{L}^{A3}$-$\mathbf{L}^{A4c}$- $\mathbf{L}^{A4b}$-*bb*; and

-$\mathbf{L}^{A4a}$-$\mathbf{L}^{A4c}$-$\mathbf{L}^{A3}$-$\mathbf{L}^{A4b}$-*bb*, wherein:

bb represents the point of attachment to $\mathbf{L}^{C}$;

$\mathbf{L}^{A3}$ is selected from the group consisting of: O and N($\mathbf{R}^{d}$);

$\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ are independently 4-12 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R}^{a}$;

$\mathbf{L}^{A4c}$ is a C_{3-10} cycloalkylene optionally substituted with 1-3 $\mathbf{R}^{a}$; and

each $\mathbf{R}^{L}$ is independently selected from the group consisting of: F, OH, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R}^{c}$ (e.g., C_{1-3} alkyl optionally substituted with 1-3 F). In some embodiments, $\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ each contain 1-2 ring nitrogen atoms and no additional ring heteroatoms. In some embodiments, one of $\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ is a 1,4-piperidinylene; and the other of $\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ is independently selected from the group consisting of: 1,4-piperidinylene and 1,4-piperazinylene, wherein each of the 1,4-piperidinylene or 1,4-piperazinylene is optionally substituted with 1-2 $\mathbf{R}^{a}$. In some embodiments, $\mathbf{L}^{A4c}$ is C_{3-4} cycloalkylene (e.g., C_4 cycloalkylene (e.g., )) optionally substituted with 1-2 $\mathbf{R}^{a}$. In some embodiments, each $\mathbf{R}^{a}$ present on $\mathbf{L}^{A4a}$, $\mathbf{L}^{A4b}$, and/or $\mathbf{L}^{A4c}$ is independently selected from the group consisting of: F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F.

In some embodiments of Formula (**II**), **L** is:

$-\mathbf{L}^{A4a}-\mathbf{L}^{A3}-\mathbf{L}^{A4c}-\mathbf{L}^{A4b}-_{bb}$, wherein:

bb represents the point of attachment to $\mathbf{L}^{C}$;

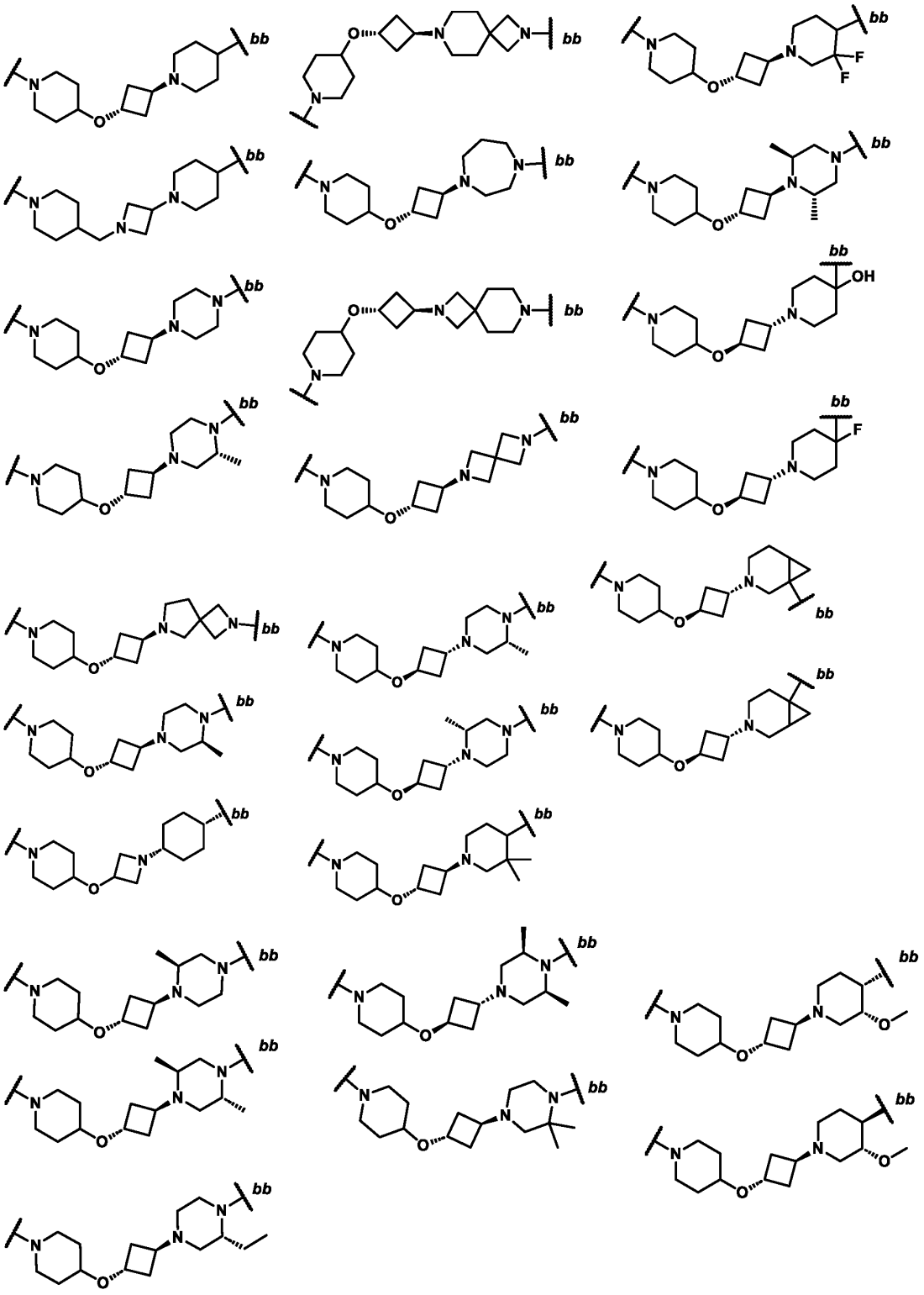
$\mathbf{L}^{A3}$ is selected from the group consisting of: O and N($\mathbf{R}^{d}$);

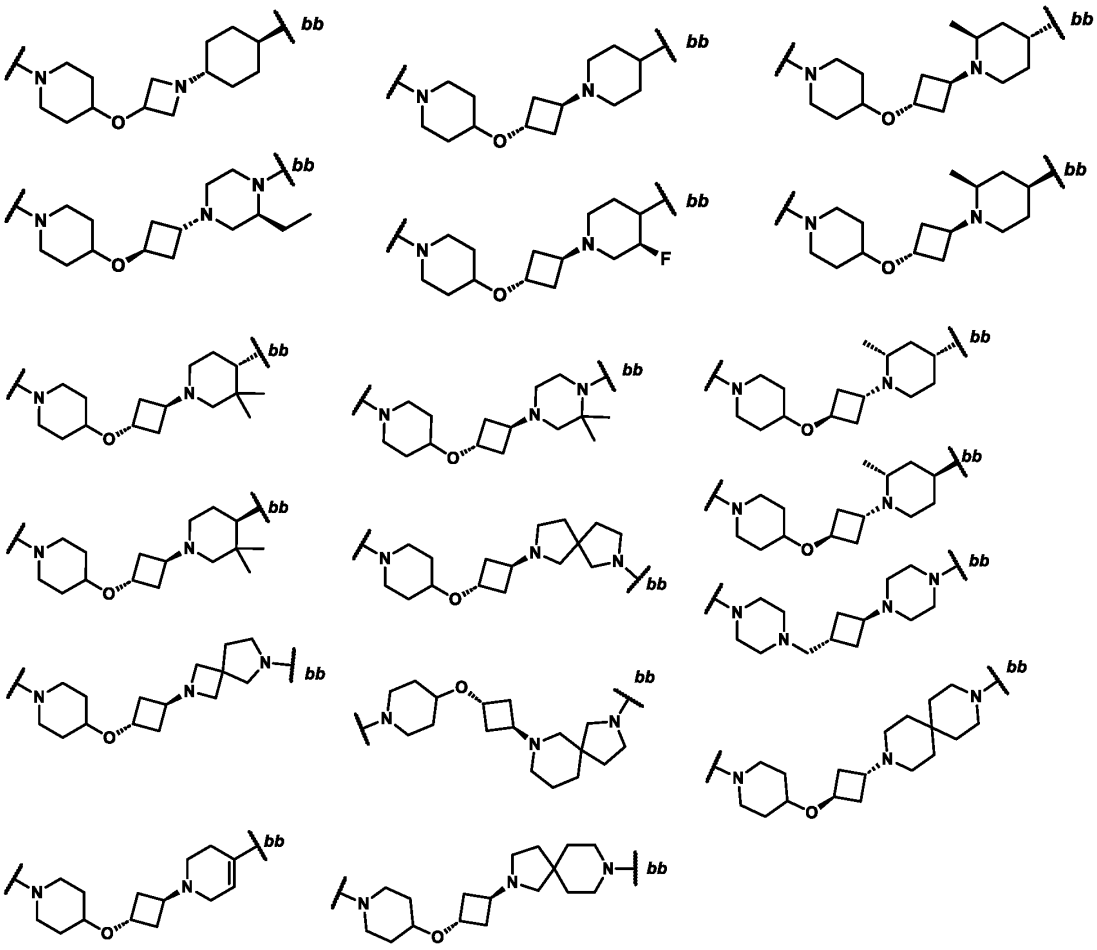
$\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ are independently 4-12 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R}^{a}$;

$\mathbf{L}^{A4c}$ is a C_{3-10} cycloalkylene optionally substituted with 1-3 $\mathbf{R}^{a}$; and

each $\mathbf{R}^{L}$ is independently selected from the group consisting of: F, OH, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R}^{c}$ (e.g., C_{1-3} alkyl optionally substituted with 1-3 F). In some embodiments, $\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ each contain 1-2 ring nitrogen atoms and no additional ring heteroatoms. In some embodiments, one of $\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ is a 1,4-piperidinylene; and the other of $\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ is independently selected from the group consisting of: 1,4-piperidinylene and 1,4-piperazinylene, wherein each of the 1,4-piperidinylene or 1,4-piperazinylene is optionally substituted with 1-2 $\mathbf{R}^{a}$. In some embodiments, $\mathbf{L}^{A4c}$ is C_{3-4} cycloalkylene (e.g., C_4 cycloalkylene (e.g., )) optionally substituted with 1-2 $\mathbf{R}^{a}$. In some embodiments, each $\mathbf{R}^{a}$ present on $\mathbf{L}^{A4a}$, $\mathbf{L}^{A4b}$, and/or $\mathbf{L}^{A4c}$ is independently selected from the group consisting of: F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F.

In some embodiments of Formula (**II**), **L** is selected from the group consisting of:





wherein ***bb*** represents the point of attachment to $\mathbf{L^C}$.

In some embodiments of Formula (**II**), **L** is selected from the group consisting of:

$-\mathbf{L^{A4a}}-\mathbf{L^{A1}}-\mathbf{L^{A4b}}-_{bb}$; and

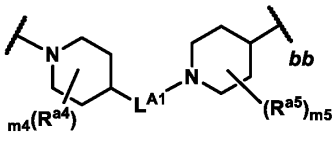
$-\mathbf{L^{A4a}}-\mathbf{L^{A3}}-\mathbf{L^{A4b}}-_{bb}$, wherein:

bb represents the point of attachment to $\mathbf{L^C}$;

$\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ are independently 4-12 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R^a}$; and

each $\mathbf{R^L}$ is independently selected from the group consisting of: F, OH, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$ (e.g., C_{1-3} alkyl optionally substituted with 1-3 F). In some embodiments, $\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ are independently monocyclic 4-6 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R^a}$. In some embodiments, one of $\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ is a 1,4-piperidinylene; and the other of $\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ is independently selected from the group consisting of: 1,4-piperidinylene and 1,4-piperazinylene, wherein each of the 1,4-

piperidinylene or 1,4-piperazinylene is optionally substituted with 1-2 R^a. In some embodiments, L^{A4a} and L^{A4b} each contain 1-2 ring nitrogen atoms and no additional ring heteroatoms. In some embodiments, each R^a present on L^{A4a} and/or L^{A4b} is independently selected from the group consisting of: F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F.

In some embodiments of Formula (**II**), **L** is , wherein:

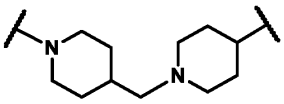
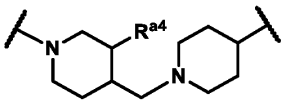
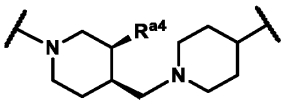
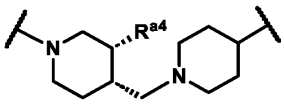
m4 and **m5** are independently 0, 1, or 2;

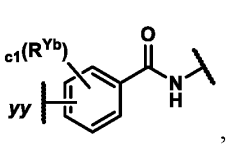
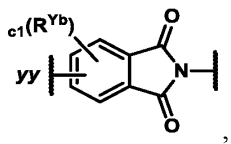
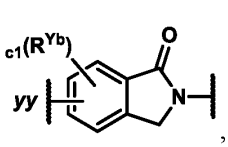
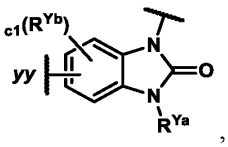
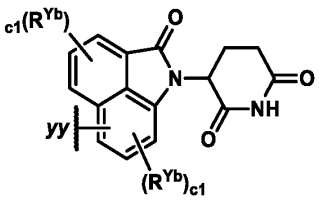
each R^{a4} and R^{a5} is independently selected from the group consisting of: F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F;

L^{A1} is CH_2 or CHR^L,

R^L is C_{1-3} alkyl optionally substituted with 1-3 R^c; and

bb represents the point of attachment to L^C. In some embodiments, each R^{a4} is independently selected from the group consisting of: F and C_{1-3} alkyl optionally substituted with 1-3 F.

In some embodiments of Formula (**II**), **L** is  or  (e.g.,  or ). In some embodiments, each R^{a4} is independently F or methyl.

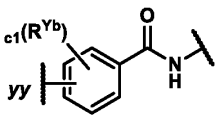
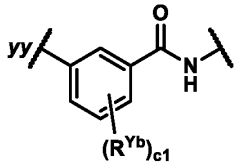
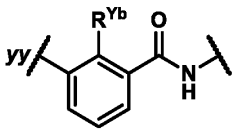
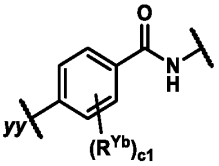
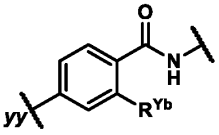
In some embodiments of Formula (**II**), L^C is selected from the group consisting of: , , , , and ;

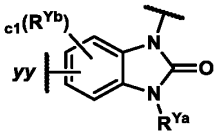
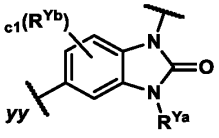
each **c1** is independently 0, 1, or 2;

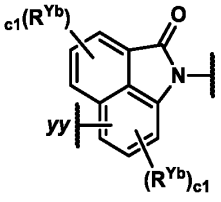
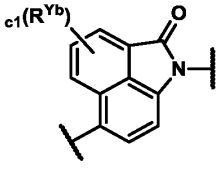
each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of $\mathbf{R^a}$ and $\mathbf{R^b}$;

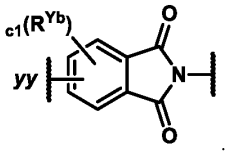
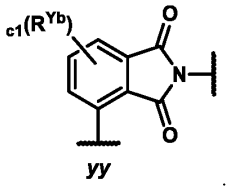
$\mathbf{R^{Ya}}$ is selected from the group consisting of: H, $\mathbf{R^a}$, and $\mathbf{R^b}$; and

yy represents the point of attachment to **L**.

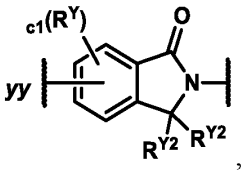
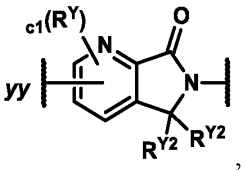
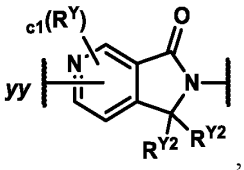
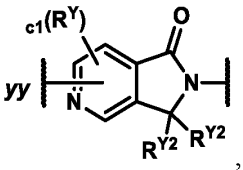
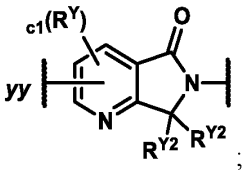
In some embodiments of Formula (**II**), $\mathbf{L^C}$ is . In some embodiments, $\mathbf{L^C}$ is  (e.g., ) or  (e.g., ), wherein **c1** is 0 or 1; and $\mathbf{R^{Yb}}$ is selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 F.

In some embodiments of Formula (**II**), $\mathbf{L^C}$ is . In some embodiments, $\mathbf{L^C}$ is , wherein $\mathbf{R^{Ya}}$ is C_{1-3} alkyl optionally substituted with 1-3 F (e.g., C_{1-3} alkyl (e.g., methyl)).

In some embodiments of Formula (**II**), $\mathbf{L^C}$ is . In some embodiments, $\mathbf{L^C}$ is .

In some embodiments of Formula (**II**), $\mathbf{L}^{C}$ is . In some embodiments, $\mathbf{L}^{C}$ is .

In some embodiments of Formula (**II**), $\mathbf{L}^{C}$ is selected from the group consisting of:

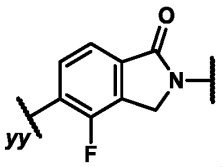
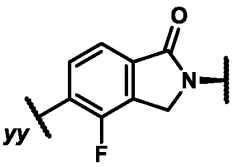
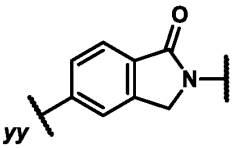
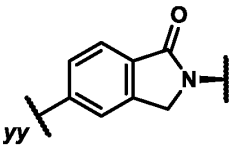
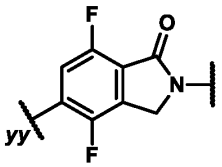
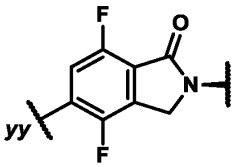
, , , , and ;

c1 is 0, 1, 2, or 3;

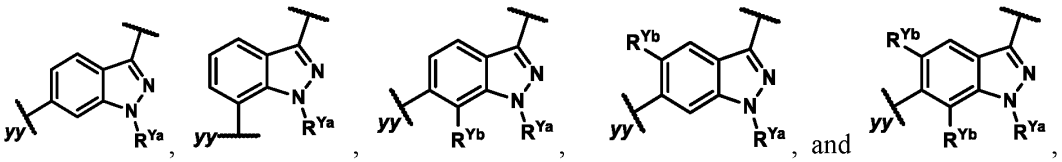
each $\mathbf{R}^{Y}$ is independently selected from the group consisting of: $\mathbf{R}^{a}$ and $\mathbf{R}^{b}$;

each $\mathbf{R}^{Y2}$ is independently selected from the group consisting of: H and $C_{1\text{-}3}$ alkyl, or both $\mathbf{R}^{Y2}$ groups taken together with the ring carbon atom to which each is attached form C=O; and *yy* represents the point of attachment to **L**.

In some embodiments, $\mathbf{L}^{C}$ is selected from the group consisting of:

, , , , , and , wherein *yy* represents the point of attachment to **L**.

In some embodiments of Formula (**II**), $\mathbf{L^C}$ is selected from the group consisting of:



wherein: $\mathbf{R^{Ya}}$ is selected from the group consisting of:

(a) H;

(b) C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$; and

(c) –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$ (e.g., C_{3-6} cycloalkyl optionally substituted with 1-3 F);

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$ (e.g., C_{1-3} alkyl optionally substituted with 1-3 F); and ***yy*** represents the point of attachment to **L**. In some embodiments, $\mathbf{R^{Ya}}$ is H or C_{1-3} alkyl optionally substituted with 1-3 F (e.g., C_{1-3} alkyl (e.g., methyl)); and each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: F and C_{1-3} alkyl optionally substituted with 1-3 F.

In some embodiments of Formula (**II**), **TBM** is (**T1a1**); and **L** is selected from the group consisting of:

$\mathbf{-L^{A4a}-L^{A3}-L^{A4c}-L^{A4b}-}$*bb*; and

$\mathbf{-L^{A4a}-L^{A4c}-L^{A3}-L^{A4b}-}$*bb*, wherein:

bb represents the point of attachment to $\mathbf{L^C}$;

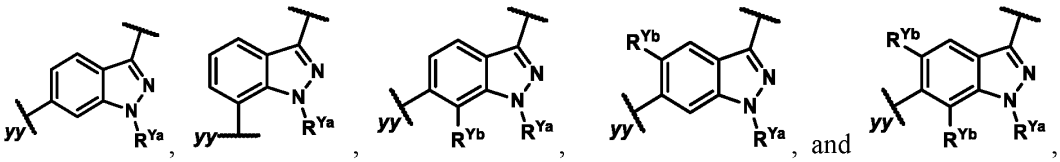
$\mathbf{L^{A3}}$ is selected from the group consisting of: O and N($\mathbf{R^d}$);

$\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ are independently 4-12 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R^a}$;

$\mathbf{L^{A4c}}$ when present is a C_{3-10} cycloalkylene optionally substituted with 1-3 $\mathbf{R^a}$. In some embodiments, $\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ each contain 1-2 ring nitrogen atoms and no additional ring heteroatoms. In some embodiments, one of $\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ is a 1,4-piperidinylene; and the other of $\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ is independently selected from the group consisting of: 1,4-piperidinylene and 1,4-piperazinylene, wherein each of the 1,4-piperidinylene or 1,4-piperazinylene is optionally substituted with 1-2 $\mathbf{R^a}$. In some embodiments, $\mathbf{L^{A4c}}$ is C_{3-4} cycloalkylene (e.g., C_4 cycloalkylene (e.g., )) optionally substituted with 1-2 $\mathbf{R^a}$. In some embodiments,

each $\mathbf{R^a}$ present on $\mathbf{L^{A4a}}$, $\mathbf{L^{A4b}}$, and/or $\mathbf{L^{A4c}}$ is independently selected from the group consisting of: F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F.

In some embodiments of Formula (**II**), $\mathbf{L^C}$ is selected from the group consisting of:



wherein: $\mathbf{R^{Ya}}$ is selected from the group consisting of:

(a) H;

(b) C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$; and

(c) –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$ (e.g., C_{3-6} cycloalkyl optionally substituted with 1-3 F); and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$ (e.g., C_{1-3} alkyl optionally substituted with 1-3 F). In some embodiments, $\mathbf{R^{Ya}}$ is H or C_{1-3} alkyl optionally substituted with 1-3 F (e.g., C_{1-3} alkyl (e.g., methyl)); and each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: F and C_{1-3} alkyl optionally substituted with 1-3 F; and

yy represents the point of attachment to **L**; and

L is selected from the group consisting of:

-$\mathbf{L^{A4a}}$-$\mathbf{L^{A3}}$-$\mathbf{L^{A4c}}$- $\mathbf{L^{A4b}}$-*bb*; and

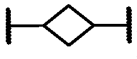
-$\mathbf{L^{A4a}}$-$\mathbf{L^{A4c}}$-$\mathbf{L^{A3}}$-$\mathbf{L^{A4b}}$-*bb*, wherein:

bb represents the point of attachment to $\mathbf{L^C}$;

$\mathbf{L^{A3}}$ is selected from the group consisting of: O and N($\mathbf{R^d}$),

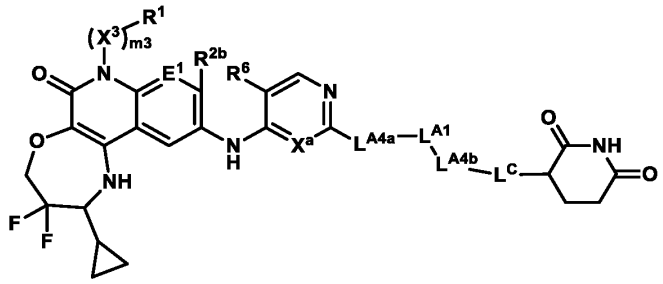
$\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ are independently 4-12 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R^a}$;

$\mathbf{L^{A4c}}$ when present is a C_{3-10} cycloalkylene optionally substituted with 1-3 $\mathbf{R^a}$. In some embodiments, $\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ each contain 1-2 ring nitrogen atoms and no additional ring heteroatoms. In some embodiments, one of $\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ is a 1,4-piperidinylene; and the other of $\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ is independently selected from the group consisting of: 1,4-piperidinylene and 1,4-piperazinylene, wherein each of the 1,4-piperidinylene or 1,4-piperazinylene is optionally substituted with 1-2 $\mathbf{R^a}$. In some embodiments, $\mathbf{L^{A4c}}$ is C_{3-4} cycloalkylene (e.g., C_4

cycloalkylene (e.g., )) optionally substituted with 1-2 R^a. In some embodiments, each R^a present on L^{A4a}, L^{A4b}, and/or L^{A4c} is independently selected from the group consisting of: F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F.

In some embodiments of Formula (**II**), **X** is CH.

Also provided herein are compounds of Formula (**II-a**):



Formula (**II-a**)

or pharmaceutically acceptable salts thereof, wherein:

E^1 is CR^{2a} or N;

R^{2a} and R^{2b} are independently selected from the group consisting of: H, halo, cyano, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, and C_{1-3} haloalkoxy;

m3 is 0 or 1;

X^3 is C_{1-3} alkylene optionally substituted with 1-3 R^c;

R^1 is selected from the group consisting of: H, halo, and R^{b1};

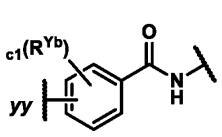
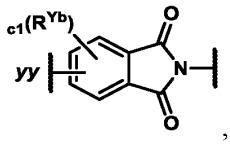
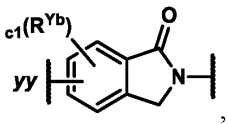
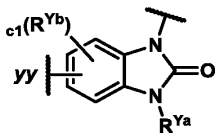
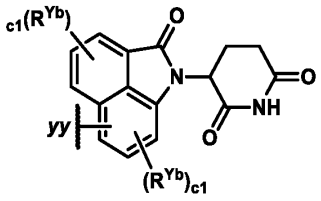
X^a is selected from the group consisting of: N and CR^{Xa};

R^6 and R^{Xa} are independently selected from the group consisting of: H, halo, C_{1-2} alkyl, C_{1-2} haloalkyl, C_{1-2} alkoxy, CN, and C≡CH;

L^{A4a} and L^{A4b} are independently 4-12 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 R^a;

L^{A1} is CH_2, CHR^L, or $C(R^L)_2$, and

each R^L is independently selected from the group consisting of: F, OH, and C_{1-3} alkyl optionally substituted with 1-3 R^c;

$\mathbf{L^C}$ is selected from the group consisting of: , , , , and ;

each **c1** is independently 0, 1, or 2;

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of $\mathbf{R^a}$ and $\mathbf{R^b}$;

$\mathbf{R^{Ya}}$ is selected from the group consisting of: H, $\mathbf{R^a}$, and $\mathbf{R^b}$; and

yy represents the point of attachment to $\mathbf{L^{A4b}}$;

each $\mathbf{R^a}$ is independently selected from the group consisting of:

(a) halo;

(b) cyano;

(c) OH;

(d) oxo;

(e) C_{1-6} alkoxy optionally substituted with 1-6 $\mathbf{R^c}$;

(f) $N\mathbf{R^d}\mathbf{R^e}$;

(g) $C(=O)C_{1-6}$ alkyl;

(h) $C(=O)OC_{1-6}$ alkyl;

(i) $C(=O)N(\mathbf{R^f})_2$;

(j) $S(O)_{0-2}(C_{1-6}$ alkyl);

(k) $S(O)_{0-2}(C_{1-6}$ haloalkyl); and

(l) C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, each optionally substituted with 1-6 $\mathbf{R^c}$;

each $\mathbf{R^b}$ is independently selected from the group consisting of: $\mathbf{-(L^b)_b-R^{b1}}$ and $\mathbf{R^{b1}}$, wherein:

each **b** is independently 1, 2, or 3;

each $\mathbf{L^b}$ is independently selected from the group consisting of: O, N(H), $N(C_{1-3}$ alkyl), $S(O)_{0-2}$, C(=O), and C_{1-3} alkylene; and

each $\mathbf{R^{b1}}$ is independently selected from the group consisting of: C_{3-6} cycloalkyl and 4-8 membered heterocyclyl, each of which is optionally substituted with 1-3 $\mathbf{R^g}$;

each $\mathbf{R^c}$ is independently selected from the group consisting of: halo, cyano, OH, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $N\mathbf{R^d}\mathbf{R^e}$, $C(=O)C_{1-6}$ alkyl, $C(=O)OC_{1-6}$ alkyl, $C(=O)N(\mathbf{R^f})_2$, $S(O)_{0-2}(C_{1-6}$ alkyl), and $S(O)_{0-2}(C_{1-6}$ haloalkyl);

each $\mathbf{R^d}$ and $\mathbf{R^e}$ is independently selected from the group consisting of: H, $C(=O)C_{1-6}$ alkyl, $C(=O)C_{1-6}$ haloalkyl, $C(=O)OC_{1-6}$ alkyl, $C(=O)OC_{1-6}$ haloalkyl, $C(=O)N(\mathbf{R^f})_2$, $S(O)_{1-2}(C_{1-6}$ alkyl), $S(O)_{1-2}(C_{1-6}$ haloalkyl), $S(O)_{1-2}N(\mathbf{R^f})_2$, and C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^h}$;

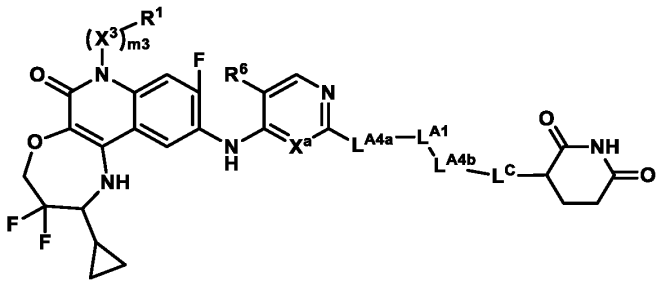
each $\mathbf{R^f}$ is independently selected from the group consisting of: H and C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^h}$;

each $\mathbf{R^g}$ is independently selected from the group consisting of: $\mathbf{R^h}$, oxo, C_{1-3} alkyl, and C_{1-3} haloalkyl; and

each $\mathbf{R^h}$ is independently selected from the group consisting of: halo, cyano, OH, $-(C_{0-3}$ alkylene)-C_{1-6} alkoxy, $-(C_{0-3}$ alkylene)-C_{1-6} haloalkoxy, $-(C_{0-3}$ alkylene)-NH_2, $-(C_{0-3}$ alkylene)-$N(H)(C_{1-3}$ alkyl), and $-(C_{0-3}$ alkylene)-$N(C_{1-3}$ alkyl)$_2$.

In some embodiments of Formula (**II-a**), **E** is $C\mathbf{R^{2a}}$ (e.g., CH).

In some embodiments, the compounds of Formula (**II-a**) are compounds of Formula (**II-a-1**):



Formula (**II-a-1**)

or pharmaceutically acceptable salts thereof.

In some embodiments of Formula (**II-a**) (e.g., Formula (**II-a-1**)), **m3** is 1; and $\mathbf{R^1}$ is H.

In some embodiments of Formula (**II-a**) (e.g., Formula (**II-a-1**)), $-(\mathbf{X^3})_{m3}\text{-}\mathbf{R^1}$ is C_{1-3} alkyl (e.g., methyl).

In some embodiments of Formula (**II-a**) (e.g., Formula (**II-a-1**)), $\mathbf{R^6}$ is F or Cl (e.g., Cl).

In some embodiments of Formula (**II-a**) (e.g., Formula (**II-a-1**)), $\mathbf{X^a}$ is N.

In some embodiments of Formula (**II-a**) (e.g., Formula (**II-a-1**)), $\mathbf{X^a}$ is N; and $\mathbf{R^6}$ is F or Cl (e.g., Cl).

In some embodiments of Formula (**II-a**) (e.g., Formula (**II-a-1**)), $\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ are independently a monocyclic 4-6 (e.g., 5-6) membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R^a}$.

In some embodiments of Formula (**II-a**) (e.g., Formula (**II-a-1**)), $\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ are independently a monocyclic 4-6 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R^a}$; and

each $\mathbf{R^a}$ present on $\mathbf{L^{A4a}}$ and/or $\mathbf{L^{A4b}}$ is independently selected from the group consisting of: F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F.

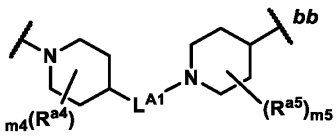
In some embodiments of Formula (**II-a**) (e.g., Formula (**II-a-1**)), one of $\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ is a 1,4-piperidinylene; and

the other of $\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ is independently selected from the group consisting of: 1,4-piperidinylene and 1,4-piperazinylene, wherein each of the 1,4-piperidinylene or 1,4-piperazinylene is optionally substituted with 1-2 $\mathbf{R^a}$, wherein:

each $\mathbf{R^a}$ present on $\mathbf{L^{A4a}}$ and/or $\mathbf{L^{A4b}}$ is independently selected from the group consisting of: F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F.

In some embodiments of Formula (**II-a**) (e.g., Formula (**II-a-1**)), each $\mathbf{R^a}$ present on $\mathbf{L^{A4a}}$ and/or $\mathbf{L^{A4b}}$ is independently selected from the group consisting of: F and C_{1-3} alkyl optionally substituted with 1-3 F (e.g., F, CH_3, CF_3, CF_2H, or CH_2F).

In some embodiments of Formula (**II-a**) (e.g., Formula (**II-a-1**)), $\mathbf{-L^{A4a}-L^{A1}-L^{A4b}-}$ is

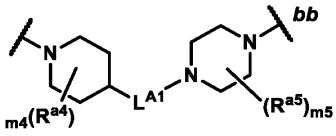


, wherein:

m4 and **m5** are independently 0, 1, or 2;

each $\mathbf{R^{a4}}$ and $\mathbf{R^{a5}}$ is independently selected from the group consisting of: F and C_{1-3} alkyl optionally substituted with 1-3 F; and

bb represents the point of attachment to $\mathbf{L^C}$. In some embodiments, **m4** is 0; and **m5** is 0.

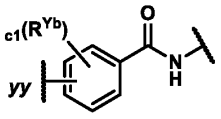
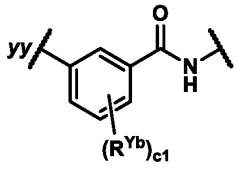
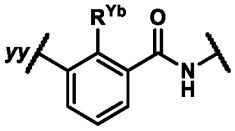
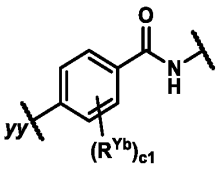
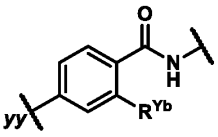
In some embodiments of Formula (**II-a**) (e.g., Formula (**II-a-1**)), -L^{A4a}-L^{A1}-L^{A4b}- is , wherein:

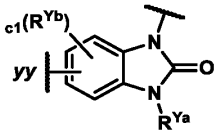
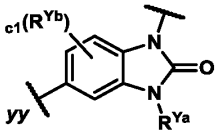
m4 and **m5** are independently 0, 1, or 2;

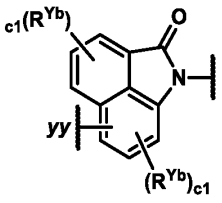
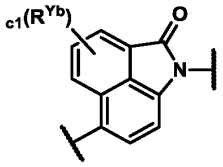
each R^{a4} is independently selected from the group consisting of: F and C_{1-3} alkyl optionally substituted with 1-3 F;

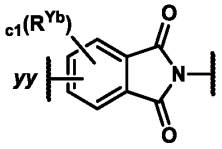
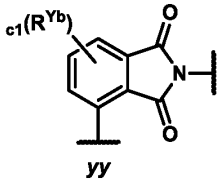
each R^{a5} is independently C_{1-3} alkyl optionally substituted with 1-3 F; and

bb represents the point of attachment to L^C. In some embodiments, **m4** is 0; and **m5** is 0.

In some embodiments of Formula (**II-a**) (e.g., Formula (**II-a-1**)), L^C is . In some embodiments, L^C is  (e.g.,  or  (e.g., ), wherein **c1** is 0 or 1; and R^{Yb} is selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 F.

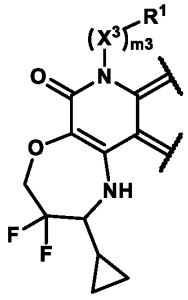
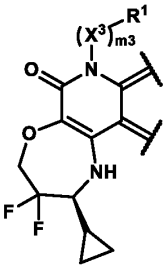
In some embodiments of Formula (**II-a**) (e.g., Formula (**II-a-1**)), L^C is . In some embodiments, L^C is , wherein R^{Ya} is C_{1-3} alkyl optionally substituted with 1-3 F (e.g., C_{1-3} alkyl (e.g., methyl)).

In some embodiments of Formula (**II-a**) (e.g., Formula (**II-a-1**)), $\mathbf{L^C}$ is  . In some embodiments, $\mathbf{L^C}$ is  .

In some embodiments of Formula (**II-a**) (e.g., Formula (**II-a-1**)), $\mathbf{L^C}$ is  . In some embodiments, $\mathbf{L^C}$ is  .

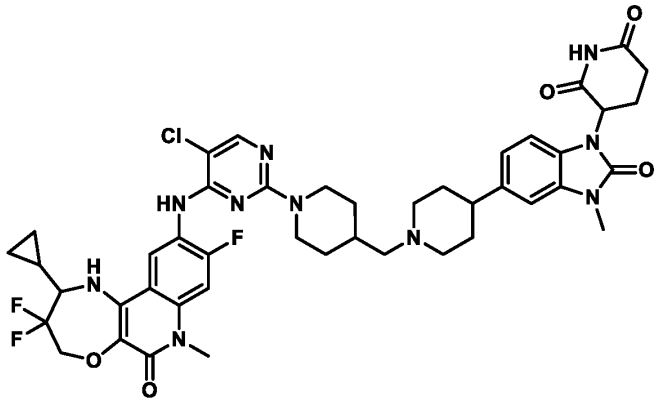
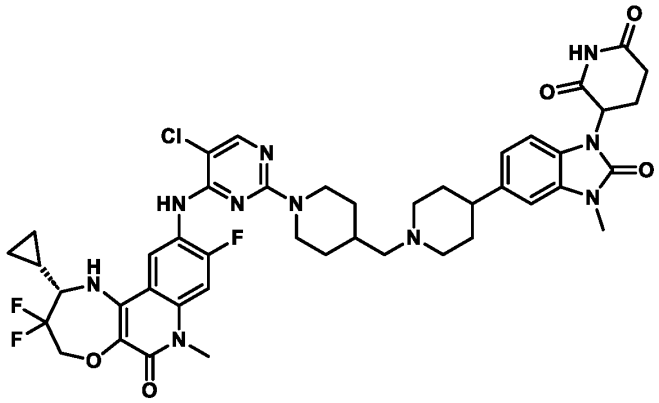
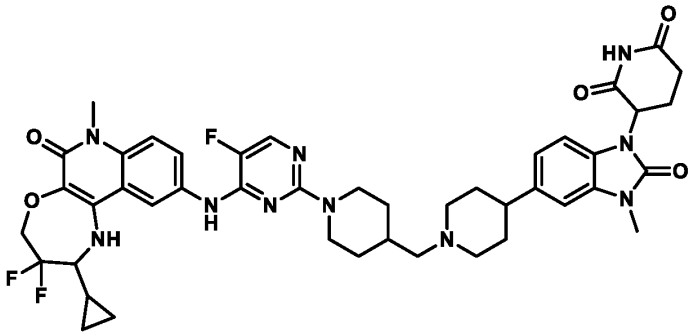
In some embodiments of Formula (**II-a**) (e.g., Formula (**II-a-1**)), each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 F.

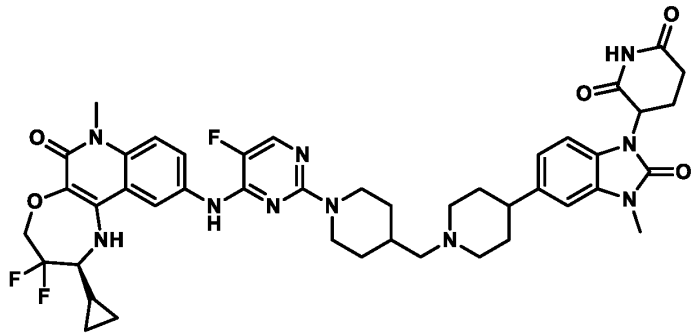
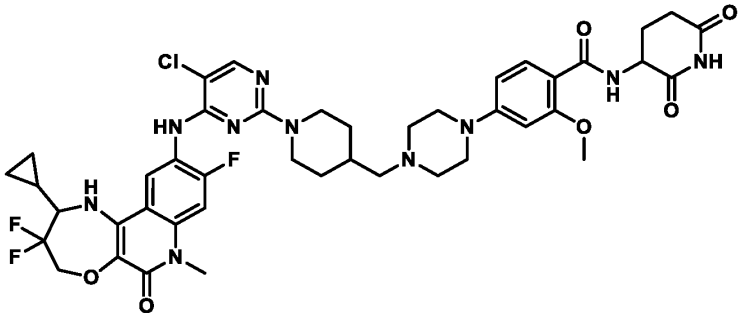
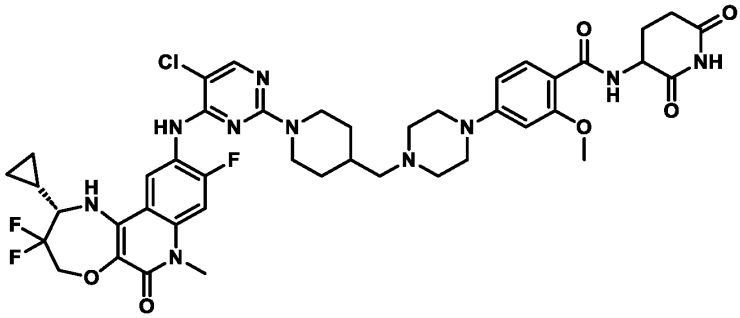
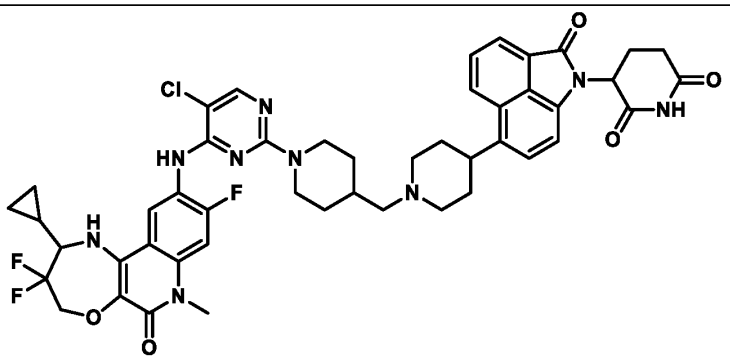
In some embodiments of Formula (**II-a**) (e.g., Formula (**II-a-1**)), **c1** is 0.

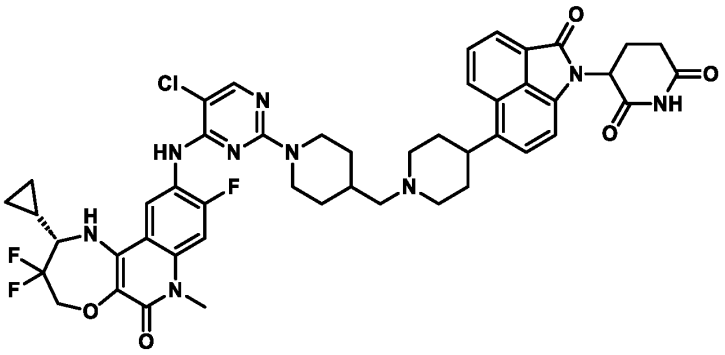
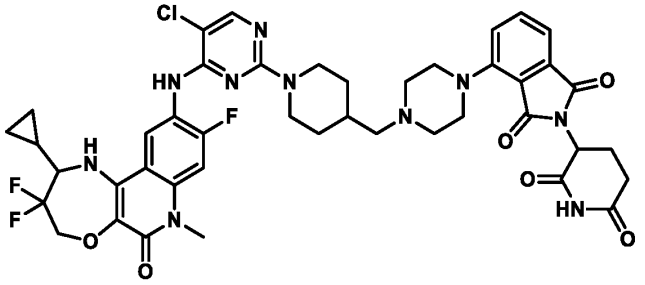
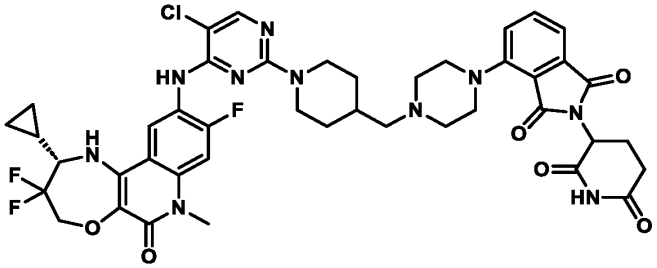
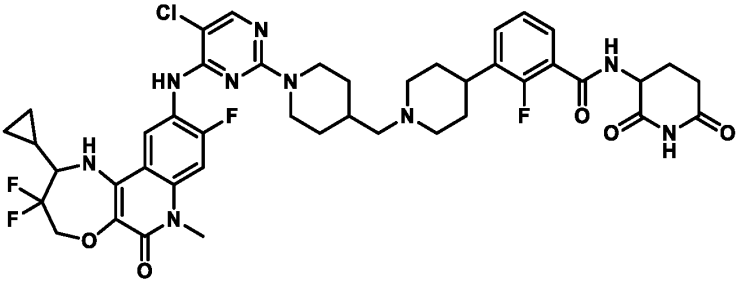
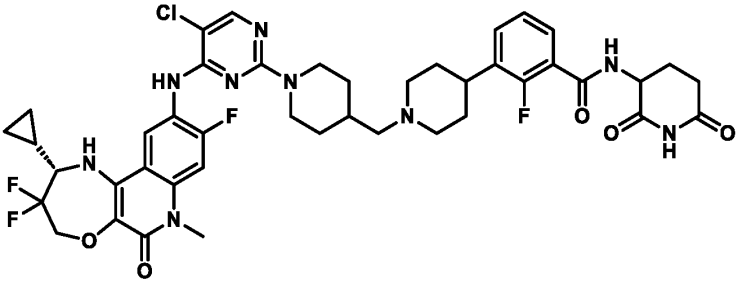
In some embodiments of Formula (**I**) (e.g., Formula (**I-1**), Formula (**I-2**), Formula (**I-a**) (e.g., Formula (**I-a-1**), (**I-a-2**), (**I-a-3**), or (**I-a-4**)), Formula (**I-b**) (e.g., Formula (**I-b-1**), (**I-b-2**), (**I-b-3**), or (**I-b-4**)), Formula (**I-c**) (e.g., Formula (**I-c-1**) or (**I-c-2**)), Formula (**I-d**) (e.g., Formula (**I-d-1**)), or Formula (**I-e**) (e.g., Formula (**I-e-1**) or (**I-e-2**))), or Formula (**II-a**) (e.g., Formula (**II-a-1**)), the  moiety is  .

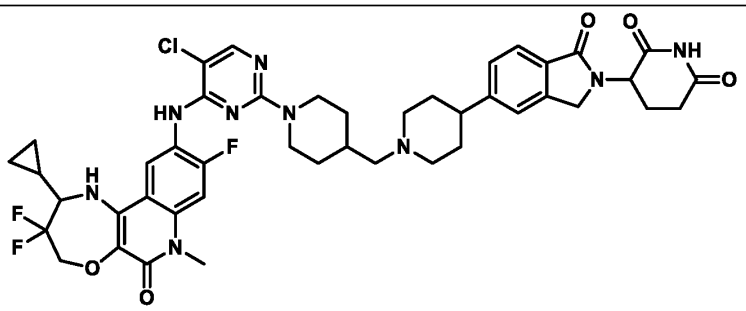
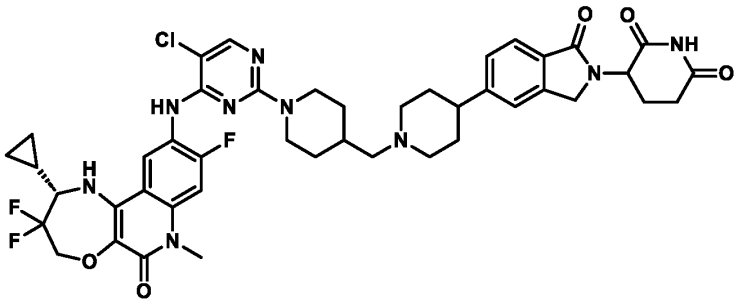
In some embodiments, the compounds of Formula (**II-a**) are selected from the group consisting of the compounds depicted in **Table C2**, or pharmaceutically acceptable salts thereof.

Table C2

No.	Structure
501	
501a	
502	

502a	
503	
503a	
504	

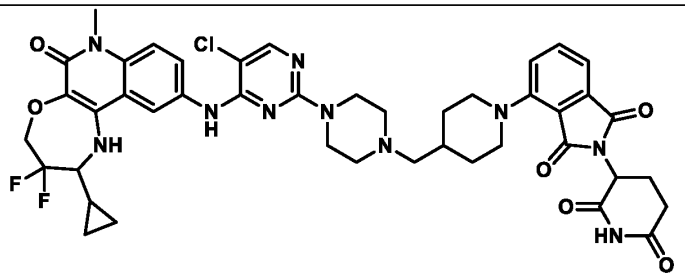
504a	
505	
505a	
506	
506a	

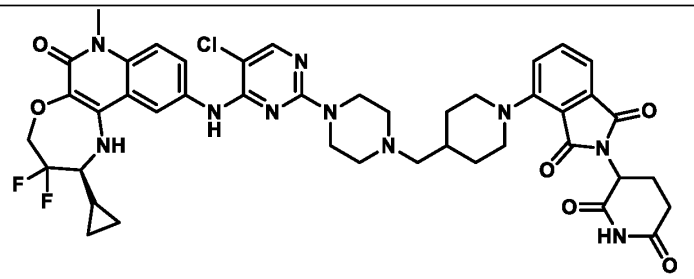
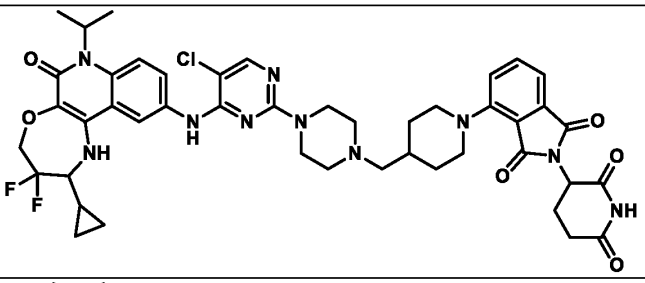
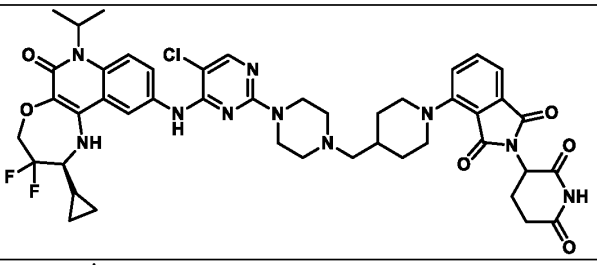
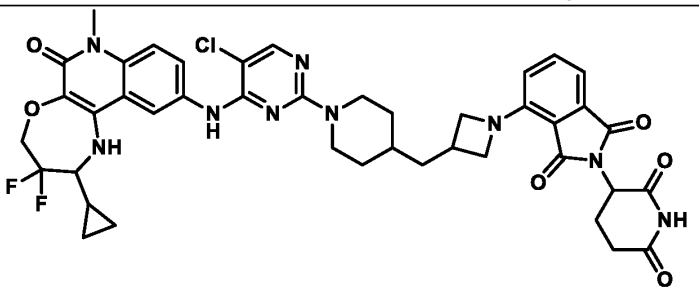
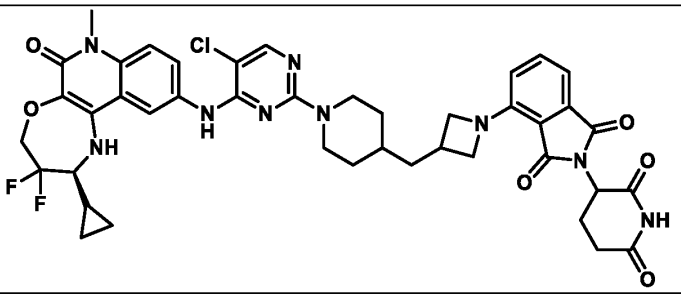
507	
507a	

In some embodiments, compounds of Formula (**II-a**), or pharmaceutically acceptable salts thereof, are other than the compounds in **Table C1** of International Patent Application No. PCT/US/23/67927 (published as WO 2023/240038), filed June 5, 2023, or pharmaceutically acceptable salts thereof, wherein the **Table C1** of International Patent Application No. PCT/US/23/67927 is incorporated herein by reference in its entirety.

In some embodiments, the compounds of Formula (**II-a**) are other than the compounds depicted in **Table R2**, or pharmaceutically acceptable salts thereof.

Table R2

No.	Compound Structure
R374	

R374a	
R375	
R375a	
R433	
R433a	

In some embodiments, the compounds of Formula (**I**) (e.g., Formula (**I-1**), Formula (**I-2**), Formula (**I-a**) (e.g., Formula (**I-a-1**), (**I-a-2**), (**I-a-3**), or (**I-a-4**)), Formula (**I-b**) (e.g., Formula (**I-b-1**), (**I-b-2**), (**I-b-3**), or (**I-b-4**)), Formula (**I-c**) (e.g., Formula (**I-c-1**) or (**I-c-2**)), Formula (**I-d**) (e.g., Formula (**I-d-1**)), or Formula (**I-e**) (e.g., Formula (**I-e-1**) or (**I-e-2**))),

Formula (**II**), or Formula (**II-a**) (e.g., Formula (**II-a-1**)), or pharmaceutically acceptable salts thereof, reduce cell viability in a cell line expressing a BCL6 protein with an EC_{50} of less than 1 μM (e.g., less than 750 nM, less than 500 nM, or less than 200 nM). In some embodiments, the compounds reduce cell viability in a cell line expressing the BCL6 protein with an EC_{50} of less than 200 nM (e.g., less than 150 nM, less than 100 nM, less than 10 nM, less than 1 nM). For example, the compounds can reduce cell viability in a cell line expressing the BCL6 protein with an EC_{50} of about 0.1 nM to about 100 nM, about 0.1 nM to about 50 nM, about 1 nM to about 50 nM, about 1 nM to about 20 nM, or about 0.1 nM to about 1 nM.

In some embodiments, the compounds of Formula (**I**) (e.g., Formula (**I-1**), Formula (**I-2**), Formula (**I-a**) (e.g., Formula (**I-a-1**), (**I-a-2**), (**I-a-3**), or (**I-a-4**)), Formula (**I-b**) (e.g., Formula (**I-b-1**), (**I-b-2**), (**I-b-3**), or (**I-b-4**)), Formula (**I-c**) (e.g., Formula (**I-c-1**) or (**I-c-2**)), Formula (**I-d**) (e.g., Formula (**I-d-1**)), or Formula (**I-e**) (e.g., Formula (**I-e-1**) or (**I-e-2**))), Formula (**II**), or Formula (**II-a**) (e.g., Formula (**II-a-1**)), or pharmaceutically acceptable salts thereof, induce degradation of a BCL6 protein in a cell line expressing the BCL6 protein with a DC_{50} of less than 1 μM (e.g., less than 750 nM, less than 500 nM, or less than 200 nM). In some embodiments, the compounds of Formula (**I**) (e.g., Formula (**I-1**), Formula (**I-2**), Formula (**I-a**) (e.g., Formula (**I-a-1**), (**I-a-2**), (**I-a-3**), or (**I-a-4**)), Formula (**I-b**) (e.g., Formula (**I-b-1**), (**I-b-2**), (**I-b-3**), or (**I-b-4**)), Formula (**I-c**) (e.g., Formula (**I-c-1**) or (**I-c-2**)), Formula (**I-d**) (e.g., Formula (**I-d-1**)), or Formula (**I-e**) (e.g., Formula (**I-e-1**) or (**I-e-2**))), Formula (**II**), or Formula (**II-a**) (e.g., Formula (**II-a-1**)), or pharmaceutically acceptable salts thereof, induce degradation of a BCL6 protein in a cell line expressing the BCL6 protein with a DC_{50} of less than 200 nM (e.g., less than 150 nM, less than 100 nM, less than 10 nM, less than 1 nM). For example, the compounds can induce degradation of a BCL6 protein in a cell line expressing the BCL6 protein with a DC_{50} of about 0.1 nM to about 100 nM, about 0.1 nM to about 50 nM, about 1 nM to about 50 nM, about 1 nM to about 20 nM, or about 0.1 nM to about 1 nM.

In some embodiments, the compounds of Formula (**I**) (e.g., Formula (**I-1**), Formula (**I-2**), Formula (**I-a**) (e.g., Formula (**I-a-1**), (**I-a-2**), (**I-a-3**), or (**I-a-4**)), Formula (**I-b**) (e.g., Formula (**I-b-1**), (**I-b-2**), (**I-b-3**), or (**I-b-4**)), Formula (**I-c**) (e.g., Formula (**I-c-1**) or (**I-c-2**)), Formula (**I-d**) (e.g., Formula (**I-d-1**)), or Formula (**I-e**) (e.g., Formula (**I-e-1**) or (**I-e-2**))), Formula (**II**), or Formula (**II-a**) (e.g., Formula (**II-a-1**)), or pharmaceutically acceptable salts thereof, induce degradation of a BCL6 protein in a cell line expressing the BCL6 protein with a Y_{min} of less than 70% (e.g., less than 50%, less than 30%, less than 20%, or less than 10%). In some embodiments, the compounds of Formula (**I**) (e.g., Formula (**I-1**), Formula (**I-2**), Formula (**I-a**) (e.g., Formula (**I-a-1**), (**I-a-2**), (**I-a-3**), or (**I-a-4**)), Formula (**I-b**) (e.g., Formula

(**I-b-1**), (**I-b-2**), (**I-b-3**), or (**I-b-4**)), Formula (**I-c**) (e.g., Formula (**I-c-1**) or (**I-c-2**)), Formula (**I-d**) (e.g., Formula (**I-d-1**)), or Formula (**I-e**) (e.g., Formula (**I-e-1**) or (**I-e-2**))), Formula (**II**), or Formula (**II-a**) (e.g., Formula (**II-a-1**)), or pharmaceutically acceptable salts thereof, induce degradation of a BCL6 protein in a cell line expressing the BCL6 protein with a Y_{min} of less than 50% (e.g., less than 40%, less than 30%, less than 20%, less than 10%, or less than 5%). In some embodiments, the compounds of Formula (**I**) (e.g., Formula (**I-1**), Formula (**I-2**), Formula (**I-a**) (e.g., Formula (**I-a-1**), (**I-a-2**), (**I-a-3**), or (**I-a-4**)), Formula (**I-b**) (e.g., Formula (**I-b-1**), (**I-b-2**), (**I-b-3**), or (**I-b-4**)), Formula (**I-c**) (e.g., Formula (**I-c-1**) or (**I-c-2**)), Formula (**I-d**) (e.g., Formula (**I-d-1**)), or Formula (**I-e**) (e.g., Formula (**I-e-1**) or (**I-e-2**))), Formula (**II**), or Formula (**II-a**) (e.g., Formula (**II-a-1**)), or pharmaceutically acceptable salts thereof, induce degradation of a BCL6 protein in a cell line expressing the BCL6 protein with a Y_{min} of less than 30% (e.g., less than 25%, less than 20%, less than 15%, less than 10%, or less than 5%). For example, the compounds can induce degradation of a BCL6 protein in a cell line expressing the BCL6 protein with a Y_{min} of about 1% to about 70% (e.g., about 5% to about 50%, about 20% to about 30%, about 20% to about 40%, or about 10% to about 30%).

Also provided herein is a BCL6 protein non-covalently bound with a compound of Formula (**I**) (e.g., Formula (**I-1**), Formula (**I-2**), Formula (**I-a**) (e.g., Formula (**I-a-1**), (**I-a-2**), (**I-a-3**), or (**I-a-4**)), Formula (**I-b**) (e.g., Formula (**I-b-1**), (**I-b-2**), (**I-b-3**), or (**I-b-4**)), Formula (**I-c**) (e.g., Formula (**I-c-1**) or (**I-c-2**)), Formula (**I-d**) (e.g., Formula (**I-d-1**)), or Formula (**I-e**) (e.g., Formula (**I-e-1**) or (**I-e-2**))), Formula (**II**), or Formula (**II-a**) (e.g., Formula (**II-a-1**)), or a pharmaceutically acceptable salt thereof.

Also provided herein is a ternary complex comprising a BCL6 protein, a compound of Formula (**I**) (e.g., Formula (**I-1**), Formula (**I-2**), Formula (**I-a**) (e.g., Formula (**I-a-1**), (**I-a-2**), (**I-a-3**), or (**I-a-4**)), Formula (**I-b**) (e.g., Formula (**I-b-1**), (**I-b-2**), (**I-b-3**), or (**I-b-4**)), Formula (**I-c**) (e.g., Formula (**I-c-1**) or (**I-c-2**)), Formula (**I-d**) (e.g., Formula (**I-d-1**)), or Formula (**I-e**) (e.g., Formula (**I-e-1**) or (**I-e-2**))), Formula (**II**), or Formula (**II-a**) (e.g., Formula (**II-a-1**)), or a pharmaceutically acceptable salt thereof, and a CRBN protein or a portion thereof.

Chemical definitions

The term "halo" refers to fluoro (F), chloro (Cl), bromo (Br), or iodo (I).

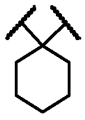
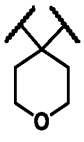
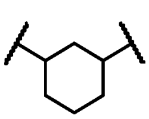
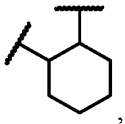
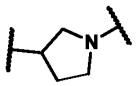
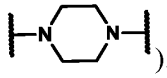
The term "oxo" refers to a divalent doubly bonded oxygen atom (i.e., "=O"). As used herein, oxo groups are attached to carbon atoms to form carbonyls.

The term "alkyl" refers to a saturated acyclic hydrocarbon radical that can be a straight chain or branched chain, containing the indicated number of carbon atoms. For example, C_{1-10}

indicates that the group can have from 1 to 10 (inclusive) carbon atoms in it. Alkyl groups can either be unsubstituted or substituted with one or more substituents. Non-limiting examples include methyl, ethyl, *iso*-propyl, *tert*-butyl, *n*-hexyl. The term "saturated" as used in this context means only single bonds present between constituent carbon atoms and other available valences occupied by hydrogen and/or other substituents as defined herein.

The term "haloalkyl" refers to an alkyl, in which one or more hydrogen atoms is/are replaced with an independently selected halo (e.g., $-CF_3$, $-CHF_2$, or $-CH_2F$).

The term "alkoxy" refers to an -O-alkyl radical (e.g., $-OCH_3$).

The term "alkylene" refers to a divalent alkyl (e.g., $-CH_2-$). Similarly, terms such as "cycloalkylene" and "heterocyclylene" refer to divalent cycloalkyl and heterocyclyl respectively. For avoidance of doubt, in "cycloalkylene" and "heterocyclylene", the two radicals can be on the same ring carbon atom (e.g., a geminal diradical such as  or ) or on different ring atoms (e.g., ring carbon and/or nitrogen atoms (e.g., vicinal ring carbon and/or nitrogen atoms)) (e.g., , , , ).

The term "alkenyl" refers to an acyclic hydrocarbon chain that can be a straight chain or branched chain having one or more carbon-carbon double bonds. The alkenyl moiety contains the indicated number of carbon atoms. For example, C_{2-6} indicates that the group can have from 2 to 6 (inclusive) carbon atoms in it. Alkenyl groups can either be unsubstituted or substituted with one or more substituents.

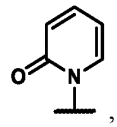
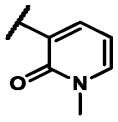
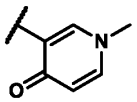
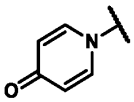
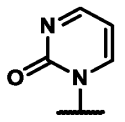
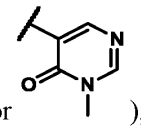
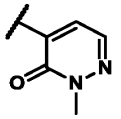
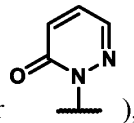
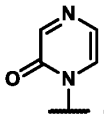
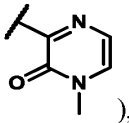
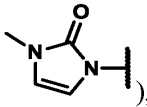
The term "alkynyl" refers to an acyclic hydrocarbon chain that can be a straight chain or branched chain having one or more carbon-carbon triple bonds. The alkynyl moiety contains the indicated number of carbon atoms. For example, C_{2-6} indicates that the group can have from 2 to 6 (inclusive) carbon atoms in it. Alkynyl groups can either be unsubstituted or substituted with one or more substituents.

The term "aryl" refers to a 6-20 carbon mono-, bi-, tri- or polycyclic group wherein at least one ring in the system is aromatic (e.g., 6-carbon monocyclic, 10-carbon bicyclic, or 14-carbon tricyclic aromatic ring system); and wherein 0, 1, 2, 3, or 4 atoms of each ring can be

substituted by a substituent. Examples of aryl groups include phenyl, naphthyl, tetrahydronaphthyl, and the like.

The term "cycloalkyl" as used herein refers to mono-, bi-, tri-, or polycyclic saturated or partially unsaturated hydrocarbon groups having, e.g., 3 to 20 ring carbons, preferably 3 to 15 ring carbons, and more preferably 3 to 12 ring carbons or 3-10 ring carbons or 3-6 ring carbons, wherein the cycloalkyl group can be optionally substituted. The term "saturated" as used in this context means only single bonds present between constituent carbon atoms. Examples of saturated cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Partially unsaturated cycloalkyl can have any degree of unsaturation provided that one or more double bonds is present in the cycloalkyl, none of the rings in the ring system are aromatic, and the partially unsaturated cycloalkyl group is not fully saturated overall. Examples of partially unsaturated cycloalkyl include, without limitation, cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl. Cycloalkyl can include multiple fused and/or bridged rings. Non-limiting examples of fused/bridged cycloalkyl includes: bicyclo[1.1.0]butyl, bicyclo[2.1.0]pentyl, bicyclo[1.1.1]pentyl, bicyclo[3.1.0]hexyl, bicyclo[2.1.1]hexyl, bicyclo[3.2.0]heptyl, bicyclo[4.1.0]heptyl, bicyclo[2.2.1]heptyl, bicyclo[3.1.1]heptyl, bicyclo[4.2.0]octyl, bicyclo[3.2.1]octyl, bicyclo[2.2.2]octyl, and the like. Cycloalkyl also includes spirocyclic rings (e.g., spirocyclic bicycle wherein two rings are connected through just one atom). Non-limiting examples of spirocyclic cycloalkyls include spiro[2.2]pentyl, spiro[2.5]octyl, spiro[3.5]nonyl, spiro[3.5]nonyl, spiro[3.5]nonyl, spiro[4.4]nonyl, spiro[2.6]nonyl, spiro[4.5]decyl, spiro[3.6]decyl, spiro[5.5]undecyl, and the like.

The term "heteroaryl", as used herein, means a mono-, bi-, tri- or polycyclic group having 5 to 20 ring atoms, alternatively 5, 6, 9, 10, or 15 ring atoms; wherein at least one ring in the system contains one or more heteroatoms independently selected from the group consisting of N, O, and S (inclusive of oxidized forms such as:  or ) and at least one ring in the system is aromatic (but does not have to be a ring which contains a heteroatom, e.g. tetrahydroisoquinolinyl, e.g., tetrahydroquinolinyl). In some embodiments, heteroaryl groups contain 1-4 (e.g., 1, 2, or 3) ring heteroatoms each independently selected from the group consisting of N, O, and S (inclusive of oxidized forms such as:  or ). Heteroaryl groups can either be unsubstituted or substituted with one or more substituents.

Examples of heteroaryl include thienyl, pyridinyl, furyl, oxazolyl, oxadiazolyl, pyrrolyl, imidazolyl, triazolyl, thiodiazolyl, pyrazolyl, isoxazolyl, thiadiazolyl, pyranyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, thiazolyl benzothienyl, benzoxadiazolyl, benzofuranyl, benzimidazolyl, benzotriazolyl, cinnolinyl, indazolyl, indolyl, isoquinolinyl, isothiazolyl, naphthyridinyl, purinyl, thienopyridinyl, pyrido[2,3-*d*]pyrimidinyl, pyrrolo[2,3-*b*]pyridinyl, quinazolinyl, quinolinyl, thieno[2,3-*c*]pyridinyl, pyrazolo[3,4-*b*]pyridinyl, pyrazolo[3,4-*c*]pyridinyl, pyrazolo[4,3-*c*]pyridinyl, pyrazolo[4,3-*b*]pyridinyl, tetrazolyl, chromanyl, 2,3-dihydrobenzo[*b*][1,4]dioxinyl, benzo[*d*][1,3]dioxolyl, 2,3-dihydrobenzofuranyl, tetrahydroquinolinyl, 2,3-dihydrobenzo[*b*][1,4]oxathiinyl, isoindolinyl, and others. In some embodiments, the heteroaryl is selected from thienyl, pyridinyl, furyl, pyrazolyl, imidazolyl, isoindolinyl, pyranyl, pyrazinyl, and pyrimidinyl. For purposes of clarification, heteroaryl also includes aromatic lactams, aromatic cyclic ureas, or vinylogous analogs thereof, in which each ring nitrogen adjacent to a carbonyl is tertiary (i.e., all three valences are occupied by non-hydrogen substituents), such as one or more of pyridone (e.g., , , , or ), pyrimidone (e.g.,  or ), pyridazinone (e.g.,  or ), pyrazinone (e.g.,  or ), and imidazolone (e.g., ), wherein each ring nitrogen adjacent to a carbonyl is tertiary (i.e., the oxo group (i.e., "=O") herein is a constituent part of the heteroaryl ring).

The term "heterocyclyl" refers to a mono-, bi-, tri-, or polycyclic saturated or partially unsaturated ring system with 3-15 ring atoms (e.g., 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-15 membered tricyclic ring system) having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic or polycyclic, the heteroatoms selected from O, N, and S (inclusive of oxidized forms such as:  or ) (e.g., carbon atoms and 1-3, 1-6, or 1-9 heteroatoms of N, O, S, or P if monocyclic, bicyclic, or tricyclic, respectively), wherein 0, 1, 2 or 3 atoms of each ring can be substituted by a substituent. The

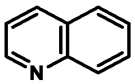
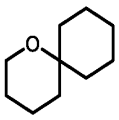
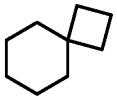
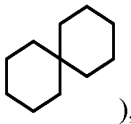
term "saturated" as used in this context means only single bonds present between constituent ring atoms and other available valences occupied by hydrogen and/or other substituents as defined herein. Examples of saturated heterocyclyl groups include piperazinyl, pyrrolidinyl, dioxanyl, morpholinyl, tetrahydrofuranyl, and the like. Partially unsaturated heterocyclyl groups can have any degree of unsaturation provided that one or more double bonds is present in the heterocyclyl, none of the rings in the ring system are aromatic, and the partially unsaturated heterocyclyl group is not fully saturated overall. Examples of partially unsaturated heterocyclyl groups include, without limitation, tetrahydropyridyl, dihydropyrazinyl, dihydropyridyl, dihydropyrrolyl, dihydrofuranyl, dihydrothiophenyl.

Heterocyclyl can include multiple fused and bridged rings. Non-limiting examples of fused/bridged heteorocyclyl includes: 2-azabicyclo[1.1.0]butyl, 2-azabicyclo[2.1.0]pentyl, 2-azabicyclo[1.1.1]pentyl, 3-azabicyclo[3.1.0]hexyl, 5-azabicyclo[2.1.1]hexyl, 3-azabicyclo[3.2.0]heptyl, octahydrocyclopenta[c]pyrrolyl, 3-azabicyclo[4.1.0]heptyl, 7-azabicyclo[2.2.1]heptyl, 6-azabicyclo[3.1.1]heptyl, 7-azabicyclo[4.2.0]octyl, 2-azabicyclo[2.2.2]octyl, 3-azabicyclo[3.2.1]octyl, 2-oxabicyclo[1.1.0]butyl, 2-oxabicyclo[2.1.0]pentyl, 2-oxabicyclo[1.1.1]pentyl, 3-oxabicyclo[3.1.0]hexyl, 5-oxabicyclo[2.1.1]hexyl, 3-oxabicyclo[3.2.0]heptyl, 3-oxabicyclo[4.1.0]heptyl, 7-oxabicyclo[2.2.1]heptyl, 6-oxabicyclo[3.1.1]heptyl, 7-oxabicyclo[4.2.0]octyl, 2-oxabicyclo[2.2.2]octyl, 3-oxabicyclo[3.2.1]octyl, and the like. Heterocyclyl also includes spirocyclic rings (e.g., spirocyclic bicycle wherein two rings are connected through just one atom). Non-limiting examples of spirocyclic heterocyclyls include 2-azaspiro[2.2]pentyl, 4-azaspiro[2.5]octyl, 1-azaspiro[3.5]nonyl, 2-azaspiro[3.5]nonyl, 7-azaspiro[3.5]nonyl, 2-azaspiro[4.4]nonyl, 6-azaspiro[2.6]nonyl, 1,7-diazaspiro[4.5]decyl, 7-azaspiro[4.5]decyl 2,5-diazaspiro[3.6]decyl, 3-azaspiro[5.5]undecyl, 2-oxaspiro[2.2]pentyl, 4-oxaspiro[2.5]octyl, 1-oxaspiro[3.5]nonyl, 2-oxaspiro[3.5]nonyl, 7-oxaspiro[3.5]nonyl, 2-oxaspiro[4.4]nonyl, 6-oxaspiro[2.6]nonyl, 1,7-dioxaspiro[4.5]decyl, 2,5-dioxaspiro[3.6]decyl, 1-oxaspiro[5.5]undecyl, 3-oxaspiro[5.5]undecyl, 3-oxa-9-azaspiro[5.5]undecyl and the like.

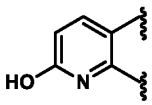
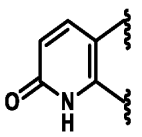
A nitrogen-containing heterocyclyl as used herein refers to a heterocyclyl having 1-2 ring nitrogen atoms and 0-2 additional ring heteroatoms selected from the group consisting of O and S (inclusive of oxidized such as:  or ). The nitrogen-containing heterocyclyl can be monocyclic, bicyclic, or polycyclic as defined elsewhere herein. Examples of monocyclic nitrogen-containing heterocyclyl include azetidinyl, pyrrolidinyl, piperidinyl,

piperazinyl, morpholinyl, and the like. Examples of bicyclic nitrogen-containing heterocyclyl include 7-azaspiro[3.5]nonyl, 1,7-diazaspiro[4.5]decyl, 3-oxa-7,9-diazabicyclo[3.3.1]nonanyl, 2,6-diazaspiro[3.3]heptanyl, and the like.

As used herein, when a ring is described as being "partially unsaturated", it means the ring has one or more additional degrees of unsaturation (in addition to the degree of unsaturation attributed to the ring itself; e.g., one or more double or triple bonds between constituent ring atoms), provided that the ring is not aromatic. Examples of such rings include: cyclopentene, cyclohexene, cycloheptene, dihydropyridine, tetrahydropyridine, dihydropyrrole, dihydrofuran, dihydrothiophene, and the like.

For the avoidance of doubt, and unless otherwise specified, for rings and cyclic groups (e.g., aryl, heteroaryl, heterocyclyl, heterocycloalkenyl, cycloalkenyl, cycloalkyl, and the like described herein) containing a sufficient number of ring atoms to form bicyclic or higher order ring systems (e.g., tricyclic, polycyclic ring systems), it is understood that such rings and cyclic groups encompass those having fused rings, including those in which the points of fusion are located (i) on adjacent ring atoms (e.g., [x.x.0] ring systems, in which 0 represents a zero atom bridge (e.g., )); (ii) a single ring atom (spiro-fused ring systems) (e.g., , , or ), or (iii) a contiguous array of ring atoms (bridged ring systems having all bridge lengths > 0) (e.g., , , or ).

In addition, atoms making up the compounds of the present embodiments are intended to include all isotopic forms of such atoms. Isotopes, as used herein, include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium, and isotopes of carbon include ^{13}C and ^{14}C.

In addition, the compounds generically or specifically disclosed herein are intended to include all tautomeric forms. Thus, by way of example, a compound containing the moiety:  encompasses the tautomeric form containing the moiety: . Similarly,

a pyridinyl or pyrimidinyl moiety that is described to be optionally substituted with hydroxyl encompasses pyridone or pyrimidone tautomeric forms.

The compounds provided herein can encompass various stereochemical forms. The compounds also encompass diastereomers as well as optical isomers, e.g., mixtures of enantiomers including racemic mixtures, as well as individual enantiomers and diastereomers, which arise as a consequence of structural asymmetry in certain compounds. Unless otherwise indicated, when a disclosed compound is named or depicted by a structure without specifying the stereochemistry and has one or more chiral centers, it is understood to represent all possible stereoisomers of the compound.

Methods of Treatment

Indications

Provided herein are methods for inducing degradation of a BCL6 protein. For example, provided herein are compounds capable of inducing degradation of a BCL6 protein useful for treating or preventing cancers. Exemplary compounds that bind to BCL6 are described in, e.g., Cerchietti, Leandro C., et al. *Cancer Cell* 17.4 (2010): 400-411, doi: 10.1016/j.ccr.2009.12.050; Cardenas, Mariano G., et al. *The Journal of Clinical Investigation* 126(9) (2016): 3351-3362, doi: 10.1172/JCI85795; Kerres, Nina, et al., *Cell Reports* 20.12 (2017): 2860-2875, doi: 10.1016/j.celrep.2017.08.081; Yasui, Takeshi, et al., *Bioorganic & Medicinal Chemistry* 25.17 (2017): 4876-4886, doi: 10.1016/j.bmc.2017.07.037; Kamada, Yusuke, et al., *Journal of Medicinal Chemistry* 60.10 (2017): 4358-4368, doi: 10.1021/acs.jmedchem.7b00313; McCoull, William, et al., *ACS Chemical Biology* 13.11 (2018): 3131-3141, doi: 10.1021/acschembio.8b00698; Guo, Weikai, et al. *Journal of Medicinal Chemistry* 63.2 (2020): 676-695, doi: 10.1021/acs.jmedchem.9b01618; Teng, Mingxing, et al., *ACS Medicinal Chemistry Letters* 11.6 (2020): 1269-1273, doi: 10.1021/acsmedchemlett.0c00111; Pearce, Andrew C., et al., *Journal of Biological Chemistry* 297.2 (2021): 100928, doi: 10.1016/j.jbc.2021.100928; Ding, Shu, Yu Rao, and Qianjin Lu, *Cellular & Molecular Immunology* (2022): 1-3, doi: 10.1038/s41423-022-00882-1; Xing, Y. et al., *Cancer Letters* (2022), doi: 10.1016/j.canlet.2021.12.035; Huckvale, R. et al., *Journal of Medicinal Chemistry* (2022), doi: 10.1021/acs.jmedchem.1c02175; Davis, O. et al., *Journal of Medicinal Chemistry* (2022), doi: 10.1021/acs.jmedchem.1c02174; International Publication Nos. WO 2008/066887; WO 2010/008436; WO 2014/204859; WO 2018/215798; WO 2018/215801; WO 2018/219281; WO 2019/119138; WO 2019/119144; WO 2019/119145;

WO 2019/153080; WO 2019/197842; WO 2020/104820; WO 2021/074620; WO 2021/077010; WO 2022/221673; WO 2023/212147; and WO 2023/114460.

The term "compound(s) provided herein" refers to compound(s) of Formula (**I**) (e.g., Formula (**I-1**), Formula (**I-2**), Formula (**I-a**) (e.g., Formula (**I-a-1**), (**I-a-2**), (**I-a-3**), or (**I-a-4**)), Formula (**I-b**) (e.g., Formula (**I-b-1**), (**I-b-2**), (**I-b-3**), or (**I-b-4**)), Formula (**I-c**) (e.g., Formula (**I-c-1**) or (**I-c-2**)), Formula (**I-d**) (e.g., Formula (**I-d-1**)), or Formula (**I-e**) (e.g., Formula (**I-e-1**) or (**I-e-2**))), Formula (**II**), or Formula (**II-a**) (e.g., Formula (**II-a-1**)) as disclosed herein.

Potency of degradation by a compound provided herein, or a pharmaceutically acceptable salt thereof, can be determined by DC_{50} value. As used herein, DC_{50} refers to the concentration of the compound provided herein, or a pharmaceutically acceptable salt thereof, that results in a 50% decrease in the concentration of a protein (e.g., BCL6 protein) in a cell compared to the concentration of the protein before the cell is contacted with the compound provided herein, or a pharmaceutically acceptable salt thereof, or compared to the concentration of the protein in a cell not contacted with the compound provided herein, or a pharmaceutically acceptable salt thereof. A compound with a lower DC_{50} value, as determined under substantially similar conditions, is a more potent inducer of degradation relative to a compound with a higher DC_{50} value. In some embodiments, a DC_{50} value can be determined (e.g., using HiBiT detection) in vitro or in vivo (e.g., in tumor cells expressing a BCL6 protein (e.g., cell lines such as A3/KAW, A4/FUK, DB, DOHH2, Farage, HT, Karpas 422, KML1, MHHPREB1, NUDHL1, OCI-Ly1, OCI-Ly3, OCI-Ly7, OCI-Ly18, OCI-Ly19, Pfeiffer, RI1, RL, SU-DHL-4, SU-DHL-5, SU-DHL-6, SU-DHL-8, SU-DHL-10, VAL, or WSU-DLCL2; see also those disclosed in, e.g., Cardenas, Mariano G., et al. *Clinical Cancer Research* 23.4 (2017): 885-893, doi: 10.1158/1078-0432.CCR-16-2071 and International Publication Nos. WO 2021/080950, WO 2021/077010, and WO 2022/221673)). In some embodiments, a cell line that is not dependent on BCL6 and/or that does not have significant expression of BCL6 can be used as a control (e.g., Toledo, H929, MM.1S, or OPM2).

Potency of degradation by a compound provided herein, or a pharmaceutically acceptable salt thereof, can be determined by EC_{50} value. As used herein, EC_{50} refers to the concentration of the compound provided herein, or a pharmaceutically acceptable salt thereof, that results in a 50% decrease in the concentration of a protein (e.g., BCL6 protein) relative to the trough concentration of the protein in a cell, when compared to the concentration of the protein before the cell is contacted with the compound provided herein, or a pharmaceutically acceptable salt thereof, or compared to the concentration of the protein in a cell not contacted with the compound provided herein, or a pharmaceutically acceptable salt thereof. A compound

with a lower EC_{50} value, as determined under substantially similar conditions, is a more potent inducer of degradation relative to a compound with a higher EC_{50} value. In some embodiments, an EC_{50} value can be determined (e.g., using HiBiT detection) in vitro or in vivo (e.g., in tumor cells expressing a BCL6 protein (e.g., cell lines such as A3/KAW, A4/FUK, DB, DOHH2, Farage, HT, Karpas 422, KML1, MHHPREB1, NUDHL1, OCI-Ly1, OCI-Ly3, OCI-Ly7, OCI-Ly18, OCI-Ly19, Pfeiffer, RI1, RL, SU-DHL-4, SU-DHL-5, SU-DHL-6, SU-DHL-8, SU-DHL-10, VAL, or WSU-DLCL2; see also those disclosed in, e.g., Cardenas, Mariano G., et al. *Clinical Cancer Research* 23.4 (2017): 885-893, doi: 10.1158/1078-0432.CCR-16-2071 and International Publication Nos. WO 2021/080950,WO 2021/077010, and WO 2022/221673)). In some embodiments, a cell line that is not dependent on BCL6 and/or that does not have significant expression of BCL6 can be used as a control (e.g., Toledo, H929, MM.1S, or OPM2).

Potency of degradation by a compound provided herein, or a pharmaceutically acceptable salt thereof, can be determined by a Y_{min} value. As used herein, Y_{min} refers to the ratio of trough concentration of a protein (e.g., BCL6 protein) in a cell compared to the concentration of the protein before the cell is contacted with the compound provided herein, or a pharmaceutically acceptable salt thereof, or compared to the concentration of the protein in a cell not contacted with the compound provided herein, or a pharmaceutically acceptable salt thereof, expressed as a percentage. As used herein, D_{max} is 1-Y_{min}. Y_{min} can be measured by a HiBiT assay (e.g., as described in Example **B1)**. A compound with a lower Y_{min} value, as determined under substantially similar conditions, is a more potent inducer of degradation relative to a compound with a higher Y_{min} value. In some embodiments, a Y_{min} value can determined (e.g., using HiBiT detection), in vitro or in vivo (e.g., in tumor cells expressing a BCL6 protein (e.g., cell lines such as A3/KAW, A4/FUK, DB, DOHH2, Farage, HT, Karpas 422, KML1, MHHPREB1, NUDHL1, OCI-Ly1, OCI-Ly3, OCI-Ly7, OCI-Ly18, OCI-Ly19, Pfeiffer, RI1, RL, SU-DHL-4, SU-DHL-5, SU-DHL-6, SU-DHL-8, SU-DHL-10, VAL, or WSU-DLCL2; see also those disclosed in, e.g., Cardenas, Mariano G., et al. *Clinical Cancer Research* 23.4 (2017): 885-893, doi: 10.1158/1078-0432.CCR-16-2071 and International Publication Nos. WO 2021/080950, WO 2021/077010, and WO 2022/221673)). In some embodiments, a cell line that is not dependent on BCL6 and/or that does not have significant expression of BCL6 can be used as a control (e.g., Toledo, H929, MM.1S, or OPM2).

In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, exhibits a Y_{min} of less than 70% (e.g., less than 50% or less than 30%) in a HiBiT based degradation assay (e.g., an assay as described in **Example B1**). In some embodiments, a

compound provided herein, or a pharmaceutically acceptable salt thereof, exhibits a Y_{min} of less than 50% (e.g., less than 30%) in a HiBiT based degradation assay. In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, exhibits a Y_{min} of less than 30% in a HiBiT based degradation assay.

In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, exhibits a Y_{min} of less than 70% (e.g., less than 50% or less than 30%) in the assay described in **Example B1**. In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, exhibits a Y_{min} of less than 50% (e.g., less than 30%) in the assay described in **Example B1**. In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, exhibits a Y_{min} of less than 30% in the assay described in **Example B1**.

In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, exhibits a Y_{min} of about 0% to about 70% (e.g., about 0% to about 50%, about 30% to about 50%, or about 0% to about 30%) in a HiBiT based degradation assay (e.g., an assay as described in **Example B1**). In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, exhibits a Y_{min} of about 0% to about 50% (e.g., about 30% to about 50% or about 0% to about 30%) in a HiBiT based degradation assay. In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, exhibits a Y_{min} of about 0% to about 30% in a HiBiT based degradation assay.

In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, exhibits a Y_{min} of about 0% to about 70% (e.g., about 0% to about 50%, about 30% to about 50%, or about 0% to about 30%) in the assay described in **Example B1**. In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, exhibits a Y_{min} of about 0% to about 50% (e.g., about 30% to about 50% or about 0% to about 30%) in the assay described in **Example B1**. In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, exhibits a Y_{min} of about 0% to about 30% in the assay described in **Example B1**.

The effect of protein degradation typically increases over time, though the appearance of degradation (e.g., as expressed by the percentage degradation compared to a control, or the parameters Y_{min}, DC_{50}, and/or D_{max}) is affected by the resynthesis rate of the protein. Accordingly, degradation can be examined after a specified period of time, such as 6 hours, 12 hours, 18 hours, 1 day, 2 days, 3 days, 5 days, 10 days, or more. For example, degradation can be expressed as the percent degradation after 24 hours.

Exemplary assays for validating the degradation-inducing mechanism of a compound

as provided herein are known in the art and are described, for example, in Wu, et al. *Nature Structural & Molecular Biology* 27.7 (2020): 605-614, doi: 10.1038/s41594-020-0438-0.

Degradation assays can be used to quantify both on- and off-target degradation-inducing effects of compounds, such as those compounds provided herein. Exemplary assays include quantitative immunoblotting, other immunoassays (e.g., MesoScale Discovery (MSD) immunoassays), homogenous time resolved florescence (HTRF), and HiBiT. In some embodiments, cells can be contacted with a compound provided herein, or a pharmaceutically acceptable salt thereof, incubated, and then the lysate can be prepared for gel electrophoresis (e.g., SDS-PAGE), followed by immunoblotting and quantification compared to a control (e.g., a DMSO-treated control). As another example, a cell line can be engineered to express a HiBiT-tagged BCL6 protein, and the amount of fluorescence observed when the complementary LgBiT peptide is added can be compared between cells treated with a compound provided herein, or a pharmaceutically acceptable salt thereof, and a control (e.g., a DMSO-treated control). See, for instance, **Example B1**. In some embodiments, off-target degradation inducing effects can be assessed for the proteins Eukaryotic peptide chain release factor GTP-binding subunit ERF3A (GSPT1), Ikaros (IKZF1), Helios (IKZF2), Aiolos (IKZF3), and/or casein kinase I isoform alpha (CK1α). See also, e.g., International Publication Nos. WO 2018/215798; WO 2018/215801; WO 2020/104820; McCoull, William, et al., *ACS Chemical Biology* 13.11 (2018): 3131-3141, doi: 10.1021/acschembio.8b00698; Bellenie, Benjamin R., et al., *Journal of Medicinal Chemistry* 63.8 (2020): 4047-4068, doi: 10.1021/acs.jmedchem.9b02076; Lloyd, Matthew G., et al., *Journal of Medicinal Chemistry* 64.23 (2021): 17079-17097, doi: 10.1021/acs.jmedchem.1c00946.

Binding affinity of a compound provided herein, or a pharmaceutically acceptable salt thereof, to BCL6 can be determined by, for example, a binding IC_{50} or K_i value (e.g., using a competition assay), or by a K_D value (e.g., using a biophysical assay). A compound with a lower binding IC_{50} value, as determined under substantially similar conditions, is a more potent binder relative to a compound with a higher binding IC_{50} value. A compound with a lower binding K_i value, as determined under substantially similar conditions, is a more potent binder relative to a compound with a higher binding K_i value. Similarly, a compound with a lower K_D value, as determined under substantially similar conditions, is a more potent binder relative to a compound with a higher K_D value. A K_D value can be determined by surface plasmon resonance (SPR) or biolayer interferometry; see, e.g., Guo, Weikai, et al., *Journal of Medicinal Chemistry* 63.2 (2020): 676-695, doi: 10.1021/acs.jmedchem.9b01618; Lloyd, Matthew G., et al., *Journal of Medicinal Chemistry* 64.23 (2021): 17079-17097, doi:

10.1021/acs.jmedchem.1c00946, and International Publication Nos. WO 2019/153080; WO 2019/119144; and WO 2019/119145.

The ability of a compound provided herein, or a pharmaceutically acceptable salt thereof, to inhibit BCL6 can be determined using an IC_{50} value. A compound with a lower IC_{50} value, as determined under substantially similar conditions, is a more potent inhibitor relative to a compound with a higher IC_{50} value. For example, an IC_{50} value can be calculated using a FRET (e.g., Homogeneous Time Resolved Fluorescence (HTRF)) assay, where a tagged (e.g., His-tagged) BCL6 protein and tagged (e.g., fluorophore-tagged (e.g., Alexa-Fluor633)) corepressor peptide (e.g., BCOR) are incubated in the presence of compounds provided herein, or pharmaceutically acceptable salts thereof, and subsequently, the FRET ratio (relative to appropriate controls) can be measured using an appropriate FRET pair (e.g., with an antibody that recognizes the tagged BCL6 protein (e.g., anti-His-Terbium cryptate)). See, e.g., International Publication Nos. WO 2018/108704; WO 2018/215798; WO 2019/197842; WO 2020/104820; WO 2021/074620. As another example, an IC_{50} value can be calculated using an enzyme-linked immunosorbent assay (ELISA) using a tagged (e.g., biotinylated) corepressor peptide (e.g., BCOR) immobilized on a substrate and a tagged (e.g., FLAG-tagged) BCL6 (e.g., a domain, such as the BTB domain, thereof), where compounds provided herein, or pharmaceutically acceptable salts thereof, can be used to prevent the interaction between the corepressor peptide and BCL6, and the interaction between the corepressor peptide and BCL6 can be measured using an antibody to the BCL6 construct (e.g., anti-FLAG antibody). See, e.g., Kamada, Yusuke, et al., *Journal of Medicinal Chemistry* 60.10 (2017): 4358-4368, doi: 10.1021/acs.jmedchem.7b00313. As yet another example, an IC_{50} value can be calculated using a florescence polarization assay with a fluorescently-tagged corepressor peptide (e.g., SMRT) where compounds provided herein, or pharmaceutically acceptable salts thereof, can be used to prevent the interaction between the corepressor peptide and BCL6. See, e.g., International Publication No. WO 2019/119144. As another example, a cellular IC_{50} value can be calculated using a BRET (Bioluminescence Resonance Energy Transfer) assay, where vectors encoding BCL6 and a corepressor peptide (e.g., SMRT), complementarily fused with NanoLuc or HaloTag, can be inserted into cells. The cells can be treated with compounds provided herein, or pharmaceutically acceptable salts thereof, to determine the effect of the compounds on inhibiting the BCL6-corepressor interaction. See, e.g., International Publication Nos. WO 2018/215798 and WO 2019/197842. In another example, an IC_{50} value for the inhibition of BCL6 repressor function can be calculated using a luciferase assay, where cells are engineered to express luciferase under the control of one or more BCL6 repressor sites, and the cells can

be incubated with compounds provided herein, or pharmaceutically acceptable salts thereof, to determine the effect of the compounds on the function of the BCL6 repressor. See, e.g., International Publication Nos. WO 2019/119144; WO 2019/119145; WO 2019/153080.

Another exemplary way of evaluating the effect of a compound provided herein, or a pharmaceutically acceptable salt thereof, is to measure the induction (e.g., fold induction) of genes that are typically repressed by BCL6 (e.g., *p53*, *ATR*, *CXCR3*, *CD69*, and *CDKN1A*) using a method such as RT-PCR. See, e.g., Guo, Weikai, et al., *Journal of Medicinal Chemistry* 63.2 (2020): 676-695, doi: 10.1021/acs.jmedchem.9b01618.

An exemplary assay for determining the potency of a compound provided herein, or a pharmaceutically acceptable salt thereof, includes measuring the effect of the compound provided herein, or a pharmaceutically acceptable salt thereof, on cell proliferation and/or viability. Cell proliferation assays can be performed in a number of formats, including 2D and 3D. Similarly, a cell proliferation assay can be performed with any appropriate cell line, including, for example, A3/KAW, A4/FUK, DB, DOHH2, Farage, HT, Karpas 422, KML1, MHHPREB1, NUDHL1, OCI-Ly1, OCI-Ly3, OCI-Ly7, OCI-Ly18, OCI-Ly19, Pfeiffer, RI1, RL, SU-DHL-4, SU-DHL-5, SU-DHL-6, SU-DHL-8, SU-DHL-10, VAL, or WSU-DLCL2. In some embodiments, a cell line that is not dependent on BCL6 and/or that does not have significant expression of BCL6 can be used as a control (e.g., Toledo, H929, MM.1S, or OPM2). As an illustrative example, a 3D cell proliferation assay can include growing cells in a 3D medium, contacting the cells with a compound provided herein, or a pharmaceutically acceptable salt thereof, measuring the cellular proliferation using an appropriate reagent (e.g., CELLTITER-GLO® 3D), and then comparing the signal from the experiment with the compound provided herein, or a pharmaceutically acceptable salt thereof, to the signal from a control experiment (e.g., lacking the compound provided herein, or a pharmaceutically acceptable salt thereof). As another illustrative example, a 2D cell proliferation assay can include plating cells onto a growth surface, optionally letting the cells grow for a period of time, contacting the cells with a compound provided herein, or a pharmaceutically acceptable salt thereof, measuring the cellular proliferation using an appropriate reagent (e.g., CELLTITER-GLO®), and then comparing the signal from an experiment with a compound provided herein, or a pharmaceutically acceptable salt thereof, to the signal from a control experiment (e.g., lacking a compound provided herein, or a pharmaceutically acceptable salt thereof). Additional cell viability assays include MTT assays, which are colorimetric assays based on the reduction of the tetrazolium dye MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) to the insoluble purple formazan, and other similar assays based

on related tetrazolium salts, ATPlite assays, and other methods are known in the art. See, for instance, **Example B2**. See also, e.g., Guo, Weikai, et al., *Journal of Medicinal Chemistry* 63.2 (2020): 676-695, doi: 10.1021/acs.jmedchem.9b01618; McCoull, William, et al. *ACS Chemical Biology* 13.11 (2018): 3131-3141, doi: 10.1021/acschembio.8b00698; Lloyd, Matthew G., et al. *Journal of Medicinal Chemistry* 64.23 (2021): 17079-17097, doi: 10.1021/acs.jmedchem.1c00946; Bellenie, Benjamin R., et al. *Journal of Medicinal Chemistry* 63.8 (2020): 4047-4068, doi: 10.1021/acs.jmedchem.9b02076; and International Publication Nos. WO 2018/215798; WO 2018/215801; WO 2018/219281; WO 2019/119145; WO 2019/153080; and WO 2020/104820.

A cell viability assay can be used to measure the effect of a compound provided herein, or a pharmaceutically acceptable salt thereof, on cell death. For example, cells expressing BCL6 protein (e.g., A3/KAW, A4/FUK, DB, DOHH2, Farage, HT, Karpas 422, KML1, MHHPREB1, NUDHL1, OCI-Ly1, OCI-Ly3, OCI-Ly7, OCI-Ly18, OCI-Ly19, Pfeiffer, RI1, RL, SU-DHL-4, SU-DHL-5, SU-DHL-6, SU-DHL-8, SU-DHL-10, VAL, or WSU-DLCL2 cells) can be incubated with various concentrations of a compound provided herein, or a pharmaceutically acceptable salt thereof, and then exposed to a detection reagent (e.g., using a CELLTITER-GLO® Cell Viability Assay kit) to determine cell viability. In some embodiments, the effect on cell viability can be compared to a cell line that is not dependent on BCL6 and/or that does not have significant expression of BCL6 (e.g., Toledo, H929, MM.1S, or OPM2).

A cell viability assay can be used to measure the effect of a compound provided herein, or a pharmaceutically acceptable salt thereof, on cell death in combination with an additional therapeutic agent. For example, cells expressing BCL6 protein (e.g., A3/KAW, A4/FUK, DB, DOHH2, Farage, HT, Karpas 422, KML1, MHHPREB1, NUDHL1, OCI-Ly1, OCI-Ly3, OCI-Ly7, OCI-Ly18, OCI-Ly19, Pfeiffer, RI1, RL, SU-DHL-4, SU-DHL-5, SU-DHL-6, SU-DHL-8, SU-DHL-10, VAL, or WSU-DLCL2 cells) can be incubated (e.g., for 72 hours or for 120 hours) in a 7x7 dose matrix at various concentrations of a compound provided herein, or a pharmaceutically acceptable salt thereof, and an additional therapeutic agent (e.g., any of the additional therapeutic agents described herein) (e.g., half-log diluted from 316 to 1 nM), and then exposed to a detection reagent (e.g., using a CELLTITER-GLO® Cell Viability Assay kit) to determine cell viability. The combination activity can be assessed by the Bliss independence model: negative values as indication of antagonism, positive as synergy, and a value of zero as additive activity. Bliss scores in the dose matrix can be added up to give a "Bliss sum" value to reflect the overall synergy activity of the compound provided herein, or a

pharmaceutically acceptable salt thereof, and the additional therapeutic agent in each cell line. In some embodiments, a cell line that is not dependent on BCL6 and/or that does not have significant expression of BCL6 can be used as a control (e.g., Toledo, H929, MM.1S, or OPM2).

As another example, the potency and/or efficacy of a compound provided herein, or a pharmaceutically acceptable salt thereof, can be evaluated in an animal model, for example, a cell line-derived (CDX) xenograft model (e.g., using an established cancer cell line such as DB, DoHH2, OCI-Ly1, OCI-Ly7, RL, Pfeiffer, SU-DHL-5, SU-DHL-6, WSU-DLCL2, REH, BALL-1, RS4;11, SEMK2, KOPN8, NALM-6, KASUMI-2, RCH-ACV, SUP-B15, BV-173, TOM-1, NALM-20, NALM-21, MUTZ-5, or MHH-CALL-4 (e.g., OCI-Ly1, OCI-Ly7, SU-DHL-5, SU-DHL-6, WSU-DLCL2, DB, RL, Pfeiffer, or DoHH2)), a genetically engineered mouse model (GEMM), or a patient-derived xenograft (PDX) model. For example, a PDX model can be run in immunodeficient mice (e.g., athymic nude, outbred homozygous (e.g., Crl:NU(NCr)-Foxn1^{nu}) or Fox Chase SCID (CB17/Icr-Prkdc^{scid}/IcrIcoCrl) mice). The mice can be female, 6-12 weeks old at tumor implantation and have access to food and water ad libitum. Approximately 70 mg of a tumor can be implanted subcutaneously in the right flank of each mouse. Following implantation, tumors can be measured weekly and once the tumor volumes reach 150-300 mm^3, the mice can be randomized into treatment and control groups. In some embodiments, one or more experimental arms can be added to evaluate pharmacokinetics and/or pharmacodynamics. The mice can be treated with a compound provided herein, or a pharmaceutically acceptable salt thereof, (e.g., via IP or PO administration) and optionally an additional therapy or therapeutic agent (e.g., any of the additional therapies or therapeutic agents described herein). Throughout the study, health condition, body weight and tumor volumes of the mice can be recorded on a weekly basis. The mice can be sacrificed at 28 days or when the tumor reaches 1 cm^3, and the tumors can be evaluated (e.g., by tumor weight, by tumor volume). At the end of each study the Best Response can be calculated for each treatment arm. Best Response is defined as the minimum value of $\Delta Volume_t$ for $t \geq 10$ days. Best Responses between the control arm(s) and the treatment arm(s) can be compared to determine if the treatment(s) work better than the control(s). In some embodiments, tumor samples can also be collected at the end of each study and relevant proteins (e.g., BCL6) can be measured to determine if the treatment has a better protein modulation profile compared to a control. In some embodiments, tumor samples and/or blood samples can also be collected at the end of each study and analyzed for altered gene expression activity (e.g., altered ARID3A, ARID3B, ATR, B2M, BANK1, BATF, BCL11A, BCL2, BCL2A1, BLIMP1, BMI1, CASP8, CCND1,

CCND2, CCR6, CCR7, CD38, CD44, CD69, CDKN1A, CDKN1B, CFLAR/FLIP, CHEK1, CXCR4, CXCR5, DR5, EBI2, ETV6, FCMR, FGD4, ID2, IFITM1, IFITM2, IFNAR2, IFNGR1, IL10, IL10RB, IL7R, CXCL10, IRF1, IRF4, IRF7, IRF9, JAK3, JARID2, JUN, KLF2, LITAF, MCL1, MIP-1a, MYC, MYD88, NFKBIE, NOTCH2, PDL1, PIM1, PPP3R1, PRDM1, PTEN, S1PR1, SHP1, STAT1, STAT3, STAT5A, TLR1, TLR4, TLR7, TLR9, TNF-R2, TOX, TP53, ZEB2, and/or ZNF608 expression levels). For pharmacokinetic and pharmacodynamic studies, tumor and/or blood samples from the mice can be obtained at the same or different time points than efficacy studies. For example, for pharmacokinetic and pharmacodynamic studies, tumor and/or blood samples from the mice can be obtained at Day 1, 3 and/or 5, with collections at 6, 12 and/or 24 hours post-dosing, and relevant proteins can be measured in the tumor samples and pharmacokinetic studies can be performed on the blood samples or a portion thereof (e.g., plasma). In some embodiments, the PDX is a model of B cell acute lymphoblastic leukemia (B-ALL) (e.g., Philadelphia chromosome positive B-ALL, Philadelphia chromosome negative B-ALL, or B-ALL with an MLL-Af4 fusion, an MLL-Af6 fusion, an MLL-Af9 fusion, an MLL-ENL fusion, or an MLL-PTD fusion), non-Hodgkin lymphoma (e.g., a mature B cell neoplasm (e.g., Burkitt lymphoma (BL), large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary large B cell lymphoma of immune-privileged sites (primary LBCL of immune-privileged sites), intravascular large B-cell lymphoma (IVLBCL), primary mediastinal large B cell lymphoma (primary mediastinal LBCL), or high grade B-cell lymphoma NOS (HBGCL-NOS)), follicular lymphoma (FL), mantle cell lymphoma (MCL), or transformations of indolent B cell lymphomas), a peripheral T-cell lymphoma (PTCL) (e.g., anaplastic large cell lymphoma (ALCL) (e.g., ALK-positive anaplastic large cell lymphoma, or ALK-negative anaplastic large cell lymphoma), nodal T follicular helper cell lymphoma (e.g., nodal T follicular helper cell lymphoma angioimmunoblastic type (also known as angioimmunoblastic T-cell lymphoma (AITL) or follicular helper T-cell lymphoma, angioimmunoblastic type), nodal T follicular helper cell lymphoma follicular type (also known as follicular helper T-cell lymphoma, follicular type), or nodal T follicular helper cell lymphoma NOS (also known as follicular helper T-cell lymphoma, NOS))), or a primary cutaneous T-cell lymphoid proliferation or lymphoma (cutaneous T-cell lymphoma (CTCL)) (e.g., primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder, mycosis fungoides, Sezary syndrome (also known as Sézary syndrome), or primary cutaneous gamma-delta T-cell lymphoma)). See, e.g., Guo,

Weikai, et al., *Journal of Medicinal Chemistry* 63.2 (2020): 676-695, doi: 10.1021/acs.jmedchem.9b01618; and Alaggio, Rita, et al. *Leukemia* 36.7 (2022): 1720-1748, doi: 10.1038/s41375-022-01620-2.

In some embodiments, the compounds provided herein, or pharmaceutically acceptable salts thereof, exhibit activity in a model of an autoimmune disease or condition. Exemplary assays can be found in, for example, International Publication Nos. WO 2020/014599 and WO 2021/074620.

In some embodiments, a compound provided herein, or pharmaceutically acceptable salt thereof, can be assessed for its ability to modulate (e.g., decrease) Ig antibody production (e.g., IgA antibody production, IgE antibody production, and/or IgG antibody production), modulate (e.g., decrease) Ig antibody affinity (e.g., IgA antibody affinity, IgE antibody affinity, and/or IgG antibody affinity), and/or modulate (e.g., decrease) germinal center formation in an animal (e.g., a mouse) following challenge with a T cell-dependent antigen (e.g., keyhole limpet haemocyanin (KLH) or sheep red blood cells (SRBC)). For example, KLH can be administered to mice (e.g., C57BL/6 mice), followed by administration of the compound provided herein, or a pharmaceutically acceptable salt thereof, for a period of time (e.g., 14 days). Following sacrifice, serum samples from the mice can be analyzed for IgG specific for KLH, for example, by ELISA. Similarly, germinal centers can be detected using immunohistological staining using, e.g., peanut agglutinin (PNA). See, e.g., Example 1 of WO 2020/014599.

In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, can be assessed for its ability to modulate (e.g., decrease) the number of germinal center B cells in an animal (e.g., mouse) following immunization with an antigen. For example, animals (e.g., mice) can be immunized with specific antigens formulated in adjuvant such as Complete Freund's Adjuvant (CFA) or Alum, and after a period of time (e.g., 8 days), the animals can be sacrificed and the spleens harvested. The spleens can be processed into a suspension and cultured in the presence of a compound provided herein, or pharmaceutically acceptable salt thereof. The cells can then be analyzed, for example, for the number of germinal center B cells (e.g., by flow cytometry using the lineage markers GL7 and CD95). See, e.g., WO 2021/074620.

In some embodiments, a compound provided herein, or pharmaceutically acceptable salt thereof, can be assessed for its ability to improve or prevent one or more symptoms, biomarkers, or other signs of an autoimmune disease or condition in an animal model of the autoimmune disease or condition.

Experimental autoimmune encephalitis (EAE) can be used as an animal model of inflammatory diseases of the CNS, including multiple sclerosis (MS) and neuromyelitis optica. In some cases, EAE can be induced in animals (e.g., mice), for example, via immunization with recombinant human myelin oligodendrocyte glycoprotein (MOG) or a fragment thereof (e.g., MOG_{1-125}), myelin basic protein, and/or proteolipid protein. Following induction of EAE, the animals can be treated with a compound provided herein, or a pharmaceutically acceptable salt thereof. The animals can be evaluated by, for example, EAE severity, B cell depletion, or both. See, e.g., Constantinescu, Cris S., et al. *British Journal of Pharmacology* 164.4 (2011): 1079-1106, doi: 10.1111/j.1476-5381.2011.01302.x; Monson, Nancy L., et al. *PloS One* 6.2 (2011): e17103, doi: 10.1371/journal.pone.0017103.

In some embodiments, the autoimmune disease or condition is an anti-drug or anti-therapy antibody. In some embodiments, the autoimmune disease or condition is an anti-drug antibody. In some embodiments, the anti-drug antibody is an antibody against an antibody drug (e.g., an anti-TNFα antibody drug). In some embodiments, the autoimmune disease or condition is an anti-therapy antibody. In some embodiments, the anti-therapy antibody is an antibody against an enzyme replacement therapy (e.g., Factor VII replacement therapy, α-galactosidase replacement therapy, or alpha-glucosidase replacement therapy). In some embodiments, the anti-therapy antibody is an antibody against a gene therapy (e.g., AAV-based gene therapy). See, e.g., Vaisman-Mentesh, Anna, et al. *Frontiers in Immunology* 11 (2020): 1951j, doi: 10.3389/fimmu.2020.01951; Lenders, Malte, and Eva Brand. *Drugs* 81.17 (2021): 1969-1981, doi: 10.1007/s40265-021-01621-y; Rana, Jyoti, Maite Melero Munoz, and Moanaro Biswas. *Cellular Immunology* (2022): 104641, doi: 10.1016/j.cellimm.2022.104641; and Butterfield, John SS, et al. *Cellular Immunology* (2023): 104742, doi: 10.1016/j.cellimm.2023.104742.

In some embodiments, the autoimmune disease or condition is anti-synthetase syndrome. For example, a model of anti-synthetase syndrome, can be induced in susceptible mice (e.g., C57BL/6, B6.G7, and/or NOD.*Idd3/5*) by immunization with histidyl-tRNA synthetase (e.g., murine histidyl-tRNA synthetase or human histidyl-tRNA synthetase), or a fragment thereof. Treatment with a compound provided herein, or a pharmaceutically acceptable salt thereof, can begin at immunization and continue for a period of time (e.g., short term (e.g., 10-14 days) or long term (e.g., 8-16 weeks)), and then the mice can be sacrificed. The mice can be evaluated, for example, for generation of histidyl-tRNA synthetase-specific antibody (e.g., via immunoprecipitation, ELISA, and/or flow cytometry), tissue (e.g., lung and/or muscle) inflammation (e.g., by pathologist review), or a combination thereof. See e.g.,

Katsumata, Yasuhiro, et al. *Journal of Autoimmunity* 29.2-3 (2007): 174-186, doi: 10.1016/j.jaut.2007.07.005; Ascherman, Dana P. *Current Rheumatology Reports* 17 (2015), doi: 10.1007/s11926-015-0532-1; and Konishi, Risa, Yuki Ichimura, and Naoko Okiyama. *Immunological Medicine* 46.1 (2023): 9-14, doi: 10.1080/25785826.2022.2137968.

In some embodiments, the autoimmune disease or condition is arthritis (e.g., rheumatoid arthritis or inflammatory arthritis). For example, a mouse model of rheumatoid arthritis, collagen induced arthritis (CIA), can be induced in susceptible mice (e.g., DBA/1 or HLA-DR) by immunization with type II collagen (CII). Treatment with a compound provided herein, or a pharmaceutically acceptable salt thereof, can begin at immunization and continue for a period of time (e.g., 6 weeks). The mice can be evaluated, for example, for clinical scores (e.g., inflammation of an arthritic limb, foot thickness, paw volume (e.g., using a plethysmometer), or a combination thereof), generation of CII-specific antibody, B cell depletion, or a combination thereof. See e.g., Example 2 of WO 2020/014599; Brand, David D., et al. *Nature Protocols* 2.5 (2007): 1269-1275, doi: 10.1038/nprot.2007.173. Additional animal models of arthritis (e.g., inflammatory arthritis) are known in the art, such as K/BxN mice. In some embodiments, such mice can be treated with a compound provided herein, or a pharmaceutically acceptable salt thereof, and evaluated, for example, in similar ways to CII-immunized mice, or additionally, titering for autoantibodies, such as those against glucose-6-phosphate isomerase. See, e.g., Huang, Haochu, Christophe Benoist, and Diane Mathis. *Proceedings of the National Academy of Sciences* 107.10 (2010): 4658-4663, doi: 10.1073/pnas.1001074107; and Pigott, Elizabeth, and Laura Mandik-Nayak. Arthritis & Rheumatism 64.7 (2012): 2169-2178, doi: 10.1002/art.34406.

In some embodiments, the autoimmune disease or condition is graft-versus-host disease (e.g., chronic graft-versus-host disease). In some cases, an animal model of graft-versus-host disease can be in animals (e.g., mice) conditioned with high-dose cyclophosphamide and lethal total-body irradiation (TBI) rescued with bone marrow optionally including allogeneic splenocytes or purified T cells. Administration of the compound provided herein, or a pharmaceutically acceptable salt thereof, for a period of time can follow. The animals can be evaluated by, for example, pulmonary function tests, by immunohistochemistry to evaluate the presence of autoantibodies, or by examining sections of the spleen for germinal centers, including for example, examining for B cell depletion (e.g., germinal center B cell depletion). See, e.g., Srinivasan, Mathangi, et al. *Blood, The Journal of the American Society of Hematology* 119.6 (2012): 1570-1580, doi: 10.1182/blood-2011-07-364414; and Paz, Katelyn, et al. *Blood, The Journal of the American Society of Hematology* 133.1 (2019): 94-99, doi:

10.1182/blood-2018-03-839993. See also, e.g., Dubovsky, Jason A., et al. *The Journal of Clinical Investigation* 124.11 (2014): 4867-4876, doi: 10.1172/JCI75328.

In some embodiments, the autoimmune disease or condition is IgG4-related disease (IgG4-RD). In some cases, an animal model of IgG4-RD can be generated by injecting mice with IgGs (e.g., IgG1 and/or IgG4) derived from human IgG4-RD patients. Such mice can be treated with a compound provided herein, or a pharmaceutically acceptable salt thereof. The animals can be evaluated by measuring, for example, pancreatic and/or salivary tissue damage, B cell depletion, or both. See, e.g., Shiokawa, Masahiro, et al. *Gut* 65.8 (2016): 1322-1332, doi: 10.1136/gutjnl-2015-310336. In some cases, an animal model of IgG4-RD can be generated by knock-in of a mutation of Linker for Activation of T cell (LAT), such as LAT Y136F. Such mice can be treated with a compound provided herein, or a pharmaceutically acceptable salt thereof. The animals can be evaluated by measuring, for example, pancreatic and/or salivary tissue damage, B cell depletion, or both. See, e.g., Yamada, Kazunori, et al. *PLoS One* 13.6 (2018): e0198417, doi: 10.1371/journal.pone.0198417.

In some embodiments, the autoimmune disease or condition is lupus (e.g., lupus erythematosus). In some cases, an animal model of lupus is MRL/*lpr* mice, which can display high expression of Tfh-associated molecules such as ICOS, PD-1, BCL6, and IL-21 and produce autoantibodies to nuclear components, develop nephritis, arthritis, and skin lesions. Such mice can be treated with a compound provided herein, or a pharmaceutically acceptable salt thereof. The animals can be evaluated by, for example, measuring B cell depletion (e.g., germinal center B cell depletion), identifying the presence and/or severity of glomerulonephritis, autoantibody titers (e.g., anti-RNA antibody titers, anti-nuclear antibody titers, and/or anti-dsDNA antibody titers), IL-21 expression, and/or amount of activated CD4+ T cells. See, e.g., Ahuja, Anupama, et al. *The Journal of Immunology* 179.5 (2007): 3351-3361, doi: 10.4049/jimmunol.179.5.3351; Shen, Chunxiu, et al. *Journal of Cellular and Molecular Medicine* 25.17 (2021): 8329-8337, doi: 10.1111/jcmm.16785; and Marinov, Anthony D., et al. *Arthritis & Rheumatology* 73.5 (2021): 826-836, doi: 10.1002/art.41608. Additional animal models of lupus are known in the art, such as NZB/W mice, which can be treated with a compound provided herein, or a pharmaceutically acceptable salt thereof, and evaluated in similar ways to the MRL/*lpr* mice. See, e.g., Wang, Wensheng, et al. The *Journal of Immunology* 192.7 (2014): 3011-3020, doi: 10.4049/jimmunol.1302003; and Kansal, Rita, et al. Science Translational Medicine 11.482 (2019): eaav1648, doi: 10.1126/scitranslmed.aav1648.

In some embodiments, the autoimmune disease or condition is myasthenia gravis (e.g.,

muscle-specific tyrosine kinase (MuSK) positive myasthenia gravis). For example, an animal model (e.g., a rat model, a mouse model, or a rabbit model) of MuSK positive myasthenia gravis can be generated by immunizing the animal with a purified chimeric protein containing the ectodomain of MuSK (e.g., the ectodomain of MuSK and the Fc region of IgG1). Following immunization, the animals are treated with a compound provided herein, or a pharmaceutically acceptable salt thereof, and the animals (e.g., rats, mice, or rabbits) can be evaluated, for example, by measuring clinical scores (e.g., grasping and/or lifting of a weight, while looking for tremor, hunched posture, muscle strength, and signs of fatigue), body weight, compound muscle action potential (e.g., using electromyography), anti-MuSK antibodies, B cell depletion, or a combination thereof. See, e.g., Shigemoto, Kazuhiro, et al. *The Journal of Clinical Investigation* 116.4 (2006): 1016-1024, doi: 10.1172/JCI21545. As another example, an animal model (e.g., a rat model, a mouse model, or a rabbit model) of MuSK positive myasthenia gravis can be generated by immunizing the animal with a purified protein containing the ectodomain of MuSK (e.g., the ectodomain of MuSK with or without a tag, just as a His-tag). Following immunization, the animals are treated with a compound provided herein, or a pharmaceutically acceptable salt thereof, and the animals (e.g., rats, mice, or rabbits) can be evaluated, for example, by measuring clinical scores (e.g., grasping and/or lifting of a weight, while looking for tremor, hunched posture, muscle strength, and signs of fatigue), body weight, compound muscle action potential (e.g., using electromyography), anti-MuSK antibodies, B cell depletion, or a combination thereof. See, e.g., Mori, Shuuichi, et al. *The American Journal of Pathology* 180.2 (2012): 798-810, doi: 10.1016/j.ajpath.2011.10.031; and Reuveni, Debby, et al. *Frontiers in Immunology* 11 (2020): 403, doi: 10.3389/fimmu.2020.00403. As another example, an animal model (e.g., a rat model, a mouse model, or a rabbit model) of myasthenia gravis can be generated by immunizing the animal with acetylcholine receptor from *Torpedo* (e.g., *Torpedo californica*) or *Electrophorus* (e.g., *Electrophorus electricus*) electric organs, or recombinant acetylcholine receptor protein or fragments thereof. Treatment with a compound provided herein, or a pharmaceutically acceptable salt thereof, can begin, for example, approximately 4 weeks after immunization, but can sometimes begin earlier or later. The animals (e.g., rats, mice, or rabbits) can be evaluated, for example, by measuring clinical scores (e.g., grasping and/or lifting of a weight, while looking for tremor, hunched posture, muscle strength, and signs of fatigue), body weight, compound muscle action potential (e.g., using electromyography), anti-acetylcholine receptor antibodies, B cell depletion, or a combination thereof. See, e.g., Mori, Shuuichi, et al. *The American Journal of Pathology* 180.2 (2012): 798-810, doi: 10.1016/j.ajpath.2011.10.031;

Xin, Ning, et al. *Molecular and Cellular Neuroscience* 58 (2014): 85-94, doi: 10.1016/j.mcn.2013.12.006; and Losen, Mario, et al. *Experimental Neurology* 270 (2015): 18-28, doi: 10.1016/j.expneurol.2015.03.010.

In some embodiments, the autoimmune disease or condition is multiple sclerosis (MS). In some embodiments, the MS is clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), primary progressive MS (PPMS), or secondary progressive MS (SPMS). In some embodiments, animal models of MS can be based on EAE, for example, relapsing-remitting EAE in SJL/J mice (e.g., via immunization with proteolipid protein$(PLP)_{139-151}$), chronic EAE in C57BL/6J mice (e.g., via immunization with MOG_{35-55}), or EAE in transgenic mice (e.g., via a T cell clone expressing Vα and Vβ chains reacting specifically to MOG_{35-55}, or a B cell heavy chain knock-in mouse). In some embodiments, the animal (e.g., mouse) model is generated via infection with a picornavirus, such as Theiler's murine encephalitis virus. In some embodiments, the animal (e.g., mouse) model is generated by feeding C57BL/6 mice with cuprizone (e.g., 0.2% for 6 weeks). In some embodiments, the animal (e.g., mouse) model is generated via lysolecithin injection (e.g., in SJL/J mice). Treatment with a compound provided herein, or a pharmaceutically acceptable salt thereof, can be followed, for example, by analysis of the animals for levels of myelin-specific T cells, B cell depletion, reduction of inflammatory lesions, axonal degeneration, protection or reversal of cuprizone or lysolecithin-induced demyelination, or a combination thereof. See, e.g., Procaccini, Claudio, et al. *European Journal of Pharmacology* 759 (2015): 182-191, doi: 10.1016/j.ejphar.2015.03.042.

In some embodiments, the autoimmune disease or condition is neuromyelitis optica (NMO). In some cases, animal models of NMO include administration of antibodies against astrocyte water channel aquaporin-4 (AQP4), called AQP4-IgG or NMO-IgG, to various CNS tissues, such as the brain. In some embodiments, the administration of the antibodies is to an animal with EAE. The AQP4-IgG can be recombinant or derived from human NMO patients. Treatment with a compound provided herein, or pharmaceutically acceptable salt thereof, can be followed, for example, by analysis of the sacrificed animal for slowing or reversal of astrocyte demyelination, number of macrophages, number of activated microglia, number of activated neutrophils, B cell depletion, or a combination thereof. See, e.g., Bennett, Jeffrey L., et al. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society* 66.5 (2009): 617-629, doi: 10.1002/ana.21802; Saini, Harleen, et al. *BMC Neurology* 13.1 (2013), doi: 10.1186/1471-2377-13-104; Oji, Satoru, et al. *PloS One* 11.3 (2016): e0151244, doi: 10.1371/journal.pone.0151244; Peschl, Patrick, et al. Journal of Neuroinflammation 14.1 (2017), doi: 10.1186/s12974-017-0984-5; and Duan, Tianjiao, and

Alan S. Verkman. *Brain Pathology* 30.1 (2020): 13-25, doi: 10.1111/bpa.12793.

In some embodiments, the autoimmune disease or condition is pemphigus (e.g., pemphigus vulgaris). In some cases, an animal (e.g., mouse) model of pemphigus can be generated using adoptive transfer of peripheral lymphocytes from *Dsg3* knockout animals to immune-deficient but desmoglein 3-expressing recipient mice to create an artificial immune state in the recipient animals. In some cases, an animal (e.g., mouse) model of pemphigus can be generated using an animal with a MHC class II-null background that expresses the pemphigus-associated HLA-DRB1*0402 allele, which after immunization with recombinant human DSG3, produce anti-human DSG3 antibodies. Treatment of these models with a compound provided herein, or a pharmaceutically acceptable salt thereof, can be followed, for example, by analysis of the B cell repertoires of the animals for anti-desmoglein B-cell clones, B cell depletion, or both. See, e.g., Kasperkiewicz, Michael, et al. *Nature Reviews Disease Primers* 3.1 (2017): 17071, doi: 10.1038/nrdp.2017.71.

In some embodiments, the autoimmune disease or condition is Sjogren's syndrome. In some cases, an animal model of Sjogren's syndrome is a NOD mouse, which sometimes has further genetic manipulation or crosses (e.g., NOD.B10.H2^b or C57BL/6.NOTDc3.NODc1t) to recapitulate the symptoms of the syndrome. Such mice can be treated with a compound provided herein, or a pharmaceutically acceptable salt thereof. The animals can be evaluated, for example, for salivary and lacrimal gland secretory flow rates, salivary protein content, autoantibodies to exocrine gland proteins (e.g., anti-Sjogren's syndrome A (SSA) antibodies, anti-Sjogren's syndrome B (SSB) antibodies, and/or anti-muscarinic acetylcholine 3 receptor (M3R) antibodies), B cell depletion, or a combination thereof. Robinson, Christopher P., et al. *Arthritis & Rheumatism* 41.1 (1998): 150-156, doi: 10.1002/1529-0131(199801)41:1<150::AID-ART18>3.0.CO;2-T; Cha, Seunghee, et al. *Arthritis & Rheumatism* 46.5 (2002): 1390-1398, doi: 10.1002/art.10258; and Ohno, Seiji, et al. *Autoimmunity* 45.7 (2012): 540-546, doi: 10.3109/08916934.2012.710860. Additional animal models of Sjogren's syndrome are known in the art and include, for example, NFS/*sld* mice, IQI/*Jic* mice, Aly/*aly* mice, and mice immunized with M3R peptides, which can be evaluated, in some cases, for the same parameters as NOD mice. See, e.g., Iizuka, Mana, et al. *Journal of Autoimmunity* 35.4 (2010): 383-389, doi: 10.1016/j.jaut.2010.08.004; and Park, Young-Seok, Adrienne E Gauna, and Seunghee Cha. *Current Pharmaceutical Design* 21.18 (2015): 2350-2364, doi: 10.2174/1381612821666150316120024.

The pharmacokinetic parameters of a compound provided herein, or a pharmaceutically acceptable salt thereof, can be evaluated in an animal model, for instance, a mouse model, a rat

model, a dog model, or a nonhuman primate (e.g., cynomolgus monkey) model. Pharmacokinetics (PK) studies can be conducted in an animal model (e.g., male CD-1 mice) by two exemplary delivery routes: intravenous (IV) injection and oral (PO), for example, oral gavage. Animals in the IV group (e.g., n = 3) are allowed free access to food and water; animals in the PO group are allowed free access to food or are fasted for 6-8 hours prior to dosing. A compound provided herein, or a pharmaceutically acceptable salt thereof, can be formulated in solution for the IV route and solution or suspension for the PO route. On each dosing day of the experiment, the compound provided herein, or a pharmaceutically acceptable salt thereof, can be administered via vein injection (e.g., at 1 mg/kg) for IV route or via oral gavage (e.g., at 3 to 300 mg/kg, at 3 to 90 mg/kg, or 3 to 10 mg/kg, such as 10 mg/kg or 30 mg/kg) for PO route. In some cases, the animals can be orally pre-dosed with a cytochrome P450 inhibitor (e.g., 1-aminobenzotriazole) prior to (e.g., 16 hours prior to) dosing the compound provided herein, or a pharmaceutically acceptable salt thereof. Blood samples can be collected via serial bleeding at multiple timepoints (e.g., at 8 timepoints from 0.83 to 24 hours post dose for a single-dose study). At each timepoint, blood (it will be understood that the volume of the blood sample will vary based on species) can be collected (e.g., via a vein, such as the saphenous vein in mice) in a tube containing an anti-coagulant (e.g., K_2EDTA). Blood samples can be put on wet ice and centrifuged (e.g., at 2000 x *g* for 4-10 minutes) to obtain plasma samples. Plasma samples can be diluted (e.g., with an equal volume of pH 3.0 phosphate buffer or with an equal volume of pH 5.0 sodium citrate) and submitted to LC-MS/MS for sample analysis. Pharmacokinetics parameters, including clearance (CL), volume of distribution (V_d), maximum plasma concentration (C_{max}), time of maximum plasma concentration (t_{max}), half-life ($t_{1/2}$), area under the curve (AUC), and oral bioavailability (%F) can be calculated using a non-compartmental model.

In some embodiments, the pharmacokinetic parameters of a compound provided herein, or a pharmaceutically acceptable salt thereof, can be measured in a rat model (e.g., a Sprague-Dawley rat model). An exemplary protocol follows.

Rats (e.g., male Sprague-Dawley rats, 7-9 weeks of age) are dosed with a compound provided herein, or a pharmaceutically acceptable salt thereof, once per day orally (e.g., via gavage) for several days (e.g., 3 days). The compound provided herein, or a pharmaceutically acceptable salt thereof, is administered to the rats at a given dose level (e.g., 1, 3, 5, 10, 25, 30, 50, or 100 mg/kg) in a solution or suspension formulation (e.g., 10% DMA/ 45% PHOSAL 50 PG/ 40% MIGLYOL® 810 N/ 5% polysorbate 80). The rats have access to food and water ad libitum.

Blood samples (e.g., 150 μL per sample) from the rats are taken at predetermined intervals, such as 1, 4, 8, 12, 24, 38, 49, 52, 60, 72, 96, and/or 120 hours after the first dose is administered. The blood is sampled via jugular vein puncture, then the blood samples (e.g., with K_2EDTA as anticoagulant) are temporarily put on ice and then centrifuged (e.g., at 4 °C and 6000 RPM for 5 minutes) within 30 minutes. Plasma samples are put on dry ice. After the completion of the last sampling, all samples are stored at -80°C or analyzed in a short time following collection. The concentration of the compound provided herein, or a pharmaceutically acceptable salt thereof, can be measured in an acidified plasma sample (e.g., diluted 1:1 v/v with pH 3 phosphate buffer) can be determined (e.g., via LC/MS/MS). For example, an acidified plasma sample is prepared for analysis using protein precipitation (e.g., by the addition of methanol), and an internal standard is spiked in at a known concentration. The spiked sample is mixed, centrifuged, and the supernatant is used in an LC/MS/MS method. The LC/MS/MS method uses a KINETEX® C18 2.6 μm 100 Å (50 mm * 2.10 mm) column with a first mobile phase of water (0.1% formic acid (FA)) and a second mobile phase of acetonitrile (0.1% FA). Multiple reaction monitoring is used to measure the analyte(s) of interest. Using the concentration of the compound provided herein, or a pharmaceutically acceptable salt thereof, in the plasma sample, pharmacokinetic parameters of $t_{1/2}$ (hr), t_{max} (hr), C_{max} (ng/mL), AUC_{last} (hr*ng/mL), AUC_{Inf} (hr*ng/mL), AUC_{Extr} (%), MRT_{Inf} (hr), AUC_{Inf}/D (hr*kg*ng/mL/mg), %F, AUC_{0-24} (hr*ng/mL), and AUC_{48-72} (hr*ng/mL) are determined.

At least one blood sample (e.g., taken at 72 hours after the first dose) is used for clinical chemistry, and levels of one or more of TBA (μmol/L), AST (U/L), ALT (U/L), GLU (mmol/L), ALP (U/L), BUN (mmol/L), CREA (μmol/L), CHOL (mmol/L), TG (mmol/L), CK (U/L), Ca (mmol/L), P (mmol/L), TBIL (μmol/L), ALB (g/L), TP (g/L), K (mmol/L), Na (mmol/L), Cl (mmol/L), A/G, and GLB (g/L) are determined.

The clinical observations, body weight and food consumption of the rats are tracked during dosing, and also for three days after the cessation of dosing. The rats are then sacrificed and grossly assessed for any macroscopic abnormalities.

In some embodiments, the pharmacokinetic parameters of a compound provided herein, or a pharmaceutically acceptable salt thereof, can be measured in a mouse model (e.g., a Balb/c model). An exemplary protocol follows.

Mice (e.g., male Balb/c mice, 9-11 weeks of age) are dosed with a compound provided herein, or a pharmaceutically acceptable salt thereof, twice per day orally (e.g., via gavage) for several days (e.g., 10 days). The compound provided herein, or a pharmaceutically acceptable salt thereof, is administered to the mice at a given dose level (e.g., 1, 3, 5, 10, 25, 30, 50, or

100 mg/kg) in a solution or suspension formulation (e.g., 10% DMA/ 45% PHOSAL 50 PG/ 40% MIGLYOL® 810 N/ 5% polysorbate 80). The mice have access to food and water ad libitum.

Blood samples (e.g., 30 µL per sample) from the mice are taken at predetermined intervals, such as 14, 12, 16, 24, 64, 136, 220, 228, 232, and 240 hours after the first dose is administered (not every mouse will have every time point sampled). The blood is sampled via saphenous vein puncture, then the blood samples (e.g., with K_2EDTA as anticoagulant) are temporarily put on ice and then centrifuged (e.g., at 4 °C and 4600 RPM for 5 minutes) within 30 minutes. Plasma samples are acidified and put on dry ice. After the completion of the last sampling, all samples are stored at -80°C or analyzed in a short time following collection. The concentration of the compound provided herein, or a pharmaceutically acceptable salt thereof, measured in an acidified plasma sample (e.g., diluted 1:1 v/v with pH 3 phosphate buffer) can be determined (e.g., via LC/MS/MS). For example, an acidified plasma sample is prepared for analysis using protein precipitation (e.g., by the addition of acetonitrile), and an internal standard is spiked in at a known concentration. The spiked sample is mixed, centrifuged, and the supernatant is used in an LC/MS/MS method. The LC/MS/MS method uses an ACQUITY UPLC BEH C18 1.7µm (2.1*50 mm) column with a first mobile phase of 5 mM NH4OAC (0.05% FA or 0.1% FA) and a second mobile phase of acetonitrile (0.1% FA). Multiple reaction monitoring is used to measure the analyte(s) of interest. Using the concentration of the compound provided herein, or a pharmaceutically acceptable salt thereof, in the plasma sample, pharmacokinetic parameters of $t_{1/2}$ (hr), t_{max} (hr), C_{max} (ng/mL), AUC_{last} (hr*ng/mL), AUC_{Inf} (hr*ng/mL), AUC_{Extr} (%), MRT_{Inf} (hr), AUC_{Inf}/D (hr*kg*ng/mL/mg), and %F, are determined.

The clinical observations, body weight and food consumption of the mice are tracked during dosing, and also for three days after the cessation of dosing. The mice are then sacrificed and grossly assessed for any macroscopic abnormalities.

In some embodiments, the %F for a compound provided herein, or a pharmaceutically acceptable salt thereof, is at least 4%. In some embodiments, the %F for a compound provided herein, or a pharmaceutically acceptable salt thereof, is at least 10%. In some embodiments, the %F for a compound provided herein, or a pharmaceutically acceptable salt thereof, is at least 20%. In some embodiments, the %F for a compound provided herein, or a pharmaceutically acceptable salt thereof, is at least 30%. In some embodiments, the %F for a compound provided herein, or a pharmaceutically acceptable salt thereof, is at least 40%. In some embodiments, the %F for a compound provided herein, or a pharmaceutically acceptable salt thereof, is at least 60%. In some embodiments, the %F for a compound provided herein, or

a pharmaceutically acceptable salt thereof, is at least 80%. In some embodiments, the %F for a compound provided herein, or a pharmaceutically acceptable salt thereof, is about 4% to about 90% (e.g., about 4% to about 80%, about 4% to about 60%, about 4% to about 40%, about 4% to about 20%, about 4% to about 10%, about 20% to about 40%, about 40% to about 60%, about 60% to about 80%, or about 70% to about 90%). In some embodiments, the %F for a compound provided herein, or a pharmaceutically acceptable salt thereof, is about 4% to about 20%. In some embodiments, the %F for a compound provided herein, or a pharmaceutically acceptable salt thereof, is about 20% to about 40%. In some embodiments, the %F for a compound provided herein, or a pharmaceutically acceptable salt thereof, is about 40% to about 60%. In some embodiments, the %F for a compound provided herein, or a pharmaceutically acceptable salt thereof, is about 50% to about 80%.

In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, is not a substrate of a human cytochrome P450 enzyme. In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, is not a substrate of a human cytochrome P450 enzyme where ≥ 25% of clearance is attributed to that enzyme. In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, is not an inhibitor and/or an inducer of one or more human cytochrome P450 enzymes. In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, is not an inhibitor and/or an inducer of one or more human cytochrome P450 enzymes, where the IC_{50} and/or EC_{50} for the one or more human cytochrome P450 enzymes, respectively, is at a concentration to be significantly greater than the estimated free fraction concentration of a compound provided herein, or a pharmaceutically acceptable salt thereof, at a clinically relevant dose.

Exemplary human cytochrome P450 enzymes include those in the CYP1, CYP2, and CYP3 families. Of those CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2J2, CYP2S1, CYP2E1, CYP3A4, and CYP3A5 are known drug metabolizing enzymes. In some embodiments, no single cytochrome P450 enzyme is responsible for greater than or equal to 25% of the elimination of a compound provided herein, or a pharmaceutically acceptable salt thereof. Cytochrome P450 inhibition and/or inducing activity can be determined using appropriate *in vitro* assays, such as those described in the guidance document “In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions” provided by the U.S. F.D.A. in January 2020, and similarly in the ICH M12 guidance finalized in May 2024 . For example, evaluation of cytochrome P450 inhibition can be performed in *in vitro* studies, in both a reversible and

time-dependent manner. In an in vitro inhibition study, the ratio of intrinsic clearance values of a probe substrate for an enzymatic pathway in the absence and in the presence of a compound provided herein, or a pharmaceutically acceptable salt thereof, can be calculated based on these in vitro results; this ratio is referred to as R_1 for reversible inhibition, where $R_1 = 1 + (I_{max,u}/K_{i,u})$, and $I_{max,u}$ is the maximal unbound plasma concentration of the compound provided herein, or a pharmaceutically acceptable salt thereof, predicted in human, and $K_{i,u}$ is the unbound inhibition constant determined in vitro. Specifically, in the case of CYP3A whereas the enzyme is also expressed at significant levels in the intestine, $R_{1,gut}$ can be calculated where $R_{1,gut} = 1 + (I_{gut} + K_{i,u})$,and where I_{gut} is predicted human intestinal luminal concentration of the compound provided herein, or a pharmaceutically acceptable salt thereof, calculated as the human oral dose/250mL. The time-dependent inhibition ratio R_2 can similarly be calculated, where $R_2 = (k_{obs} + k_{deg}) / k_{deg}$, and kobs is the observed (apparent first order) inactivation rate of the affected cytochrome P450 calculated by $k_{obs} = (k_{inact}*I_{max,u}) / (K_{I,u} + *I_{max,u})$, k_{deg} is the apparent first-order degradation rate constant of the affected cytochrome P450, $K_{I,u}$ is the unbound concentration of the compound provided herein, or a pharmaceutically acceptable salt thereof, causing half maximal inactivation, and k_{inact} is the maximal inactivation rate constant. Utilizing these equations for R_1, $R_{1,gut}$, and R_2, the compound provided herein, or a pharmaceutically acceptable salt thereof, can be evaluated for their potential to be an inhibitor of a cytochrome P450, and the drug-drug interaction (DDI) potential can be further investigated using mechanistic or physiological-based pharmacokinetic models of the liver and intestine and/or conducting a clinical DDI study with a sensitive index substrate. Additionally, a compounds propensity to activate nuclear receptors (e.g., PXR, CAR, or AhR) is evaluated through in vitro cytochrome P450 hepatocyte induction studies and the resulting data can be evaluated via the fold-change method, wherein the fold-change in cytochrome P450 enzyme mRNA levels, when incubated with the compound provided herein, or a pharmaceutically acceptable salt thereof, based on cutoff determined from known positive and negative controls to calibrate the system. For example, a compound provided herein, or a pharmaceutically acceptable salt thereof, is determined an inducer if: (1) it increases mRNA expression of a cytochrome P450 enzyme in a concentration-dependent manner; and (2) the fold change of cytochrome P450 mRNA expression relative to the vehicle control is $\geq$ 2-fold at the expected hepatic concentrations of the drug. Additionally, evaluation of cytochrome P450 induction can be performed by a correlation method, wherein correlation methods are used to predict the magnitude of a clinical induction effect (e.g., AUC ratio of an index substrate in the presence and absence of inducers) of a compound provided herein, or a pharmaceutically acceptable salt thereof, according to a

calibration curve of relative induction scores (RIS) or $I_{max,u}/EC_{50}$ for a set of known inducers of the same cytochrome P450. If the predicted magnitude is more than a predefined cut-off (e.g., AUC ratio $\leq$ 0.8), a compound provided herein, or a pharmaceutically acceptable salt thereof, is considered to have induction potential in vivo.

In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, can be tested for its potency in inhibiting hERG potassium channels. The cardiac potassium channel hERG is responsible for a rapid delayed rectifier current (I_{Kr}) in human ventricle and inhibition of I_{Kr} is the most common cause of cardiac action potential prolongation by non-cardiac drugs. Increased action potential duration causes prolongation of the QT interval that has been associated with a dangerous ventricular arrhythmia, *torsade de pointes*. There are several methods of testing hERG inhibition potency, including Fastpatch hERG and manual patch clamp experiments.

In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, is tested for its potency in inhibiting hERG potassium channels using a manual patch clamp assay. For example, in some embodiments, solutions or suspensions of a compound provided herein, or a pharmaceutically acceptable salt thereof, at several concentrations (e.g., 0.3, 1, 3 and 10 μM) can be exposed to single cells. The effect of the compound provided herein, or a pharmaceutically acceptable salt thereof, on the inhibition of hERG potassium channels can be measured in this system using an electrical pulse pattern, the data plotted, and an IC_{50} value calculated for the inhibition of hERG by the compound provided herein, or a pharmaceutically acceptable salt thereof. An exemplary protocol follows.

In this experiment, hERG potassium channels are expressed in a human embryonic kidney cell line that lacks endogenous I_{Kr} (HEK-293 (ATCC 293T, CRL-3216™)). See, e.g., Brown, Arthur M., and David Rampe. *Pharmaceutical News* 7.4 (2000): 15-20; Weirich, Jörg, and H. Antoni, *Basic Research in Cardiology* 93 (1998): s125-s132, doi: 10.1007/s003950050236; and Yap, Yee Guan, and A. J. Camm. *Clinical & Experimental Allergy* 29 (1999): 174-181, doi: 10.1046/j.1365-2222.1999.0290s3174.x.

All chemicals used in solution preparations are purchased from a commercial supplier (e.g., Sigma-Aldrich) and are of ACS reagent grade purity or higher. Stock solutions of the compound provided herein, or a pharmaceutically acceptable salt thereof, positive control compound(s), and reference substance(s) are prepared in dimethyl sulfoxide (DMSO) and stored frozen. Solutions of each compound provided herein, or a pharmaceutically acceptable salt thereof, positive control compound, and reference substance concentrations are prepared fresh daily by diluting stock solutions into HEPES-buffered physiological saline solution (HB-

PS; 137 mM NaCl, 4 mM KCl, 1.8 mM $CaCl_2$, 1 mM $MgCl_2$, 10 mM HEPES, and 10 mM glucose, pH 7.4). Since previous results have shown that ≤ 0.3% DMSO does not affect channel current, all test and control solutions can contain 0.3% DMSO.

In some embodiments, a positive control compound can be included in the experiment. In some such embodiments, the positive control compound can be terfenadine (Sigma-Aldrich), for example, in a HB-PS and 0.3% DMSO solution.

In some embodiments, a reference compound can be included in the experiment. In some such embodiments, the reference compound can be E-4031 (Sigma-Aldrich), for example, in a HB-PS and 0.3% DMSO solution.

If necessary, test article solutions are sonicated to facilitate dissolution. Visible precipitate observed during preparation or exposure of test article formulations to the test system is noted for reference.

The effect of a compound provided herein, or a pharmaceutically acceptable salt thereof, are initially evaluated at concentration range of 1 to 10 μM. Subsequent concentrations are evaluated based on the inhibition observed at that concentration.

HEK-293 cells are transfected with hERG cDNA. Stable transfectants are selected by coexpression of the G418-resistance gene incorporated into the expression plasmid. Selection pressure is maintained by including G418 in the culture medium. Cells are cultured in Dulbecco's Modified Eagle's Medium / Ham's Nutrient Mixture F-12 (DMEM/F-12) supplemented with 10% fetal bovine serum and the appropriate concentrations of penicillin G sodium, streptomycin sulfate, and G418.

All experiments are performed at near-physiological temperature (33 – 35 °C). Each cell acts as its own control.

The effect of a compound provided herein, or a pharmaceutically acceptable salt thereof, is evaluated at multiple (e.g., up to four) concentrations. Each concentration will be tested in at least three cells ($n \geq 3$). Additional concentration(s) may be tested due to the limits imposed by the physiochemical effects of the compound provided herein, or a pharmaceutically acceptable salt thereof (e.g., solubility or cytotoxicity).

The positive control compound is tested in at least two (2) cells ($n \geq 2$).

Cells are transferred to the recording chamber and superfused with vehicle control solution. Pipette (intracellular) solution for whole cell recordings is composed of 130 mM potassium aspartate, 5 mM $MgCl_2$, 5 mM EGTA, 4 mM ATP, and 10 mM HEPES, pH 7.2. Pipette solution is prepared in batches, aliquoted, stored frozen and a fresh aliquot thawed each day. The recording is performed at a temperature of 33 to 35 °C using a combination of in-line

solution pre-heater, chamber heater, and feedback temperature controller. Temperature is measured using a thermistor probe in the recording chamber. Micropipettes for patch clamp recording are made from glass capillary tubing using a P-97 micropipette puller (Sutter Instruments). A commercial patch clamp amplifier (Molecular Devices) is used for whole patch clamp cell recordings. Before digitization, current records are low-pass filtered.

Cells stably expressing hERG are held at -80 mV. Onset and steady state inhibition of hERG potassium current due to the compound provided herein, or a pharmaceutically acceptable salt thereof, are measured using a pulse pattern with fixed amplitudes (conditioning prepulse of +20 mV for 1 second; repolarizing test ramp to –80 mV (at –0.5 V/second) repeated at 5 second intervals). Each recording ends with an application of a supramaximal concentration of the reference substance (e.g., E-4031 at 500 nM) to assess the contribution of endogenous currents. The remaining uninhibited current is subtracted off-line digitally from the data to determine the potency of the compound provided herein, or a pharmaceutically acceptable salt thereof, for hERG inhibition. Peak current is measured during the test ramp. A steady state is maintained for at least 20 seconds before applying the compound provided herein, or a pharmaceutically acceptable salt thereof, positive control compound, or reference substance. Peak tail currents are measured until a new steady state is achieved. If a steady state cannot be reached within 12 minutes, the response at 12 minutes is substituted for the steady state value and a notation made.

Data acquisition and analyses are performed using the commercial suite of pCLAMP programs (Molecular Devices). Steady state is defined by the limiting constant rate of change with time (linear time dependence). The steady state before and after application of each compound provided herein, or a pharmaceutically acceptable salt thereof, is used to calculate the percentage of current inhibited at each concentration.

In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, is tested for its potency in inhibiting hERG potassium channels (e.g., encoded by the *KCNH2* gene and expressed in HEK293 cells) using a Fastpatch hERG assay. For example, in some embodiments, solutions or suspensions of a compound provided herein, or a pharmaceutically acceptable salt thereof, at several concentrations (e.g., 0.3, 1, 3 and 10 μM) can be exposed to cells in an automatic parallel patch clamp system. The effect of the compound provided herein, or a pharmaceutically acceptable salt thereof, on the inhibition of hERG potassium channels can be measured in this system using an electrical pulse pattern, the data plotted, and an IC_{50} value calculated for the inhibition of hERG by the compound provided herein, or a pharmaceutically acceptable salt thereof. An exemplary protocol follows.

The in vitro effects of a compound provided herein, or a pharmaceutically acceptable salt thereof, are evaluated at room temperature using the QPATCH HT® (Sophion Bioscience A/S, Denmark), an automatic parallel patch clamp system. The compound provided herein, or a pharmaceutically acceptable salt thereof, is exposed to hERG at 0.3, 1, 3 and 10 μM in at least five cells ($n \geq 5$). The duration of exposure to each compound concentration is at least three minutes.

Solutions or suspensions of the compound(s) provided herein, or a pharmaceutically acceptable salt thereof, are prepared daily. Various concentrations are prepared by diluting stock solutions into an appropriate HEPES-buffered physiological saline solution (HB-PS).

Previous results have shown that 0.3% DMSO does not affect channel current. Therefore, all test and control solutions can contain up to 0.3% DMSO.

Each formulation of a compound provided herein, or a pharmaceutically acceptable salt thereof, can be sonicated (e.g., Model 2510/5510, Branson Ultrasonics, Danbury, CT), e.g., at room temperature, to facilitate dissolution.

In some embodiments, a positive control can be included in the experiment. In some such embodiments, the positive control compound can be cisapride (Tocris Bioscience), for example, in a 0.3% DMSO solution.

In preparation for the recording session, a glass-lined 96-well compound plate is loaded with the appropriate amounts of solutions of compound(s) provided herein, or a pharmaceutically acceptable salt thereof, and control solutions, and placed in the plate well of the QPATCH® (Sophion Bioscience A/S, Denmark).

HEK293 (ATCC 293T, CRL-3216™) cells are stably transfected with the appropriate ion channel cDNA(s). Except for cells that have been stored frozen, stable transfectants are maintained in the culture medium with the appropriate selection pressure and antibiotics.

All experiments are performed at room temperature. Each cell acts as its own control.

Vehicle is applied via the QPATCH® robot pipetting system to naive cells for a 5-10 minute exposure interval. After vehicle application, various concentrations of a compound provided herein, or a pharmaceutically acceptable salt thereof, are applied in at least three (3) minute intervals ($n \sim 3$, where n = the number of cells/concentration). Each solution exchange on the QPATCH® is performed multiple times, which results in 100% replacement of the compound in the QPlate.

Positive control(s) are applied in the same manner as the compound provided herein, or a pharmaceutically acceptable salt thereof, to verify sensitivity to ion channel blockade.

In preparation for a recording session, an intracellular solution (e.g., 137 mM NaCl, 4 mM KCl, 1.8 mM $CaCl_2$, 1 mM $MgCl_2$, 10 mM HEPES, and 10 mM glucose, pH 7.4) is loaded into the intracellular compartments of the QPlate and cell suspension is pipetted into the extracellular compartments. After establishment of a whole-cell configuration, membrane currents are recorded using up to 48 parallel patch clamp amplifiers in the QPATCH® system.

Valid whole-cell recordings meet the following criteria:

1. Membrane resistance $\geq$ 200 MΩ.

2. Leak current $\leq$ 25% channel current or subtracted.

Onset and block of hERG current is measured using a stimulus voltage pattern consisting of a 500 ms prepulse to -40 mV (leakage subtraction), a 2-second activating pulse to +40 mV followed by a 2-second test pulse to -40 mV. The pulse pattern is repeated continuously at 10 s intervals from a holding potential of -80 mV. Peak tail current is measured during the -40 mV test pulse. Leakage current is calculated from the current amplitude evoked by the -40 mV prepulse and subtracted from the total membrane current record.

Data acquisition and analyses are performed using conventional software. Steady state is defined by the limiting constant rate of change with time (linear time dependence). The steady state before and after application of a compound provided herein, or a pharmaceutically acceptable salt thereof, will be used to calculate the percentage of current inhibited at each concentration. If current is blocked ≥50%, estimated IC_{50} values will be calculated using the following formula:

$$\% \text{ Inhibition} = \{1\text{-}1/[1+([\text{Test}]/IC_{50})^{N}]\}*100$$

Where [Test] is the concentration of the compound provided herein, or a pharmaceutically acceptable salt thereof, IC_{50} is the concentration of the compound provided herein, or a pharmaceutically acceptable salt thereof, at half-maximal inhibition, N is the Hill coefficient, and % Inhibition is the percentage of current inhibited at each test article concentration. Nonlinear least squares fits are solved with the Solver add-in for Excel (Microsoft, WA). Overestimation of current inhibition, due to rundown, is avoided by a manual adjustment that uses an exponential compensation formula in the QPATCH® analysis software.

In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, is not a hERG inhibitor. In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, inhibits hERG with an IC_{50} of greater than 60 nM

(e.g., greater than 100 nM, 300 nM, 500 nM, 1 μM, 3 μM, 5 μM, 10 μM, 20 μM, or 30 μM). For example, a compound provided herein, or a pharmaceutically acceptable salt thereof, inhibits hERG with an IC_{50} of greater than 500 nM (e.g., greater than 1 μM, 3 μM, 5 μM, 10 μM, 20 μM, or 30 μM). In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, inhibits hERG with an IC_{50} of greater than 1 μM (e.g., greater than 3 μM, 5 μM, 10 μM, 20 μM, or 30 μM). In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, inhibits hERG with an IC_{50} of greater than 10 μM (e.g., greater than 20 μM or 30 μM). In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, inhibits hERG with an IC_{50} of greater than 30 μM.

In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, can be evaluated for potential secondary pharmacology. For example, in some embodiments, solutions of a compound provided herein, or a pharmaceutically acceptable salt thereof, at a single or several concentrations can be exposed to a panel of primary cells, cell lines or isolated tissues expressing known pharmacological receptors, enzymes or transporters. The effect of the compound provided herein, or a pharmaceutically acceptable salt thereof, the secondary pharmacological target of interest can be determined, the data is initially plotted as a percent inhibition. For secondary targets exceeding an inhibition threshold (typically ≥ 50%), an IC_{50} value is generated and calculated following an 8-point concentration curve of the compound provided herein, or a pharmaceutically acceptable salt thereof.

An exemplary list of assays is included in **Table 1** below. One or more of these assays can be used to assess the secondary pharmacological characteristics of a compound provided herein. Exemplary protocols are described in Valentin, Jean-Pierre, and Tim Hammond. *Journal of Pharmacological and Toxicological Methods* 58.2 (2008): 77-87; doi: 10.1016/j.vascn.2008.05.007; Wakefield, Ian D., et al. *Fundamental & Clinical Pharmacology* 16.3 (2002): 209-218, doi: 10.1046/j.1472-8206.2002.00099.x; Whitebread, Steven, et al. *Drug Discovery Today* 10.21 (2005): 1421-1433, doi: 10.1016/S1359-6446(05)03632-9; and Lounkine, Eugen, et al. *Nature* 486.7403 (2012): 361-367, doi: 10.1038/nature11159.

Table 1.

Protein	Organism	Assay Type	Family
Acetylcholinesterase	Human	Enzymatic	Neurotransmitter Metabolism

Angiotensin-converting peptidase	Human	Enzymatic	Protease
ATPase (Na/K)	Pig	Enzymatic	Transporter
Cathespin G chymotrypsin peptidase	Human	Enzymatic	Protease
Cyclooxygenase 1	Human	Enzymatic	Lipid Metabolism
Cyclooxygenase 2	Human	Enzymatic	Lipid Metabolism
Monoamine Oxidase A	Human	Enzymatic	Oxireductase
Monoamine Oxidase B	Human	Enzymatic	Oxireductase
Phosphodiesterase 3A	Human	Enzymatic	PDE
Phosphodiesterase 4D2	Human	Enzymatic	PDE
Insulin Receptor Kinase	Human	Enzymatic	Kinase
lrc Kinase	Human	Enzymatic	Kinase
PKC alpha Kinase	Human	Enzymatic	Kinase
Adenosine A1 Receptor	Human	Binding	GPCR
Adenosine Transporter	Human	Binding	Transporter
Alpha 1A Adrenergic Receptor	Human	Binding	GPCR
Alpha 1B Adrenergic Receptor	Human	Binding	GPCR
Alpha 1D Adrenergic Receptor	Human	Binding	GPCR
Alpha 2A Adrenergic Receptor	Human	Binding	GPCR
Alpha 2B Adrenergic Receptor	Human	Binding	GPCR
Beta 1 Adrenergic Receptor	Human	Binding	GPCR
Beta 2 Adrenergic Receptor	Human	Binding	GPCR
Androgen Receptor	Human	Binding	Nuclear Hormone Receptor
Angiotensin 1 Receptor	Human	Binding	GPCR
Bradyknin 2 Receptor	Human	Binding	GPCR

Cav1.2 (L-type Diltizem) Calcium Channel	Rat	Binding	Ion Channel
Cav1.2 (L-type Dihydropyridine) Calcium Channel	Rat	Binding	Ion Channel
Cav1.2 (L-type Verpamil) Calcium Channel	Rat	Binding	Ion Channel
Cav2.2 (N-typel) Calcium Channel	Rat	Binding	Ion Channel
Cannabinoid 1	Human	Binding	GPCR
Cannabinoid 2	Human	Binding	GPCR
Chemokine Receptor 1	Human	Binding	GPCR
Cholecystokinin 1 Receptor	Human	Binding	GPCR
Cholecystokinin 2 Receptor	Human	Binding	GPCR
Dopamine 1 Receptor	Human	Binding	GPCR
Dopamine 2L Receptor	Human	Binding	GPCR
Dopamine 2L Receptor	Human	Binding	GPCR
Dopamine Transporter	Human	Binding	Transporter
Endothelial Receptor A	Human	Binding	GPCR
Estrogen Receptor Alpha	Human	Binding	Nuclear Hormone Receptor
GABA (nonselective) Transporter	Rat	Binding	Transporter
GABA A (nonselective) Flunitrazepam	Rat	Binding	Ion Channel
GABA A (nonselective) Ro-15-1788	Rat	Binding	Ion Channel
GABA A (nonselective) TBOB	Rat	Binding	Ion Channel
GABA B Receptor B1a/B2	Human	Binding	GCPR

Glucocorticoid Receptor	Human	Binding	Nuclear Hormone Receptor
Glutamate AMPA (nonselective)	Rat	Binding	Ion Channel
Glutamate Kainate (nonselective)	Rat	Binding	Ion Channel
Glutamate NMDA (nonselective) MDL 105,519	Rat	Binding	Ion Channel
Glutamate NMDA (nonselective) TCP	Rat	Binding	Ion Channel
Glutamate NMDA (nonselective) Ifenprodil	Rat	Binding	Ion Channel
Metabotropic glutatmate Receptor 5	Human	Binding	GPCR
Glycine (nonselective) Strychine	Rat	Binding	Ion Channel
Histamine Receptor 1	Human	Binding	GPCR
Histamine Receptor 2	Human	Binding	GPCR
CXC Receptor 2	Human	Binding	GPCR
Cys Leukotriene Receptor 1	Human	Binding	GPCR
Melanocortin Receptor 1	Human	Binding	GPCR
Melanocortin Receptor 4	Human	Binding	GPCR
Muscarinic Receptor 1	Human	Binding	GPCR
Muscarinic Receptor 2	Human	Binding	GPCR
Muscarinic Receptor 3	Human	Binding	GPCR
Muscarinic Receptor 4	Human	Binding	GPCR
Neurokinin 1 Receptor	Human	Binding	GPCR
Neuropeptide Y Receptor	Human	Binding	GPCR
N Acetylcholine Receptor Alpha 1	Human	Binding	Ion Channel
N Acetylcholine Receptor Alpha 3/Beta4	Human	Binding	Ion Channel

Delta Opioid Receptor	Human	Binding	GPCR
Kappa Opioid Receptor	Human	Binding	GPCR
Mu-Opioid Receptor	Human	Binding	GPCR
Potassium ATP Receptor	Hamster	Binding	Ion Channel
hERG Potassium Channel Dofetilide	Human	Binding	Ion Channel
Peroxisomes proliferator Receptor (agonist)	Human	Binding	Nuclear Hormone Receptor
Serotonin 1A Receptor (Antagonist)	Human	Binding	GPCR
Serotonin 2A Receptor (Agonist)	Human	Binding	GPCR
Serotonin 2B Receptor (Antagonist)	Human	Binding	GPCR
Serotonin 2C Receptor (Antagonist)	Human	Binding	GPCR
Serotonin 3 Receptor (Antagonist)	Human	Binding	Ion Channel
Serotonin Transporter	Human	Binding	Transporter
Sodium (Nav1.5) Channel Site 2	Human	Binding	Ion Channel
Vasopressin 1A Receptor Oxytocin	Human	Binding	GPCR
Progesterone Receptor	Human	Binding	Nuclear Hormone Receptor
Platelet Activating Factor (agonist)	Human	Binding	GPCR

In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, can be evaluated for potential to induce phospholipidosis. For example, in some embodiments, solutions or suspensions of a compound provided herein, or a pharmaceutically acceptable salt thereof, at several concentrations can be exposed to cells in a dye-based assay using a dye that binds to phospholipids. The effect of the compound provided herein, or a

pharmaceutically acceptable salt thereof, on the accumulation of phospholipids can be determined, the data plotted, and an IC_{50} value calculated for Cell Loss due to phospholipidosis by the compound provided herein, or a pharmaceutically acceptable salt thereof. An exemplary protocol follows.

HepG2 culture medium is prepared by supplementing Dulbecco's Modified Eagle's Medium (DMEM) low glucose media with 1% 2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulfonic acid (HEPES), 10% Fetal bovine serum (FBS), 1% non-essential amino ascids (NEAA) and 1% of a penicillin, streptomycin mixture (PS).

HepG2 cells are cultivated (e.g., in T-75 flasks in a cell culture incubator set at 37 °C, 5% CO_2, 95% relative humidity). Cells are allowed to reach 80-90% confluence before detaching and splitting. The HepG2 culture medium is aspirated from the HepG2 cells (e.g., from a T75 flask) and 10 mL of phosphate buffer is added, and the cells are washed two times. The phosphate buffer is aspirated, 3-5 mL of Trypsin-EDTA is added, and the flask is incubated at 37 °C for 5 min. Once the cells are detached, a 3-fold volume of HepG2 culture medium is added into the flask to neutralize the trypsin effect, and the flask contents are transferred to 50 mL vial. The vial with cells is centrifuged (e.g., at 150 × *g* for 5 min at room temperature). The supernatant is aspirated carefully, and the cell pellet is re-suspended with culture medium. The cell density is adjusted to 6×10^4 cells/mL and cell suspension (e.g., 100 µL) is seeded into each well of Poly-D-lysine coated 96-well plate (The stock solution of poly-D-lysine is 100 µg/mL, diluted to 50 µg/mL by phosphate buffer, then directly added to 70 µL of blank 96-well plate. The plate is incubated overnight at 37 °C. After incubation, the incubation solution is discarded, and the plate is dried for use).

Culture medium with 24 µg/mL (*N*-(7-Nitrobenz-2-Oxa-1,3-Diazol-4-yl)-1,2-Dihexadecanoyl-*sn*-Glycero-3-Phosphoethanolamine, Triethylammonium Salt) (NBD-PE) is prepared and filtered (e.g., with a 0.2 µm filter) before using. A volume of NBD-PE medium (e.g., 120 µL) is transferred to each well of the Poly-D-lysine coated 96-well cell culture plate seeded with HepG2 cells, and the plate is incubated for 24 hours at 37 °C with 95% humidity and 5% CO_2 atmosphere.

After the incubation, the cell plate is moved out of the incubator. The working solutions are aspirated from the wells, and cells are fixed with 4% paraformaldehyde at room temperature for approximately 20 min. Then wells are washed twice with phosphate buffer (e.g., 100 µL), and Hoechst 33342 (e.g., 5 µM, 100 µL per well) is added into the plate. The plate is incubated at humidified, 37 °C, 5% CO_2 atmosphere for 30 min. After 30 min of incubation at 37 °C, the dye is removed from the wells and the wells are washed twice with phosphate buffer (e.g., 100

μL for each wash). Phosphate buffer (e.g., 100 μL) is added to each well. The plate is scanned using a high-content imaging machine. Nine fields for each well are scanned and the fluorescence signals of NBD-PE and Hoechst 33342 are recorded simultaneously based on different florescence channels. The mean values of the fluorescence signals of 9 fields are output by the instrument for each well. The assays are performed in duplicate. The fluorescence of NBD-PE is used for the phospholipidosis calculation, while the fluorescence of Hoechst 33342 is used for the cell loss calculation.

Data analysis is performed (e.g., using Microsoft Excel). A phospholipidosis Fold Change of a particular concentration of test compound can be calculated using the following equation:

$$\text{Fold Change} = (\text{Read}_{\text{test compound}} / \text{Read}_{\text{Vehicle}})$$

The Fold Change values are plotted against the concentration of the compound provided herein, or a pharmaceutically acceptable salt thereof, and the data are fit to a sigmoidal dose-response curve with a variable slope (e.g., using GraphPad Prism 8.0.2). The EC_{50} value of the compound provided herein, or a pharmaceutically acceptable salt thereof, can be calculated from the curve using the following equation:

$$Y = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1+10^{((\text{Log}EC_{50} - X)*\text{HillSlope})})$$

Where X is the log of the concentration of the compound provided herein, Bottom is the minimum Fold Change observed with the compound provided herein, and Top is the maximum Fold Change observed with the compound provided herein.

A data point can be excluded if it is an outlier or an abnormal value due to cell death.

Cell Loss is calculated using the following equation:

$$\text{Cell Loss (\% Vehicle Control)} = (\text{Read}_{\text{test compound}} / \text{Read}_{\text{Vehicle Control}})*100\%$$

The Cell Loss as a percentage of Vehicle Control is plotted against the concentration of test compound, and the data are fit to a sigmoidal dose-response curve with a variable slope (e.g., using GraphPad Prism 8.0.2). The IC_{50} of Cell Loss for the compound provided herein, or a pharmaceutically acceptable salt thereof, can be calculated from the curve using the following equation:

$$Y = 100/(1+ 10^{((\text{Log}IC_{50} - X) \times \text{HillSlope})})$$

Where X is the log of the concentration of the compound provided herein.

Heterobifunctional degraders can, in some cases, induce the degradation of off-target proteins. For heterobifunctional degraders that utilize CRBN, common off-target proteins that can be degraded include GSPT1, IKZF1, IKZF2, IKZF3, and/or CK1α. This degradation is generally believed to be due to the E3 binding moiety of the heterobifunctional degrader facilitating ternary complex formation between the off-target protein and CRBN. GSPT1 is a translation termination factor, and CK1α is a kinase that is involved in many key cellular processes including cell cycle progression and chromosome segregation; these are both commonly essential genes, so undesired degradation of either or both can lead to nonspecific cytotoxicity. The IKZF proteins are zinc finger transcription factors that are involved with cell fate during hematopoiesis, and degradation of these proteins has been associated with hematotoxicity. See, e.g., Moreau, Kevin, et al. *British Journal of Pharmacology* 177.8 (2020): 1709-1718, doi: 10.1111/bph.15014.

In some embodiments, the compounds provided herein, or pharmaceutically acceptable salts thereof, can exhibit potent and selective induction of degradation of a BCL6 protein. In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt thereof, can selectively target a BCL6 protein for degradation over a second protein (e.g., GSPT1, IKZF1, IKZF2, IKZF3, CK1α, C6orf132, CAMP (cathelicidin antimicrobial peptide), CCNA2 (cyclin-A2), FSP1 (ferroptosis suppressor protein 1, also known as AIFM2), JCHAIN (immunoglobin J chain), NLRP7 (NACHT, LRR, PYD domains-containing protein 7), PTTG1 (securin), and/or TPX2 (targeting protein for Xklp2)). CAMP is an antimicrobial protein that is an integral part of the innate immune system, and it binds to bacterial lipopolysaccharides. CCNA2 controls both the G1/S and the G2/M transition phases of the cell cycle. FSP1 is an oxidoreductase that is an inhibitor of ferroptosis. JCHAIN links two monomer units of either IgM or IgA; the J chain-joined dimer is a nucleating unit of the IgM pentamer, and the J chain-joined dimer of IgA induces dimers or larger polymers. NLRP7 Inhibits CASP1/caspase-1-dependent IL1B secretion. PTTG1 is key for chromosomal stability and negatively regulates TP53. TPX2 is required for the normal assembly of mitotic spindles.

As used herein, “selective” or “selectively”, when referring to a compound provided herein, or a pharmaceutically acceptable salt thereof, in a protein degradation assay, indicates at least a 5-fold (e.g., at least a 10-fold, at least a 25-fold, at least a 50-fold, or at least a 100-fold) superior performance in the protein degradation assay for a specified protein with reference to a comparator protein in the assay.

In some embodiments, the compounds provided herein can exhibit potency (e.g.,

nanomolar potency) against a BCL6 protein with minimal activity (e.g., single digit micromolar potency, for example, potency greater than 1 μM (e.g., greater than 3 μM, 5 μM, 10 μM, 20 μM, or 30 μM)) against a second protein. In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, can exhibit potent degradation of a BCL6 protein and have minimal potency in degrading (e.g., as measured by Y_{min}, $DC_{50,}$ and/or D_{max} values) a second protein (e.g., GSPT1, IKZF1, IKZF2, IKZF3, CK1α, C6orf132, CAMP, CCNA2, FSP1, JCHAIN, NLRP7, PTTG1, and/or TPX2). In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, can exhibit greater induction of degradation of a BCL6 protein relative to induction of degradation (e.g., as measured by Y_{min}, $DC_{50,}$ and/or D_{max} values) of a second protein (e.g., GSPT1, IKZF1, IKZF2, IKZF3, CK1α, C6orf132, CAMP, CCNA2, FSP1, JCHAIN, NLRP7, PTTG1, and/or TPX2). In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, can exhibit at least 2-fold, 3-fold, 5-fold, 10-fold, 25-fold, 50-fold, or 100-fold greater induction of degradation of a BCL6 protein relative to induction of degradation of a second protein. In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, can exhibit up to 1000-fold greater induction of degradation of a BCL6 protein relative to induction of degradation of a second protein. In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, can exhibit from about 2-fold to about 10-fold greater induction of degradation of a BCL6 protein relative to induction of degradation of a second protein (e.g., GSPT1, IKZF1, IKZF2, IKZF3, CK1α, C6orf132, CAMP, CCNA2, FSP1, JCHAIN, NLRP7, PTTG1, and/or TPX2) (e.g., as measured by Y_{min}, $DC_{50,}$ and/or D_{max} values). In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, can exhibit from about 10-fold to about 100-fold greater induction of degradation of a BCL6 protein relative to induction of degradation of a second protein. In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, can exhibit from about 100-fold to about 1000-fold greater induction of degradation of a BCL6 protein relative to induction of degradation of a second protein. In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, can exhibit from about 1000-fold to about 10000-fold greater induction of degradation of a BCL6 protein relative to induction of degradation of a second protein. In some embodiments, the second protein is selected from the group consisting of GSPT1, IKZF1, IKZF2, IKZF3, CK1α, C6orf132, CAMP, CCNA2, FSP1, JCHAIN, NLRP7, PTTG1, and TPX2. In some embodiments, the second protein is selected from the group consisting of GSPT1, IKZF1, IKZF2, IKZF3, and CK1α. In some embodiments, the second protein is selected from the group consisting of C6orf132, CAMP,

CCNA2, FSP1, JCHAIN, NLRP7, PTTG1, and TPX2. In some embodiments, the second protein is C6orf132. In some embodiments, the second protein is CAMP. In some embodiments, the second protein is CCNA2. In some embodiments, the second protein is FSP1. In some embodiments, the second protein is JCHAIN. In some embodiments, the second protein is NLRP7. In some embodiments, the second protein is PTTG1. In some embodiments, the second protein is TPX2.

In some embodiments, the compounds provided herein can exhibit potency against a BCL6 protein with similar activity against a second protein (i.e., less than 2-fold greater activity against a BCL6 protein than against a second protein and no more than 2-fold greater activity against the second protein than against the BCL6 protein). In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, can exhibit similar induction of degradation of a BCL6 protein relative to induction of degradation (e.g., as measured by Y_{min}, $DC_{50,}$ and/or D_{max} values) of a second protein (i.e., less than 2-fold difference greater induction of degradation of a BCL6 protein than induction of degradation of a second protein and no more than 2-fold greater activity against the second protein than against a BCL6 protein) (e.g., GSPT1, IKZF1, IKZF2, IKZF3, CK1α, C6orf132, CAMP, CCNA2, FSP1, JCHAIN, NLRP7, PTTG1, and/or TPX2). In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, can exhibit less than 2-fold greater induction of degradation of a BCL6 protein relative to induction of degradation of a second protein. In some embodiments, the second protein is selected from the group consisting of GSPT1, IKZF1, IKZF2, IKZF3, CK1α, C6orf132, CAMP, CCNA2, FSP1, JCHAIN, NLRP7, PTTG1, and TPX2. In some embodiments, the second protein is selected from the group consisting of GSPT1, IKZF1, IKZF2, IKZF3, and CK1α. In some embodiments, the second protein is selected from the group consisting of C6orf132, CAMP, CCNA2, FSP1, JCHAIN, NLRP7, PTTG1, and TPX2. In some embodiments, the second protein is C6orf132. In some embodiments, the second protein is CAMP. In some embodiments, the second protein is CCNA2. In some embodiments, the second protein is FSP1. In some embodiments, the second protein is JCHAIN. In some embodiments, the second protein is NLRP7. In some embodiments, the second protein is PTTG1. In some embodiments, the second protein is TPX2.

In some embodiments, the compounds provided herein can exhibit potency against a BCL6 protein with minimal activity against a second protein (e.g., as measured by a proteomics assay, for example, a < 20% reduction in protein abundance as measured in the proteomics assay described herein). In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, can exhibit potent degradation of a BCL6 protein and

have minimal potency in degrading (e.g., as measured by abundance in a proteomic assay) a second protein (e.g., C6orf132, CAMP, CCNA2, FSP1, JCHAIN, NLRP7, PTTG, and/or TPX2) (e.g., as measured by abundance in a proteomic assay, for example, the proteomics assay as described herein). In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, can exhibit greater induction of degradation of a BCL6 protein relative to induction of degradation (e.g., as measured by abundance in a proteomic assay, for example, the proteomics assay as described herein)of a second protein (e.g., C6orf132, CAMP, CCNA2, FSP1, JCHAIN, NLRP7, PTTG1, and/or TPX2). In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, can exhibit at least 2-fold, 3-fold, 5-fold, 10-fold, 25-fold, 50-fold, or 100-fold greater induction of degradation of a BCL6 protein relative to induction of degradation of a second protein (e.g., C6orf132, CAMP, CCNA2, FSP1, JCHAIN, NLRP7, PTTG1, and/or TPX2) (e.g., as measured by abundance in a proteomic assay, for example, the proteomics assay as described herein). In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, can exhibit up to 1000-fold greater induction of degradation of a BCL6 protein relative to induction of degradation of a second protein (e.g., C6orf132, CAMP, CCNA2, FSP1, JCHAIN, NLRP7, PTTG1, and/or TPX2) (e.g., as measured by abundance in a proteomic assay, for example, the proteomics assay as described herein). In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, can exhibit from about 2-fold to about 10-fold greater induction of degradation of a BCL6 protein relative to induction of degradation of a second protein (e.g., C6orf132, CAMP, CCNA2, FSP1, JCHAIN, NLRP7, PTTG1, and/or TPX2) (e.g., as measured by abundance in a proteomic assay, for example, the proteomics assay as described herein). In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, can exhibit from about 10-fold to about 100-fold greater induction of degradation of a BCL6 protein relative to induction of degradation of a second protein (e.g., C6orf132, CAMP, CCNA2, FSP1, JCHAIN, NLRP7, PTTG1, and/or TPX2) (e.g., as measured by abundance in a proteomic assay, for example, the proteomics assay as described herein). In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, can exhibit from about 100-fold to about 1000-fold greater induction of degradation of a BCL6 protein relative to induction of degradation of a second protein (e.g., C6orf132, CAMP, CCNA2, FSP1, JCHAIN, NLRP7, PTTG1, and/or TPX2) (e.g., as measured by abundance in a proteomic assay, for example, the proteomics assay as described herein). In some embodiments, the second protein is selected from the group consisting of GSPT1, IKZF1, IKZF2, IKZF3, CK1α, C6orf132, CAMP, CCNA2, FSP1,

JCHAIN, NLRP7, PTTG1, and TPX2. In some embodiments, the second protein is selected from the group consisting of GSPT1, IKZF1, IKZF2, IKZF3, and CK1α. In some embodiments, the second protein is selected from the group consisting of C6orf132, CAMP, CCNA2, FSP1, JCHAIN, NLRP7, PTTG1, and TPX2. In some embodiments, the second protein is C6orf132. In some embodiments, the second protein is CAMP. In some embodiments, the second protein is CCNA2. In some embodiments, the second protein is FSP1. In some embodiments, the second protein is JCHAIN. In some embodiments, the second protein is NLRP7. In some embodiments, the second protein is PTTG1. In some embodiments, the second protein is TPX2.

In some embodiments, the compounds provided herein can exhibit potency against a BCL6 protein with minimal activity against any other detectable protein (e.g., as measured by a proteomics assay, for example, a < 20% reduction in protein abundance as measured in the proteomics assay described herein). In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, can exhibit potent degradation of a BCL6 protein and have minimal potency in degrading (e.g., as measured by abundance in a proteomic assay, for example, the proteomics assay as described herein) any other detectable protein. In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, can exhibit greater induction of degradation of a BCL6 protein relative to induction of degradation (e.g., as measured by abundance in a proteomic assay, for example, the proteomics assay as described herein) of any other detectable protein. In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, can exhibit at least 2-fold, 3-fold, 5-fold, 10-fold, 25-fold, 50-fold, or 100-fold greater induction of degradation of a BCL6 protein relative to induction of degradation of any other detectable protein (e.g., as measured by abundance in a proteomic assay, for example, the proteomics assay as described herein). In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, can exhibit up to 1000-fold greater induction of degradation of a BCL6 protein relative to induction of degradation of any other detectable protein (e.g., as measured by abundance in a proteomic assay, for example, the proteomics assay as described herein). In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, can exhibit from about 2-fold to about 10-fold greater induction of degradation of a BCL6 protein relative to induction of degradation of any other detectable protein (e.g., as measured by abundance in a proteomic assay, for example, the proteomics assay as described herein). In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, can exhibit from about 10-fold to about 100-fold greater induction of degradation of a

BCL6 protein relative to induction of degradation of any other detectable protein (e.g., as measured by abundance in a proteomic assay, for example, the proteomics assay as described herein).

In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, can exhibit potent degradation of a BCL6 protein and have minimal potency in degrading one or more additional proteins as measured by abundance in a proteomic assay. An exemplary proteomic experiment follows. OCI-Ly1 (DSMZ: ACC 722) cells are incubated with 100 nM of a compound provided herein, or a pharmaceutically acceptable salt thereof, or dimethyl sulfoxide (DMSO), for six hours. The cells are then washed two times with phosphate buffered saline and collected. Cells are lysed to extract total proteins, and total proteins are prepared for mass spectrometry analysis according to the protocol for the EASYPEP™ MS Sample Prep Kit (Fisher Scientific). In brief, proteins are reduced with dithiothreitol, alkylated with iodoacetamide, and digested with Trypsin and LysC enzyme. The resulting peptides are labeled with TMTPRO™ 18plex reagents (Fisher Scientific) according to the manufacturer protocol. Labeled peptides from each sample are mixed together in equal volumes, and the peptide mixture is separated by basic reverse-phase chromatography. A total of 85 fractions are combined into 18 pooled fractions. The pooled fractions are dried with a centrivap and resuspended in 5% acetonitrile, 0.1% formic acid for mass spectrometry analysis. Peptide abundance is quantified by tandem mass spectrometry using a Vanquish Neo chromatography system (Fisher Scientific) and Orbitrap FUSION™ LUMOS™ mass spectrometer (Fisher Scientific). Briefly, two micrograms of total peptides are loaded on a two-centimeter C8 trap column followed by a 50-centimeter C18 column. Data-dependent acquisition is performed to obtain peptide sequence and abundance information. Peptide and protein abundances are determined using the PROTEOME DISCOVERER™ software and the *Homo sapiens* proteome database (TaxID 9606), and the results are filtered to FDR<0.01. Significance thresholds are set to p-value <0.001 and abundance fold-change < 50%.

In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, can degrade a BCL6 protein and minimally degrade one or more additional proteins as measured by abundance in a proteomic assay, for example, a proteomic assay that measures peptides on a proteome-wide basis following exposure of cells to a compound provided herein, or a pharmaceutically acceptable salt thereof, for a period of time. The abundance of measured peptides can be compared to a control experiment, and proteins increased or decreased following exposure to the compound provided herein, or a pharmaceutically acceptable salt thereof, can be identified. An exemplary protocol follows.

Cells (e.g., OCI-Ly1 DSMZ: ACC 722) are incubated with a solution of 100 nM or 500 nM of a compound provided herein, or a pharmaceutically acceptable salt thereof, for 6 or 24 hours. After incubation, cells are washed two times with phosphate buffered saline, pelleted, and flash frozen in liquid nitrogen. Pellets are prepared for mass spectrometry analysis by using the Accelerome TMT 16-plex kit (Thermo Fisher #PIA50949) and an Accelerome (Thermo Fisher). Briefly, cells are lysed with lysis buffer containing universal nuclease and a cocktail of phosphatase and protease inhibitors (Thermo Fisher #78440). Protein extracts are digested with trypsin and LysC, reduced with dithiothreitol, and modified with iodoacetamide. Peptides are labeled with isobaric TMTpro reagent and combined. The combined, labeled peptides are separated by high-pH reverse phase fractionation using a C18 column (Phenomenex #00F-4893-AN) on an Agilent 1260 Infinity II HPLC. A total of 85 fractions are combined into 18 pooled fractions. The pooled fractions are dried with a centrivap and resuspended in 0.1% formic acid, 5% acetonitrile for analysis on an Orbitrap Ascend mass spectrometer (Thermo Fisher). Peptides are resolved using a 90-minute reverse phase gradient and a 50 cm C18 column (Thermo Fisher #ES903). A data-dependent SPS-MS3 analysis method is used with the default settings (e.g., MS1 scan with 120000 orbitrap resolution, Scan Range of 400-1600 m/z, and RF Lens of 60%; MS2 scan with CID fragmentation, 30% Collision Energy, Ion Trap detector, Turbo Scan Rate, and 45 ms injection time; MS3 scan with HCD fragmentation, 55% Collision Energy, Orbitrap detector, 45000 resolution, TurboTMT off, and 200 ms injection time). Real-time search is enabled with the *Homo sapiens* proteome database (Uniprot 9606, downloaded 7/10/23), Static Modifications of "Carbamidomethyl" and "TMTpro16plex", and Variable Modification "Oxidation M". Raw files are processed to identify and quantify proteins using Proteome Discoverer version 3.0. Data are searched against the human proteome (above). Processing method "PWF_Tribrid_TMTpro_Quan_SPS_MS3_SequestFT_Percolator" and Consensus method "CWF_Comprehensive_Enhanced Annotation_Reporter_Quan_MS3" are used to generate protein quantitation values. The Sequest HT node included dynamic modifications of oxidation on Met, phosphorylation on Ser, Thr, and Tyr, and static modifications of TMTpro on Lys and peptide N-terminus and Carbamidomethyl on Cys.

As used herein, "determining BCL6 expression status," means assessing whether or not BCL6 is expressed, e.g., at the mRNA or protein level. In some embodiments, the assessment includes the level of BCL6 expression (e.g., BCL6 expression above or below a threshold value). BCL6 expression status can be assessed by a variety of methods (e.g., measuring protein levels, mRNA levels, or both) and can be assessed quantitatively or qualitatively, e.g., using a scale or threshold accepted by, e.g., a regulatory agency or by a pathologist. In some

embodiments, the assessment includes consulting the medical record of a subject. In some embodiments, the BCL6 expression status is positive (e.g., the sample from the subject is positive for BCL6 expression). In some embodiments the BCL6 expression status is not positive for BCL6 expression (e.g., the sample from the subject is negative or indeterminate, for example, BCL6 expression is below a threshold value or below the lower limit of detection for a particular assay).

In some embodiments, a BCL6 expression status can be determined for a sample from a subject. In some embodiments, the BCL6 expression status can be determined by expression profiling (e.g., mRNA expression profiling) (e.g., of a sample of the cancer or from a blood sample). In some embodiments, the BCL6 expression status can be determined by an mRNA-based test, such as RNA sequencing (RNA-seq), reverse transcription polymerase chain reaction (RT-PCR), digital PCR (dPCR), or in-situ hybridization (ISH). In some embodiments, the BCL6 expression status can be determined by an IHC test, using any appropriate IHC method and reagents. For example, a pathologist or an automated system (e.g., the BOND RX system (Leica), the BOND-PRIME system (Leica), the AutoStainer Link 48 system (Agilent), the AutoStainer PLUS system (Agilent), the Dako Omnis system (Agilent), the BenchMark ULTRA system (Roche), or the BenchMark ULTRA PLUS system (Roche)) can determine that a sample of the cancer (e.g., a biopsy sample) from the subject subjected to IHC with an appropriate BCL6 antibody is positive for BCL6 expression. As another example, an IHC test can result in an IHC score of 0, 1, 2, or 3; in some such embodiments, a positive BCL6 expression status can be indicated by a score of 1, 2, or 3 (e.g., 2 or 3) (e.g., as determined by a pathologist or an automated system). As yet another example, an IHC test may result in a percent nuclear positivity score from 0% to 100%; in some such embodiments, a positive BCL6 expression status can be indicated by a percent nuclear positivity score of greater than or equal to 1% (e.g., greater than or equal to 5%, greater than or equal to 10%, greater than or equal to 15%, or greater than or equal to 20%). In some embodiments, a positive BCL6 expression status can be indicated by a percent nuclear positivity score of greater than or equal to 30% (e.g., greater than or equal to 35%, greater than or equal to 40%, or greater than or equal to 50%) (e.g., as determined by a pathologist or an automated system). See, e.g., Hans, Christine P., et al. *Blood* 103.1 (2004): 275-282, doi: 10.1182/blood-2003-05-1545. In some such embodiments, the sample from the subject can have a percent nuclear positivity score of greater than or equal to 75% (e.g., greater than or equal to 80%, greater than or equal to 90%, or greater than or equal to 95%) (e.g., as determined by a pathologist or an automated system). As another example, an IHC test can result in an H-score from 0 to 300; in some such embodiments, a

positive BCL6 expression status can be indicated by an H-score of greater than or equal to 10 (e.g., greater than or equal to 30, greater than or equal to 50, greater than or equal to 60, greater than or equal to 75, greater than or equal to 100, greater than or equal to 150, or greater than or equal to 200). In some embodiments, an H-score is calculated as 3 x percentage of strongly staining nuclei + 2 x percentage of moderately staining nuclei + percentage of weakly staining nuclei.

Non-limiting examples of antibodies suitable for an IHC test of BCL6 expression include clone PG-B6p (e.g., Dako/Agilent product number IR625), clone GI191E/A8 (e.g., Roche/Ventana product number 760-4241), clone LN22 (e.g., Lecia Biosystems product number PA0204), clone GI191E/A8 (e.g., Sigma/Cell Marque product number 227M-98), and clone EP278 (e.g., Sigma/Cell Marque product number 227R-27).

Provided herein is a method of treating a cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound provided herein, or a pharmaceutically acceptable salt thereof. In some embodiments, the cancer in the subject is positive for BCL6 expression. In some embodiments, the cancer in the subject is negative for BCL6 expression. Accordingly, also provided herein is a method of treating cancer in a subject in need thereof, the method comprising (a) determining the BCL6 expression status of the cancer (e.g., by performing an assay or a test, or consulting the subject's medical record); and (b) administering to the subject a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound provided herein, or a pharmaceutically acceptable salt thereof. Also provided herein is a method of treating cancer in a subject in need thereof, the method comprising: (a) determining that the cancer in the subject is positive for BCL6 expression (e.g., determining that the cancer is positive for BCL6 expression by an IHC test); and (b) administering to the subject a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound provided herein, or a pharmaceutically acceptable salt thereof.

Also provided herein is a method of treating cancer in a subject in need thereof, the method comprising: (a) determining the BCL6 expression status of the cancer; and (b) administering to the subject a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound provided herein, or a pharmaceutically acceptable salt thereof. In some such

embodiments, the cancer in the subject is positive for BCL6 expression. In other such embodiments, the cancer in the subject is not positive for BCL6 expression.

Also provided herein is a method of treating cancer, the method comprising administering to a subject determined to have a cancer that is positive for BCL6 expression (e.g., a subject determined to have a cancer that is positive for BCL6 expression by an IHC test) a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound provided herein, or a pharmaceutically acceptable salt thereof.

Also provided herein is a method of treating cancer, the method comprising administering to a subject having a cancer previously tested for BCL6 expression status (e.g., a subject having a cancer previously tested for BCL6 expression by an IHC test) a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound provided herein, or a pharmaceutically acceptable salt thereof. In some such embodiments, the cancer in the subject is positive for BCL6 expression. In other such embodiments, the cancer in the subject is not positive for BCL6 expression.

Also provided herein is a method of treating cancer, the method comprising administering to a subject who has a record (e.g., a medical record) that indicates that the cancer in the subject is positive for BCL6 expression (e.g., a subject previously identified as having a cancer that is positive for BCL6 expression by an IHC test) a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound provided herein, or a pharmaceutically acceptable salt thereof.

Also provided herein is a method of treating cancer, the method comprising administering to a subject who has a record (e.g., a medical record) that indicates that the cancer in the subject was previously tested for BCL6 expression (e.g., a subject identified as having a cancer that was previously tested for BCL6 expression by an IHC test) a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound provided herein, or a pharmaceutically acceptable salt thereof. In some such embodiments, the cancer in the subject is positive for BCL6 expression. In other such embodiments, the cancer in the subject is not positive for BCL6 expression.

Also provided herein is a method of treating cancer, the method comprising administering a therapeutically effective amount of a compound provided herein, or a

pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound provided herein, or a pharmaceutically acceptable salt thereof, to a subject determined to have a cancer that is positive for BCL6 expression (e.g., a cancer that is positive for BCL6 expression by an IHC test).

Also provided herein is a method of treating cancer, the method comprising administering a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound provided herein, or a pharmaceutically acceptable salt thereof, to a subject determined to have a cancer previously tested for BCL6 expression (e.g., a cancer previously tested for BCL6 expression by an IHC test). In some such embodiments, the cancer in the subject is positive for BCL6 expression. In other such embodiments, the cancer in the subject is not positive for BCL6 expression.

In some embodiments, provided herein is a method of treating cancer in a subject that includes performing an assay on a sample (e.g., a tumor sample) obtained from the subject to determine that the cancer in the subject is positive for BCL6 expression, and administering a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound provided herein, or a pharmaceutically acceptable salt thereof, to the subject having a cancer determined to be positive for BCL6 expression.

In some embodiments, provided herein is a method of treating cancer in a subject that includes performing an assay on a sample (e.g., a tumor sample) obtained from the subject to determine the BCL6 expression status of the cancer, and administering a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound provided herein, or a pharmaceutically acceptable salt thereof, to the subject. In some such embodiments, the cancer in the subject is positive for BCL6 expression. In other such embodiments, the cancer in the subject is not positive for BCL6 expression.

In some embodiments of any of these methods, the BCL6 expression status of the cancer is determined after administration of at least one dose (e.g., two doses, three doses, four doses, five doses, or more) of a compound provided herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound provided herein, or a pharmaceutically acceptable salt thereof, to the subject (e.g., the BCL6 expression status of the cancer is determined via a biopsy or a blood sample).

In some embodiments, the subject is suspected of having a cancer that is positive for

BCL6 expression, is presenting with one or more symptoms of a cancer expressing BCL6, or has an elevated risk of developing a cancer that is positive for BCL6 expression. In some embodiments, the subject is treatment naïve with respect to the cancer. In some embodiments, the subject has received one or more lines of previous therapy for the cancer.

In some embodiments of any of these methods, the compound provided herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound provided herein, or a pharmaceutically acceptable salt thereof, is administered to the subject as a monotherapy. Some embodiments of these methods further include administering to the subject an additional therapy or therapeutic agent.

In some embodiments, the cancer is a large B cell lymphoma (LBCL) (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary LBCL of immune-privileged sites, primary mediastinal LBCL, or HBGCL-NOS). In some embodiments, the LBCL is positive for BCL6 expression as determined by an IHC test (e.g., indicated by a percent nuclear positivity score of greater than or equal to 30% in an IHC test). In some embodiments, the cancer is DLBCL-NOS; in some such embodiments, the DLBCL-NOS is positive for BCL6 expression as determined by an IHC test (e.g., indicated by a percent nuclear positivity score of greater than or equal to 30% in an IHC test). In some embodiments, the cancer is HGBCL-MYC/BCL-2 or HGBCL-NOS; in some such embodiments, the HGBCL-MYC/BCL-2 or HGBCL-NOS is positive for BCL6 expression as determined by an IHC test (e.g., indicated by a percent nuclear positivity score of greater than or equal to 30% in an IHC test). In some embodiments, the cancer is primary LBCL of immune-privileged sites; in some such embodiments, the primary LBCL of immune-privileged sites is positive for BCL6 expression as determined by an IHC test (e.g., indicated by a percent nuclear positivity score of greater than or equal to 30% in an IHC test). In some embodiments, the cancer is primary mediastinal LBCL; in some such embodiments, the primary mediastinal LBCL is positive for BCL6 expression as determined by an IHC test (e.g., indicated by a percent nuclear positivity score of greater than or equal to 30% in an IHC test).

In some embodiments, the cancer is a transformed indolent B cell lymphoma. In some embodiments, the transformed indolent B cell lymphoma is positive for BCL6 expression as determined by an IHC test (e.g., indicated by a percent nuclear positivity score of greater than or equal to 1% in an IHC test; e.g., a percent nuclear positivity score of greater than or equal to 30% in an IHC test).

In some embodiments, the cancer is FL. In some embodiments, the FL is positive for BCL6 expression as determined by an IHC test (e.g., indicated by a percent nuclear positivity score of greater than or equal to 1% in an IHC test; e.g., a percent nuclear positivity score of greater than or equal to 30% in an IHC test).

In some embodiments, the cancer is BL. In some embodiments, the BL is positive for BCL6 expression as determined by an IHC test (e.g., indicated by a percent nuclear positivity score of greater than or equal to 1% in an IHC test; e.g., a percent nuclear positivity score of greater than or equal to 30% in an IHC test).

In some embodiments, the cancer is NLPHL. In some embodiments, the NLPHL is positive for BCL6 expression as determined by an IHC test (e.g., indicated by a percent nuclear positivity score of greater than or equal to 1% in an IHC test; e.g., a percent nuclear positivity score of greater than or equal to 30% in an IHC test).

In some embodiments, the cancer is a peripheral T-cell lymphoma (PTCL) (e.g., anaplastic large cell lymphoma (ALCL) (e.g., ALK-positive anaplastic large cell lymphoma, or ALK-negative anaplastic large cell lymphoma), nodal T follicular helper cell lymphoma (e.g., nodal T follicular helper cell lymphoma angioimmunoblastic type (also known as angioimmunoblastic T-cell lymphoma (AITL) or follicular helper T-cell lymphoma, angioimmunoblastic type), nodal T follicular helper cell lymphoma follicular type (also known as follicular helper T-cell lymphoma, follicular type), or nodal T follicular helper cell lymphoma NOS (also known as follicular helper T-cell lymphoma, NOS))) or a primary cutaneous T-cell lymphoid proliferation or lymphoma (cutaneous T-cell lymphoma (CTCL)) (e.g., primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder, mycosis fungoides, Sezary syndrome, or primary cutaneous gamma-delta T-cell lymphoma). In some embodiments, the PTCL or CTCL is positive for BCL6 expression as determined by an IHC test (e.g., indicated by a percent nuclear positivity score of greater than or equal to 1% in an IHC test; e.g., a percent nuclear positivity score of greater than or equal to 30% in an IHC test). In some embodiments, the cancer is a nodal T follicular helper cell lymphoma (e.g., nodal T follicular helper cell lymphoma angioimmunoblastic type (also known as angioimmunoblastic T-cell lymphoma (AITL) or follicular helper T-cell lymphoma, angioimmunoblastic type), nodal T follicular helper cell lymphoma follicular type (also known as follicular helper T-cell lymphoma, follicular type), or nodal T follicular helper cell lymphoma NOS (also known as follicular helper T-cell lymphoma, NOS)). In some such embodiments, the nodal T follicular helper cell lymphoma (e.g., nodal T follicular helper cell lymphoma angioimmunoblastic type (also known as angioimmunoblastic T-cell lymphoma

(AITL) or follicular helper T-cell lymphoma, angioimmunoblastic type), nodal T follicular helper cell lymphoma follicular type (also known as follicular helper T-cell lymphoma, follicular type), or nodal T follicular helper cell lymphoma NOS (also known as follicular helper T-cell lymphoma, NOS)) is positive for BCL6 expression as determined by an IHC test (e.g., indicated by a percent nuclear positivity score of greater than or equal to 1% in an IHC test; e.g., a percent nuclear positivity score of greater than or equal to 30% in an IHC test). In some embodiments, the cancer is nodal T follicular helper cell lymphoma follicular type. In some such embodiments, the nodal T follicular helper cell lymphoma follicular type is positive for BCL6 expression as determined by an IHC test (e.g., indicated by a percent nuclear positivity score of greater than or equal to 1% in an IHC test; e.g., a percent nuclear positivity score of greater than or equal to 30% in an IHC test). In some embodiments, the cancer is nodal T follicular helper cell lymphoma angioimmunoblastic type. In some such embodiments, the nodal T follicular helper cell lymphoma angioimmunoblastic type is positive for BCL6 expression as determined by an IHC test (e.g., indicated by a percent nuclear positivity score of greater than or equal to 1% in an IHC test; e.g., a percent nuclear positivity score of greater than or equal to 30% in an IHC test). In some embodiments, the cancer is anaplastic large cell lymphoma (ALCL) (e.g., ALK-positive anaplastic large cell lymphoma, or ALK-negative anaplastic large cell lymphoma). In some such embodiments, the anaplastic large cell lymphoma (ALCL) (e.g., ALK-positive anaplastic large cell lymphoma, or ALK-negative anaplastic large cell lymphoma) is positive for BCL6 expression as determined by an IHC test (e.g., indicated by a percent nuclear positivity score of greater than or equal to 1% in an IHC test; e.g., a percent nuclear positivity score of greater than or equal to 30% in an IHC test). In some embodiments, the cancer is nodal T follicular helper cell lymphoma NOS. In some such embodiments, the nodal T follicular helper cell lymphoma NOS is positive for BCL6 expression as determined by an IHC test (e.g., indicated by a percent nuclear positivity score of greater than or equal to 1% in an IHC test; e.g., a percent nuclear positivity score of greater than or equal to 30% in an IHC test). In some embodiments, the cancer is a primary cutaneous T-cell lymphoid proliferation or lymphoma (cutaneous T-cell lymphoma (CTCL)) (e.g., primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder, mycosis fungoides, Sezary syndrome, or primary cutaneous gamma-delta T-cell lymphoma). In some such embodiments, the primary cutaneous T-cell lymphoid proliferation or lymphoma (cutaneous T-cell lymphoma (CTCL)) (e.g., primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder, mycosis fungoides, Sezary syndrome, or primary cutaneous gamma-delta T-cell lymphoma) is positive for BCL6 expression as determined by

an IHC test (e.g., indicated by a percent nuclear positivity score of greater than or equal to 1% in an IHC test; e.g., a percent nuclear positivity score of greater than or equal to 30% in an IHC test). In some embodiments, the cancer is mycosis fungoides. In some such embodiments, the mycosis fungoides is positive for BCL6 expression as determined by an IHC test (e.g., indicated by a percent nuclear positivity score of greater than or equal to 1% in an IHC test; e.g., a percent nuclear positivity score of greater than or equal to 30% in an IHC test). In some embodiments, the cancer is primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder. In some such embodiments, the primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder is positive for BCL6 expression as determined by an IHC test (e.g., indicated by a percent nuclear positivity score of greater than or equal to 1% in an IHC test; e.g., a percent nuclear positivity score of greater than or equal to 30% in an IHC test). In some embodiments, the cancer is mycosis fungoides. In some such embodiments, the mycosis fungoides is positive for BCL6 expression as determined by an IHC test (e.g., indicated by a percent nuclear positivity score of greater than or equal to 1% in an IHC test; e.g., a percent nuclear positivity score of greater than or equal to 30% in an IHC test). In some embodiments, the cancer is primary cutaneous gamma-delta T-cell lymphoma. In some such embodiments, the primary cutaneous gamma-delta T-cell lymphoma is positive for BCL6 expression as determined by an IHC test (e.g., indicated by a percent nuclear positivity score of greater than or equal to 1% in an IHC test; e.g., a percent nuclear positivity score of greater than or equal to 30% in an IHC test). In some embodiments, the cancer is Sezary syndrome. In some such embodiments, the Sezary syndrome is positive for BCL6 expression as determined by an IHC test (e.g., indicated by a percent nuclear positivity score of greater than or equal to 1% in an IHC test; e.g., a percent nuclear positivity score of greater than or equal to 30% in an IHC test).

In some cases, treatment of a cancer or a model of a cancer (e.g., a PDX or CDX model) with a compound provided herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound provided herein, or a pharmaceutically acceptable salt thereof, can result in a regression (e.g., greater than or equal to 50% regression) of the cancer or the model of the cancer. In some cases, treatment of a cancer or a model of a cancer (e.g., a PDX or CDX model) with a compound provided herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound provided herein, or a pharmaceutically acceptable salt thereof, as a monotherapy can result in a regression (e.g., greater than or equal to 50% regression) of the cancer or the model of the cancer. In some such embodiments, the PDX model is positive for BCL6 expression as

determined by an IHC test (e.g., indicated by a percent nuclear positivity score of greater than or equal to 30% in an IHC test). In some embodiments, the PDX model is positive for MYC expression as determined by an IHC test (e.g., indicated by a percent nuclear positivity score of greater than or equal to 30% in an IHC test). In some such embodiments, the PDX model is positive for BCL6 expression as determined by an IHC test (e.g., indicated by a percent nuclear positivity score of greater than or equal to 30% in an IHC test) and positive for MYC expression as determined by an IHC test (e.g., indicated by a percent nuclear positivity score of greater than or equal to 30% in an IHC test).

Provided herein is use of a compound provided herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, for the treatment of cancer, for example, any of the cancers provided herein. Also provided herein is use of a compound provided herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, for the treatment of a cancer that is positive for BCL6 expression (e.g., as determined by an IHC test).

Provided herein is use of a compound provided herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, as a medicament for the treatment of cancer, for example, any of the cancers provided herein. Also provided herein is use of a compound provided herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, as a medicament for the treatment of a cancer that is positive for BCL6 expression (e.g., as determined by an IHC test).

Provided herein is use of a compound provided herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer, for example, any of the cancers provided herein. Also provided herein is use of a compound provided herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a cancer that is positive for BCL6 expression (e.g., as determined by an IHC test).

Provided herein is a compound provided herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, for use as a medicament. Also provided herein is a compound provided herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, for use as a medicament for the treatment of cancer, for example, any of the cancers provided herein. Also provided herein is a compound provided herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, for use as a medicament in the treatment of a cancer that is positive for BCL6 expression (e.g., as determined by an IHC test).

Provided herein is a compound provided herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, for use in treating a cancer, for example, any

of the cancers provided herein. Also provided is a compound provided herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, for use in treating a cancer that is positive for BCL6 expression in a subject identified or diagnosed as having a cancer that is positive for BCL6 expression through a step of performing a test (e.g., an IHC test) on a sample (e.g., a tumor sample) obtained from the subject to determine whether the cancer in the subject that is positive for BCL6 expression (e.g., as determined by an IHC test).

As used herein, treatment of a cancer can include treatment of a primary tumor (i.e., non-metastatic cancer) (e.g., as first, second, third, or later line of therapy, including, but not limited to, the relapsed/refractory setting), treatment of a metastatic (or secondary) tumor, neoadjuvant therapy (e.g., before treatment with an additional therapy or therapeutic agent, such as surgery, radiation, chemotherapy, or a line of therapy), adjuvant therapy (e.g., following treatment with an additional therapy or therapeutic agent, such as surgery, radiation, chemotherapy, or a line of therapy), or maintenance therapy (e.g., treatment following response to an additional therapy or therapeutic agent, such as surgery, radiation, chemotherapy, or a line of therapy).

In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof is used in the treatment of a primary tumor. In some embodiments, the subject is treatment naïve with respect to the cancer. In some embodiments, the subject has received one or more lines of therapy for the cancer. In some embodiments, the subject has received chemotherapy, cell-based therapy (e.g., adoptive cell therapy (e.g., CAR T therapy, cytokine-induced killer cells (CIKs), natural killer cells (e.g., CAR-modified NK cells)) or antibody-armed cell therapy), or both. In some embodiments, the subject has received R-CHOP, G-CHOP, R-EPOCH, CVP, CVAD, R^2, R-CODOX-M, R-IVAC, DA-EPOCH-R, cell-based therapy, or two or more thereof. In some embodiments, the subject has received a rituximab-containing regimen. In some embodiments, the subject has received an obinutuzumab-containing regimen. In some embodiments, the subject has received a mosunetuzumab-containing regimen. In some embodiments, the subject has received an epcoritamab-containing regimen. In some embodiments, the compound provided herein, or a pharmaceutically acceptable salt thereof is used in the treatment of a subject who has received one or more lines of systemic therapy for the cancer. In some embodiments, the compound provided herein, or a pharmaceutically acceptable salt thereof is used in the treatment of a subject who has received two or more lines of systemic therapy for the cancer.

In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof is used in the treatment of a metastatic tumor. In some embodiments, the subject is treatment naïve with respect to the metastatic tumor. In some embodiments, the subject has received one or more lines of therapy for the secondary tumor. In some embodiments, the subject has received chemotherapy, cell-based therapy (e.g., adoptive cell therapy (e.g., CAR T therapy, cytokine-induced killer cells (CIKs), natural killer cells (e.g., CAR-modified NK cells)) or antibody-armed cell therapy), or both. In some embodiments, the subject has received R-CHOP, G-CHOP, R-EPOCH, CVP, CVAD, R^2, R-CODOX-M, R-IVAC, DA-EPOCH-R, cell-based therapy, or two or more thereof. In some embodiments, the subject has received a rituximab-containing regimen. In some embodiments, the subject has received an obinutuzumab-containing regimen. In some embodiments, the subject has received a mosunetuzumab-containing regimen. In some embodiments, the subject has received an epcoritamab-containing regimen. In some embodiments, the compound provided herein, or a pharmaceutically acceptable salt thereof is used in the treatment of a subject who has received one or more lines of systemic therapy for the cancer. In some embodiments, the compound provided herein, or a pharmaceutically acceptable salt thereof is used in the treatment of a subject who has received two or more lines of systemic therapy for the cancer.

In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof is used as neoadjuvant therapy. In some embodiments, the neoadjuvant therapy precedes surgery (e.g., surgical resection, such as partial surgical resection or complete, total, or full surgical resection). In some embodiments, the neoadjuvant therapy precedes radiation therapy. In some embodiments, the neoadjuvant therapy precedes chemotherapy.

In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof is an adjuvant therapy. In some embodiments, the subject has received chemotherapy, cell-based therapy (e.g., adoptive cell therapy (e.g., CAR T therapy, cytokine-induced killer cells (CIKs), natural killer cells (e.g., CAR-modified NK cells)) or antibody-armed cell therapy), or both. In some embodiments, the subject has received R-CHOP, G-CHOP, R-EPOCH, CVP, CVAD, R^2, R-CODOX-M, R-IVAC, DA-EPOCH-R, cell-based therapy, or two or more thereof. In some embodiments, the subject has received a rituximab-containing regimen. In some embodiments, the subject has received an obinutuzumab-containing regimen. In some embodiments, the subject has received a mosunetuzumab-containing regimen. In some embodiments, the subject has received an epcoritamab-containing regimen. In some embodiments, the compound provided herein, or a pharmaceutically acceptable salt thereof is used in the treatment of a subject who has received one or more lines

of systemic therapy for the cancer. In some embodiments, the compound provided herein, or a pharmaceutically acceptable salt thereof is used in the treatment of a subject who has received two or more lines of systemic therapy for the cancer. In some embodiments, the adjuvant therapy follows surgery (e.g., surgical resection, such as partial surgical resection or complete, total, or full surgical resection). In some embodiments, the adjuvant therapy follows radiation therapy. In some embodiments, the adjuvant therapy follows chemotherapy.

In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof is a maintenance therapy. In some embodiments, the subject has received chemotherapy, cell-based therapy (e.g., adoptive cell therapy (e.g., CAR T therapy, cytokine-induced killer cells (CIKs), natural killer cells (e.g., CAR-modified NK cells)) or antibody-armed cell therapy), a stem cell transplant, or a combination thereof. In some embodiments, the subject has received R-CHOP, G-CHOP, R-EPOCH, CVP, CVAD, R^2, R-CODOX-M, R-IVAC, DA-EPOCH-R, cell-based therapy, or two or more thereof. In some embodiments, the subject has received a rituximab-containing regimen. In some embodiments, the subject has received an obinutuzumab-containing regimen. In some embodiments, the subject has received a mosunetuzumab-containing regimen. In some embodiments, the subject has received an epcoritamab-containing regimen. In some embodiments, the subject has received a stem cell transplant. In some embodiments, the subject has received a cell-based therapy (e.g., CAR T therapy). In some embodiments, the compound provided herein, or a pharmaceutically acceptable salt thereof is used in the treatment of a subject who has received one or more lines of systemic therapy for the cancer. In some embodiments, the compound provided herein, or a pharmaceutically acceptable salt thereof is used in the treatment of a subject who has received two or more lines of systemic therapy for the cancer.

As used herein, “monotherapy”, when referring to a compound provided herein, or a pharmaceutically acceptable salt thereof, means that the compound provided herein, or a pharmaceutically acceptable salt thereof, is the only therapeutic agent or therapy (e.g., anticancer agent or therapy) administered to the subject during the treatment cycle (e.g., no additional targeted therapeutics, anticancer agents, chemotherapeutics, or checkpoint inhibitors are administered to the subject during the treatment cycle). As a person of ordinary skill in the art would understand, monotherapy does not exclude the co-administration of medicaments for the treatment of side effects or general symptoms associated with the cancer or treatment, such as pain, rash, edema, photosensitivity, pruritis, skin discoloration, hair brittleness, hair loss, brittle nails, cracked nails, discolored nails, swollen cuticles, fatigue, weight loss, general malaise, shortness of breath, infection, anemia, or gastrointestinal symptoms, including nausea,

diarrhea, and lack of appetite.

As used herein, "the subject has received one or more lines of therapy for the cancer" means that the subject has been previously administered one or more therapeutic agents or therapies (e.g., anticancer agent or therapy) for the cancer other than a compound provided herein, or a pharmaceutically acceptable salt thereof, during a prior treatment cycle. In some embodiments, the subject cannot tolerate the one or more therapeutic agents or therapies previously administered for the cancer. In some embodiments, the subject did not respond to the one or more therapeutic agents or therapies previously administered for the cancer. In some embodiments, the subject did not adequately respond to one or more therapeutic agents or therapies previously administered for the cancer. In some embodiments, the subject has stopped responding to the one or more therapeutic agents or therapies previously administered for the cancer. In some embodiments, a lack of response, an inadequate response, or a discontinued response can be determined by objective criteria (e.g., tumor volume, or by criteria such as RECIST 1.1, the Lugano 2014 criteria (Cheson, Bruce D., et al. *Journal of Clinical Oncology* 32.27 (2014): 3059-3067; doi: 10.1200/JCO.2013.54.8800) or the Global Response Criteria (Olsen, Elise A., et al. *Blood, The Journal of the American Society of Hematology* 140.5 (2022): 419-437; doi: 10.1182/blood.2021012057)). In some embodiments, a lack of response, an inadequate response, or a discontinued response can be determined by the subject's physician.

As used herein, "the subject is treatment naïve with respect to the cancer" means that the subject has not been previously administered one or more therapeutic agents or therapies for the cancer.

For any of the solid tumors described herein, the solid tumor can be primary tumors or metastatic (or secondary) tumors. As used herein, "primary" tumors are those located at the site where the tumor began to grow (i.e., where it originated). As used herein, "metastatic" (or "secondary") tumors are those that have spread to other parts of body from the original tumor site. In some embodiments, the metastatic or secondary tumors are the same type of cancer as the primary tumor. In some embodiments, the metastatic or secondary tumors are not genetically identical to the primary tumor.

In some embodiments of any of the methods or uses described herein, the cancer is breast cancer (e.g., breast invasive carcinoma, breast invasive ductal carcinoma), central or peripheral nervous system tissue cancer (e.g., brain cancer (e.g., astrocytoma, glioblastoma, glioma, oligoastrocytoma)), endocrine or neuroendocrine cancer (e.g., adrenal cancer (e.g., adrenocortical carcinoma, pheochromocytoma, paraganglioma), multiple neuroendocrine type I and type II tumors, parathyroid cancer, pituitary tumors, thyroid cancer (e.g., papillary thyroid

cancer)), eye cancer (e.g., uveal cancer (e.g., uveal melanoma)), gastrointestinal cancer (e.g., anal cancer, bile duct cancer (e.g., cholangiocarcinoma), colorectal cancer (e.g., colon adenocarcinoma, rectal adenocarcinoma, mucinous adenocarcinoma, mucinous carcinoma), esophageal cancer (e.g., esophageal adenocarcinoma), gallbladder cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor, liver cancer (e.g., hepatocellular carcinoma, intrahepatic bile duct cancer), pancreatic cancer (e.g., pancreatic adenocarcinoma, pancreatic islet cell cancer), small intestine cancer, or stomach cancer (e.g., stomach adenocarcinoma, signet ring cell carcinoma of the stomach)), genitourinary cancer (e.g., bladder cancer (e.g., bladder urothelial carcinoma), kidney cancer (e.g., renal clear cell carcinoma, renal papillary cell carcinoma, kidney chromophobe), prostate cancer (e.g., prostate adenocarcinoma), testicular cancer (e.g., testicular germ cell tumors), or ureter cancer), gynecologic cancer (e.g., cervical cancer (e.g., cervical squamous cell carcinoma, endocervical adenocarcinoma, mucinous carcinoma), ovarian cancer (e.g., serous ovarian cancer, ovarian serous cystadenocarcinoma), uterine cancer (e.g., uterine carcinosarcoma, uterine endometrioid carcinoma, uterine serous carcinoma, uterine papillary serous carcinoma, uterine corpus endometrial carcinoma), or vulvar cancer), head and neck cancer (e.g., ear cancer (e.g., middle ear cancer), head and neck squamous cell carcinoma, nasal cavity cancer, oral cancer, pharynx cancer (e.g., hypopharynx cancer, nasopharynx cancer, oropharyngeal cancer), hematological cancer (e.g., leukemia (e.g., acute lymphocytic leukemia (ALL) (e.g., Philadelphia chromosome positive ALL, Philadelphia chromosome negative ALL), acute myeloid leukemia (AML) (e.g., acute promyelocytic leukemia (APL)), chronic myeloid leukemia (CML), or early T-precursor lymphoblastic leukemia, or myelodysplastic syndrome), lymphoma (e.g., Hodgkin lymphoma (e.g., nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) or classic Hodgkin lymphoma), non-Hodgkin lymphoma (e.g., B cell lymphoid proliferations and lymphomas (e.g., tumor-like lesions with B-cell predominance (e.g., IgG4-related disease), precursor B cell neoplasms (e.g., B lymphoblastic lymphomas), mature B cell neoplasms (e.g., chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), marginal zone lymphoma, Burkitt lymphoma (BL), large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), T-cell/histiocyte-rich large B-cell lymphoma, diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), ALK-positive large B-cell lymphoma, large B cell lymphoma with IRF4 rearrangements, high-grade B cell lymphoma with 11q aberration, lymphomatoid granulomatosis, Epstein-Barr virus (EBV)-positive large B-cell lymphoma, diffuse large B-cell lymphoma associated with chronic

inflammation, fibrin-associated large B-cell lymphoma, fluid-overload large B-cell lymphoma, plasmablastic lymphoma, primary large B cell lymphoma of immune-privileged sites (primary LBCL of immune-privileged sites), primary cutaneous large B-cell lymphoma leg type, intravascular large B-cell lymphoma (IVLBCL), primary mediastinal large B cell lymphoma (primary mediastinal LBCL), mediastinal grey zone lymphoma, or high grade B-cell lymphoma NOS), follicular lymphoma (FL), transformations of indolent B cell lymphomas, mantle cell lymphoma (MCL), or plasma cell neoplasms (e.g., multiple myeloma))), T-cell and NK-cell lymphoid proliferations and lymphomas (e.g., tumor-like lesions with T-cell predominance (e.g., autoimmune lymphoproliferative syndrome), precursor T-cell neoplasms (e.g., early T-precursor lymphoblastic leukemia/lymphoma or T-lymphoblastic leukemia/lymphoma NOS), mature T-cell and NK-cell neoplasms (e.g., mature T-cell and NK-cell leukemias (e.g., T-prolymphocytic leukemia, T-large granular lymphocytic leukemia, NK-large granular lymphocytic leukemia, adult T-cell leukemia/lymphoma, or aggressive NK-cell leukemia), primary cutaneous T-cell lymphoid proliferations and lymphomas (cutaneous T-cell lymphoma (CTCL)) (e.g., primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder, primary cutaneous acral CD8-positive T-cell lymphoproliferative disorder, mycosis fungoides, Sezary syndrome, primary cutaneous CD30-positive T-cell lymphoproliferative disorder: lymphomatoid papulosis, primary cutaneous CD30-positive T-cell lymphoproliferative disorder: primary cutaneous anaplastic large cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, primary cutaneous gamma-delta T-cell lymphoma, primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma, or primary cutaneous peripheral T-cell lymphoma NOS), peripheral T-cell lymphoma (PTCL) (e.g., intestinal T-cell and NK-cell lymphoid proliferations and lymphomas (e.g., indolent T-cell lymphoma of the gastrointestinal tract, indolent NK-cell lymphoproliferative disorder of the gastrointestinal tract, enteropathy-associated T-cell lymphoma, monomorphic epitheliotropic intestinal T-cell lymphoma, or intestinal T-cell lymphoma NOS)),hepatosplenic T-cell lymphoma, anaplastic large cell lymphoma (ALCL) (e.g., ALK-positive anaplastic large cell lymphoma, ALK-negative anaplastic large cell lymphoma, or breast implant-associated anaplastic large cell lymphoma), nodal T follicular helper cell lymphoma (e.g., nodal T follicular helper cell lymphoma angioimmunoblastic type (also known as angioimmunoblastic T-cell lymphoma (AITL) or follicular helper T-cell lymphoma, angioimmunoblastic type), nodal T follicular helper cell lymphoma follicular type (also known as follicular helper T-cell lymphoma, follicular type), or nodal T follicular helper cell lymphoma NOS (also known as follicular helper T-cell lymphoma, NOS)), other peripheral

T-cell lymphomas (e.g., peripheral T-cell lymphoma NOS), or EBV-positive T-cell and NK-cell lymphomas (e.g., EBV-positive nodal T- and NK-cell lymphoma or extranodal NK/T-cell lymphoma)))))), Li-Fraumeni tumors, mesentery cancer (e.g., omentum cancer, peritoneal cancer), pleural cancer, respiratory cancer (e.g., larynx cancer, lung cancer (e.g., lung squamous cell carcinoma, lung adenocarcinoma, mesothelioma, non-small cell lung cancer (NSCLC)), tracheal cancer), sarcoma (e.g., bone cancer (e.g., osteosarcoma, chondrosarcoma) or soft tissue sarcoma (Ewing sarcoma, leiomyosarcoma, myxofibrosarcoma, rhabdomyosarcoma)), skin cancer (e.g., melanoma), thymus cancer (e.g., thymoma), or a combination thereof.

In some embodiments, the cancer is breast cancer (e.g., breast invasive carcinoma, breast invasive ductal carcinoma), central or peripheral nervous system tissue cancer (e.g., brain cancer (e.g., astrocytoma, glioblastoma, glioma, oligoastrocytoma)), endocrine or neuroendocrine cancer (e.g., adrenal cancer (e.g., adrenocortical carcinoma, pheochromocytoma, paraganglioma), thyroid cancer (e.g., papillary thyroid cancer)), eye cancer (e.g., uveal cancer (e.g., uveal melanoma)), gastrointestinal cancer (e.g., bile duct cancer (e.g., cholangiocarcinoma), colorectal cancer (e.g., colon adenocarcinoma, rectal adenocarcinoma, mucinous adenocarcinoma, mucinous carcinoma), esophageal cancer (e.g., esophageal adenocarcinoma), liver cancer (e.g., hepatocellular carcinoma), pancreatic cancer (e.g., pancreatic adenocarcinoma), or stomach cancer (e.g., stomach adenocarcinoma, signet ring cell carcinoma of the stomach)), genitourinary cancer (e.g., bladder cancer (e.g., bladder urothelial carcinoma), kidney cancer (e.g., renal clear cell carcinoma, renal papillary cell carcinoma, kidney chromophobe), prostate cancer (e.g., prostate adenocarcinoma), or testicular cancer (e.g., testicular germ cell tumors)), gynecologic cancer (e.g., cervical cancer (e.g., cervical squamous cell carcinoma, endocervical adenocarcinoma, mucinous carcinoma), ovarian cancer (e.g., serous ovarian cancer, ovarian serous cystadenocarcinoma), or uterine cancer (e.g., uterine carcinosarcoma, uterine endometrioid carcinoma, uterine serous carcinoma, uterine papillary serous carcinoma, uterine corpus endometrial carcinoma)), head and neck cancer (e.g., head and neck squamous cell carcinoma), hematological cancer (e.g., lymphoma (e.g., Hodgkin lymphoma (e.g., nodular lymphocyte predominant Hodgkin lymphoma (NLPHL)), non-Hodgkin lymphoma (e.g., B cell lymphoid proliferations and lymphomas (e.g., mature B cell neoplasms (e.g., Burkitt lymphoma (BL), large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), T-cell/histiocyte-rich large B-cell lymphoma, diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-

MYC/BCL-2)), primary large B cell lymphoma of immune-privileged sites (primary LBCL of immune-privileged sites), primary mediastinal large B cell lymphoma (primary mediastinal LBCL), or high grade B-cell lymphoma NOS), follicular lymphoma (FL), or transformations of indolent B cell lymphomas)), T-cell and NK-cell lymphoid proliferations and lymphomas (e.g., mature T-cell and NK-cell neoplasms (e.g., mature T-cell and NK-cell leukemias (e.g., adult T-cell leukemia/lymphoma), primary cutaneous T-cell lymphoid proliferations and lymphomas (cutaneous T-cell lymphoma (CTCL)) (e.g., primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder, mycosis fungoides, Sezary syndrome, primary cutaneous CD30-positive T-cell lymphoproliferative disorder: lymphomatoid papulosis, primary cutaneous CD30-positive T-cell lymphoproliferative disorder: primary cutaneous anaplastic large cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, primary cutaneous gamma-delta T-cell lymphoma, or primary cutaneous peripheral T-cell lymphoma NOS), peripheral T-cell lymphoma (PTCL) (e.g., anaplastic large cell lymphoma (ALCL) (e.g., ALK-positive anaplastic large cell lymphoma, or ALK-negative anaplastic large cell lymphoma), nodal T follicular helper cell lymphoma (e.g., nodal T follicular helper cell lymphoma angioimmunoblastic type (also known as angioimmunoblastic T-cell lymphoma (AITL) or follicular helper T-cell lymphoma, angioimmunoblastic type), nodal T follicular helper cell lymphoma follicular type (also known as follicular helper T-cell lymphoma, follicular type), or nodal T follicular helper cell lymphoma NOS (also known as follicular helper T-cell lymphoma, NOS)), or other peripheral T-cell lymphomas (e.g., peripheral T-cell lymphoma NOS))))), respiratory cancer (e.g., lung cancer (e.g., lung squamous cell carcinoma, lung adenocarcinoma, mesothelioma, non-small cell lung cancer (NSCLC))), sarcoma (e.g., leiomyosarcoma, myxofibrosarcoma), skin cancer (e.g., melanoma), thymus cancer (e.g., thymoma), or a combination thereof.

In some embodiments, the cancer is a hematological cancer (e.g., lymphoma (e.g., non-Hodgkin lymphoma (e.g., B cell lymphoid proliferations and lymphomas (e.g., mature B cell neoplasms (e.g., large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), or primary mediastinal large B cell lymphoma (primary mediastinal LBCL)), follicular lymphoma (FL), or transformations of indolent B cell lymphomas)), T-cell and NK-cell lymphoid proliferations and lymphomas (e.g., mature T-cell and NK-cell neoplasms (e.g., primary cutaneous T-cell lymphoid proliferations and lymphomas (cutaneous T-cell lymphoma (CTCL)) (e.g., primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder, mycosis fungoides, or Sezary syndrome), or peripheral T-cell lymphoma (PTCL) (e.g., nodal T follicular helper cell lymphoma (e.g., nodal T follicular helper

cell lymphoma angioimmunoblastic type (also known as angioimmunoblastic T-cell lymphoma (AITL) or follicular helper T-cell lymphoma, angioimmunoblastic type), nodal T follicular helper cell lymphoma follicular type (also known as follicular helper T-cell lymphoma, follicular type), or nodal T follicular helper cell lymphoma NOS (also known as follicular helper T-cell lymphoma, NOS)), or other peripheral T-cell lymphomas (e.g., peripheral T-cell lymphoma NOS))))), breast cancer, gastrointestinal cancer, brain cancer (e.g., glioblastoma) or lung cancer (e.g., NSCLC).

In some embodiments, the cancer is a mature B cell neoplasm (e.g., chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), Burkitt lymphoma (BL), large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), T-cell/histiocyte-rich large B-cell lymphoma, diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary large B cell lymphoma of immune-privileged sites (primary LBCL of immune-privileged sites), intravascular large B-cell lymphoma (IVLBCL), primary mediastinal large B cell lymphoma (primary mediastinal LBCL), or high grade B-cell lymphoma NOS (HBGCL-NOS)), follicular lymphoma (FL), mantle cell lymphoma (MCL), or transformations of indolent B cell lymphomas), a peripheral T-cell lymphoma (PTCL) (e.g., anaplastic large cell lymphoma (ALCL) (e.g., ALK-positive anaplastic large cell lymphoma, or ALK-negative anaplastic large cell lymphoma), nodal T follicular helper cell lymphoma (e.g., nodal T follicular helper cell lymphoma angioimmunoblastic type (also known as angioimmunoblastic T-cell lymphoma (AITL) or follicular helper T-cell lymphoma, angioimmunoblastic type), nodal T follicular helper cell lymphoma follicular type (also known as follicular helper T-cell lymphoma, follicular type), or nodal T follicular helper cell lymphoma NOS (also known as follicular helper T-cell lymphoma, NOS))), a primary cutaneous T-cell lymphoid proliferation or lymphoma (cutaneous T-cell lymphoma (CTCL)) (e.g., primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder, mycosis fungoides, Sezary syndrome, or primary cutaneous gamma-delta T-cell lymphoma), nodular lymphocyte predominant Hodgkin lymphoma (NLPHL), diffuse histiocytic lymphoma (DHL), acute lymphocytic leukemia (ALL), chronic myeloid leukemia (CML), or early T-precursor lymphoblastic leukemia. In some embodiments, the cancer is a mature B cell neoplasm (e.g., BL, large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary LBCL of immune-privileged sites, primary mediastinal LBCL, or HBGCL-NOS), FL,

MCL, or transformations of indolent B cell lymphomas), a peripheral T-cell lymphoma (PTCL) (e.g., anaplastic large cell lymphoma (ALCL) (e.g., ALK-positive anaplastic large cell lymphoma, or ALK-negative anaplastic large cell lymphoma), nodal T follicular helper cell lymphoma (e.g., nodal T follicular helper cell lymphoma angioimmunoblastic type (also known as angioimmunoblastic T-cell lymphoma (AITL) or follicular helper T-cell lymphoma, angioimmunoblastic type), nodal T follicular helper cell lymphoma follicular type (also known as follicular helper T-cell lymphoma, follicular type), or nodal T follicular helper cell lymphoma NOS (also known as follicular helper T-cell lymphoma, NOS))), a primary cutaneous T-cell lymphoid proliferation or lymphoma (cutaneous T-cell lymphoma (CTCL)) (e.g., primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder, mycosis fungoides, Sezary syndrome, or primary cutaneous gamma-delta T-cell lymphoma), or ALL (e.g., B-ALL). In some embodiments, the cancer is a mature B cell neoplasm (e.g., a large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary LBCL of immune-privileged sites, primary mediastinal LBCL, or HBGCL-NOS), FL, or transformations of indolent B cell lymphomas). In some embodiments, the cancer is a mature B cell neoplasm (e.g., large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary LBCL of immune-privileged sites, primary mediastinal LBCL, or HBGCL-NOS), FL, MCL, or transformations of indolent B cell lymphomas), or ALL (e.g., B-ALL). In some embodiments, the cancer is a peripheral T-cell lymphoma (PTCL) (e.g., anaplastic large cell lymphoma (ALCL) (e.g., ALK-positive anaplastic large cell lymphoma, or ALK-negative anaplastic large cell lymphoma), nodal T follicular helper cell lymphoma (e.g., nodal T follicular helper cell lymphoma angioimmunoblastic type (also known as angioimmunoblastic T-cell lymphoma (AITL) or follicular helper T-cell lymphoma, angioimmunoblastic type), nodal T follicular helper cell lymphoma follicular type (also known as follicular helper T-cell lymphoma, follicular type), or nodal T follicular helper cell lymphoma NOS (also known as follicular helper T-cell lymphoma, NOS))). See, e.g., Leeman-Neill and Bhagat, *Expert Opinion on Therapeutic Targets* 22.2 (2018): 143-152, doi: 10.1080/14728222.2018.1420782; Mlynarczyk and Melnick. *Immunological Reviews* 288.1 (2019): 214-239, doi: 10.1111/imr.12755; Hurtz, Christian, et al., *Journal of Experimental Medicine* 208.11 (2011): 2163-2174, doi: 10.1084/jem.20110304; Deb, Dhruba, et al. *Cancer Research* 77.11 (2017):

3070-3081, doi: 10.1158/0008-5472.CAN-15-3052; Cardenas, Mariano G., et al., *Clinical Cancer Research* 23.4 (2017): 885-893, doi: 10.1158/1078-0432.CCR-16-2071; Walker, Sarah R., et al., *Oncogene* 34.9 (2015): 1073-1082, doi: 10.1038/onc.2014.61; See, e.g., Alaggio, Rita, et al. *Leukemia* 36.7 (2022): 1720-1748, doi: 10.1038/s41375-022-01620-2; Paik, Jin Ho, et al. *Human Pathology* 131 (2023): 47-60, doi: 10.1016/j.humpath.2022.12.003; and International Publication Nos. WO 2021/080950, WO 2021/077010, and WO 2022/221673.

In some embodiments, the cancer is a non-Hodgkin lymphoma (e.g., a mature B cell neoplasm (e.g., chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), Burkitt lymphoma (BL), large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary large B cell lymphoma of immune-privileged sites (primary LBCL of immune-privileged sites), intravascular large B-cell lymphoma (IVLBCL), primary mediastinal large B cell lymphoma (primary mediastinal LBCL), or high grade B-cell lymphoma NOS (HBGCL-NOS)), follicular lymphoma (FL), mantle cell lymphoma (MCL), or transformations of indolent B cell lymphomas), a peripheral T-cell lymphoma (PTCL) (e.g., anaplastic large cell lymphoma (ALCL) (e.g., ALK-positive anaplastic large cell lymphoma, or ALK-negative anaplastic large cell lymphoma), nodal T follicular helper cell lymphoma (e.g., nodal T follicular helper cell lymphoma angioimmunoblastic type (also known as angioimmunoblastic T-cell lymphoma (AITL) or follicular helper T-cell lymphoma, angioimmunoblastic type), nodal T follicular helper cell lymphoma follicular type (also known as follicular helper T-cell lymphoma, follicular type), or nodal T follicular helper cell lymphoma NOS (also known as follicular helper T-cell lymphoma, NOS))), or a primary cutaneous T-cell lymphoid proliferation or lymphoma (cutaneous T-cell lymphoma (CTCL)) (e.g., primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder, mycosis fungoides, Sezary syndrome, or primary cutaneous gamma-delta T-cell lymphoma)). In some embodiments, the non-Hodgkin lymphoma is B-cell non-Hodgkin lymphoma. In some embodiments, the non-Hodgkin lymphoma is CD20-positive. In some embodiments, the non-Hodgkin lymphoma is CD20-positive B-cell non-Hodgkin lymphoma. In some embodiments, the subject has not been previously treated for the non-Hodgkin lymphoma. In some embodiments, the subject has previously received chemotherapy. In some embodiments, the subject has been previously treated with rituximab or obinutuzumab as a monotherapy or in combination with an additional therapy or therapeutic agent. In some embodiments, the subject has been previously treated with rituximab as a monotherapy or in combination with an

additional therapy or therapeutic agent. In some embodiments, the subject has been previously treated with obinutuzumab as a monotherapy or in combination with an additional therapy or therapeutic agent. In some embodiments, the subject has previously been treated with R-CHOP (RITUXAN® (rituximab), cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone), or G-CHOP (GAZYVA® (obinutuzumab)), cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone). In some cases, the subject has previously been treated with etoposide and R-CHOP (called R-EPOCH). In some cases, the subject has been previously treated with R-CHOP combined with lenalidomide, venetoclax, ibrutinib, acalabrutinib, obinutuzumab, polatuzumab, pembrolizumab, durvalumab, or mosunetuzumab. In some embodiments, the subject has been previously treated with cyclophosphamide, vincristine, and prednisone (CVP), with or without rituximab or obinutuzumab. In some embodiments, the subject has received one or more lines of systemic therapy. In some embodiments, the subject has received two or more lines of systemic therapy. In some embodiments, the subject has previously been treated with a cell-based therapy (e.g., adoptive cell therapy (e.g., CAR T therapy, cytokine-induced killer cells (CIKs), natural killer cells (e.g., CAR-modified NK cells)) or antibody-armed cell therapy). In some embodiments, the non-Hodgkin lymphoma is non-progressing (including stable disease) non-Hodgkin lymphoma. In some embodiments, the non-Hodgkin lymphoma is relapsed or refractory non-Hodgkin lymphoma. In some embodiments, the subject is a subject who relapsed after, or is refractory to, a rituximab-containing regimen. In some embodiments, the subject is a subject who relapsed after, or is refractory to, an obinutuzumab-containing regimen. In some such embodiments, treatment effect can be measured by progression-free survival (PFS), event-free survival (EFS), overall survival (OS), time to treatment failure, response rate (e.g., overall response rate, complete response, partial response, or a combination thereof), duration of response, or a combination thereof. In some embodiments, cancer is a non-Hodgkin lymphoma, and a compound provided herein, or a pharmaceutically acceptable salt thereof, is administered as a monotherapy.

In some embodiments, the cancer is a large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary LBCL of immune-privileged sites, primary mediastinal LBCL, or HBGCL-NOS). In some embodiments, the DLBCL (e.g., DLBCL-NOS) is characterized by a *BCL2* translocation, a *BCL6* translocation, a *CD79B* mutation (e.g., H225Y, A205D, Y196del, Y196F, Y196D, Y207X, Y196N, A205fs, Y196S, Y196H, A205fs, T206fs,

H194_E197delinsQ, E197G, K219T, E192fs, or Y196C), an *EZH2* mutation (e.g., a Y646F, Y646N, A682G, or A692V mutation), a *MYC* translocation, a *MYD88* mutation (e.g., a L265P mutation), a *NOTCH1* mutation (e.g., Q2394X, Q2501X, Q2459X, Y2490X, G2427fs, Q2444X, P2514fs, or P2517S), a *NOTCH2* mutation (e.g., Q2285K, S2136fs, Q2361X, P2288fs, L2415fs, G2410fs, Q2409X, S2388X, I2304fs, Q2364X, Q2360fs, S2395X, E2261fs, M2267fs, Q2285fs, R2400X, P2303fs, Q2285fs, A2273fs, K2133fs, Q2389X, E2399X, E2290X, Q2325X, Y2340X, Y2392X, or E2411fs), a *TP53* mutation (e.g., R181C, E336A, R248W, P98fs, P152L, R280I, S149fs, P151H, G245D, Y236D, S127F, A161T, D148fs, M246I, Y126C, H179R, A159P, C238G, L93fs, Y220C, R283fs, G244D, G245S, E171X, R209X, T155_R156dup, E271K, R306X, G105D, L93fs, G262V, W53X, G244V, H214Y, R282W, R337C, Q331fs, R273G, R273C, C176Y, S215R, R213Q, I195T, G245R, I232T, R175H, Y126D, R273H, R196X, Y205C, C141Y, C229X, Y126N, P278S, P151S, Y236H, R282G, Y103X, V216M, G244S, G266E, V173A, V173fs, I254S, T125M, R342X, P152fs, Y205D, V274L, L257P, C135Y, C176R, Y234N, R248Q, G244R, Y234H, R248G, M237I, R213X, E258D, V173M, L252_I254del, L252I, Y234C, or C176F), *17p* deletion, *18q* gain, or a combination thereof. In some embodiments, the DLBCL (e.g., DLBCL-NOS) has a *BCL6* rearrangement, a *NOTCH2* mutation (e.g., Q2285K, S2136fs, Q2361X, P2288fs, L2415fs, G2410fs, Q2409X, S2388X, I2304fs, Q2364X, Q2360fs, S2395X, E2261fs, M2267fs, Q2285fs, R2400X, P2303fs, Q2285fs, A2273fs, K2133fs, Q2389X, E2399X, E2290X, Q2325X, Y2340X, Y2392X, E2411fs), or a combination thereof. In some embodiments, the large B cell lymphoma (e.g., DLBCL-NOS) is large B cell lymphoma having a germinal center B cell (GCB) cell of origin. In some embodiments, the large B cell lymphoma (e.g., DLBCL-NOS) is a BN2-type large B cell lymphoma (e.g., having a *BCL6* rearrangement and/or a *NOTCH2* mutation). In some embodiments, the large B cell lymphoma (e.g., DLBCL-NOS) is an EZB-type large B cell lymphoma (e.g., having an *EZH2* mutation and/or a *BCL2* translocation). In some embodiments, the large B cell lymphoma (e.g., DLBCL-NOS) is a C1 genetic cluster large B cell lymphoma (e.g., having a *BCL6* rearrangement and/or a *NOTCH2* mutation). See, e.g., Schmitz, Roland, et al. *New England Journal of Medicine* 378.15 (2018): 1396-1407, doi: 10.1056/NEJMoa1801445; Chapuy, Bjoern, et al. *Nature Medicine* 24.5 (2018): 679-690, doi: 10.1038/s41591-018-0016-8 for additional description of these classifications.

In some embodiments, the cancer is a FL. In some embodiments, the FL has a *BCL2* translocation (e.g., a t(14;18) translocation). In some embodiments, the FL has an *EZH2* mutation (e.g., a Y646F, Y646N, A682G, or A692V mutation). See, e.g., Kridel, Robert, Laurie

H. Sehn, and Randy D. Gascoyne. *The Journal of Clinical Investigation* 122.10 (2012): 3424-3431, doi: 10.1172/JCI63186. In some embodiments, the cancer is a FL, and a compound provided herein, or a pharmaceutically acceptable salt thereof, is administered as a monotherapy.

In some embodiments, the cancer is a B-ALL. In some embodiments, the B-ALL has an *MLL* rearrangement (e.g., an MLL-Af4 fusion, an MLL-Af6 fusion, an MLL-Af9 fusion, an MLL-ENL fusion, or an MLL-PTD fusion), is pre-B cell receptor positive (Pre-BCR+), has the Philadelphia chromosome, is Philadelphia chromosome-like, is dependent on Ras signaling, has a *BCL2* amplification, has a *JAK2* mutation (with or without high cytokine receptor-like factor 2 (CRLF2) expression), or a combination thereof. See, e.g., Knight, Thomas, and Julie Anne Elizabeth Irving. *Frontiers in Oncology* 4 (2014): 160, doi: 10.3389/fonc.2014.00160; Geng, Huimin, et al. *Cancer Cell* 27.3 (2015): 409-425, doi: 10.1016/j.ccell.2015.02.003; Jain, Nitin, et al. *Blood*, 129.5 (2017): 572-581, doi: 10.1182/blood-2016-07-726588; and Hurtz, Christian, et al. *Genes & Development* 33 (2019): 1265-1279, doi: 10.1101/gad.327593.119. In some embodiments, the cancer is a B-ALL, and a compound provided herein, or a pharmaceutically acceptable salt thereof, is administered as a monotherapy. In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, is used in the treatment of subject having a B-ALL. In some embodiments, the B-ALL is a relapsed or refractory B-ALL after two or more lines of systemic therapy.

In some embodiments, the subject has previously been treated with another anticancer agent, a chemotherapeutic agent, surgery, radiation, a multi-kinase inhibitor, or a combination thereof.

In some embodiments, the cancer is a large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary LBCL of immune-privileged sites, primary mediastinal LBCL, or HBGCL-NOS). In some embodiments, the subject has not been previously treated for the large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary LBCL of immune-privileged sites, primary mediastinal LBCL, or HBGCL-NOS). In some embodiments, the subject has previously received chemotherapy. In some embodiments, the subject has been previously treated with rituximab or obinutuzumab as a monotherapy or in combination with an additional therapy or therapeutic agent. In some embodiments, the subject has been

previously treated with rituximab as a monotherapy or in combination with an additional therapy or therapeutic agent. In some embodiments, the subject has been previously treated with obinutuzumab as a monotherapy or in combination with an additional therapy or therapeutic agent. In some embodiments, the subject has previously been treated with lenalidomide in combination with rituximab or obinutuzumab. In some embodiments, the subject has previously been treated with cyclophosphamide, vincristine and prednisone (CVP), optionally in combination with rituximab or obinutuzumab. In some embodiments, the subject has previously been treated with R-CHOP (RITUXAN® (rituximab), cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone), or G-CHOP (GAZYVA® (obinutuzumab)), cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone). In some cases, the subject has previously been treated with etoposide and R-CHOP (called R-EPOCH). In some cases, the subject has been previously treated with R-CHOP combined with lenalidomide, venetoclax, ibrutinib, acalabrutinib, obinutuzumab, polatuzumab, pembrolizumab, durvalumab, or mosunetuzumab. In some embodiments, the subject has been previously treated with a rituximab-containing regimen. In some embodiments, the subject has been previously treated with an obinutuzumab-containing regimen. In some embodiments, the subject has been previously treated with a mosunetuzumab-containing regimen. In some embodiments, the subject has been previously treated with an epcoritamab-containing regimen. In some embodiments, the subject has received one or more lines of systemic therapy. In some embodiments, the subject has received two or more lines of systemic therapy. In some embodiments, the subject has previously been treated with a cell-based therapy (e.g., adoptive cell therapy (e.g., CAR T therapy, cytokine-induced killer cells (CIKs), natural killer cells (e.g., CAR-modified NK cells)) or antibody-armed cell therapy). In some embodiments, the large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary LBCL of immune-privileged sites, primary mediastinal LBCL, or HBGCL-NOS) is non-progressing (including stable disease) LBCL. In some embodiments, the large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary LBCL of immune-privileged sites, primary mediastinal LBCL, or HBGCL-NOS), is relapsed or refractory LBCL. In some embodiments, the subject is a subject who relapsed after, or is refractory to, a rituximab-containing regimen. In some embodiments, the subject is a subject who relapsed after, or is refractory to, an obinutuzumab-

containing regimen. In some such embodiments, treatment effect can be measured by progression-free survival (PFS), event-free survival (EFS), overall survival (OS), time to treatment failure, response rate (e.g., overall response rate, complete response, partial response, or a combination thereof), duration of response, or a combination thereof. In some embodiments, the cancer is a large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary LBCL of immune-privileged sites, primary mediastinal LBCL, or HBGCL-NOS), and a compound provided herein, or a pharmaceutically acceptable salt thereof, is administered as a monotherapy. In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof is used in the treatment of subject having a large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary LBCL of immune-privileged sites, primary mediastinal LBCL, or HBGCL-NOS). In some embodiments, the large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary LBCL of immune-privileged sites, primary mediastinal LBCL, or HBGCL-NOS) is a relapsed or refractory LBCL after two or more lines of systemic therapy.

In some embodiments, the cancer is a FL. In some embodiments, the subject has not been previously treated for the FL. In some embodiments, the subject has previously received chemotherapy. In some embodiments, the subject has been previously treated with rituximab or obinutuzumab as a monotherapy or in combination with an additional therapy or therapeutic agent. In some embodiments, the subject has been previously treated with rituximab as a monotherapy or in combination with an additional therapy or therapeutic agent. In some embodiments, the subject has been previously treated with obinutuzumab as a monotherapy or in combination with an additional therapy or therapeutic agent. In some embodiments, the subject has previously been treated with rituximab or obinutuzumab monotherapy. In some embodiments, the subject has previously been treated with bendamustine in combination with rituximab or obinutuzumab. In some embodiments, the subject has previously been treated with lenalidomide in combination with rituximab or obinutuzumab (the combination of lenalidomide with rituximab is sometimes called "R^2"). In some embodiments, the subject has previously been treated with cyclophosphamide, vincristine and prednisone (CVP), optionally

in combination with rituximab or obinutuzumab. In some embodiments, the subject has previously been treated with R-CHOP or G-CHOP. In some embodiments, the subject has received one or more lines of systemic therapy. In some embodiments, the subject has received two or more lines of systemic therapy. In some embodiments, the subject has previously been treated with a cell-based therapy (e.g., adoptive cell therapy (e.g., CAR T therapy, cytokine-induced killer cells (CIKs), natural killer cells (e.g., CAR-modified NK cells)) or antibody-armed cell therapy). In some embodiments, the non-Hodgkin lymphoma is non-progressing (including stable disease) FL. In some embodiments, the FL is relapsed or refractory FL. In some embodiments, the subject is a subject who relapsed after, or is refractory to, a rituximab-containing regimen. In some embodiments, the subject is a subject who relapsed after, or is refractory to, an obinutuzumab-containing regimen. In some such embodiments, treatment effect can be measured by progression-free survival (PFS), event-free survival (EFS), overall survival (OS), time to treatment failure, response rate (e.g., overall response rate, complete response, partial response, or a combination thereof), duration of response, or a combination thereof. In some embodiments, the cancer is a FL, and a compound provided herein, or a pharmaceutically acceptable salt thereof, is administered as a monotherapy. In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof is used in the treatment of subject having a FL. In some embodiments, the FL is a relapsed or refractory FL after two or more lines of systemic therapy.

In some embodiments, the cancer is a BL. In some embodiments, the subject has not been previously treated for the BL. In some embodiments, the subject has previously received chemotherapy. In some embodiments, the subject has been previously treated with rituximab or obinutuzumab as a monotherapy or in combination with an additional therapy or therapeutic agent. In some embodiments, the subject has been previously treated with rituximab as a monotherapy or in combination with an additional therapy or therapeutic agent. In some embodiments, the subject has been previously treated with obinutuzumab as a monotherapy or in combination with an additional therapy or therapeutic agent. In some embodiments, the subject has previously been treated with rituximab or obinutuzumab monotherapy. In some embodiments, the subject has previously been treated with bendamustine in combination with rituximab or obinutuzumab. In some embodiments, the subject has previously been treated with R-CHOP or G-CHOP. In some embodiments, the subject has previously been treated with rituximab, cyclophosphamide, vincristine, doxorubicin, and methotrexate (R-CODOX-M). In some embodiments, the subject has previously been treated with rituximab, ifosfamide, etoposide, and cytarabine (R-IVAC). In some embodiments, the subject has previously been

treated with rituximab with dose-adjusted etoposide, prednisolone, vincristine, cyclophosphamide, and doxorubicin (DA-EPOCH-R). In some embodiments, the subject has received one or more lines of systemic therapy. In some embodiments, the subject has received two or more lines of systemic therapy. In some embodiments, the subject has previously been treated with a cell-based therapy (e.g., adoptive cell therapy (e.g., CAR T therapy, cytokine-induced killer cells (CIKs), natural killer cells (e.g., CAR-modified NK cells)) or antibody-armed cell therapy). In some embodiments, the BL is non-progressing (including stable disease) BL. In some embodiments, the BL is relapsed or refractory BL. In some embodiments, the subject is a subject who relapsed after, or is refractory to, a rituximab-containing regimen. In some embodiments, the subject is a subject who relapsed after, or is refractory to, an obinutuzumab-containing regimen. In some such embodiments, treatment effect can be measured by progression-free survival (PFS), event-free survival (EFS), overall survival (OS), time to treatment failure, response rate (e.g., overall response rate, complete response, partial response, or a combination thereof), duration of response, or a combination thereof. In some embodiments, the cancer is a BL, and a compound provided herein, or a pharmaceutically acceptable salt thereof, is administered as a monotherapy. In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof is used in the treatment of subject having a BL. In some embodiments, the BL is a relapsed or refractory BL after two or more lines of systemic therapy.

In some embodiments, the cancer is a peripheral T-cell lymphoma (PTCL) (e.g., anaplastic large cell lymphoma (ALCL) (e.g., ALK-positive anaplastic large cell lymphoma, or ALK-negative anaplastic large cell lymphoma), nodal T follicular helper cell lymphoma (e.g., nodal T follicular helper cell lymphoma angioimmunoblastic type (also known as angioimmunoblastic T-cell lymphoma (AITL) or follicular helper T-cell lymphoma, angioimmunoblastic type), nodal T follicular helper cell lymphoma follicular type (also known as follicular helper T-cell lymphoma, follicular type), or nodal T follicular helper cell lymphoma NOS (also known as follicular helper T-cell lymphoma, NOS))) or a primary cutaneous T-cell lymphoid proliferation or lymphoma (cutaneous T-cell lymphoma (CTCL)) (e.g., primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder, mycosis fungoides, Sezary syndrome, or primary cutaneous gamma-delta T-cell lymphoma) In some embodiments, the subject has not been previously treated for the PTCL or CTCL. In some embodiments, the subject has previously received chemotherapy. In some embodiments, the subject has been previously treated with rituximab or obinutuzumab as a monotherapy or in combination with an additional therapy or therapeutic agent. In some embodiments, the subject

has been previously treated with rituximab as a monotherapy or in combination with an additional therapy or therapeutic agent. In some embodiments, the subject has been previously treated with obinutuzumab as a monotherapy or in combination with an additional therapy or therapeutic agent. In some embodiments, the subject has previously been treated with rituximab or obinutuzumab monotherapy. In some embodiments, the subject has previously been treated with bendamustine in combination with rituximab or obinutuzumab. In some embodiments, the subject has previously been treated with lenalidomide in combination with rituximab or obinutuzumab (the combination with rituximab is sometimes called "R^2"). In some embodiments, the subject has previously been treated with cyclophosphamide, vincristine and prednisone (CVP), optionally in combination with rituximab or obinutuzumab (R-CVP or G-CVP, respectively). In some embodiments, the subject has previously been treated with R-CHOP or G-CHOP. In some embodiments, the subject has received one or more lines of systemic therapy. In some embodiments, the subject has received two or more lines of systemic therapy. In some embodiments, the subject has previously been treated with a cell-based therapy (e.g., adoptive cell therapy (e.g., CAR T therapy, cytokine-induced killer cells (CIKs), natural killer cells (e.g., CAR-modified NK cells)) or antibody-armed cell therapy). In some embodiments, the PTCL or CTCL is non-progressing (including stable disease) PTCL or CTCL. In some embodiments, the PTCL or CTCL is relapsed or refractory PTCL or CTCL. In some embodiments, the subject is a subject who relapsed after, or is refractory to, a rituximab-containing regimen. In some embodiments, the subject is a subject who relapsed after, or is refractory to, an obinutuzumab-containing regimen. In some such embodiments, treatment effect can be measured by progression-free survival (PFS), event-free survival (EFS), overall survival (OS), time to treatment failure, response rate (e.g., overall response rate, complete response, partial response, or a combination thereof), duration of response, or a combination thereof. In some embodiments, the cancer is a PTCL or CTCL, and a compound provided herein, or a pharmaceutically acceptable salt thereof, is administered as a monotherapy. In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof is used in the treatment of a subject having a PTCL or CTCL. In some embodiments, the PTCL or CTCL is a relapsed or refractory PTCL or CTCL after two or more lines of systemic therapy.

In some embodiments, the cancer is B-ALL. In some embodiments, the B-ALL is Philadelphia chromosome positive B-ALL. In some embodiments, the B-ALL is Philadelphia chromosome negative B-ALL. In some embodiments, the subject has previously received chemotherapy. In some embodiments, the subject has previously been treated with at least one cycle of induction, consolidation, intensification, and optional maintenance. In some cases,

induction therapy can include an anthracycline, vincristine, a corticosteroid, and cyclophosphamide. In some embodiments, the anthracycline is doxorubicin. In some embodiments, the corticosteroid is dexamethasone. In some cases, the combination of doxorubicin, vincristine, dexamethasone, and cyclophosphamide is known as CVAD. In some embodiments, induction therapy can further include a tyrosine kinase inhibitor (e.g., a BCR-ABL inhibitor for subjects with this fusion). In some embodiments, induction therapy can further include asparaginase (e.g., for pediatric subjects). In some cases, consolidation therapy can include methotrexate, cytarabine, vincristine, 6-mercaptopurine, 6-thioguanine, cyclophosphamide, and etoposide. In some embodiments, consolidation therapy can further include a tyrosine kinase inhibitor (e.g., a BCR-ABL inhibitor for subjects with this fusion). In some embodiments, consolidation therapy can further include asparaginase (e.g., for pediatric subjects). In some cases, intensification therapy can include an anthracycline, vincristine, a corticosteroid, and cyclophosphamide. In some embodiments, intensification therapy can further include a tyrosine kinase inhibitor (e.g., a BCR-ABL inhibitor for subjects with this fusion). In some embodiments, intensification therapy can further include asparaginase (e.g., for pediatric subjects). Typically, pediatric and young adult regimens include higher cumulative doses of asparaginase and vincristine but can have lower cumulative doses of anthracycline and cyclophosphamide compared to adult regimens. In any of these cycle phases, an anti-CD20 immunotherapy (e.g., rituximab) can be added for subjects expressing the CD20 protein on the cells. See, e.g., Muffly, Lori, and Emily Curran. *Hematology 2014, the American Society of Hematology Education Program Book* 2019.1 (2019): 17-23, doi: 10.1182/hematology.2019000009. In some embodiments, the subject has received one or more lines of systemic therapy. In some embodiments, the subject has received two or more lines of systemic therapy. In some embodiments, the B-ALL is relapsed or refractory B-ALL. In some such embodiments, treatment effect can be measured by progression-free survival (PFS), event-free survival (EFS), overall survival (OS), time to treatment failure, response rate (e.g., overall response rate, complete response, partial response, or a combination thereof), duration of response, or a combination thereof. In some embodiments, the cancer is a B-ALL, and a compound provided herein, or a pharmaceutically acceptable salt thereof, is administered as a monotherapy. In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof is used in the treatment of subject having a B-ALL. In some embodiments, the B-ALL is a relapsed or refractory B-ALL after two or more lines of systemic therapy.

Also provided herein is a method of treating a subject having a cancer, wherein the

method comprises:

administering a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable salt thereof, as a monotherapy or in conjunction with a first anticancer agent to the subject who has been administered one or more doses of the first anticancer agent for a period of time.

Also provided herein is a method of treating a subject having a cancer, wherein the method comprises:

(a) administering one or more doses of a first anticancer agent to the subject for a period of time; and

(b) after (a), administering a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable salt thereof, as a monotherapy or in conjunction with the first anticancer agent to the subject.

Also provided herein is a method of treating a subject having a cancer, wherein the method comprises:

(a) administering one or more doses of a first anticancer agent to the subject for a period of time; and

(b) after (a), administering a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable salt thereof, as a monotherapy or in conjunction with a second anticancer agent to the subject.

In some embodiments of any of the methods of treating cancers provided herein, the compound provided herein, or a pharmaceutically acceptable salt thereof, is dosed q.d. (once daily) to the subject. In some embodiments of any of the methods of treating cancers provided herein, the compound provided herein, or a pharmaceutically acceptable salt thereof, is dosed b.i.d. (twice daily) to the subject. In some embodiments of any of the methods of treating cancers provided herein, the compound provided herein, or a pharmaceutically acceptable salt thereof, is dosed t.i.d. (three times daily) to the subject. In some embodiments of any of the methods of treating cancers provided herein, the compound provided herein, or a pharmaceutically acceptable salt thereof, is dosed q.i.d. (four times daily) to the subject. In some embodiments of any of the methods of treating cancers provided herein, the compound provided herein, or a pharmaceutically acceptable salt thereof, is dosed q.o.d. (every other day) to the subject. In some embodiments of any of the methods of treating cancers provided herein, the compound provided herein, or a pharmaceutically acceptable salt thereof, is dosed q.week (once weekly) to the subject. In some embodiments of any of the methods of treating cancers provided herein, the compound provided herein, or a pharmaceutically acceptable salt thereof,

is dosed b.i.w. (twice weekly) to the subject. In some embodiments of any of the methods of treating cancers provided herein, the compound provided herein, or a pharmaceutically acceptable salt thereof, is dosed t.i.w. (three times weekly) to the subject.

BCL6 activity has also been implicated in autoimmunity. See, for example, Li, Qing, et al. *European Journal of Immunology* 50.4 (2020): 525-536, doi: 10.1002/eji.201948299; Pearce, Andrew C., et al. *Journal of Biological Chemistry* 297.2 (2021): 100928, doi: 10.1016/j.jbc.2021.100928; Venkatadri, Rajkumar, et al. *European Journal of Immunology* 52.5 (2022): 825-834, doi: 10.1002/eji.202149324; Patel, Preeyam S., et al. *Science Advances* 8.25 (2022): eabo1782, doi: 10.1126/sciadv.abo1782; Ding, Shu, Yu Rao, and Qianjin Lu. *Cellular & Molecular Immunology* 19 (2022): 863-865, doi: 10.1038/s41423-022-00882-1. Accordingly, also provided herein is a method of treating or preventing an autoimmune disease or condition in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound provided herein, or a pharmaceutically acceptable salt thereof.

Provided herein is use of a compound provided herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, for the treatment or prevention of an autoimmune disease or condition, for example, any of the autoimmune diseases or conditions provided herein.

Provided herein is use of a compound provided herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, as a medicament for the treatment or prevention of an autoimmune disease or condition, for example, any of the autoimmune diseases or conditions provided herein.

Provided herein is use of a compound provided herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prevention of an autoimmune diseases or condition, for example, any of the autoimmune diseases or conditions provided herein.

Provided herein is a compound provided herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, for use as a medicament for the treatment or prevention of an autoimmune disease or condition, for example, any of the autoimmune diseases or conditions provided herein.

Provided herein is a compound provided herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, for use in treating or preventing an autoimmune disease or condition, for example, any of the autoimmune diseases or conditions

provided herein.

In some embodiments, the autoimmune disease or condition is acquired hemophilia, Addison's disease, ankylosing spondylitis, anti-neutrophil cytoplasmic antibody associated vasculitis (ANCA vasculitis), anti-synthetase syndrome, atherosclerosis, autoimmune hemolytic anemia, autoimmune hepatitis, autoimmune sclerosing cholangitis, autoimmune thyroiditis, autoimmune uveitis, Crohn's disease, dermatomyositis, diffuse scleroderma, Goodpasture's syndrome, graft-versus-host disease (GVHD) (e.g., chronic graft-versus-host disease (cGVHD)), Graves' disease, Guillain-Barre syndrome, Hashimoto's thyroiditis, Hughes' syndrome, IgG4-related disease, immune thrombocytopenic purpura (ITP), inflammatory bowel disease, limited scleroderma, multiple sclerosis, myasthenia gravis (MG), neuromyelitis optica spectrum disorders (NMOSD) (e.g., neuromyelitis optica (NMO)), pemphigoid, pemphigus, pernicious anemia, polymyositis, primary biliary cirrhosis, psoriasis, psoriatic arthritis, rheumatoid arthritis, seronegative spondyloarthropathies, Sjogren's syndrome, systemic lupus erythematosus, thrombocytopenic purpura, Type 1 diabetes, ulcerative colitis, vitiligo, or a combination thereof. In some embodiments, the autoimmune disease or condition is rheumatoid arthritis, systemic lupus erythematosus, or a combination thereof. In some embodiments, the autoimmune disease or condition is ANCA vasculitis, GVHD (e.g., cGVHD), myasthenia gravis, NMO, or a combination thereof. In some embodiments, the autoimmune disease or condition is ANCA vasculitis, anti-synthetase syndrome, arthritis (e.g., rheumatoid arthritis or inflammatory arthritis), GVHD (e.g., cGVHD), IgG4-RD, lupus (e.g., lupus erythematosus), ITP, MG (e.g., muscle-specific tyrosine kinase (MuSK) positive MG), MS, NMOSD (e.g., NMO), pemphigus (e.g., pemphigus vulgaris), Sjogren's syndrome, or a combination thereof. In some embodiments, the autoimmune disease or condition is ANCA vasculitis, anti-synthetase syndrome, GVHD (e.g., cGVHD), TIP, MG (e.g., muscle-specific tyrosine kinase (MuSK) positive MG), NMOSD (e.g., NMO), pemphigus, or a combination thereof. In some embodiments, the autoimmune disease or condition is arthritis (e.g., rheumatoid arthritis or inflammatory arthritis), GVHD (e.g., cGVHD), IgG4-RD, lupus (e.g., lupus erythematosus), MG (e.g., muscle-specific tyrosine kinase (MuSK) positive MG), MS, NMOSD (e.g., NMO), pemphigus (e.g., pemphigus vulgaris), Sjogren's syndrome, or a combination thereof See, e.g., Pearce, Andrew C., et al. *Journal of Biological Chemistry* 297.2 (2021): 100928, doi: 10.1016/j.jbc.2021.100928; Ding, Shu, Yu Rao, and Qianjin Lu, *Cellular & Molecular Immunology* (2022): 863–865; doi: 10.1038/s41423-022-00882-1; Lee, Dennis SW, Olga L. Rojas, and Jennifer L. Gommerman, *Nature Reviews Drug Discovery* 20.3 (2021): 179-199, doi: 10.1038/s41573-020-00092-2; and

International Publication Nos. WO 2020/014599; WO 2021/074620.

In some embodiments of any of the methods of treating or preventing autoimmune diseases or conditions provided herein, the compound provided herein, or a pharmaceutically acceptable salt thereof, is dosed q.d. (once daily) to the subject. In some embodiments of any of the methods of treating or preventing autoimmune diseases or conditions provided herein, the compound provided herein, or a pharmaceutically acceptable salt thereof, is dosed b.i.d. (twice daily) to the subject. In some embodiments of any of the methods of treating or preventing autoimmune diseases or conditions provided herein, the compound provided herein, or a pharmaceutically acceptable salt thereof, is dosed t.i.d. (three times daily) to the subject. In some embodiments of any of the methods of treating or preventing autoimmune diseases or conditions provided herein, the compound provided herein, or a pharmaceutically acceptable salt thereof, is dosed q.i.d. (four times daily) to the subject. In some embodiments of any of the methods of treating or preventing autoimmune diseases or conditions provided herein, the compound provided herein, or a pharmaceutically acceptable salt thereof, is dosed q.o.d. (every other day) to the subject. In some embodiments of any of the methods of treating or preventing autoimmune diseases or conditions provided herein, the compound provided herein, or a pharmaceutically acceptable salt thereof, is dosed q.week (once weekly) to the subject. In some embodiments of any of the methods of treating or preventing autoimmune diseases or conditions provided herein, the compound provided herein, or a pharmaceutically acceptable salt thereof, is dosed b.i.w. (twice weekly) to the subject. In some embodiments of any of the methods of treating or preventing autoimmune diseases or conditions provided herein, the compound provided herein, or a pharmaceutically acceptable salt thereof, is dosed t.i.w. (three times weekly) to the subject.

Also provided herein is a method of treating a lymphoproliferative disorder in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound provided herein, or a pharmaceutically acceptable salt thereof.

Provided herein is use of a compound provided herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, for the treatment of a lymphoproliferative disorder, for example, any of the lymphoproliferative disorders provided herein.

Provided herein is use of a compound provided herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, as a medicament for the treatment of a lymphoproliferative disorder, for example, any of the lymphoproliferative disorders provided

herein.

Provided herein is use of a compound provided herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a lymphoproliferative disorder, for example, any of the lymphoproliferative disorders provided herein.

Provided herein is a compound provided herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, for use as a medicament for the treatment of a lymphoproliferative disorder, for example, any of the lymphoproliferative disorders provided herein.

Provided herein is a compound provided herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, for use in treating a lymphoproliferative disorder, for example, any of the lymphoproliferative disorders provided herein.

In some embodiments, the lymphoproliferative disorder is Epstein-Barr Virus-associated lymphoproliferative disorder.

Also provided is a method for modulating (e.g., decreasing) BCL6 protein activity in a cell, comprising contacting the cell with a compound provided herein, or a pharmaceutically acceptable salt thereof. In some embodiments, the contacting is in vitro. In some embodiments, the contacting is in vivo. In some embodiments, the contacting is ex vivo. In some embodiments, the contacting is in vivo, wherein the method comprises administering an effective amount of a compound provided herein, or a pharmaceutically acceptable salt thereof, to a subject. In some embodiments, the cell is a cancer cell. In some embodiments, the cell is a mammalian cell. In some embodiments, the cell is a mammalian cancer cell. In some embodiments, the cancer cell is any cancer as described herein.

As used herein, the term "contacting" refers to the bringing together of indicated moieties in an in vitro system, an in vivo system, or an ex vivo system. For example, "contacting" a cell with a compound provided herein includes the administration of a compound provided herein to the cell, in vitro or in vivo, including, for example, introducing a compound provided herein into a sample containing cells (e.g., grown in culture or derived from a subject), an organoid, or an organism (e.g., an animal (e.g., an animal bearing a tumor), or a human).

Also provided is a method of modulating (e.g., decreasing) the level of BCL6 protein in a cell, comprising contacting the cell with a compound provided herein, or a pharmaceutically acceptable salt thereof. In some embodiments, the level of BCL6 protein is decreased by at least 30% (e.g., at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 97%, or at least 99%) compared to a cell not contacted

with the compound provided herein, or a pharmaceutically acceptable salt thereof. In some embodiments, the contacting is in vitro. In some embodiments, the contacting is in vivo. In some embodiments, the contacting is in vivo, wherein the method comprises administering an effective amount of a compound provided herein, or a pharmaceutically acceptable salt thereof, to a subject having a cell having a BCL6 protein. In some embodiments, the cell is a cancer cell. In some embodiments, the cell is a mammalian cell. In some embodiments, the cell is a mammalian cancer cell. In some embodiments, the cancer cell is any cancer as described herein.

Also provided is a method of inducing ubiquitination of a BCL6 protein in a cell, comprising contacting the cell with a compound provided herein, or a pharmaceutically acceptable salt thereof. In some embodiments, the contacting is in vitro. In some embodiments, the contacting is in vivo. In some embodiments, the contacting is in vivo, wherein the method comprises administering an effective amount of a compound provided herein, or a pharmaceutically acceptable salt thereof, to a subject having a cell having a BCL6 protein. In some embodiments, the cell is a cancer cell. In some embodiments, the cell is a mammalian cell. In some embodiments, the cell is a mammalian cancer cell. In some embodiments, the cancer cell is any cancer as described herein.

Also provided is a method of forming a ternary complex comprising a BCL6 protein, a compound provided herein, or a pharmaceutically acceptable salt thereof, and a CRBN protein or fragment thereof in a cell, comprising contacting the cell with a compound provided herein, or a pharmaceutically acceptable salt thereof. In some embodiments, the contacting is in vitro. In some embodiments, the contacting is in vivo. In some embodiments, the contacting is in vivo, wherein the method comprises administering an effective amount of a compound provided herein, or a pharmaceutically acceptable salt thereof, to a subject having a cell having a BCL6 protein. In some embodiments, the cell is a cancer cell. In some embodiments, the cell is a mammalian cell. In some embodiments, the cell is a mammalian cancer cell. In some embodiments, the cancer cell is any cancer as described herein.

Also provided herein is a method for inducing degradation of a BCL6 protein in a mammalian cell, the method comprising contacting the mammalian cell with an effective amount of a compound provided herein, or a pharmaceutically acceptable salt thereof.

Also provided herein is a method of inhibiting cell proliferation, in vitro or in vivo, the method comprising contacting a cell with an effective amount of a compound provided herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof as defined herein.

Further provided herein is a method of increasing cell death, in vitro or in vivo, the method comprising contacting a cell with an effective amount of a compound provided herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof as defined herein. Also provided herein is a method of increasing tumor cell death in a subject, the method comprising administering to the subject a compound provided herein, or a pharmaceutically acceptable salt thereof, in an amount effective to increase tumor cell death.

When employed as pharmaceuticals, the compounds provided herein, or pharmaceutically acceptable salts thereof, can be administered in the form of pharmaceutical compositions as described herein.

Combinations

In any of the indications described herein, a compound provided herein, or a pharmaceutically acceptable salt thereof, can be used as a monotherapy. In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, can be used prior to administration of an additional therapeutic agent or additional therapy. For example, a subject in need thereof can be administered one or more doses of a compound provided herein, or a pharmaceutically acceptable salt thereof, for a period of time and then undergo at least partial resection of the tumor. In some embodiments, the treatment with one or more doses of a compound provided herein, or a pharmaceutically acceptable salt thereof, reduces the size of the tumor (e.g., the tumor burden) prior to the at least partial resection of the tumor.

In some embodiments, a subject in need thereof can be administered one or more doses of a compound provided herein, or a pharmaceutically acceptable salt thereof, for a period of time and undergo one or more rounds of radiation therapy. In some embodiments, the treatment with one or more doses of a compound provided herein, or a pharmaceutically acceptable salt thereof, reduces the size of the tumor (e.g., the tumor burden) prior to the one or more rounds of radiation therapy.

In some embodiments of any the methods described herein, the compound provided herein, or a pharmaceutically acceptable salt thereof, is administered in combination with a therapeutically effective amount of at least one additional therapeutic (e.g., chemotherapeutic) agent.

Non-limiting examples of additional therapeutic agents include: RAS pathway targeted therapeutic agents (e.g., Ras/RAF/MEK/PI3K pathway inhibitors, (e.g., Ras inhibitors, KRas-targeted therapeutic agents, SOS1 inhibitors, SOS1/Ras protein-protein interaction inhibitors, SHP2 inhibitors, PI3K-AKT-mTOR pathway inhibitors)), kinase-targeted therapeutics (e.g.,

MEK inhibitors, ERK inhibitors, Raf inhibitors (e.g., BRaf inhibitors), PI3K inhibitors, AKT inhibitors, BTK inhibitors, mTOR inhibitors, CDK4/5 inhibitors, CDK4/6 inhibitors, MET inhibitors, JAK inhibitors (e.g., JAK2 inhibitors), FAK inhibitors, ErbB family inhibitors (e.g., EGFR inhibitors, Her2 inhibitors), Src inhibitors), menin inhibitors, mTORC1 inhibitors, YAP inhibitors, proteasome inhibitors, farnesyl transferase inhibitors, HSP90 inhibitors, PTEN inhibitors, inhibitors of the polycomb repressive complex 2 (PRC2) (e.g., EZH1/2 or EZH2 inhibitors), signal transduction pathway inhibitors, checkpoint inhibitors, modulators of the apoptosis pathway (e.g., BCL-2 inhibitors, BCL-X_L inhibitors), XPO1 inhibitors, steroids, chemotherapeutics, angiogenesis-targeted therapies, immune-targeted agents including immunomodulatory imide drugs (sometimes called "IMiDs" or "CELMoDs"), immunotherapy (e.g., anti-PD1, anti-PD-L1, anti-CD19, anti-CD20, anti-CD22, anti-CD3, anti-CD30, anti-CD79B, or anti-CD47 therapies, including antibodies (e.g., single-targeted antibodies targeting one or more of PD1, PD-L1, CD19, CD20, CD22, CD3, CD30, CD79B, or CD47, bispecific antibodies (including bispecific T cell engagers (BiTEs)) targeting one or more of PD1, PD-L1, CD19, CD20, CD22, CD3, CD30, CD79B, or CD47, and antibody-drug conjugates (ADCs) incorporating one or more of PD1, PD-L1, CD19, CD20, CD22, CD3, CD30, CD79B, or CD47 antibodies) or antigen-binding fragments thereof, a PD-1 inhibitor, or a PD-L1 inhibitor), cell-based therapeutics (e.g., adoptive cell therapy (e.g., CAR T therapy, cytokine-induced killer cells (CIKs), natural killer cells (e.g., CAR-modified NK cells)) or antibody-armed cell therapy), and radiotherapy.

As used herein, a biosimilar antibody refers to an antibody or antigen-binding fragment that has the same primary amino acid sequence as compared to a reference antibody and optionally, can have detectable differences in post-translation modifications (e.g., glycosylation and/or phosphorylation) as compared to the reference antibody (e.g., a different glycoform).

In some embodiments, the additional therapeutic agent is a PI3K inhibitor, an Abl inhibitor (e.g., a BCR-Abl inhibitor), a BTK inhibitor, a JAK inhibitor (e.g., a JAK2 inhibitor), a BRaf inhibitor, a MEK inhibitor, a menin inhibitor, a BCL-2 inhibitor, a BCL-X_L inhibitor, an MCL-1 inhibitor, an XPO1 inhibitor, an inhibitor of the polycomb repressive complex 2 (e.g., an EZH1/2 or EZH2 inhibitor), an immunomodulatory imide drug, a steroid, anti-CD19 therapy, anti-CD20 therapy, anti-CD3 therapy, chemotherapy, or a combination thereof.

Without being bound by any particular theory, it is believed that targeting BCL6 can result in the induction of genes that it typically represses, such as *BCL2*. In some embodiments, the additional therapeutic agent is a BCL-2 inhibitor (e.g., foselutoclax (UBX-1325),

lacutoclax, lisaftoclax, navitoclax, obatoclax, pelcitoclax, venetoclax, sonrotoclax (BGB-11417), surzetoclax, oblimersen (e.g., oblimersen sodium), beclanorsen, AZD-0466, ICP-248, TQB-3909, UBX-1967, ZN-d5, or a combination thereof).

In some embodiments, the PI3K inhibitor is alpelisib (BYL719), amdizalisib, apitolisib (GDC-0980), bimiralisib, buparlisib (BKM120), copanlisib (ALIQOPA™, BAY80-6946) (e.g., copanlisib dihydrochloride or a hydrate of copanlisib dihydrochloride), dactolisib (NVP-BEZ235, BEZ-235), dezapelisib, dordaviprone, duvelisib (e.g., a hydrate of duvelisib), eganelisib, fimepinostat, gedatolisib (PF-05212384, PKI-587), idelalisib, inavolisib, leniolisib (e.g., leniolisib phosphate), linperlisib, omipalisib (GSK2126458, GSK458), parsaclisib, pictilisib (GDC-0941), pilaralisib (XL147, SAR245408), paxalisib, rigosertib, risovalisib, seletalisib, serabelisib (TAK-117, MLN1117, INK 1117), sonolisib (PX-866), taselisib (GDC-0032, RG7604), umbralisib (e.g., umbralisib tosylate), voxtalisib (XL756, SAR245409), wortmannin, zandelisib, AMG 511, AMG319, ASN003, AZD8835, BGT-226 (NVP-BGT226), CH5132799, CUDC-907, GDC-0077, GDC-0084 (RG7666), GS-9820, GSK1059615, GSK2636771, KIN-193 (AZD-6428), LY2023414, LY294002, PF-04691502, PI-103, PKI-402, PQR309, SAR260301, SF1126, SHC-014748-M, TQ-B-3525, VS-5584 (SB2343), WX-037, XL-765, ZSTK474, or a combination thereof. In some embodiments, the PI3K inhibitor is alpelisib, amdizalisib, apitolisib, bimiralisib, buparlisib, copanlisib (e.g., copanlisib dihydrochloride or a hydrate of copanlisib dihydrochloride), dactolisib, dezapelisib, dordaviprone, duvelisib (e.g., a hydrate of duvelisib), eganelisib, fimepinostat, gedatolisib, idelalisib, inavolisib, leniolisib (e.g., leniolisib phosphate), linperlisib, parsaclisib, paxalisib, risovalisib, seletalisib, serabelisib, sonolisib, tenalisib, umbralisib (e.g., umbralisib tosylate), zandelisib, PF-04691502, SHC-014748-M, TQ-B-3525, or a combination thereof.

In some embodiments, the Abl inhibitor (e.g., BCR-Abl inhibitor) is asciminib (e.g., asciminib hydrochloride), bafetinib, bosutinib (e.g., bosutinib monohydrate), danusertib, dasatinib (e.g., dasatinib monohydrate), flumatinib (e.g., flumatinib mesylate), imatinib (e.g., imatinib mesylate), nilotinib (e.g., nilotinib monochloride monohydrate), olverembatinib (e.g., olverembatinib mesylate), ponatinib (e.g., ponatinib hydrochloride), radotinib (e.g., radotinib dihydrochloride), risvodetinib (IkT-148009), ruserontinib, vamotinib, vandetanib, AN-019, AT-9283, NPB-001-056, or a combination thereof.

In some embodiments, the cancer is a B-ALL, and the additional therapy or therapeutic agent is an Abl inhibitor. In some embodiments, the cancer is a Philadelphia chromosome positive B-ALL and the additional therapy or therapeutic agent is an Abl inhibitor. In some embodiments, the cancer is a Philadelphia chromosome-like B-ALL, and the additional therapy

or therapeutic agent is an Abl inhibitor. In some embodiments, the Abl inhibitor is selected from the group consisting of imatinib, dasatinib, ponatinib, or a combination thereof.

In some embodiments, the BTK inhibitor is abivertinib, acalabrutinib, atuzabrutinib, branebrutinib, dasatinib (e.g., dasatinib monohydrate), edralbrutinib (SHR-1459), elsubrutinib, evobrutinib, fenebrutinib, ibrutinib, luxeptinib, nemtabrutinib, olafertinib, nemtabrutinib, orelabrutinib, pirtobrutinib, remibrutinib, rilzabrutinib, spebrutinib, sunvozertinib, tirabrutinib (e.g., tirabrutinib hydrochloride), tolebrutinib, vecabrutinib, zanubrutinib, AC-0058 (AC-0058TA), BMS-986142, CT-1530, DTRMWXHS-12, LY-3337641 (HM-71224), M-7583, TAS-5315, or a combination thereof. In some embodiments, the BTK inhibitor is abivertinib, acalabrutinib, atuzabrutinib, branebrutinib, dasatinib (e.g., dasatinib monohydrate), edralbrutinib, elsubrutinib, evobrutinib, fenebrutinib, ibrutinib, nemtabrutinib, orelabrutinib, pirtobrutinib, remibrutinib, rilzabrutinib, rocbrutinib, spebrutinib, sunvozertinib, tirabrutinib (e.g., tirabrutinib hydrochloride), tolebrutinib, zanubrutinib, AC-0058, BIIB-091, BMS-986142, DTRMWXHS-12, LY-3337641, TAS-5315, TL-925, or a combination thereof.

In some embodiments, the cancer is a B-ALL, and the additional therapy or therapeutic agent is a BTK inhibitor. In some embodiments, the cancer is a pre-BCR+ B-ALL, and the additional therapy or therapeutic agent is a BTK inhibitor. In some embodiments, the cancer is a B-ALL dependent on Ras signaling, and the additional therapy or therapeutic agent is a BTK inhibitor. In some embodiments, the BTK inhibitor is ibrutinib or acalabrutinib.

In some embodiments, the JAK inhibitor is abrocitinib, baricitinib, brepocitinib, decernotinib, delgocitinib, deuruxolitinib, elsubrutinib, fedratinib (e.g., fedratinib dihydrochloride monohydrate), filgotinib (e.g., filgotinib maleate), gandotinib, gusacitinib, ilginatinib, itacitinib, ivarmacitinib, izencitinib, jaktinib, momelotinib, nezulcitinib, pacritinib (e.g., pacritinib citrate), peficitinib (e.g., peficitinib hydrobromide), povorcitinib (INCB-54707), ropsacitinib, ruxolitinib (e.g., ruxolitinib phosphate), solcitinib, tasocitinib (e.g., tofacitinib citrate), tinengotinib, upadacitinib (e.g., upadacitinib hydrate), zasocitinib, AGA-201, ATI-1777, ATI-501, ESK-001, GLPG-3667, INCB-52793, LNK-01001, LNK-01003, R-348, TD-8236, TLL-018, TQ-05105, VTX-958, or a combination thereof. In some embodiments, the JAK inhibitor is abrocitinib, baricitinib, brepocitinib, decernotinib, delgocitinib, deuruxolitinib, fedratinib (e.g., fedratinib dihydrochloride monohydrate), filgotinib (e.g., filgotinib maleate), gandotinib, golidocitinib, gusacitinib, ilginatinib, itacitinib, ivarmacitinib, izencitinib, jaktinib, lepzacitinib (ATI-1777), londamocitinib, momelotinib, nezulcitinib, pacritinib (e.g., pacritinib citrate), peficitinib (e.g., peficitinib hydrobromide), povorcitinib (INCB-54707), ritlecitinib (e.g., ritlecitinib tosylate), tasocitinib, ropsacitinib,

ruxolitinib (e.g., ruxolitinib phosphate), solcitinib, tofacitinib (e.g., tofacitinib citrate), tinengotinib, upadacitinib (e.g., upadacitinib hydrate), zasocitinib, AGA-201, ATI-501, CPL-409116, ESK-001, GLPG-3667, LNK-01001, LNK-01003, KL-130008, NS-229, R-348, TD-8236, TDM-180935, TLL-018, TQ-05105, VC-005, VTX-958, VVN-461, or a combination thereof.

In some embodiments, the JAK2 inhibitor is adelatinib, baricitinib, brepocitinib, deuruxolitinib, fedratinib (e.g., fedratinib dihydrochloride monohydrate), filgotinib (e.g., filgotinib maleate), gandotinib, gusacitinib, ilginatinib, izencitinib, jaktinib, momelotinib (e.g., momelotinib dihydrochloride), nezulcitinib, pacritinib (e.g., pacritinib citrate), peficitinib (e.g., peficitinib hydrobromide), ropsacitinib, ruxolitinib (e.g., ruxolitinib phosphate), tasocitinib (e.g., tofacitinib citrate), AT-9283, CPL-409116, KL-130008, TQ-05105, or a combination thereof.

In some embodiments, the cancer is a B-ALL, and the additional therapy or therapeutic agent is a JAK inhibitor. In some embodiments, the cancer is a JAK2 (e.g., $JAK2^{R683G}$ or $JAK2^{I682F}$) mutant B-ALL, and the additional therapy or therapeutic agent is a JAK inhibitor. In some embodiments, the cancer is a JAK2 (e.g., $JAK2^{R683G}$ or $JAK2^{I682F}$) mutant B-ALL with high CRLF2 expression, and the additional therapy or therapeutic agent is a JAK inhibitor (e.g., a JAK2 inhibitor) and a BCL-2 inhibitor (e.g., venetoclax).

In some embodiments, the BRaf inhibitor is avutometinib (RO5126766), dabrafenib (e.g., dabrafenib mesylate, GSK2118436), encorafenib (e.g., BRAFTOVI™, LGX818), naporafenib (LXH254), sorafenib (e.g., sorafenib tosylate), vemurafenib (e.g., ZELBORAF®, RO5185426), ARQ-736, AZ304, BMS-908662 (XL281), C17071479-F, CHIR-265 (RAF265), FORE-8394 (PLX-8394), GDC-0879, GDC-5573 (HM95573), HLX-208, PLX-3603, PLX-4720, or a combination thereof. In some embodiments, the BRaf inhibitor is avutometinib, dabrafenib (e.g., dabrafenib mesylate), encorafenib, naporafenib, sorafenib (e.g., sorafenib tosylate), vemurafenib, C17071479-F, CHIR-265, FORE-8394, HLX-208, or a combination thereof.

In some embodiments, the MEK inhibitor is avutometinib, binimetinib, cobimetinib (e.g., cobimetinib fumarate), mirdametinib, nedometinib, pimasertib, refametinib, selumetinib (e.g., selumetinib sulfate), trametinib (e.g., trametinib dimethyl sulfoxide, GSK-1120212), tunlametinib, zapnometinib, FCN-159, NFX-179, TAK-733, or a combination thereof. In some embodiments, the MEK inhibitor is a MEK-Raf protein-protein interaction stabilizer, such as NST-628 or avutometinib (VS6766).

In some embodiments, the menin inhibitor is revumenib (e.g., revumenib fumarate), icovamenib (BMF-219), ziftomenib, DS-1594, DSP-5336, HMPL-506, JNJ-6617, or a combination thereof.

In some embodiments, the cancer is a B-ALL, and the additional therapy or therapeutic agent is a menin inhibitor. In some embodiments, the cancer is an *MLL*-rearranged (e.g., an MLL-Af4 fusion, an MLL-Af6 fusion, an MLL-Af9 fusion, an MLL-ENL fusion, or an MLL-PTD fusion) B-ALL, and the additional therapy or therapeutic agent is a menin inhibitor.

In some embodiments, the BCL-2 inhibitor is foselutoclax (UBX-1325), lacutoclax, lisaftoclax, navitoclax, obatoclax, pelcitoclax, venetoclax, sonrotoclax (BGB-11417), surzetoclax, oblimersen (e.g., oblimersen sodium), beclanorsen, AZD-0466, ICP-248, TQB-3909, UBX-1967, ZN-d5, or a combination thereof. In some embodiments, the BCL-2 inhibitor is foselutoclax (UBX-1325), lisaftoclax, navitoclax, obatoclax, pelcitoclax, venetoclax, sonrotoclax, oblimersen (e.g., oblimersen sodium), beclanorsen, or a combination thereof.

In some embodiments, the cancer is a B-ALL, and the additional therapy or therapeutic agent is a BCL-2 inhibitor. In some embodiments, the cancer is an *MLL*-rearranged (e.g., an MLL-Af4 fusion, an MLL-Af6 fusion, an MLL-Af9 fusion, an MLL-ENL fusion, or an MLL-PTD fusion) B-ALL, and the additional therapy or therapeutic agent is a BCL-2 inhibitor. In some embodiments, the cancer is a *BCL2* amplified B-ALL, and the additional therapy or therapeutic agent is a BCL-2 inhibitor. In some embodiments, the BCL-2 inhibitor is venetoclax.

In some embodiments, the cancer is a large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary large B cell lymphoma of immune-privileged sites (primary LBCL of immune-privileged sites), intravascular large B-cell lymphoma (IVLBCL), primary mediastinal large B cell lymphoma (primary mediastinal LBCL), or high grade B-cell lymphoma NOS (HBGCL-NOS)), follicular lymphoma (FL), mantle cell lymphoma (MCL), or a transformation of an indolent B cell lymphoma, and the additional therapy or therapeutic agent is a BCL-2 inhibitor. In some embodiments, the cancer is a large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary large B cell lymphoma of immune-privileged sites (primary LBCL of immune-privileged sites), intravascular large B-cell lymphoma (IVLBCL), primary mediastinal large B cell lymphoma (primary mediastinal

LBCL), or high grade B-cell lymphoma NOS (HBGCL-NOS)), and the additional therapy or therapeutic agent is a BCL-2 inhibitor. In some embodiments, the cancer is a transformation of an indolent B cell lymphoma, and the additional therapy or therapeutic agent is a BCL-2 inhibitor. In some embodiments, the cancer is a DLBCL-NOS, and the additional therapy or therapeutic agent is a BCL-2 inhibitor. In some embodiments, the BCL-2 inhibitor is venetoclax.

In some embodiments, the cancer is a FL, and the additional therapy or therapeutic agent is a BCL-2 inhibitor. In some embodiments, the BCL-2 inhibitor is venetoclax.

In some embodiments, the cancer is an MCL, and the additional therapy or therapeutic agent is a BCL-2 inhibitor. In some embodiments, the BCL-2 inhibitor is venetoclax.

In some embodiments, the cancer is a T-ALL, and the additional therapy or therapeutic agent is a BCL-2 inhibitor. In some embodiments, the BCL-2 inhibitor is venetoclax.

In some embodiments, the BCL-X_L inhibitor is lisaftoclax, navitoclax, obatoclax, pelcitoclax, mirzotamab clezutoclax, ABBV-155, APG-1252-12A, AZD-0466, DT-2216, PA-15227, UBX-1325, UBX-1967, XZ-739, 753-B, or a combination thereof. In some embodiments, the BCL-X_L inhibitor is lisaftoclax, navitoclax, obatoclax, or a combination thereof.

In some embodiments, the MCL-1 inhibitor or degrader is omacetaxine (e.g., omacetaxine mepesuccinate), murizatoclax, tapotoclax, ABBV-467, GS-9716 S-64315, or a combination thereof.

In some embodiments, the XPO1 inhibitor is eltanexor, felezonexor, selinexor, verdinexor, BIIB-100, JS-110, or a combination thereof. In some embodiments, the XPO1 inhibitor is selinexor.

In some embodiments, the inhibitor of the PRC2 is lirametostat, mevrometostat, tazemetostat (e.g., tazemetostat hydrobromide), valemetostat (e.g., valemetostat tosylate), tulmimetostat (CPI-0209), EBI-2511, HH-2853, HM-97662, SHR-2554, XNW-5004, or a combination thereof. In some embodiments, the inhibitor of the PRC2 is an EZH1/2 inhibitor. In some embodiments, the EZH1/2 inhibitor is valemetostat (e.g., valemetostat tosylate), tulmimetostat (CPI-0209), HH-2853, HM-97662, or a combination thereof. In some embodiments, the inhibitor of the PRC2 is an EZH2 inhibitor. In some embodiments, the EZH2 inhibitor is lirametostat, mevrometostat, tazemetostat (e.g., tazemetostat hydrobromide), EBI-2511, SHR-2554, XNW-5004, or a combination thereof. Non-limiting examples of EZH2 and/or EZH1/2 inhibitors are described in International Publication Nos. WO 2011/140325, WO 2012/005805, WO 2012/050532, WO 2012/118812, WO 2012/142513, WO

2012/142504, WO 2013/049770, WO 2013/039988, WO 2013/067300, WO 2015/141616, WO 2017/084494, WO 2018/210296, WO 2018/210302, WO 2019/091450, WO 2019/204490, WO 2019/226491, WO 2020/063863, WO 2020/171606, WO 2020/228591, WO 2021/016414, WO 2021/063332, WO 2021/063340, WO 2021/180235, and WO 2022/035303.

In some embodiments, the cancer is a large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary large B cell lymphoma of immune-privileged sites (primary LBCL of immune-privileged sites), intravascular large B-cell lymphoma (IVLBCL), primary mediastinal large B cell lymphoma (primary mediastinal LBCL), or high grade B-cell lymphoma NOS (HBGCL-NOS)), follicular lymphoma (FL), mantle cell lymphoma (MCL), or a transformation of an indolent B cell lymphoma, and the additional therapy or therapeutic agent is an inhibitor of the PRC2 (e.g., an EZH1/2 or EZH2 inhibitor). In some embodiments, the cancer is a large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary large B cell lymphoma of immune-privileged sites (primary LBCL of immune-privileged sites), intravascular large B-cell lymphoma (IVLBCL), primary mediastinal large B cell lymphoma (primary mediastinal LBCL), or high grade B-cell lymphoma NOS (HBGCL-NOS)), and the additional therapy or therapeutic agent is an inhibitor of the PRC2 (e.g., an EZH1/2 or EZH2 inhibitor). In some embodiments, the cancer is a DLBCL-NOS, and the additional therapy or therapeutic agent is an inhibitor of the PRC2 (e.g., an EZH1/2 or EZH2 inhibitor). In some embodiments, the cancer is a diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), and the additional therapy or therapeutic agent is an inhibitor of the PRC2 (e.g., an EZH1/2 or EZH2 inhibitor). In some embodiments, the cancer is a HBGCL-NOS, and the additional therapy or therapeutic agent is an inhibitor of the PRC2 (e.g., an EZH1/2 or EZH2 inhibitor). In some embodiments, the cancer is a primary mediastinal large B cell lymphoma, and the additional therapy or therapeutic agent is an inhibitor of the PRC2 (e.g., an EZH1/2 or EZH2 inhibitor). In some embodiments, the cancer is a primary large B cell lymphoma of immune-privileged sites (primary LBCL of immune-privileged sites), and the additional therapy or therapeutic agent is an inhibitor of the PRC2 (e.g., an EZH1/2 or EZH2 inhibitor). In some embodiments, the cancer is a follicular lymphoma (FL), and the additional therapy or

therapeutic agent is an inhibitor of the PRC2 (e.g., an EZH1/2 or EZH2 inhibitor). In some embodiments, the cancer is a mantle cell lymphoma (MCL), and the additional therapy or therapeutic agent is an inhibitor of the PRC2 (e.g., an EZH1/2 or EZH2 inhibitor). In some embodiments, the cancer is a transformation of an indolent B cell lymphoma, and the additional therapy or therapeutic agent is an inhibitor of the PRC2 (e.g., an EZH1/2 or EZH2 inhibitor).

In some embodiments, the cancer is a BL, and the additional therapy or therapeutic agent is an inhibitor of the PRC2 (e.g., an EZH1/2 or EZH2 inhibitor).

In some embodiments, the cancer is a NLPHL, and the additional therapy or therapeutic agent is an inhibitor of the PRC2 (e.g., an EZH1/2 or EZH2 inhibitor).

In some embodiments, the cancer is a B-ALL (e.g., Philadelphia chromosome positive B-ALL, Philadelphia chromosome negative B-ALL, or B-ALL with an *MLL* rearrangement (e.g., an MLL-Af4 fusion, an MLL-Af6 fusion, an MLL-Af9 fusion, an MLL-ENL fusion, or an MLL-PTD fusion)), and the additional therapy or therapeutic agent is an inhibitor of the PRC2. In some embodiments, the cancer is a FL, and the additional therapy or therapeutic agent is an inhibitor of the PRC2 (e.g., an EZH1/2 or EZH2 inhibitor). In some embodiments, the cancer is an MCL, and the additional therapy or therapeutic agent is an inhibitor of the PRC2 (e.g., an EZH1/2 or EZH2 inhibitor).

In some embodiments, the cancer is peripheral T-cell lymphoma (PTCL) (e.g., anaplastic large cell lymphoma (ALCL) (e.g., ALK-positive anaplastic large cell lymphoma, or ALK-negative anaplastic large cell lymphoma), nodal T follicular helper cell lymphoma (e.g., nodal T follicular helper cell lymphoma angioimmunoblastic type (also known as angioimmunoblastic T-cell lymphoma (AITL) or follicular helper T-cell lymphoma, angioimmunoblastic type), nodal T follicular helper cell lymphoma follicular type (also known as follicular helper T-cell lymphoma, follicular type), or nodal T follicular helper cell lymphoma NOS (also known as follicular helper T-cell lymphoma, NOS))), or a primary cutaneous T-cell lymphoid proliferation or lymphoma (cutaneous T-cell lymphoma (CTCL)) (e.g., primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder, mycosis fungoides, Sezary syndrome, or primary cutaneous gamma-delta T-cell lymphoma), and the additional therapy or therapeutic agent is an inhibitor of the PRC2 (e.g., an EZH1/2 or EZH2 inhibitor). In some embodiments, the cancer is peripheral T-cell lymphoma (PTCL) (e.g., anaplastic large cell lymphoma (ALCL) (e.g., ALK-positive anaplastic large cell lymphoma, or ALK-negative anaplastic large cell lymphoma), nodal T follicular helper cell lymphoma (e.g., nodal T follicular helper cell lymphoma angioimmunoblastic type (also known as angioimmunoblastic T-cell lymphoma (AITL) or follicular helper T-cell lymphoma,

angioimmunoblastic type), nodal T follicular helper cell lymphoma follicular type (also known as follicular helper T-cell lymphoma, follicular type), or nodal T follicular helper cell lymphoma NOS (also known as follicular helper T-cell lymphoma, NOS))), and the additional therapy or therapeutic agent is an inhibitor of the PRC2 (e.g., an EZH1/2 or EZH2 inhibitor). In some embodiments, the cancer is anaplastic large cell lymphoma (ALCL) (e.g., ALK-positive anaplastic large cell lymphoma, or ALK-negative anaplastic large cell lymphoma), and the additional therapy or therapeutic agent is an inhibitor of the PRC2 (e.g., an EZH1/2 or EZH2 inhibitor). In some embodiments, the cancer is ALK-positive anaplastic large cell lymphoma, and the additional therapy or therapeutic agent is an inhibitor of the PRC2 (e.g., an EZH1/2 or EZH2 inhibitor). In some embodiments, the cancer is ALK-negative anaplastic large cell lymphoma, and the additional therapy or therapeutic agent is an inhibitor of the PRC2 (e.g., an EZH1/2 or EZH2 inhibitor). In some embodiments, the cancer is nodal T follicular helper cell lymphoma (e.g., nodal T follicular helper cell lymphoma angioimmunoblastic type (also known as angioimmunoblastic T-cell lymphoma (AITL) or follicular helper T-cell lymphoma, angioimmunoblastic type), nodal T follicular helper cell lymphoma follicular type (also known as follicular helper T-cell lymphoma, follicular type), or nodal T follicular helper cell lymphoma NOS (also known as follicular helper T-cell lymphoma, NOS)), and the additional therapy or therapeutic agent is an inhibitor of the PRC2 (e.g., an EZH1/2 or EZH2 inhibitor). In some embodiments, the cancer is nodal T follicular helper cell lymphoma angioimmunoblastic type (also known as angioimmunoblastic T-cell lymphoma (AITL) or follicular helper T-cell lymphoma, angioimmunoblastic type), and the additional therapy or therapeutic agent is an inhibitor of the PRC2 (e.g., an EZH1/2 or EZH2 inhibitor). In some embodiments, the cancer is nodal T follicular helper cell lymphoma follicular type (also known as follicular helper T-cell lymphoma, follicular type), and the additional therapy or therapeutic agent is an inhibitor of the PRC2 (e.g., an EZH1/2 or EZH2 inhibitor). In some embodiments, the cancer is nodal T follicular helper cell lymphoma NOS (also known as follicular helper T-cell lymphoma, NOS), and the additional therapy or therapeutic agent is an inhibitor of the PRC2 (e.g., an EZH1/2 or EZH2 inhibitor). In some embodiments, the cancer is a primary cutaneous T-cell lymphoid proliferation or lymphoma (cutaneous T-cell lymphoma (CTCL)) (e.g., primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder, mycosis fungoides, Sezary syndrome, or primary cutaneous gamma-delta T-cell lymphoma), and the additional therapy or therapeutic agent is an inhibitor of the PRC2 (e.g., an EZH1/2 or EZH2 inhibitor). In some embodiments, the cancer is mycosis fungoides, and the additional therapy or therapeutic agent is an inhibitor of the PRC2 (e.g., an EZH1/2 or EZH2 inhibitor).

In some embodiments, the cancer is Sezary syndrome, and the additional therapy or therapeutic agent is an inhibitor of the PRC2 (e.g., an EZH1/2 or EZH2 inhibitor).

An exemplary wild-type human EZH2 sequence is shown below. This is one of several isoforms of EZH2, and it will be understood that residue numbering can change based on the reference isoform.

SEQ ID NO: 1 (UniParc ID UPI000006D77C):

MGQTGKKSEKGPVCWRKRVKSEYMRLRQLKRFRRADEVKSMFSSNRQKILE
RTEILNQEWKQRRIQPVHILTSVSSLRGTRECSVTSDLDFPTQVIPLKTLNAVASVPIM
YSWSPLQQNFMVEDETVLHNIPYMGDEVLDQDGTFIEELIKNYDGKVHGDRECGFIN
DEIFVELVNALGQYNDDDDDDDGDDPEEREEKQKDLEDHRDDKESRPPRKFPSDKIF
EAISSMFPDKGTAEELKEKYKELTEQQLPGALPPECTPNIDGPNAKSVQREQSLHSFH
TLFCRRCFKYDCFLHRKCNYSFHATPNTYKRKNTETALDNKPCGPQCYQHLEGAKE
FAAALTAERIKTPPKRPGGRRRGRLPNNSSRPSTPTINVLESKDTDSDREAGTETGGE
NNDKEEEEKKDETSSSSEANSRCQTPIKMKPNIEPPENVEWSGAEASMFRVLIGTYYD
NFCAIARLIGTKTCRQVYEFRVKESSIIAPAPAEDVDTPPRKKKRKHRLWAAHCRKIQ
LKKDGSSNHVYNYQPCDHPRQPCDSSCPCVIAQNFCEKFCQCSSECQNRFPGCRCKA
QCNTKQCPCYLAVRECDPDLCLTCGAADHWDSKNVSCKNCSIQRGSKKHLLLAPSD
VAGWGIFIKDPVQKNEFISEYCGEIISQDEADRRGKVYDKYMCSFLFNLNNDFVVDA
TRKGNKIRFANHSVNPNCYAKVMMVNGDHRIGIFAKRAIQTGEELFFDYRYSQADA
LKYVGIEREMEIP

In some embodiments, the steroid is dexamethasone, prednisone, or a combination thereof.

In some embodiments, the immunomodulatory imide drug is avadomide, lenalidomide, iberdomide, pomalidomide, thalidomide, CC-99282, or a combination thereof.

In some embodiments, the additional therapy or therapeutic agent is lenalidomide and rituximab or obinutuzumab.

In some embodiments, the anti-CD19 therapy is blinatumomab (e.g., BLINCYTO® (blinatumomab) or a biosimilar thereof), coltuximab ravtansine, inebilizumab (e.g., inebilizumab-cdon, or a biosimilar thereof), loncastuximab tesirine (e.g., loncastuximab tesirine-lpyl, or a biosimilar thereof), obexelimab, tafasitamab (e.g., tafasitamab-cxix, or a biosimilar thereof), dDT-2219, LY-3541860, biosimilars thereof, or a combination thereof. In some embodiments, the anti-CD19 therapy is a bispecific antibody or antigen-binding fragment thereof (e.g., BLINCYTO® (blinatumomab) or a biosimilar thereof). In some embodiments, the anti-CD19 therapy is an anti-CD19 and anti-CD3 bispecific antibody or antigen-binding

fragment thereof (e.g., BLINCYTO® (blinatumomab) or a biosimilar thereof). In some embodiments, the anti-CD19 therapy is an antibody-drug conjugate (e.g., coltuximab ravtansine, loncastuximab tesirine (e.g., loncastuximab tesirine-lpyl, or a biosimilar thereof), or a biosimilar thereof).

In some embodiments, the anti-CD20 therapy is divozilimab, epcoritamab (e.g., epcoritamab-bysp, or a biosimilar thereof), glofitamab (e.g., COLUMVI® (glofitamab), or a biosimilar thereof), ibritumomab tiuxetan (e.g., ZEVALIN® (ibritumomab tiuxetan), or a biosimilar thereof), mosunetuzumab (e.g., mosunetuzumab-axgb, or a biosimilar thereof), obinutuzumab (e.g., GAZYVA® (obinutuzumab), or a biosimilar thereof), ocrelizumab (e.g., OCREVUS® (ocrelizumab), or a biosimilar thereof), odronextamab, ofatumumab (e.g., ARZERRA® (ofatumumab), or a biosimilar thereof), plamotamab, rituximab (e.g., RITUXAN® (rituximab), or a biosimilar thereof (e.g., rituximab-abbs, rituximab-arrx, rituximab-pvvr, ACELLBIA® (rituximab), HALPRYZA® (rituximab), HANLIKON® (rituximab), RIXATHON® (rituximab), REDITUX™ (rituximab), Retuxira (rituximab), BI-695500, GB-241, Mabion-CD20, RTXM-83, SAIT-101), ublituximab (e.g., ublituximab-xiiy, or a biosimilar thereof), veltuzumab, zuberitamab, MIL-62, SCT-400, TQB-2303, biosimilars thereof, or a combination thereof. In some embodiments, the anti-CD20 therapy is a bispecific antibody or antigen-binding fragment thereof (e.g., epcoritamab (e.g., epcoritamab-bysp, or a biosimilar thereof), glofitamab (e.g., COLUMVI® (glofitamab), or a biosimilar thereof), mosunetuzumab (e.g., mosunetuzumab-axgb, or a biosimilar thereof), plamotamab, odronextamab, biosimilars thereof, or a combination thereof. In some embodiments, the anti-CD20 therapy is an anti-CD20 and anti-CD3 bispecific antibody or antigen-binding fragment thereof (e.g., epcoritamab (e.g., epcoritamab-bysp, or a biosimilar thereof), glofitamab (e.g., COLUMVI® (glofitamab), or a biosimilar thereof), mosunetuzumab (e.g., mosunetuzumab-axgb, or a biosimilar thereof), plamotamab, odronextamab, biosimilars thereof, or a combination thereof. In some embodiments, the anti-CD20 therapy is an antibody-drug conjugate (e.g., ibritumomab tiuxetan (e.g., ZEVALIN® (ibritumomab tiuxetan), or a biosimilar thereof).

In some embodiments, the additional therapy or therapeutic agent is rituximab. In some such embodiments, the combination of rituximab and a compound provided herein, or a pharmaceutically acceptable salt thereof, is used as maintenance therapy. In some such embodiments, the cancer is a FL.

In some embodiments, the additional therapy or therapeutic agent is obinutuzumab. In some such embodiments, the combination of obinutuzumab and a compound provided herein,

or a pharmaceutically acceptable salt thereof, is used as maintenance therapy. In some such embodiments, the cancer is a FL.

In some embodiments, the cancer is a large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary large B cell lymphoma of immune-privileged sites (primary LBCL of immune-privileged sites), intravascular large B-cell lymphoma (IVLBCL), primary mediastinal large B cell lymphoma (primary mediastinal LBCL), or high grade B-cell lymphoma NOS (HBGCL-NOS)), follicular lymphoma (FL), mantle cell lymphoma (MCL), or transformations of indolent B cell lymphomas, and the additional therapy or therapeutic agent is anti-CD20 therapy. In some embodiments, the cancer is a large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary large B cell lymphoma of immune-privileged sites (primary LBCL of immune-privileged sites), intravascular large B-cell lymphoma (IVLBCL), primary mediastinal large B cell lymphoma (primary mediastinal LBCL), or high grade B-cell lymphoma NOS (HBGCL-NOS)), and the additional therapy or therapeutic agent is anti-CD20 therapy. In some embodiments, the cancer is mantle cell lymphoma (MCL), and the additional therapy or therapeutic agent is anti-CD20 therapy. In some embodiments, the cancer is a transformation of an indolent B cell lymphoma, and the additional therapy or therapeutic agent is anti-CD20 therapy. In some embodiments, the anti-CD20 therapy is rituximab, obinutuzumab, or a combination thereof.

In some embodiments, the cancer is a FL, and the additional therapy or therapeutic agent is anti-CD20 therapy. In some embodiments, the anti-CD20 therapy is rituximab, obinutuzumab, or a combination thereof.

In some embodiments, the anti-CD22 therapy is bectumomab, epratuzumab, inotuzumab ozogamicin (e.g., BESPONSA® (inotuzumab ozogamicin), or a biosimilar thereof), moxetumomab pasudotox (e.g., LUMOXITI® (moxetumomab pasudotox), or a biosimilar thereof), pinatuzumab vedotin, suciraslimab, dDT-2219, biosimilars thereof, or a combination thereof. In some embodiments, the anti-CD22 therapy is an antibody-drug conjugate (e.g., inotuzumab ozogamicin (e.g., BESPONSA® (inotuzumab ozogamicin), or a biosimilar thereof), pinatuzumab vedotin, dDT-2219, biosimilars thereof, or a combination thereof. In some embodiments, the anti-CD22 therapy is an immunotoxin (e.g., moxetumomab

pasudotox (e.g., LUMOXITI® (moxetumomab pasudotox), or a biosimilar thereof)). In some embodiments, the anti-CD22 therapy is inotuzumab ozogamicin.

In some embodiments, the cancer is a B-ALL, and the additional therapy or therapeutic agent is anti-CD22 therapy. In some embodiments, the anti-CD22 therapy is an anti-CD22 antibody-drug conjugate (e.g., inotuzumab ozogamicin, or a biosimilar thereof).

In some embodiments, the anti-CD3 therapy is blinatumomab (e.g., BLINCYTO® (blinatumomab), or a biosimilar thereof), catumaxomab, elranatamab, epcoritamab, ertumaxomab, glofitamab (e.g., COLUMVI® (glofitamab), or a biosimilar thereof), linvoseltamab, mosunetuzumab (e.g., mosunetuzumab-axgb, or a biosimilar thereof), odronextamab, otelixizumab, plamotamab, talquetamab, tarlatamab, tebentafusp (e.g., tebentafusp-tebn, or a biosimilar thereof), teclistamab (e.g., teclistamab-cqyv, or a biosimilar thereof), teplizumab (e.g., teplizumab-mzwv, or a biosimilar thereof), visilizumab, biosimilars thereof, or a combination thereof. In some embodiments, the anti-CD3 therapy is bispecific antibody or antigen-binding fragment thereof (e.g., blinatumomab (e.g., BLINCYTO® (blinatumomab), or a biosimilar thereof), catumaxomab, elranatamab, epcoritamab (e.g., epcoritamab-bysp, or a biosimilar thereof), ertumaxomab, glofitamab (e.g., COLUMVI® (glofitamab), or a biosimilar thereof), linvoseltamab, mosunetuzumab (e.g., mosunetuzumab-axgb, or a biosimilar thereof), plamotamab, odronextamab, talquetamab, tarlatamab, tebentafusp (e.g., tebentafusp-tebn, or a biosimilar thereof), teclistamab (e.g., teclistamab-cqyv, or a biosimilar thereof), biosimilars thereof, or a combination thereof. In some embodiments, the anti-CD3 therapy is an anti-CD3 and anti-CD19 bispecific antibody or antigen-binding fragment thereof (e.g., BLINCYTO® (blinatumomab) or a biosimilar thereof). In some embodiments, the anti-CD3 therapy is an anti-CD20 and anti-CD3 bispecific antibody or antigen-binding fragment thereof (e.g., epcoritamab (e.g., epcoritamab-bysp, or a biosimilar thereof), glofitamab (e.g., COLUMVI® (glofitamab), or a biosimilar thereof), mosunetuzumab (e.g., mosunetuzumab-axgb, or a biosimilar thereof), plamotamab, odronextamab, biosimilars thereof, or a combination thereof.

In some embodiments, the anti-CD30 therapy is acimtamig, brentuximab, brentuximab vedotin (e.g., ADCETRIS®, or a biosimilar thereof), iratumumab, biosimilars thereof, or a combination thereof. In some embodiments, the anti-CD30 therapy is a bispecific antibody or antigen-binding fragment thereof (e.g., acimtamig), or a biosimilar thereof. In some embodiments, the anti-CD30 therapy is an antibody-drug conjugate (e.g., brentuximab vedotin (e.g., ADCETRIS®, or a biosimilar thereof), or a biosimilar thereof.

In some embodiments, the anti-CD79B therapy is polatuzumab (e.g., polatuzumab vedotin (e.g., polatuzumab vedotin-piiq, or a biosimilar thereof)), MGD-010, RG-7986, biosimilars thereof, or a combination thereof. In some embodiments, the anti-CD79B therapy is polatuzumab (e.g., polatuzumab vedotin (e.g., polatuzumab vedotin-piiq, or a biosimilar thereof)), MGD-010, biosimilars thereof, or a combination thereof. In some embodiments, the anti-CD79B therapy is a bispecific antibody or antigen-binding fragment thereof (e.g., MGD-010). In some embodiments, the anti-CD79B therapy is an antibody-drug conjugate (e.g., polatuzumab vedotin (e.g., polatuzumab vedotin-piiq, or a biosimilar thereof)).

In some embodiments, the anti-PD1 therapy is balstilimab, budigalimab, cadonilimab, camrelizumab, cemiplimab (e.g., cemiplimab-rwlc, or a biosimilar thereof), cetrelimab, dostarlimab (e.g., dostarlimab-gxly, or a biosimilar thereof), enlonstobart (SG-001), ezabenlimab, geptanolimab, ivonescimab, nivolumab (e.g., OPDIVO® (nivolumab), or a biosimilar thereof), nofazinlimab, pembrolizumab (e.g., KEYTRUDA® (pembrolizumab), or a biosimilar thereof), penpulimab, pidilizumab, pimivalimab, prolgolimab, pucotenlimab, retifanlimab (e.g., retifanlimab-dlwr, or a biosimilar thereof), rilvegostomig, rosnilimab, rulonilimab, sasanlimab, serplulimab, sintilimab (e.g., TYVYT® (sintilimab), or a biosimilar thereof), spartalizumab, tebotelimab, tislelizumab, toripalimab, volrustomig, vudalimab, zimberelimab, QL-1604, HX-009, INCB-086550, RG-6139, BAT-1306, BAT-1308, biosimilars thereof, or a combination thereof. In some embodiments, the anti-PD1 therapy is a bispecific antibody or antigen-binding fragment thereof (e.g., cadonilimab, ivonescimab, rilvegostomig, tebotelimab, volrustomig, vudalimab, AZD7709, HX-009, RG-6139, biosimilars thereof, or a combination thereof). In some embodiments, the anti-PD1 therapy is an anti-PD1 and anti-CD47 bispecific antibody or antigen-binding fragment thereof (e.g., HX-009, or a biosimilar thereof).

In some embodiments, the anti-PD-L1 therapy is adebrelimab, atezolizumab (e.g., TECENTRIQ® (atezolizumab), or a biosimilar thereof), avelumab (e.g., BAVENCIO® (avelumab), or a biosimilar thereof), benmelstobart (APL-502), bintrafusp alfa, cosibelimab, danburstotug, durvalumab (e.g., IMFINZI® (durvalumab), or a biosimilar thereof), envafolimab (e.g., ENWEIDA® (envafolimab), or a biosimilar thereof), erfonrilimab, lesabelimab, pacmilimab, socazolimab, sugemalimab (e.g., CEJEMLY® (sugemalimab), or a biosimilar thereof), tagitanlimab (A-167), AUPM-170, BNT-311, SHR-1701, biosimilars thereof, or a combination thereof. In some embodiments, the anti-PD-L1 therapy is a bispecific antibody or antigen-binding fragment thereof (e.g., erfonrilimab, BNT-311, biosimilars thereof, or a combination thereof).

In some embodiments, the PD-L1 inhibitor is INCB-086550 or INCB-099280.

In some embodiments, the anti-CD47 therapy is lemzoparlimab, letaplimab, magrolimab, 6MW-3211, AO-176, CPO-107, HX-009, TTI-621, TTI-622, biosimilars thereof, or a combination thereof. In some embodiments, the anti-CD47 therapy is lemzoparlimab, ligufalimab, magrolimab, HX-009, PF-07901801 (TTI-622), TTI-621, biosimilars thereof, or a combination thereof. In some embodiments, the anti- anti-CD47 therapy is a bispecific antibody or antigen-binding fragment thereof (e.g., HX-009). In some embodiments, the anti-CD47 therapy is an anti-CD47 and anti-PD1 bispecific antibody or antigen-binding fragment thereof (e.g., HX-009, or a biosimilar thereof).

In some embodiments, the cell-based therapy is adoptive cell therapy (e.g., CAR T therapy, cytokine-induced killer cells (CIKs), natural killer cells (e.g., CAR-modified NK cells)) or antibody-armed cell therapy. In some embodiments, the cell-based therapy is actalycabtagene autoleucel, axicabtagene ciloleucel (e.g., YESCARTA® (axicabtagene ciloleucel), or a biosimilar thereof), brexucabtagene autoleucel (e.g., TECARTUS® (brexucabtagene autoleucel), or a biosimilar thereof), cemacabtagene ansegedleucel, inaticabtagene autoleucel, lisocabtagene maraleucel (e.g., BREYANZI® (lisocabtagene maraleucel), or a biosimilar thereof), obecabtagene autoleucel, rapcabtagene autoleucel, relmacabtagene autoleucel (e.g., CARTEYVA® (relmacabtagene autoleucel), or a biosimilar thereof), tisagenlecleucel (e.g., KYMRIAH® (tisagenlecleucel), or a biosimilar thereof), varnimcabtagene autoleucel (e.g., IMN-003A, or a biosimilar thereof), zamtocabtagene autoleucel, BZ-019, CD19CAR CTL, CTL-119, TAK-007, XLCART-001, biosimilars thereof, or a combination thereof. In some embodiments, the cell-based therapy is a CD19 targeted cell-based therapy (e.g., actalycabtagene autoleucel, axicabtagene ciloleucel (e.g., YESCARTA® (axicabtagene ciloleucel), or a biosimilar thereof), brexucabtagene autoleucel (e.g., TECARTUS® (brexucabtagene autoleucel), or a biosimilar thereof), cemacabtagene ansegedleucel, inaticabtagene autoleucel, lisocabtagene maraleucel (e.g., BREYANZI® (lisocabtagene maraleucel), or a biosimilar thereof), obecabtagene autoleucel, rapcabtagene autoleucel, relmacabtagene autoleucel (e.g., CARTEYVA® (relmacabtagene autoleucel), or a biosimilar thereof), tisagenlecleucel (e.g., KYMRIAH® (tisagenlecleucel), or a biosimilar thereof), varnimcabtagene autoleucel (e.g., IMN-003A, or a biosimilar thereof), zamtocabtagene autoleucel, BZ-019, CD19CAR CTL, CTL-119, TAK-007, XLCART-001, biosimilars thereof, or a combination thereof.) In some embodiments, the cell-based therapy is a CD20 targeted cell-based therapy (e.g., zamtocabtagene autoleucel).

In some embodiments, the additional therapy or therapeutic agent is chemotherapy. In some embodiments, the chemotherapy is CVAD, hyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone), CHOP, R-CHOP, G-CHOP, EPOCH, R-EPOCH, Pola-R-CHP (polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone), R-CODOX-M, R-IVAC, DA-EPOCH-R, CVP, R-CVP, G-CVP, CVD (cyclophosphamide, vincristine, dacarbazine, including mini-CVD), cyclophosphamide, bendamustine with rituximab or obinutuzumab, methotrexate-cytarabine, vincristine (with or without steroids (e.g., dexamethasone)), nelarabine, a hypomethylating agent (e.g., azacitidine and/or decitabine), CALGB8811, or pediatric-inspired multi-agent chemotherapy (e.g., GRAALL-2003, COG AALL-0434, CCG-1961, CALGB 10403, or the DFCI regimen). In some embodiments, the chemotherapy is cyclophosphamide.

In some embodiments, the cancer is a large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary large B cell lymphoma of immune-privileged sites (primary LBCL of immune-privileged sites), intravascular large B-cell lymphoma (IVLBCL), primary mediastinal large B cell lymphoma (primary mediastinal LBCL), or high grade B-cell lymphoma NOS (HBGCL-NOS)), follicular lymphoma (FL), mantle cell lymphoma (MCL), or a transformation of an indolent B cell lymphoma, and the additional therapy or therapeutic agent is chemotherapy. In some embodiments, the cancer is a large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary large B cell lymphoma of immune-privileged sites (primary LBCL of immune-privileged sites), intravascular large B-cell lymphoma (IVLBCL), primary mediastinal large B cell lymphoma (primary mediastinal LBCL), or high grade B-cell lymphoma NOS (HBGCL-NOS)), and the additional therapy or therapeutic agent is chemotherapy. In some embodiments, the cancer is a DLBCL-NOS, and the additional therapy or therapeutic agent is chemotherapy. In some embodiments, the cancer is a diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), and the additional therapy or therapeutic agent is chemotherapy. In some embodiments, the cancer is a HBGCL-NOS, and the additional therapy or therapeutic agent is chemotherapy. In some embodiments, the cancer is a primary mediastinal large B cell lymphoma, and the additional therapy or therapeutic agent is chemotherapy. In some embodiments, the cancer is a primary large B cell lymphoma of

immune-privileged sites (primary LBCL of immune-privileged sites), and the additional therapy or therapeutic agent is chemotherapy. In some embodiments, the cancer is a follicular lymphoma (FL), and the additional therapy or therapeutic agent is chemotherapy. In some embodiments, the cancer is a mantle cell lymphoma (MCL), and the additional therapy or therapeutic agent is chemotherapy. In some embodiments, the cancer is a transformation of an indolent B cell lymphoma, and the additional therapy or therapeutic agent is chemotherapy.

In some embodiments, the cancer is a BL, and the additional therapy or therapeutic agent is chemotherapy.

In some embodiments, the cancer is a NLPHL, and the additional therapy or therapeutic agent is chemotherapy.

In some embodiments, the cancer is a B-ALL (e.g., Philadelphia chromosome positive B-ALL, Philadelphia chromosome negative B-ALL, or B-ALL with an *MLL* rearrangement (e.g., an MLL-Af4 fusion, an MLL-Af6 fusion, an MLL-Af9 fusion, an MLL-ENL fusion, or an MLL-PTD fusion)), and the additional therapy or therapeutic agent is an inhibitor of the PRC2. In some embodiments, the cancer is a FL, and the additional therapy or therapeutic agent is chemotherapy. In some embodiments, the cancer is an MCL, and the additional therapy or therapeutic agent is chemotherapy.

In some embodiments, the cancer is peripheral T-cell lymphoma (PTCL) (e.g., anaplastic large cell lymphoma (ALCL) (e.g., ALK-positive anaplastic large cell lymphoma, or ALK-negative anaplastic large cell lymphoma), nodal T follicular helper cell lymphoma (e.g., nodal T follicular helper cell lymphoma angioimmunoblastic type (also known as angioimmunoblastic T-cell lymphoma (AITL) or follicular helper T-cell lymphoma, angioimmunoblastic type), nodal T follicular helper cell lymphoma follicular type (also known as follicular helper T-cell lymphoma, follicular type), or nodal T follicular helper cell lymphoma NOS (also known as follicular helper T-cell lymphoma, NOS))), or a primary cutaneous T-cell lymphoid proliferation or lymphoma (cutaneous T-cell lymphoma (CTCL)) (e.g., primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder, mycosis fungoides, Sezary syndrome, or primary cutaneous gamma-delta T-cell lymphoma), and the additional therapy or therapeutic agent is chemotherapy. In some embodiments, the cancer is peripheral T-cell lymphoma (PTCL) (e.g., anaplastic large cell lymphoma (ALCL) (e.g., ALK-positive anaplastic large cell lymphoma, or ALK-negative anaplastic large cell lymphoma), nodal T follicular helper cell lymphoma (e.g., nodal T follicular helper cell lymphoma angioimmunoblastic type (also known as angioimmunoblastic T-cell lymphoma (AITL) or follicular helper T-cell lymphoma, angioimmunoblastic type), nodal T follicular

helper cell lymphoma follicular type (also known as follicular helper T-cell lymphoma, follicular type), or nodal T follicular helper cell lymphoma NOS (also known as follicular helper T-cell lymphoma, NOS))), and the additional therapy or therapeutic agent is chemotherapy. In some embodiments, the cancer is anaplastic large cell lymphoma (ALCL) (e.g., ALK-positive anaplastic large cell lymphoma, or ALK-negative anaplastic large cell lymphoma), and the additional therapy or therapeutic agent is chemotherapy. In some embodiments, the cancer is ALK-positive anaplastic large cell lymphoma, and the additional therapy or therapeutic agent is chemotherapy. In some embodiments, the cancer is ALK-negative anaplastic large cell lymphoma, and the additional therapy or therapeutic agent is chemotherapy. In some embodiments, the cancer is nodal T follicular helper cell lymphoma (e.g., nodal T follicular helper cell lymphoma angioimmunoblastic type (also known as angioimmunoblastic T-cell lymphoma (AITL) or follicular helper T-cell lymphoma, angioimmunoblastic type), nodal T follicular helper cell lymphoma follicular type (also known as follicular helper T-cell lymphoma, follicular type), or nodal T follicular helper cell lymphoma NOS (also known as follicular helper T-cell lymphoma, NOS)), and the additional therapy or therapeutic agent is chemotherapy. In some embodiments, the cancer is nodal T follicular helper cell lymphoma angioimmunoblastic type (also known as angioimmunoblastic T-cell lymphoma (AITL) or follicular helper T-cell lymphoma, angioimmunoblastic type), and the additional therapy or therapeutic agent is chemotherapy. In some embodiments, the cancer is nodal T follicular helper cell lymphoma follicular type (also known as follicular helper T-cell lymphoma, follicular type), and the additional therapy or therapeutic agent is chemotherapy. In some embodiments, the cancer is nodal T follicular helper cell lymphoma NOS (also known as follicular helper T-cell lymphoma, NOS), and the additional therapy or therapeutic agent is chemotherapy. In some embodiments, the cancer is a primary cutaneous T-cell lymphoid proliferation or lymphoma (cutaneous T-cell lymphoma (CTCL)) (e.g., primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder, mycosis fungoides, Sezary syndrome, or primary cutaneous gamma-delta T-cell lymphoma), and the additional therapy or therapeutic agent is chemotherapy. In some embodiments, the cancer is mycosis fungoides, and the additional therapy or therapeutic agent is chemotherapy. In some embodiments, the cancer is Sezary Syndrome, and the additional therapy or therapeutic agent is chemotherapy.

In some embodiments, the cancer is a B-ALL, and the additional therapy or therapeutic agent is chemotherapy (e.g., CVAD). In some embodiments, the cancer is an *MLL*-rearranged (e.g., an MLL-Af4 fusion, an MLL-Af6 fusion, an MLL-Af9 fusion, an MLL-ENL fusion, or

an MLL-PTD fusion) B-ALL, and the additional therapy or therapeutic agent is chemotherapy (e.g., CVAD). In some embodiments, the cancer is a Philadelphia chromosome positive B-ALL, and the additional therapy or therapeutic agent is chemotherapy (e.g., CVAD). In some embodiments, the cancer is a Philadelphia chromosome-like B-ALL, and the additional therapy or therapeutic agent is chemotherapy (e.g., CVAD). In some embodiments, the cancer is a pre-BCR+ B-ALL, and the additional therapy or therapeutic agent is chemotherapy (e.g., CVAD). In some embodiments, the cancer is a B-ALL dependent on Ras signaling, and the additional therapy or therapeutic agent is a chemotherapy (e.g., CVAD).

In some embodiments, the cancer is a FL, and the additional therapy or therapeutic agent is R-CHOP. In some such embodiments, the combination of R-CHOP and a compound provided herein, or a pharmaceutically acceptable salt thereof, is used as treatment for a primary tumor. In some such embodiments, the combination of R-CHOP and a compound provided herein, or a pharmaceutically acceptable salt thereof, is used as maintenance therapy.

In some embodiments, the cancer is a large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary large B cell lymphoma of immune-privileged sites (primary LBCL of immune-privileged sites), intravascular large B-cell lymphoma (IVLBCL), primary mediastinal large B cell lymphoma (primary mediastinal LBCL), or high grade B-cell lymphoma NOS (HBGCL-NOS)), follicular lymphoma (FL), mantle cell lymphoma (MCL), and transformations of indolent B cell lymphomas, and the additional therapy or therapeutic agent is R-CHOP. In some embodiments, the cancer is a large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary large B cell lymphoma of immune-privileged sites (primary LBCL of immune-privileged sites), intravascular large B-cell lymphoma (IVLBCL), primary mediastinal large B cell lymphoma (primary mediastinal LBCL), or high grade B-cell lymphoma NOS (HBGCL-NOS)), and the additional therapy or therapeutic agent is R-CHOP. In some such embodiments, the combination of R-CHOP and a compound provided herein, or a pharmaceutically acceptable salt thereof, is used as treatment for a primary tumor. In some such embodiments, the combination of R-CHOP and a compound provided herein, or a pharmaceutically acceptable salt thereof, is used as maintenance therapy.

In some embodiments, the cancer is a large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade

B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary large B cell lymphoma of immune-privileged sites (primary LBCL of immune-privileged sites), intravascular large B-cell lymphoma (IVLBCL), primary mediastinal large B cell lymphoma (primary mediastinal LBCL), or high grade B-cell lymphoma NOS (HBGCL-NOS)), follicular lymphoma (FL), mantle cell lymphoma (MCL), and transformations of indolent B cell lymphomas, and the additional therapy or therapeutic agent is R-EPOCH. In some embodiments, the cancer is a large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary large B cell lymphoma of immune-privileged sites (primary LBCL of immune-privileged sites), intravascular large B-cell lymphoma (IVLBCL), primary mediastinal large B cell lymphoma (primary mediastinal LBCL), or high grade B-cell lymphoma NOS (HBGCL-NOS)), and the additional therapy or therapeutic agent is R-EPOCH.In some such embodiments, the combination of R-EPOCH and a compound provided herein, or a pharmaceutically acceptable salt thereof, is used as treatment for a primary tumor. In some such embodiments, the combination of R-EPOCH and a compound provided herein, or a pharmaceutically acceptable salt thereof, is used as maintenance therapy.

In some embodiments, the cancer is a large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary large B cell lymphoma of immune-privileged sites (primary LBCL of immune-privileged sites), intravascular large B-cell lymphoma (IVLBCL), primary mediastinal large B cell lymphoma (primary mediastinal LBCL), or high grade B-cell lymphoma NOS (HBGCL-NOS)), follicular lymphoma (FL), mantle cell lymphoma (MCL), and transformations of indolent B cell lymphomas, and the additional therapy or therapeutic agent is Pola-R-CHP. In some embodiments, the cancer is a large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary large B cell lymphoma of immune-privileged sites (primary LBCL of immune-privileged sites), intravascular large B-cell lymphoma (IVLBCL), primary mediastinal large B cell lymphoma (primary mediastinal LBCL), or high grade B-cell lymphoma NOS (HBGCL-NOS)), and the additional therapy or therapeutic agent is Pola-R-CHP. In some such embodiments, the combination of Pola-R-CHP

and a compound provided herein, or a pharmaceutically acceptable salt thereof, is used as treatment for a primary tumor. In some such embodiments, the combination of Pola-R-CHP and a compound provided herein, or a pharmaceutically acceptable salt thereof, is used as maintenance therapy.

In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof is used in combination with one or more steps of induction, consolidation, intensification, or maintenance in a chemotherapeutic regimen.

Also provided herein is a method of treating cancer, comprising administering to a subject in need thereof (a) a compound provided herein, or a pharmaceutically acceptable salt thereof, and (b) an additional therapeutic agent, for simultaneous, separate or sequential use for the treatment of cancer, wherein the amounts of the compound provided herein, or a pharmaceutically acceptable salt thereof, and the additional therapeutic agent are together effective in treating the cancer. In some embodiments, the method comprises administering (c) at least one pharmaceutically acceptable carrier.

In some such embodiments, the additional therapeutic agent is an inhibitor of the PRC2 (e.g., an EZH1/2 inhibitor or an EZH2 inhibitor (e.g., any of the EZH1/2 inhibitors or EZH2 inhibitors described herein)), and the cancer is a cancer having an EZH2 alteration. In an aspect of this embodiment, the EZH2 alteration is a mutation is at residue 27, residue 34, residue 59, residue 141, residue 162, residue 172, residue 197, residue 238, residue 239, residue 246, residue 395, residue 401, residue 452, residue 510, residue 516, residue 556, residue 583, residue 618, residue 644, residue 646, residue 682, residue 690, residue 692, residue 716, residue 732, residue 744, residue 745, or a combination thereof, relative to SEQ ID NO. 1. In another aspect of this embodiment, the EZH2 alteration is a translocation. In another aspect of this embodiment, the EZH2 mutation is R27*, R34*, E59*, Q141*, E162*, V172Cfs*11, E197Rfs*12, E238*, E239*, E246*, G395Efs*29, E401Kfs*22, E401*, Y452*, K510Yfs*3, X516_splice, S556*, R583*, X618_splice, S644*, Y646F, Y646N, Y646S, R690G, R690H, A692V, F716Lfs*24, X732_splice, I744Mfs*25, E745Afs*24, EZH2-AUTS2, EZH2-TMEM176B, GALNT11-EZH2, or a combination thereof. In another aspect of this embodiment, the EZH2 mutation is at residue 646, residue 682, or residue 692 relative to SEQ ID NO. 1. In another aspect of this embodiment, the EZH2 mutation is Y646F, Y646N, A682G, or A692V relative to SEQ ID NO: 1. In another aspect of this embodiment, the cancer is a large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary large B cell lymphoma

of immune-privileged sites (primary LBCL of immune-privileged sites), intravascular large B-cell lymphoma (IVLBCL), primary mediastinal large B cell lymphoma (primary mediastinal LBCL), or high grade B-cell lymphoma NOS (HBGCL-NOS)), follicular lymphoma (FL), mantle cell lymphoma (MCL), or transformations of indolent B cell lymphomas, and the EZH2 mutation is Y646F, Y646N, A682G, or A692V relative to SEQ ID NO: 1. In another aspect of this embodiment, the cancer is a large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary large B cell lymphoma of immune-privileged sites (primary LBCL of immune-privileged sites), intravascular large B-cell lymphoma (IVLBCL), primary mediastinal large B cell lymphoma (primary mediastinal LBCL), or high grade B-cell lymphoma NOS (HBGCL-NOS)), and the EZH2 mutation is Y646F, Y646N, A682G, or A692V relative to SEQ ID NO: 1.

These additional therapeutic agents can be administered with one or more doses of the compound provided herein, or a pharmaceutically acceptable salt thereof, or pharmaceutical composition comprising a compound provided herein, or a pharmaceutically acceptable salt thereof, as part of the same or separate dosage forms, via the same or different routes of administration, and/or on the same or different administration schedules according to standard pharmaceutical practice known to one skilled in the art. In some embodiments, the compound provided herein, or a pharmaceutically acceptable salt thereof, and the additional therapeutic agent are administered simultaneously as separate dosages. In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, and the additional therapeutic agent are administered as separate dosages simultaneously, separately, or sequentially in any order, in jointly therapeutically effective amounts, e.g., in daily or intermittent dosages. In some embodiments, the compound provided herein, or a pharmaceutically acceptable salt thereof, and the additional therapeutic agent are administered simultaneously as a combined dosage. When administered simultaneously, the two agents can be administered as a single dosage form (e.g., a fixed dosage form) or as separate dosages (e.g., non-fixed dosage forms).

As used herein, the terms “treat” or “treatment” refer to therapeutic or palliative measures. Beneficial or desired clinical results include, but are not limited to, alleviation, in whole or in part, of symptoms associated with a disease or disorder or condition, diminishment of the extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state (e.g., one or more symptoms of the disease), and remission (whether partial or total), whether detectable or undetectable.

"Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment.

As used herein, the terms "prevent" or "prevention" refer to prophylactic measures. Beneficial or desired clinical results include, but are not limited to, the delay, arrest, or preclusion of the onset, recurrence or spread, in whole or in part, of a disease or condition, or a symptom thereof, such as any of those provided herein.

As used herein, the terms "subject," "individual," or "patient," are used interchangeably, and refer to any animal, including mammals such as mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, primates, and humans. In some embodiments, the subject is a human. In some embodiments, the subject has experienced and/or exhibited at least one symptom of the disease, disorder, or condition to be treated and/or prevented.

In some embodiments, the subject is a pediatric subject.

The term "pediatric subject" as used herein refers to a subject under the age of 21 years at the time of diagnosis or treatment. The term "pediatric" can be further be divided into various subpopulations including: neonates (from birth through the first month of life); infants (1 month up to two years of age); children (two years of age up to 12 years of age); and adolescents (12 years of age through 21 years of age (up to, but not including, the twenty-second birthday)). Berhman RE, Kliegman R, Arvin AM, Nelson WE. Nelson *Textbook of Pediatrics*, 15th Ed. Philadelphia: W.B. Saunders Company, 1996; Rudolph AM, et al. *Rudolph's Pediatrics*, 21st Ed. New York: McGraw-Hill, 2002; and Avery MD, First LR. *Pediatric Medicine*, 2nd Ed. Baltimore: Williams & Wilkins; 1994. In some embodiments, a pediatric subject is from birth through the first 28 days of life, from 29 days of age to less than two years of age, from two years of age to less than 12 years of age, or 12 years of age through 21 years of age (up to, but not including, the twenty-second birthday). In some embodiments, a pediatric subject is from birth through the first 28 days of life, from 29 days of age to less than 1 year of age, from one month of age to less than four months of age, from three months of age to less than seven months of age, from six months of age to less than 1 year of age, from 1 year of age to less than 2 years of age, from 2 years of age to less than 3 years of age, from 2 years of age to less than seven years of age, from 3 years of age to less than 5 years of age, from 5 years of age to less than 10 years of age, from 6 years of age to less than 13 years of age, from 10 years of age to less than 15 years of age, or from 15 years of age to less than 22 years of age.

The term "regulatory agency" refers to a country's agency for the approval of the medical use of pharmaceutical agents with the country. For example, a non-limiting example of a regulatory agency is the U.S. Food and Drug Administration (FDA).

The phrase "therapeutically effective amount" means an amount of compound that, when administered to a subject in need thereof, is sufficient to (i) treat a disease, disorder, or condition, (ii) attenuate, ameliorate, or eliminate one or more symptoms of the particular disease, disorder, or condition, or (iii) delay the onset of one or more symptoms of the particular disease, disorder, or condition described herein. The amount of a compound provided herein, or a pharmaceutically acceptable salt thereof, that will correspond to such an amount will vary depending upon factors such as the particular compound, disease condition and its severity, the identity (e.g., weight) of the subject in need of treatment, but can nevertheless be routinely determined by one skilled in the art.

As used herein, an "effective amount" refers to an amount of the compound sufficient to effect a beneficial or desired result. For example, an "effective amount" as used herein can refer to an amount of the compound sufficient to modulate (e.g., increase or decrease) (1) activity or amount of a protein; (2) proliferation of a cell (e.g., a cancer cell); and/or (3) one or more cellular signaling pathways associated with a protein's activity.

Pharmaceutical Compositions and Administration

General

In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, is administered as a pharmaceutical composition that includes the compound, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients, and optionally one or more additional therapeutic agents as described herein.

In some embodiments, the compounds can be administered in combination with one or more conventional pharmaceutical excipients. Pharmaceutically acceptable excipients include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems (SEDDS) such as d-α-tocopherol polyethylene glycol 1000 succinate, surfactants used in pharmaceutical dosage forms such as Tweens, poloxamers or other similar polymeric delivery matrices, serum proteins, such as human serum albumin, buffer substances such as phosphates, tris, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium-chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethyl cellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, and wool fat. Cyclodextrins such as α-, β-, and γ-cyclodextrin, or chemically modified derivatives such as hydroxyalkylcyclodextrins, including

2- and 3-hydroxypropyl-β-cyclodextrins, or other solubilized derivatives can also be used to enhance delivery of compounds described herein. Dosage forms or compositions containing a compound as described herein in the range of 0.005% to 100% with the balance made up from non-toxic excipient can be prepared. The contemplated compositions can contain 0.001%-100% of a compound provided herein, in one embodiment 0.1-95%, in another embodiment 75-85%, in a further embodiment 20-80%. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see *Remington: The Science and Practice of Pharmacy*, 22nd Edition (Pharmaceutical Press, London, UK. 2012).

Routes of Administration and Composition Components

In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition thereof, can be administered to a subject in need thereof by any accepted route of administration. Acceptable routes of administration include, but are not limited to, buccal, cutaneous, endocervical, endosinusial, endotracheal, enteral, epidural, interstitial, intra-abdominal, intra-arterial, intrabronchial, intrabursal, intracerebral, intracisternal, intracoronary, intradermal, intraductal, intraduodenal, intradural, intraepidermal, intraesophageal, intragastric, intragingival, intraileal, intralymphatic, intramedullary, intrameningeal, intramuscular, intraovarian, intraperitoneal, intraprostatic, intrapulmonary, intrasinal, intraspinal, intrasynovial, intratesticular, intrathecal, intratubular, intratumoral, intrauterine, intravascular, intravenous, nasal, nasogastric, oral, parenteral, percutaneous, peridural, rectal, respiratory (inhalation), subcutaneous, sublingual, submucosal, topical, transdermal, transmucosal, transtracheal, ureteral, urethral and vaginal. In certain embodiments, a preferred route of administration is parenteral (e.g., intratumoral).

In some embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition thereof, can be administered orally to a subject in need thereof. Without being bound by any particular theory, it is believed that oral dosing (e.g., versus IV dosing) can be preferred by subjects for convenience, perception of efficacy, and/or past experience.

Compositions can be formulated for parenteral administration, e.g., formulated for injection via the intravenous, intramuscular, sub-cutaneous, or even intraperitoneal routes. Typically, such compositions can be prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for use to prepare solutions or suspensions upon the addition of a liquid prior to injection can also be prepared; and the preparations can also be emulsified.

The preparation of such formulations will be known to those of skill in the art in light of the present disclosure.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions; formulations including sesame oil, peanut oil, or aqueous propylene glycol; and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that it can be easily injected. It also should be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi.

The carrier also can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion, and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques, which yield a powder of the active ingredient, plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Intratumoral injections are discussed, e.g., in Lammers, et al., *"Effect of Intratumoral Injection on the Biodistribution and the Therapeutic Potential of HPMA Copolymer-Based Drug Delivery Systems" Neoplasia*. **2006,** *10*, 788–795.

Pharmacologically acceptable excipients usable in the rectal composition as a gel, cream, enema, or rectal suppository, include, without limitation, any one or more of cocoa butter glycerides, synthetic polymers such as polyvinylpyrrolidone, PEG (like PEG ointments),

glycerine, glycerinated gelatin, hydrogenated vegetable oils, poloxamers, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol Vaseline, anhydrous lanolin, shark liver oil, sodium saccharinate, menthol, sweet almond oil, sorbitol, sodium benzoate, anoxid SBN, vanilla essential oil, aerosol, parabens in phenoxyethanol, sodium methyl p-oxybenzoate, sodium propyl p-oxybenzoate, diethylamine, carbomers, carbopol, methyloxybenzoate, macrogol cetostearyl ether, cocoyl caprylocaprate, isopropyl alcohol, propylene glycol, liquid paraffin, xanthan gum, carboxy-metabisulfite, sodium edetate, sodium benzoate, potassium metabisulfite, grapefruit seed extract, methyl sulfonyl methane (MSM), lactic acid, glycine, vitamins, such as vitamin A and E and potassium acetate.

In certain embodiments, suppositories can be prepared by mixing the compound described herein with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum and release the active compound. In other embodiments, compositions for rectal administration are in the form of an enema.

In other embodiments, the compounds described herein, or a pharmaceutical composition thereof, are suitable for local delivery to the digestive or GI tract by way of oral administration (e.g., solid or liquid dosage forms.).

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the compound is mixed with one or more pharmaceutically acceptable excipients, such as sodium citrate or dicalcium phosphate and/or: a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form can also comprise buffering agents. Solid compositions of a similar type can also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

In one embodiment, the compositions will take the form of a unit dosage form such as a pill or tablet and thus the composition can contain, along with a compound, or pharmaceutically acceptable salt thereof, as provided herein, a diluent such as lactose, sucrose, dicalcium phosphate, or the like; a lubricant such as magnesium stearate or the like; and a binder such as starch, gum acacia, polyvinylpyrrolidine, gelatin, cellulose, cellulose derivatives, or the like. In another solid dosage form, a powder, marume, solution or suspension (e.g., in propylene carbonate, vegetable oils, PEGs, poloxamer 124 or triglycerides) is encapsulated in a capsule (gelatin or cellulose base capsule). Unit dosage forms in which one or more compounds provided herein or additional active agents are physically separated are also contemplated; e.g., capsules with granules (or tablets in a capsule) of each drug; two-layer tablets; two-compartment gel caps, etc. Enteric coated or delayed release oral dosage forms are also contemplated.

Other physiologically acceptable compounds include wetting agents, emulsifying agents, dispersing agents or preservatives that are particularly useful for preventing the growth or action of microorganisms. Various preservatives are well known and include, for example, phenol and ascorbic acid.

In certain embodiments the excipients are sterile and generally free of undesirable matter. These compositions can be sterilized by conventional, well-known sterilization techniques. For various oral dosage form excipients such as tablets and capsules sterility is not required. The USP/NF standard is usually sufficient.

In certain embodiments, solid oral dosage forms can include one or more components that chemically and/or structurally predispose the composition for delivery of the compounds to the stomach or the lower GI; e.g., the ascending colon and/or transverse colon and/or distal colon and/or small bowel. Exemplary formulation techniques are described in, e.g., Filipski, K.J., et al., *Current Topics in Medicinal Chemistry*, **2013**, *13*, 776-802.

Examples include upper-GI targeting techniques, e.g., Accordion Pill (Intec Pharma), floating capsules, and materials capable of adhering to mucosal walls.

Other examples include lower-GI targeting techniques. For targeting various regions in the intestinal tract, several enteric/pH-responsive coatings and excipients are available. These materials are typically polymers that are designed to dissolve or erode at specific pH ranges, selected based upon the GI region of desired drug release. These materials also function to protect acid labile drugs from gastric fluid or limit exposure in cases where the active ingredient can be irritating to the upper GI (e.g., hydroxypropyl methylcellulose phthalate series, Coateric (polyvinyl acetate phthalate), cellulose acetate phthalate, hydroxypropyl methylcellulose

acetate succinate, Eudragit series (methacrylic acid–methyl methacrylate copolymers), and Marcoat). Other techniques include dosage forms that respond to local flora in the GI tract, Pressure-controlled colon delivery capsule, and Pulsincap.

Ocular compositions can include, without limitation, one or more of any of the following: viscogens (e.g., Carboxymethylcellulose, Glycerin, Polyvinylpyrrolidone, Polyethylene glycol); Stabilizers (e.g., Pluronic (triblock copolymers), Cyclodextrins); Preservatives (e.g., Benzalkonium chloride, ETDA, SofZia (boric acid, propylene glycol, sorbitol, and zinc chloride; Alcon Laboratories, Inc.), Purite (stabilized oxychloro complex; Allergan, Inc.)).

Topical compositions can include ointments and creams. Ointments are semisolid preparations that are typically based on petrolatum or other petroleum derivatives. Creams containing the selected active agent are typically viscous liquid or semisolid emulsions, often either oil-in-water or water-in-oil. Cream bases are typically water-washable, and contain an oil phase, an emulsifier, and an aqueous phase. The oil phase, also sometimes called the "internal" phase, is generally comprised of petrolatum and a fatty alcohol such as cetyl or stearyl alcohol; the aqueous phase usually, although not necessarily, exceeds the oil phase in volume, and generally contains a humectant. The emulsifier in a cream formulation is generally a nonionic, anionic, cationic, or amphoteric surfactant. As with other carriers or vehicles, an ointment base should be inert, stable, nonirritating, and non-sensitizing.

In any of the foregoing embodiments, pharmaceutical compositions described herein can include one or more one or more of the following: lipids, interbilayer crosslinked multilamellar vesicles, biodegradable poly(D,L-lactic-co-glycolic acid) [PLGA]-based or poly anhydride-based nanoparticles or microparticles, and nanoporous particle-supported lipid bilayers.

Dosages

The dosages can be varied depending on the requirement of the subject, the severity of the condition being treated, and the particular compound being employed. Determination of the proper dosage for a particular situation can be determined by one skilled in the medical arts. The total daily dosage can be divided and administered in portions throughout the day or by means providing continuous delivery.

In some embodiments, the compounds described herein are administered at a dosage of from about 0.001 mg/kg to about 500 mg/kg (e.g., from about 0.001 mg/kg to about 200 mg/kg; from about 0.01 mg/kg to about 200 mg/kg; from about 0.01 mg/kg to about 150 mg/kg; from

about 0.01 mg/kg to about 100 mg/kg; from about 0.01 mg/kg to about 50 mg/kg; from about 0.01 mg/kg to about 10 mg/kg; from about 0.01 mg/kg to about 5 mg/kg; from about 0.01 mg/kg to about 1 mg/kg; from about 0.01 mg/kg to about 0.5 mg/kg; from about 0.01 mg/kg to about 0.1 mg/kg; from about 0.1 mg/kg to about 200 mg/kg; from about 0.1 mg/kg to about 150 mg/kg; from about 0.1 mg/kg to about 100 mg/kg; from about 0.1 mg/kg to about 50 mg/kg; from about 0.1 mg/kg to about 10 mg/kg; from about 0.1 mg/kg to about 5 mg/kg; from about 0.1 mg/kg to about 1 mg/kg; from about 0.1 mg/kg to about 0.5 mg/kg).

Regimens

The foregoing dosages can be administered on a daily basis (e.g., as a single dose or as two or more divided doses) or non-daily basis (e.g., every other day, every two days, every three days, once weekly, twice weeks, once every two weeks, once a month).

In some embodiments, the period of administration of a compound described herein is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, or more. In a further embodiment, a period of during which administration is stopped is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, or more. In an embodiment, a therapeutic compound is administered to an individual for a period of time followed by a separate period of time. In another embodiment, a therapeutic compound is administered for a first period and a second period following the first period, with administration stopped during the second period, followed by a third period where administration of the therapeutic compound is started and then a fourth period following the third period where administration is stopped. In an aspect of this embodiment, the period of administration of a therapeutic compound followed by a period where administration is stopped is repeated for a determined or undetermined period of time. In a further embodiment, a period of administration is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, or more. In a further embodiment, a period of during which administration is stopped is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9

days, 10 days, 11 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, or more.

The term "acceptable" with respect to a formulation, composition, or ingredient, as used herein, means having no persistent detrimental effect on the general health of the subject being treated.

"API" refers to an active pharmaceutical ingredient.

The term "excipient" or "pharmaceutically acceptable excipient" means a pharmaceutically acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, carrier, solvent, or encapsulating material. In one embodiment, each component is "pharmaceutically acceptable" in the sense of being compatible with the other ingredients of a pharmaceutical formulation, and suitable for use in contact with the tissue or organ of humans and animals without excessive toxicity, irritation, allergic response, immunogenicity, or other problems or complications, commensurate with a reasonable benefit/risk ratio. *See, e.g., Remington: The Science and Practice of Pharmacy, 21st ed.*; Lippincott Williams & Wilkins: Philadelphia, PA, 2005; *Handbook of Pharmaceutical Excipients, 6th ed.*; Rowe *et al.*, Eds.; The Pharmaceutical Press and the American Pharmaceutical Association: 2009; *Handbook of Pharmaceutical Additives, 3rd ed.*; Ash and Ash Eds.; Gower Publishing Company: 2007; *Pharmaceutical Preformulation and Formulation, 2nd ed.*; Gibson Ed.; CRC Press LLC: Boca Raton, FL, 2009.

The term "pharmaceutically acceptable salt" refers to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In certain instances, pharmaceutically acceptable salts are obtained by reacting a compound described herein, with acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. In some instances, pharmaceutically acceptable salts are obtained by reacting a compound having acidic group described herein with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, *N*-methyl-D-glucamine, tris(hydroxymethyl)methylamine, and salts with amino acids such as arginine, lysine, and the like, or by other methods previously determined. The term "pharmacologically acceptable salts" is not specifically limited as far as it can be used in medicaments. Examples of a salt that the compounds described herein form with a base include the following: salts

thereof with inorganic bases such as sodium, potassium, magnesium, calcium, and aluminum; salts thereof with organic bases such as methylamine, ethylamine, and ethanolamine; salts thereof with basic amino acids such as lysine and ornithine; and ammonium salt. The salts can be acid addition salts, which are specifically exemplified by acid addition salts with the following: mineral acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, and phosphoric acid:organic acids such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, and ethanesulfonic acid; acidic amino acids such as aspartic acid and glutamic acid.

In some embodiments, a pharmaceutically acceptable salt is an anion salt selected from the group consisting of: a mesylate salt, a besylate salt, an acetate salt, a benzenesulfonate salt, a benzoate salt, a bicarbonate salt, a bitartrate salt, a bromide salt, a calcium edetate salt, a camsylate salt, a carbonate salt, a chloride salt, a citrate salt, a dihydrochloride salt, an edetate salt, an edisylate salt, an estolate salt, an esylate salt, a fumarate salt, a gluceptate salt, a gluconate salt, a glucuronate salt, a glutamate salt, a glycollylarsanilate salt, a hexylresorcinol salt, a hydramine salt, a hydrobromide salt, a hydrochloride salt, a hydroxynaphthoate salt, an iodide salt, an isethionate salt, a lactate salt, a lactobionate salt, a malate salt, a maleate salt, a mandelate salt, a mesylate salt, a methylbromide salt, a methylnitrate salt, a methylsulfate salt, a mucate salt, a napsylate salt, a nitrate salt, a pamoate (embonate) salt, a pantothenate salt, a phosphate/diphosphate salt, a polygalacturonate salt, a salicylate salt, a stearate salt, a subacetate salt, a succinate salt, a sulfate salt, an oleate salt, a tannate salt, a tartrate salt, a teoclate salt, and a triethiodide salt.

In some embodiments, a pharmaceutically acceptable salt is a cation salt selected from the group consisting of: a benzathine salt, a chloroprocaine salt, a choline salt, a tromethamine salt, a diethanolamine salt, an ethylenediamine salt, a meglumine salt, a procaine salt, an aluminum salt, a calcium salt, a lithium salt, a magnesium salt, a potassium salt, a sodium salt, and a zinc salt.

Examples of pharmaceutically acceptable salts also include those disclosed in e.g., Berge, Stephen M., Lyle D. Bighley, and Donald C. Monkhouse. "Pharmaceutical salts." *Journal of pharmaceutical sciences* 66.1 (1977): 1-19 doi: 10.1002/jps.2600660104, Bharate, Sonali S. "Recent developments in pharmaceutical salts: FDA approvals from 2015 to 2019." *Drug Discovery Today* 26.2 (2021): 384-398 doi: 10.1016/j.drudis.2020.11.016, and Bharate, Sonali S. "Modulation of biopharmaceutical properties of drugs using sulfonate counterions:

A critical analysis of FDA-approved pharmaceutical salts." *Journal of Drug Delivery Science and Technology* 66 (2021): 102913 doi: 10.1016/j.jddst.2021.102913.

The term "pharmaceutical composition" refers to a mixture of a compound described herein with other chemical components (referred to collectively herein as "excipients"), such as carriers, stabilizers, diluents, dispersing agents, suspending agents, and/or thickening agents. The pharmaceutical composition facilitates administration of the compound to a subject. Multiple techniques of administering a compound exist in the art including, but not limited to: rectal, oral, intravenous, aerosol, parenteral, ophthalmic, pulmonary, and topical administration.

Compound Preparation

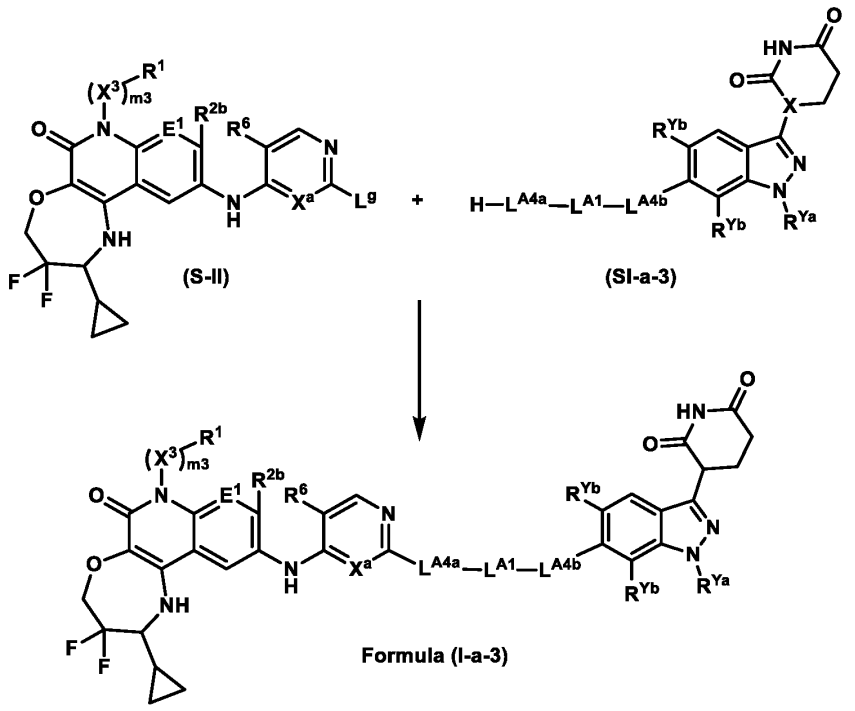
The compounds disclosed herein can be prepared in a variety of ways using commercially available starting materials, compounds known in the literature, or from readily prepared intermediates, by employing standard synthetic methods and procedures either known to those skilled in the art, or in light of the teachings herein.

Standard synthetic methods and procedures for the preparation of organic molecules and functional group transformations and manipulations can be obtained from the relevant scientific literature or from standard textbooks in the field. Although not limited to any one or several sources, classic texts such as R. Larock, Comprehensive Organic Transformations, VCH Publishers (1989); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); Smith, M. B., March, J., March' s Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 5th edition, John Wiley & Sons: New York, 2001 ; and Greene, T.W., Wuts, P.G. M., Protective Groups in Organic Synthesis, 3rd edition, John Wiley & Sons: New York, 1999, are useful and recognized reference textbooks of organic synthesis known to those in the art. The following descriptions of synthetic methods are designed to illustrate, but not to limit, general procedures for the preparation of compounds of the present disclosure.

The synthetic processes disclosed herein can tolerate a wide variety of functional groups; therefore, various substituted starting materials can be used. The processes generally provide the desired final compound at or near the end of the overall process, although it can be desirable in certain instances to further convert the compound to a pharmaceutically acceptable salt thereof.

Also provided herein are methods of preparing compounds of Formula (**I-a-3**) as depicted in **Scheme 1**, the methods comprising reacting compounds of Formula (**S-II**) with compounds of Formula (**SI-a-3**) to provide compounds of Formula (**I-a-3**):

Scheme 1



wherein:

X is CH;

$\mathbf{L^g}$ is a leaving group such as halo (e.g., Cl); and

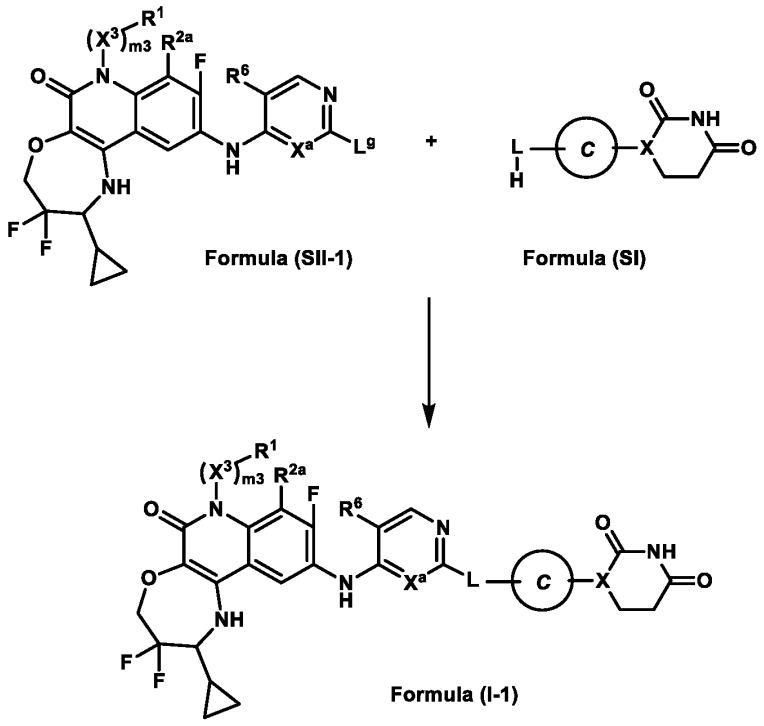
m3, $\mathbf{X^3}$, $\mathbf{R^1}$, $\mathbf{E^1}$, $\mathbf{R^{2b}}$, $\mathbf{R^6}$, $\mathbf{X^a}$, $\mathbf{L^{A4a}}$, $\mathbf{L^{A1}}$, $\mathbf{L^{A4b}}$, $\mathbf{R^{Yb}}$, and $\mathbf{R^{Ya}}$ are as defined for Formula (**I-a-3**) anywhere herein.

In some embodiments, the methods comprise reacting the compounds of Formula (**S-II**) with the compounds of Formula (**SI-a-3**) under conditions suitable for S_NAr reactions. In some embodiments, the methods comprise reacting the compounds of Formula (**S-II**) with the compounds of Formula (**SI-a-3**) in the presence of a base (e.g., triethylamine or diisopropylethylamine) in an appropriate solvent. In some embodiments, the solvent is a polar aprotic solvent (e.g., DMSO or MeCN). In some embodiments, the methods comprise heating the compounds of Formula (**S-II**) with the compounds of Formula (**SI-a-3**) at a temperature of at least 60°C (e.g., heating the reaction at 60-135°C, 70-120°C, 70-110°C, or 80-110°C).

In some embodiments, the compounds of Formula (**I-a-3**) are compounds of Formula (**I-a-4**), or salts thereof. In some embodiments, the compounds of Formula (**I-a-3**) are compounds of Formula (**I-b-3**), or salts thereof. In some embodiments, the compounds of Formula (**I-a-3**) are compounds of Formula (**I-b-4**), or salts thereof.

Also provided herein are methods of preparing compounds of Formula (**I-1**) as depicted in **Scheme 2**, the methods comprising reacting compounds of Formula (**SII-1**) with compounds of Formula (**SI**) to provide compounds of Formula (**I-1**):

Scheme 2



wherein:

L^g is a leaving group such as halo (e.g., Cl); and

m3, X^3, R^1, R^{2a}, R^6, X^a, **L**, **Ring C**, and **X** are as defined for Formula (**I-1**) anywhere herein.

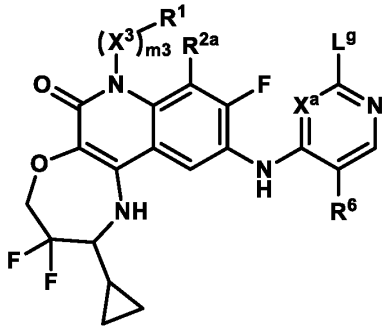
In some embodiments, the methods comprise reacting the compounds of Formula (**SII-1**) with the compounds of Formula (**SI**) under conditions suitable for S_NAr reactions. In some embodiments, the methods comprise reacting the compounds of Formula (**SII-1**) with the

compounds of Formula (**SI**) in the presence of a base (e.g., triethylamine or diisopropylethylamine) in an appropriate solvent. In some embodiments, the solvent is a polar aprotic solvent (e.g., DMSO or MeCN). In some embodiments, the methods comprise heating the compounds of Formula (**SII-1**) with the compounds of Formula (**SI**) at a temperature of at least 60°C (e.g., heating the reaction at 60-135°C, 70-120°C, 70-110°C, or 80-110°C).

In some embodiments, the compounds of Formula (**I-1**) are compounds of Formula (**I-a-1**), or salts thereof. In some embodiments, the compounds of Formula (**I-1**) are compounds of Formula (**I-b-1**), or salts thereof. In some embodiments, the compounds of Formula (**I-1**) are compounds of Formula (**I-c-1**), or salts thereof. In some embodiments, the compounds of Formula (**I-1**) are compounds of Formula (**I-d-1**), or salts thereof. In some embodiments, the compounds of Formula (**I-1**) are compounds of Formula (**I-e-1**), or salts thereof.

Also provided herein are compounds useful in the synthesis of compounds of Formula (**I**) (e.g., Formula (**I-1**), Formula (**I-2**), Formula (**I-a**) (e.g., Formula (**I-a-1**), (**I-a-2**), (**I-a-3**), or (**I-a-4**)), Formula (**I-b**) (e.g., Formula (**I-b-1**), (**I-b-2**), (**I-b-3**), or (**I-b-4**)), Formula (**I-c**) (e.g., Formula (**I-c-1**) or (**I-c-2**)), Formula (**I-d**) (e.g., Formula (**I-d-1**)), or Formula (**I-e**) (e.g., Formula (**I-e-1**) or (**I-e-2**))).

Also provided herein are compounds of Formula (**SII-1**):



Formula (**SII-1**)

or salts thereof, wherein:

m3 is 0 or 1;

$\mathbf{X^3}$ is C_{1-3} alkylene optionally substituted with 1-3 $\mathbf{R^c}$;

$\mathbf{R^1}$ is selected from the group consisting of: H, halo, and $\mathbf{R^{b1}}$;

$\mathbf{R^{2a}}$ is selected from the group consisting of: H, halo, cyano, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, and C_{1-3} haloalkoxy;

X^a is selected from the group consisting of: N and CR^{Xa};

R^6 and R^{Xa} are independently selected from the group consisting of: H, halo, C_{1-2} alkyl, C_{1-2} haloalkyl, C_{1-2} alkoxy, CN, and C≡CH;

L^g is a leaving group such as halo (e.g., Cl);

each R^{b1} is independently selected from the group consisting of: C_{3-6} cycloalkyl and 4-8 membered heterocyclyl, each of which is optionally substituted with 1-3 R^g;

each R^c is independently selected from the group consisting of: halo, cyano, OH, C_{1-6} alkoxy, C_{1-6} haloalkoxy, NR^dR^e, $C(=O)C_{1-6}$ alkyl, $C(=O)OC_{1-6}$ alkyl, $C(=O)N(R^f)_2$, $S(O)_{0-2}(C_{1-6}$ alkyl), and $S(O)_{0-2}(C_{1-6}$ haloalkyl);

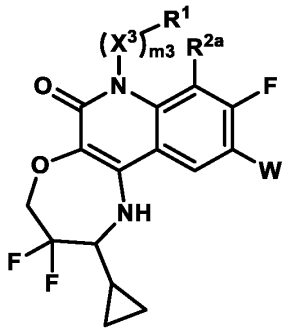
each R^d and R^e is independently selected from the group consisting of: H, $C(=O)C_{1-6}$ alkyl, $C(=O)C_{1-6}$ haloalkyl, $C(=O)OC_{1-6}$ alkyl, $C(=O)OC_{1-6}$ haloalkyl, $C(=O)N(R^f)_2$, $S(O)_{1-2}(C_{1-6}$ alkyl), $S(O)_{1-2}(C_{1-6}$ haloalkyl), $S(O)_{1-2}N(R^f)_2$, and C_{1-6} alkyl optionally substituted with 1-3 R^h;

each R^f is independently selected from the group consisting of: H and C_{1-6} alkyl optionally substituted with 1-3 R^h;

each R^g is independently selected from the group consisting of: R^h, oxo, C_{1-3} alkyl, and C_{1-3} haloalkyl; and

each R^h is independently selected from the group consisting of: halo, cyano, OH, $-(C_{0-3}$ alkylene)-C_{1-6} alkoxy, $-(C_{0-3}$ alkylene)-C_{1-6} haloalkoxy, $-(C_{0-3}$ alkylene)-NH_2, $-(C_{0-3}$ alkylene)-N(H)(C_{1-3} alkyl), and $-(C_{0-3}$ alkylene)-N(C_{1-3} alkyl)$_2$.

Also provided herein are compounds of Formula (**SIII-1**):



Formula (**SIII-1**)

or salts thereof, wherein:

m3 is 0 or 1;

$\mathbf{X^3}$ is C_{1-3} alkylene optionally substituted with 1-3 $\mathbf{R^c}$;

$\mathbf{R^1}$ is selected from the group consisting of: H, halo, and $\mathbf{R^{b1}}$;

$\mathbf{R^{2a}}$ is selected from the group consisting of: H, halo, cyano, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, and C_{1-3} haloalkoxy;

W is selected from the group consisting of: NH_2 and halo;

each $\mathbf{R^{b1}}$ is independently selected from the group consisting of: C_{3-6} cycloalkyl and 4-8 membered heterocyclyl, each of which is optionally substituted with 1-3 $\mathbf{R^g}$;

each $\mathbf{R^c}$ is independently selected from the group consisting of: halo, cyano, OH, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -$N\mathbf{R^d}\mathbf{R^e}$, $C(=O)C_{1-6}$ alkyl, $C(=O)OC_{1-6}$ alkyl, $C(=O)N(\mathbf{R^f})_2$, $S(O)_{0-2}(C_{1-6}$ alkyl), and $S(O)_{0-2}(C_{1-6}$ haloalkyl);

each $\mathbf{R^d}$ and $\mathbf{R^e}$ is independently selected from the group consisting of: H, $C(=O)C_{1-6}$ alkyl, $C(=O)C_{1-6}$ haloalkyl, $C(=O)OC_{1-6}$ alkyl, $C(=O)OC_{1-6}$ haloalkyl, $C(=O)N(\mathbf{R^f})_2$, $S(O)_{1-2}(C_{1-6}$ alkyl), $S(O)_{1-2}(C_{1-6}$ haloalkyl), $S(O)_{1-2}N(\mathbf{R^f})_2$, and C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^h}$;

each $\mathbf{R^f}$ is independently selected from the group consisting of: H and C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^h}$;

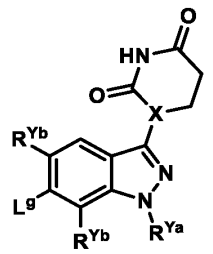
each $\mathbf{R^g}$ is independently selected from the group consisting of: $\mathbf{R^h}$, oxo, C_{1-3} alkyl, and C_{1-3} haloalkyl; and

each $\mathbf{R^h}$ is independently selected from the group consisting of: halo, cyano, OH, -(C_{0-3} alkylene)-C_{1-6} alkoxy, -(C_{0-3} alkylene)-C_{1-6} haloalkoxy, -(C_{0-3} alkylene)-NH_2, -(C_{0-3} alkylene)-N(H)(C_{1-3} alkyl), and –(C_{0-3} alkylene)-N(C_{1-3} alkyl)$_2$.

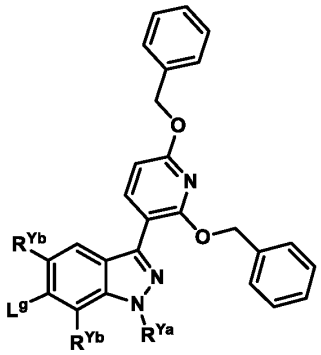
In some embodiments of Formula (**SII-1**) or (**SIII-1**), $\mathbf{R^{2a}}$ is H.

In some embodiments of Formula (**SII-1**) or (**SIII-1**), -$(\mathbf{X^3})_{m3}$-$\mathbf{R^1}$ is C_{1-3} alkyl (e.g., methyl).

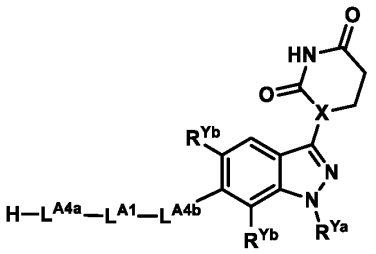
Also provided herein are compounds of Formula (**SI-a-2**), Formula (**SI-aa-2**), Formula (**SI-a-3**), and Formula (**SI-aa-3**):



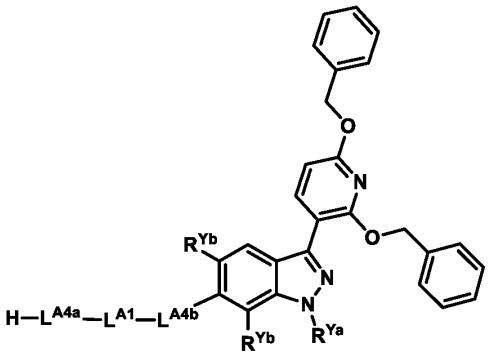
(SI-a-2)



(SI-aa-2)



(SI-a-3)



(SI-aa-3)

or salts thereof, wherein:

$\mathbf{L^g}$ is a leaving group such as halo (e.g., -Br);

X is CH or N;

$\mathbf{R^{Ya}}$ is selected from the group consisting of:

H, C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$, and –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$ (e.g., C_{3-6} cycloalkyl optionally substituted with 1-3 F);

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$ (e.g., C_{1-3} alkyl optionally substituted with 1-3 F);

$\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ are independently 4-12 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R^a}$;

$\mathbf{L^{A1}}$ is CH_2 or $CH\mathbf{R^L}$;

$\mathbf{R^L}$ is selected from the group consisting of: F, OH, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$, wherein:

each $\mathbf{R^a}$ is independently selected from the group consisting of:

(a) halo;

(b) cyano;

(c) OH;

(d) oxo;

(e) C_{1-6} alkoxy optionally substituted with 1-6 $\mathbf{R^c}$;

(f) $-N\mathbf{R^d}\mathbf{R^e}$;

(g) $C(=O)C_{1-6}$ alkyl;

(h) $C(=O)OC_{1-6}$ alkyl;

(i) $C(=O)N(\mathbf{R^f})_2$;

(j) $S(O)_{0-2}(C_{1-6}$ alkyl);

(k) $S(O)_{0-2}(C_{1-6}$ haloalkyl); and

(l) C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, each optionally substituted with 1-6 $\mathbf{R^c}$;

each $\mathbf{R^c}$ is independently selected from the group consisting of: halo, cyano, OH, C_{1-6} alkoxy, $-C_{1-6}$ haloalkoxy, $-N\mathbf{R^d}\mathbf{R^e}$, $C(=O)C_{1-6}$ alkyl, $C(=O)OC_{1-6}$ alkyl, $C(=O)N(\mathbf{R^f})_2$, $S(O)_{0-2}(C_{1-6}$ alkyl), and $S(O)_{0-2}(C_{1-6}$ haloalkyl);

each $\mathbf{R^d}$ and $\mathbf{R^e}$ is independently selected from the group consisting of: H, $C(=O)C_{1-6}$ alkyl, $C(=O)C_{1-6}$ haloalkyl, $C(=O)OC_{1-6}$ alkyl, $C(=O)OC_{1-6}$ haloalkyl, $C(=O)N(\mathbf{R^f})_2$, $S(O)_{1-2}(C_{1-6}$ alkyl), $S(O)_{1-2}(C_{1-6}$ haloalkyl), $S(O)_{1-2}N(\mathbf{R^f})_2$, and C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^h}$;

each $\mathbf{R^f}$ is independently selected from the group consisting of: H and C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^h}$;

each $\mathbf{R^g}$ is independently selected from the group consisting of: $\mathbf{R^h}$, oxo, C_{1-3} alkyl, and C_{1-3} haloalkyl; and

each $\mathbf{R^h}$ is independently selected from the group consisting of: halo, cyano, OH, $-(C_{0-3}$ alkylene)-C_{1-6} alkoxy, $-(C_{0-3}$ alkylene)-C_{1-6} haloalkoxy, $-(C_{0-3}$ alkylene)-NH_2, $-(C_{0-3}$ alkylene)-$N(H)(C_{1-3}$ alkyl), and $-(C_{0-3}$ alkylene)-$N(C_{1-3}$ alkyl)$_2$.

In some embodiments of Formula (**SI-a-2**) or (**SI-aa-2**), each $\mathbf{R^{Yb}}$ is independently halo (e.g., F).

In some embodiments of Formula (**SI-a-2**) or (**SI-aa-2**), each $\mathbf{R^{Yb}}$ is F.

In some embodiments of Formula (**SI-a-2**) or (**SI-aa-2**), $\mathbf{R^{Ya}}$ is $C_{1\text{-}3}$ alkyl optionally substituted with 1-3 F (e.g., $C_{1\text{-}3}$ alkyl (e.g., methyl)).

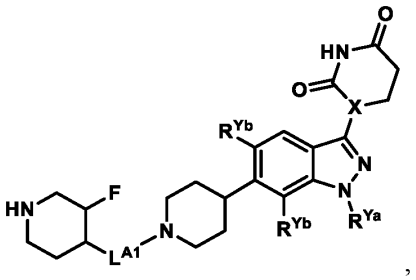
In some embodiments of Formula (**SI-a-3**) or (**SI-aa-3**), each $\mathbf{R^{Yb}}$ is independently halo (e.g., F).

In some embodiments of Formula (**SI-a-3**) or (**SI-aa-3**), each $\mathbf{R^{Yb}}$ is F.

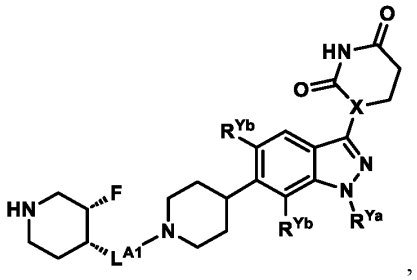
In some embodiments of Formula (**SI-a-3**) or (**SI-aa-3**), $\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ are independently monocyclic 4-6 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R^a}$.

In some embodiments of Formula (**SI-a-3**) or (**SI-aa-3**), $\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ are independently monocyclic 4-6 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R^a}$ wherein, $\mathbf{R^a}$ is each selected from the group consisting of: F and $C_{1\text{-}3}$ alkyl (e.g., methyl).

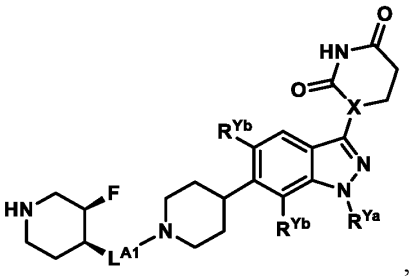
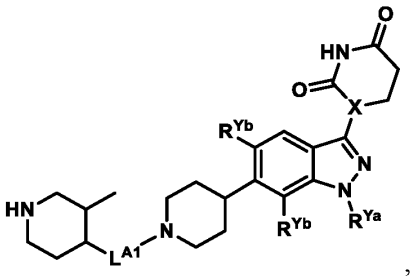
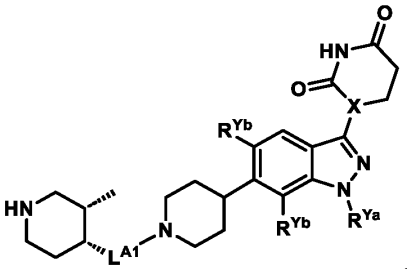
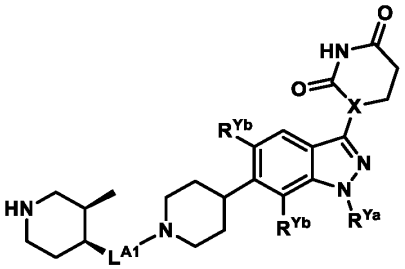
For example, compounds of Formula (**SI-a-3**) can be



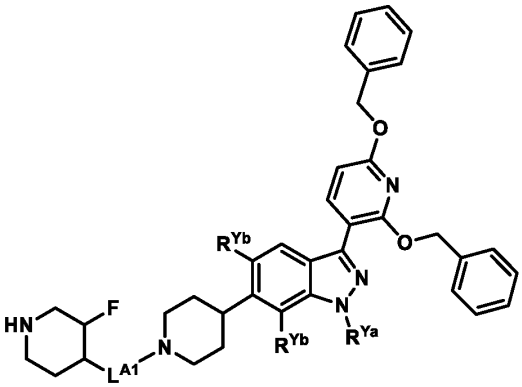
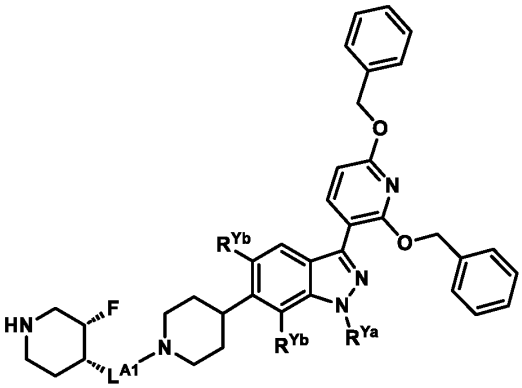
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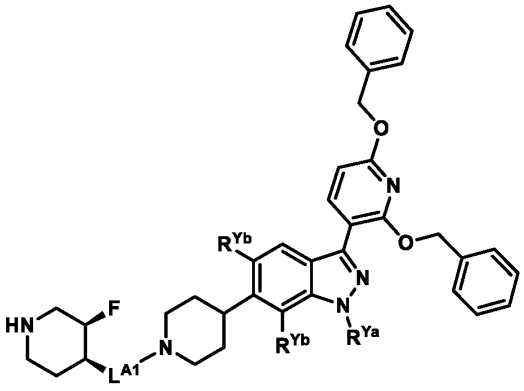


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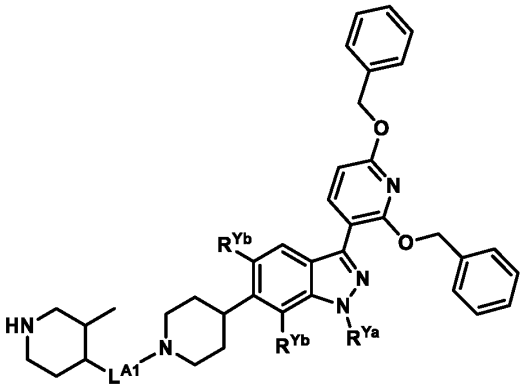

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, or

, or salts thereof.

For example, compounds of Formula (**SI-aa-3**) can be

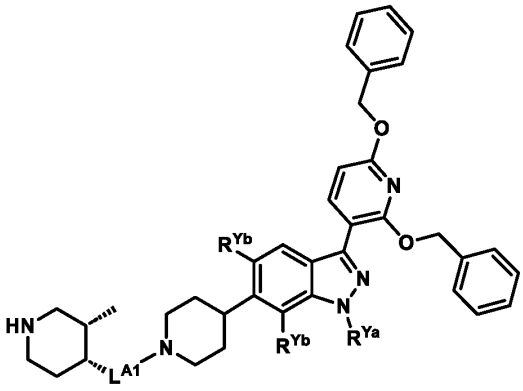

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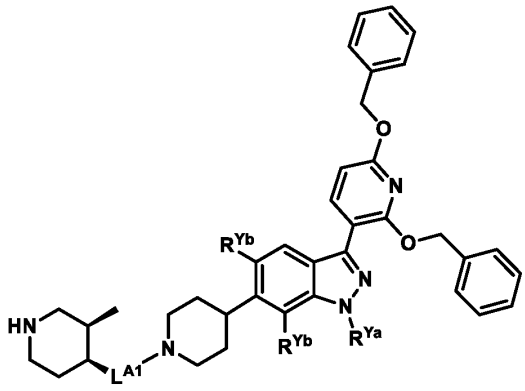
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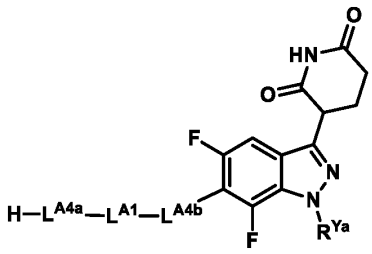


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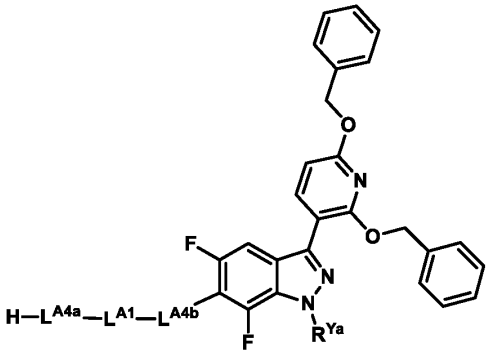


, or salts thereof.

In some embodiments, the compounds of Formula (**SI-a-3**) or (**SI-aa-3**) are compounds of Formula (**SI-a-4**) or Formula (**SI-aa-4**), respectively:



Formula (**SI-a-4**)



Formula (**SI-aa-4**)

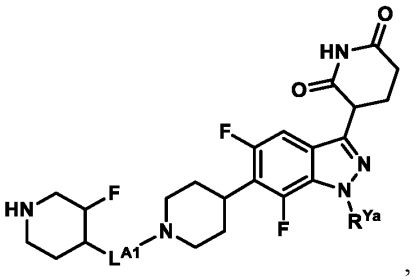
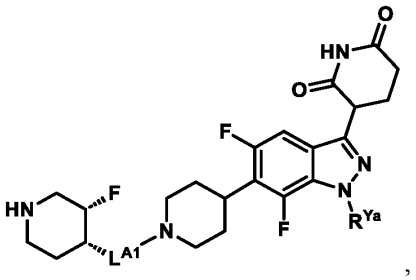
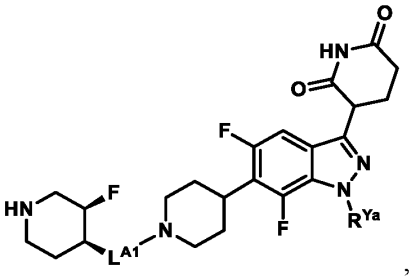
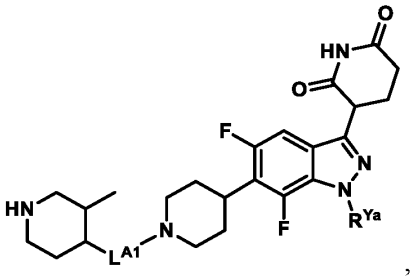
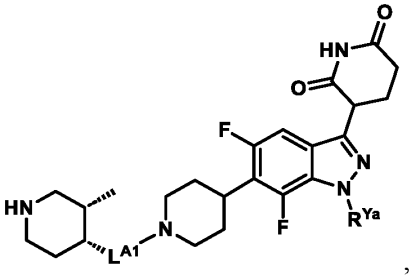
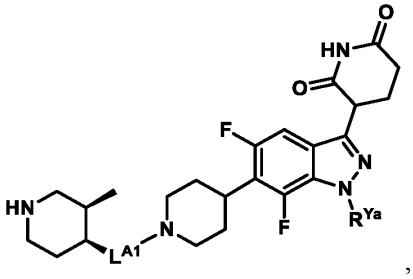
or salts thereof, wherein:

$\mathbf{R}^{Ya}$ is C_{1-3} alkyl optionally substituted with 1-3 F (e.g., C_{1-3} alkyl (e.g., methyl)).

In some embodiments of Formula (**SI-a-4**) or (**SI-aa-4**), $\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ are independently monocyclic 4-6 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R}^{a}$.

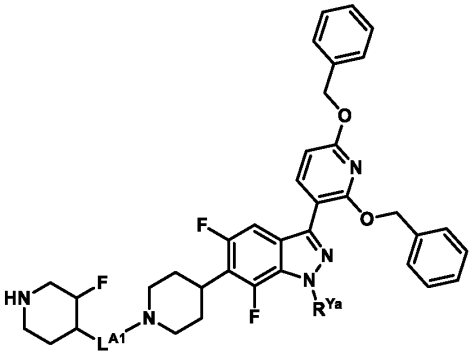
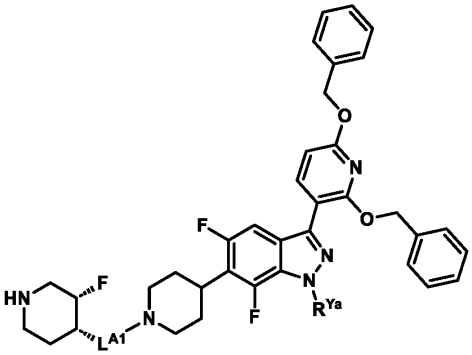
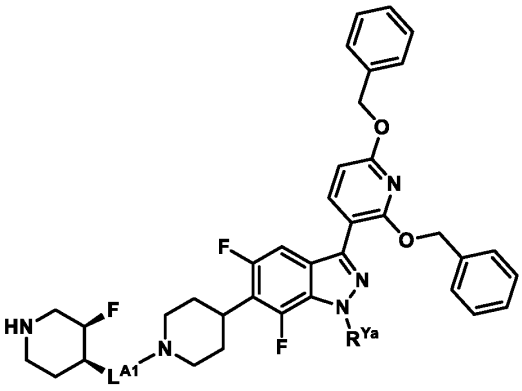
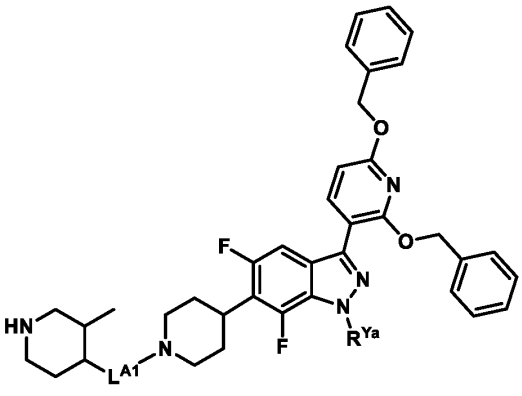
In some embodiments of Formula (**SI-a-4**) or (**SI-aa-4**), $\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ are independently monocyclic 4-6 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R}^{a}$ wherein, $\mathbf{R}^{a}$ is selected from the group consisting of: F and C_{1-3} alkyl (e.g., methyl).

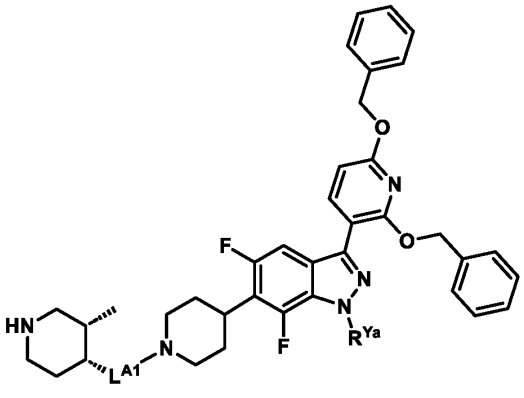
For example, compounds of Formula (**SI-a-4**) can be

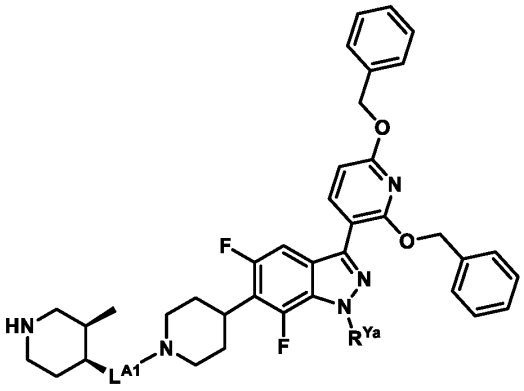
, or salts thereof.

For example, compounds of Formula (**SI-aa-4**) can be


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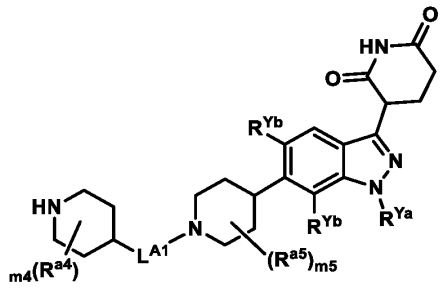


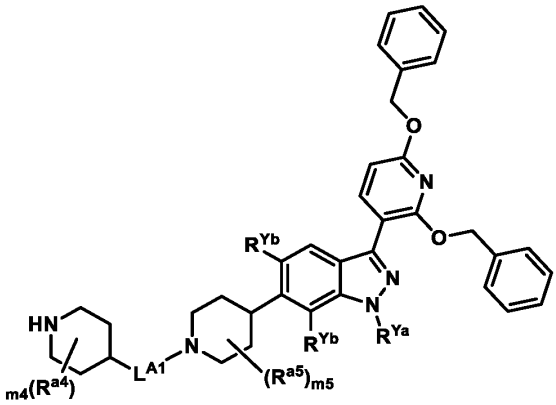
, or



, or salts thereof.

In some embodiments, the compounds of Formula (**SI-a-3**) or (**SI-aa-3**) are compounds of Formula (**SI-b-3**) or (**SI-bb-3**), respectively:





Formula (**SI-b-3**) Formula (**SI-bb-3**)

or salts thereof, wherein:

$\mathbf{R^{Ya}}$ is C_{1-3} alkyl optionally substituted with 1-3 F (e.g., C_{1-3} alkyl (e.g., methyl));

each $\mathbf{R^{Yb}}$ is independently halo (e.g., F);

m4 and **m5** are each independently 0, 1, or 2; and

each $\mathbf{R^{a4}}$ and $\mathbf{R^{a5}}$ is independently selected from the group consisting of: F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F.

In some embodiments of Formula (**SI-b-3**) or (**SI-bb-3**), **m4** and **m5** are each independently 0 or 1.

In some embodiments of Formula (**SI-b-3**) or (**SI-bb-3**), each $\mathbf{R^{a4}}$ and $\mathbf{R^{a5}}$ is independently selected from the group consisting of: F and C_{1-3} alkyl (e.g., methyl).

In some embodiments of Formula (**SI-b-3**) or (**SI-bb-3**), **m4** and **m5** are each independently 0 or 1; and

each $\mathbf{R^{a4}}$ and $\mathbf{R^{a5}}$ is independently selected from the group consisting of: F and C_{1-3} alkyl (e.g., methyl).

In some embodiments of Formula (**SI-b-3**) or (**SI-bb-3**), each $\mathbf{R^{Yb}}$ is an independently selected halo (e.g., F);

m4 is 0; and

m5 is 0.

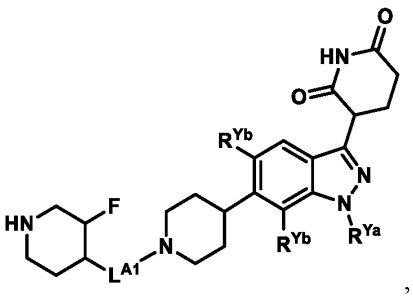
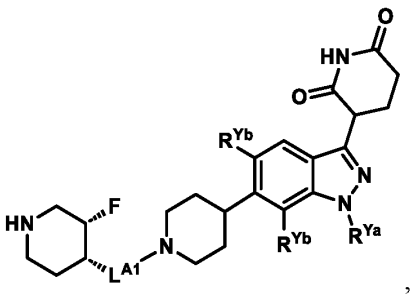
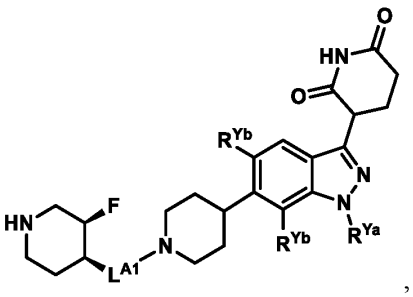
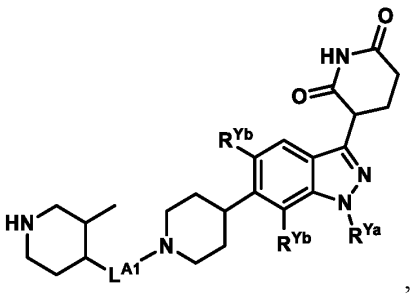
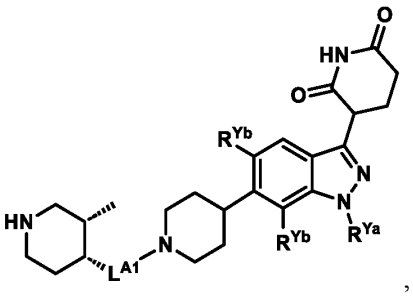
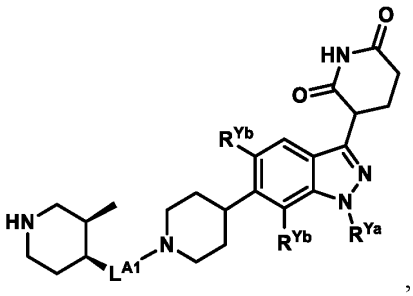
In some embodiments of Formula (**SI-b-3**) or (**SI-bb-3**), each $\mathbf{R^{Yb}}$ is an independently selected halo (e.g., F);

m4 is 1;

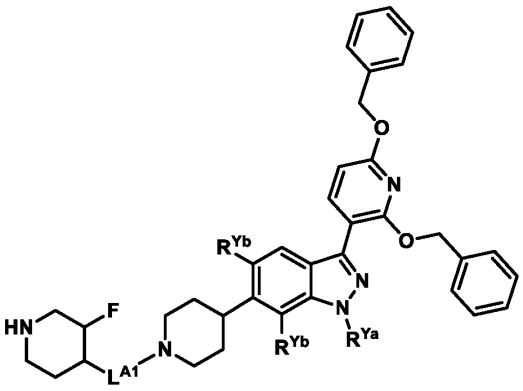
m5 is 0; and

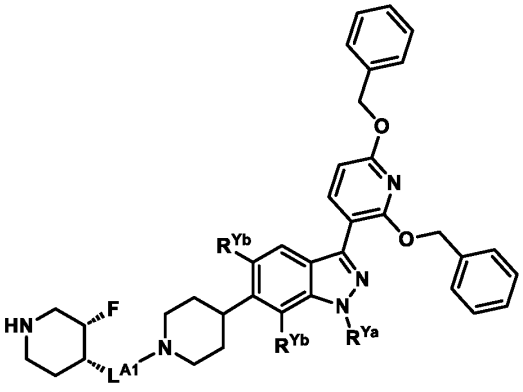
$\mathbf{R^{a4}}$ is F or $C_{1\text{-}3}$ alkyl (e.g., methyl).

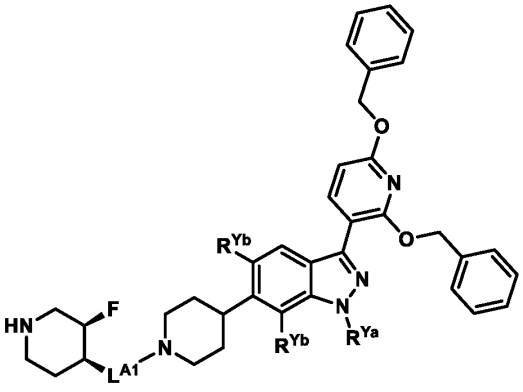
For example, compounds of Formula (**SI-b-3**) can be

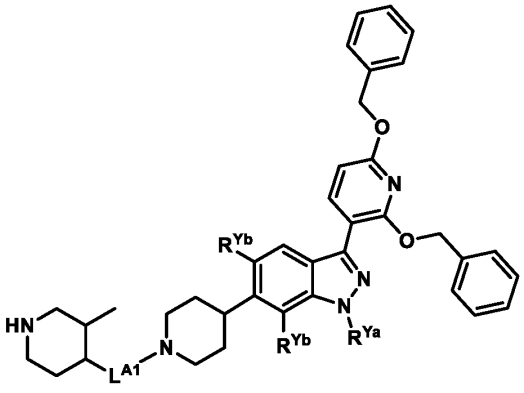

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, or

, or salts thereof.

For example, compounds of Formula (**SI-bb-3**) can be

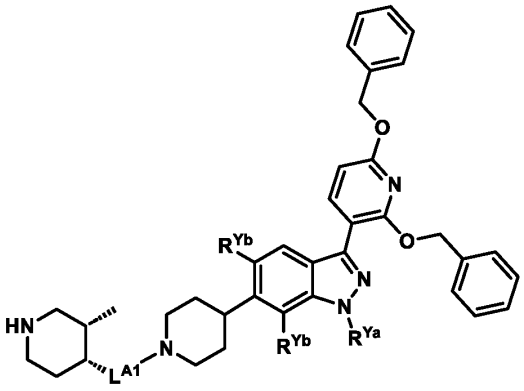

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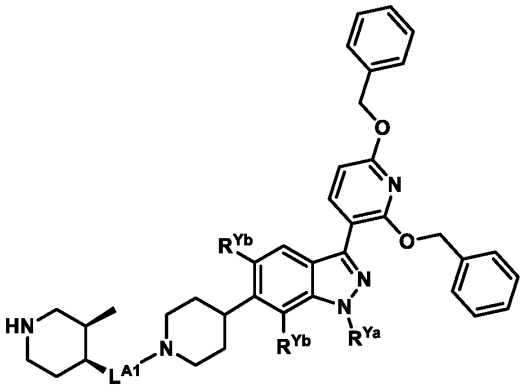

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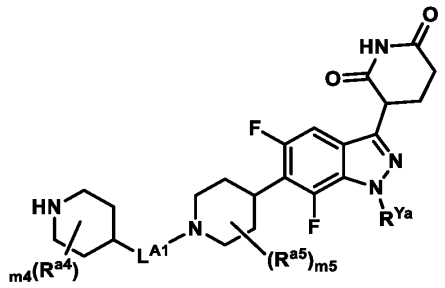


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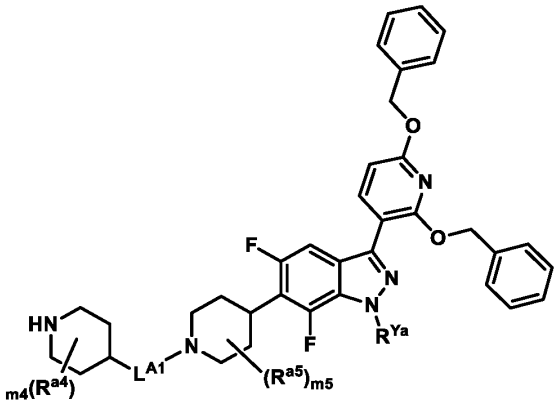


, or salts thereof.

In some embodiments, the compounds of Formula (**SI-a-3**) and Formula (**SI-aa-3**) are compounds of Formula (**SI-b-4**) and Formula (**SI-bb-4**), respectively:



Formula (**SI-b-4**)



Formula (**SI-bb-4**)

or salts thereof, wherein:

$\mathbf{R^{Ya}}$ is C_{1-3} alkyl optionally substituted with 1-3 F (e.g., C_{1-3} alkyl (e.g., methyl));

m4 and **m5** are independently 0, 1, or 2; and

each $\mathbf{R^{a4}}$ and $\mathbf{R^{a5}}$ is independently selected from the group consisting of: F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F.

In some embodiments of Formula (**SI-b-4**) or (**SI-bb-4**), **m4** and **m5** are independently 0 or 1.

In some embodiments of Formula (**SI-b-4**) or (**SI-bb-4**), each $\mathbf{R^{a4}}$ and $\mathbf{R^{a5}}$ is independently selected from the group consisting of: F and C_{1-3} alkyl (e.g., methyl).

In some embodiments of Formula (**SI-b-4**) or Formula (**SI-bb-4**),

m4 and **m5** are independently 0 or 1; and

each $\mathbf{R^{a4}}$ and $\mathbf{R^{a5}}$ is independently selected from the group consisting of: F and C_{1-3} alkyl (e.g., methyl).

In some embodiments of Formula (**SI-b-4**) or (**SI-bb-4**), each $\mathbf{R^{Yb}}$ is an independently selected halo (e.g., F);

m4 is 0; and

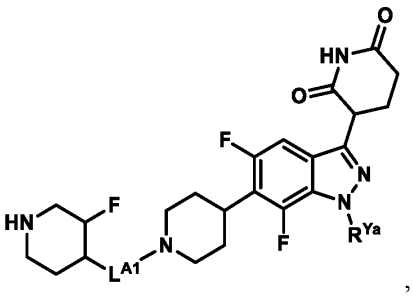
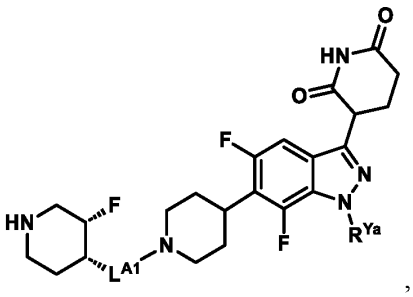
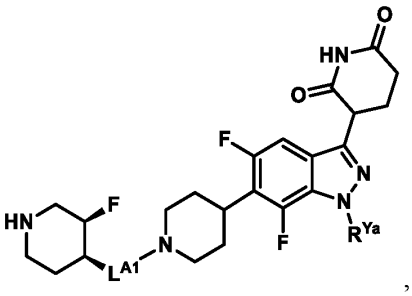
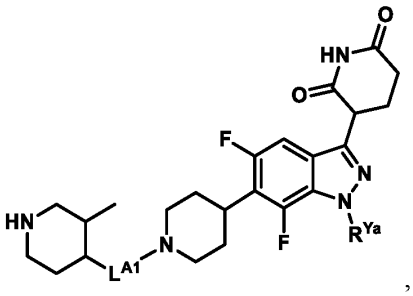
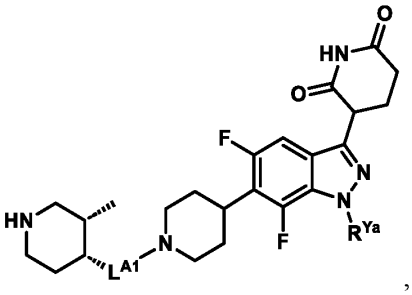
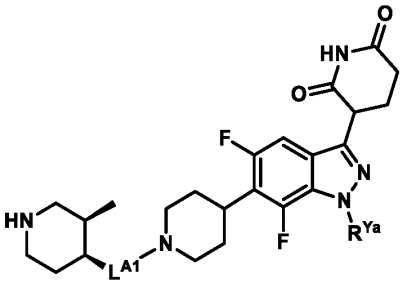
m5 is 0.

In some embodiments of Formula (**SI-b-4**) and Formula (**SI-bb-4**), **m4** is 1;

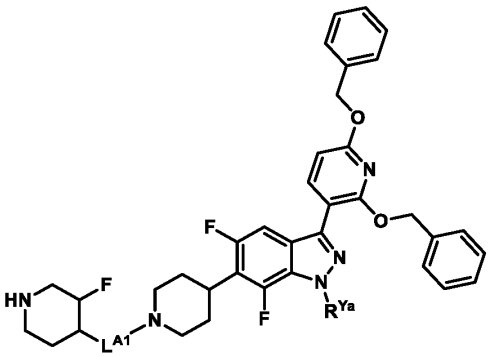
m5 is 0; and

$\mathbf{R^{a4}}$ is F or $C_{1\text{-}3}$ alkyl (e.g., methyl).

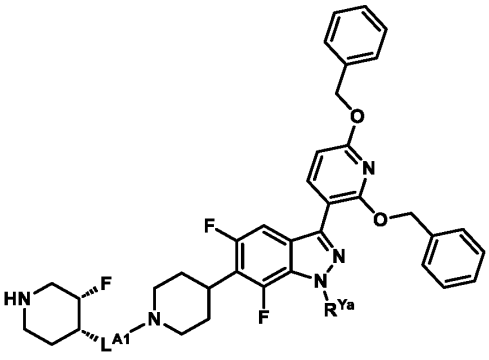
For example, compounds of Formula (**SI-b-4**) can be


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, or

, or salts thereof.

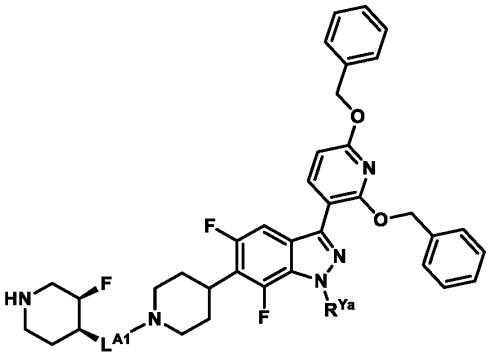
For example, compounds of Formula (**SI-bb-4**) can be



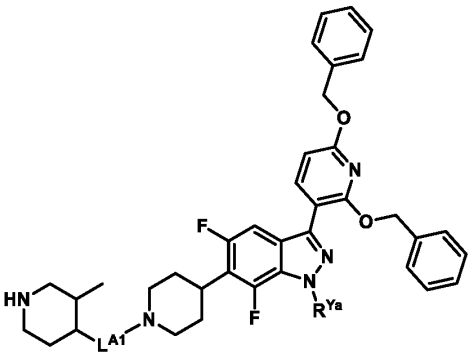
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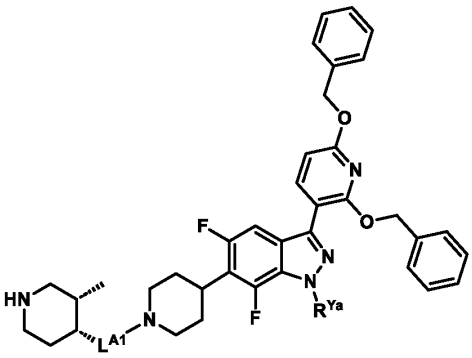
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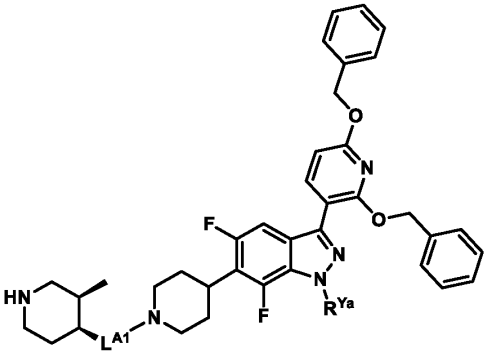
,



,



, or



, or salts thereof.

5

EXAMPLES

In some of the examples disclosed herein, the final product of a described chemical reaction sequence is structurally depicted with enhanced stereochemical notation(s) at one or more stereogenic center(s). Examples of such notations include *or1*, *or2*, and the like. In some such examples, in the chemical name of the same compound, each of such stereogenic center(s) is assigned a tentative configuration (e.g., (*R*)- or (*S*)-) based on the wedge/dash representation of the structural formula. However, the stereogenic center(s) should be understood to have configurations consistent with the enhanced stereochemical notation(s), as described herein. Accordingly, unless otherwise specified, starting materials and intermediates leading to these compounds incorporate the enhanced stereochemical notations at the corresponding stereogenic centers, notwithstanding the tentative assignments provided in their chemical names.

For example, based on the *or1* notation, **Compound 131a** in **Example 11** is a single stereoisomer selected from:

3-(6-(4-(((S)-1-(5-chloro-4-(((S)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione; and

3-(6-(4-(((R)-1-(5-chloro-4-(((S)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione.

The starting material used to prepare **Compound 131a**, as described in **Example 11**, incorporates the *or1* notation. It is therefore a single stereoisomer selected from:

3-(6-(4-(((S)-3,3-dimethylpiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione; and

3-(6-(4-(((R)-3,3-dimethylpiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione.

For further clarification, a chemical name that takes into account the enhanced stereochemical notation(s) is provided for the final product having enhanced stereochemical notation(s) at one or more stereogenic centers. This chemical name is enclosed in brackets (i.e., "[]").

When a defined stereogenic center (i.e., a stereogenic center depicted with wedge and/or dash) is labelled with an asterisk ("*") in a chemical name of a compound having more than one defined stereogenic centers, the defined stereogenic center labeled with the asterisk is resolved, but its absolute configuration is either (R)- or (S)-. As such, in a chemical name wherein one defined stereogenic center is labelled with the asterisk, that defined stereogenic center should be labelled with an *or1* enhanced stereochemical notation in its corresponding structure.

For example, the chemical name containing an asterisk for **Compound 131a** is: [3-(6-(4-(((S*)-1-(5-chloro-4-(((S)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione], as included in **Example 11**.

When the chemical name of a compound contains two defined stereogenic centers labelled with asterisks, these two defined stereogenic centers can have (R) or (S) configurations, either concertedly or independently, in conformity with the *orx* (e.g., *or1* or *or2*) notations in **Table C1** for the corresponding compound.

When two defined stereogenic centers are labelled *or1* and *or1* in a compound structure, and they are labelled with asterisks in the chemical name, then the relative stereochemistry between the two defined stereogenic centers (e.g., *syn* or *anti* relationship) is as represented by the name, but the absolute configurations of the two defined stereogenic centers can vary concertedly (e.g., a compound designated (R*,R*) is one stereoisomer selected from (R,R) and (S,S); for avoidance of doubt, the compound designated (R*,R*) does not have (S,R) or (R,S) configurations across these stereogenic centers). For example, the chemical name of a compound having two asterisks for **Compound 131a** is:

[3-(6-((3S*,4S*)-4-((9-(5-chloro-4-(((S)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione], as included in **Example 11**.

When two defined stereogenic centers are labelled *or1* and *or2* in a compound structure, and they are labelled with asterisks in the chemical name, then the configuration of the two defined stereogenic centers can vary independently (e.g., a compound designated (R*,R*) is one stereoisomer selected from (R,R), (S,S), (R,S), and (S,R)).

Work-Up Methods

Work-up A: The reaction mixture was quenched with cold water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to obtain crude product which was purified by flash chromatography.

Work-up B: The reaction mixture was quenched with cold water and extracted with ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to obtain crude product which was triturated with n-pentane.

Work-up C: The reaction mixture was diluted with saturated Na_2SO_3 and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography.

Work-up D: The reaction mixture was filtered and concentrated under reduced pressure to give a residue which was used in the next step without further purification.

Work-up E: The reaction mixture was concentrated and dried under vacuum to afford crude product which was used in the next step without further purification.

Work-up F: The reaction mixture was quenched with ice cold water and the precipitated solid was filtered and washed with n-pentane to afford crude product which was used in the next step without further purification.

Work-up G: The reaction mixture was quenched with H_2O, filtered, and concentrated under reduced pressure to give a residue which was triturated with petroleum ether at 25 °C for 10 min.

Work-up H: The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography.

Work-Up I: Reaction mixture was concentrated under reduced pressure, co-distilled with DCM, and triturated with diethyl-ether.

Work-up J: The reaction was diluted with H_2O and extracted with DCM. The combined organic layers were washed with brine dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue which was used in the next step without further purification.

Work-up K: The reaction mixture was filtered through celite and the filtrate was concentrated under reduced pressure to give a crude product which was purified by flash chromatography.

Work-up L: The reaction mixture was quenched with ice-cold water, solid was filtered to get crude product. The Crude product was triturated with diethyl-ether and dried under vacuum.

Work-up M: Reaction was concentrated under reduced pressure then dissolved in methanol and refluxed at 80 °C for 2 – 4 hours. The mixture was then concentrated under reduced pressure to give crude product which was purified by flash column chromatography.

Work-up N: The reaction mixture was quenched by addition $NaHCO_3$, and then extracted with DCM. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give a residue which was used in the next step without further purification.

Work-up O: The reaction mixture was dried under reduced pressure and washed with n-pentane to get crude product.

Work-up P: The reaction mixture was quenched with cold methanol and diluted with H_2O. The mixture was extracted with ethyl acetate and washed with brine. The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to obtain crude product which was purified by flash chromatography.

Work-up Q: The reaction was diluted with H_2O and extracted with ethyl acetate. The combined organic layers were washed with brine dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue which was used in the next step without further purification.

Work-up R: The reaction mixture was quenched with H_2O, filtered and concentrated under reduced pressure to give a residue which was purified by flash column chromatography.

Work-up S: The reaction mixture was quenched with cold water and extracted with DCM. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to obtain crude product which was purified by flash chromatography.

Work-up T: The reaction mixture was filtered and concentrated under reduced pressure to give a residue which was purified by prep-HPLC.

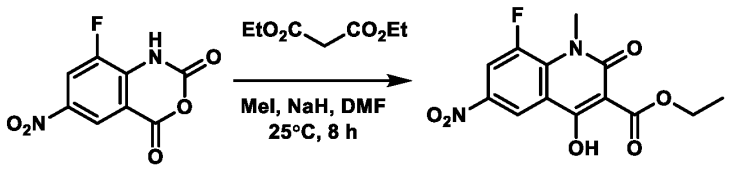
Work-up U: The reaction mixture was quenched by addition $NaHCO_3$, and then extracted with DCM. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give a residue which was purified by flash column chromatography.

Work-up V: The reaction mixture was quenched with $NaHCO_3$ to pH ~ 7-9. Then the mixture was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4,

filtered and concentrated under reduced pressure to give a residue which was purified by re-crystallization from ethyl acetate.

Synthesis of Intermediates

Example P1



To a stirred suspension of NaH (1.85 g, 46.35 mmol, 1 *equiv.*) in DMF (15 mL) was added a solution of 8-fluoro-6-nitro-2H-benzo[d][1,3]oxazine-2,4(1H)-dione (3.0 g, 13.26 mmol, 1 *equiv.*) in DMF (15 mL) at 0 °C. The resulting reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was cooled to 0 °C and added diethylmalonate (6.3 mL, 39.78 mmol, 1 *equiv.*). The resulting reaction mixture was stirred at room temperature for 6 hours. The reaction mixture was acidified with 1N HCl solution and the precipitated solid was filtered and dried under vacuum to afford ethyl-8-fluoro-4-hydroxy-1-methyl-6-nitro-2-oxo-1,2-dihydroquinoline-3-carboxylate (2.0 g) as an off white solid. **LC-MS (ESI):** m/z = 311.21 $[M+H]^+$

The compounds shown in the "**Product**" column of **Table P1** were synthesized using the method of **Example P1**, with variations noted in **Table P1**.

Table P1

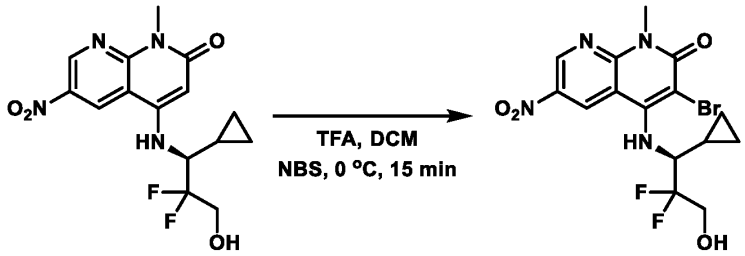
Reactant	Variation from Example P1	Product
3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl-2-(methylamino)-5-nitronicotinate	K_2CO_3 (1 *equiv.*) was added to the reaction; reaction temperature: 100 °C; reaction time: 16 hours	ethyl-4-hydroxy-1-methyl-6-nitro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate
8-fluoro-6-nitro-2H-benzo[d][1,3]oxazine-2,4(1H)-dione		ethyl-8-fluoro-4-hydroxy-1-methyl-6-nitro-2-oxo-1,2-dihydroquinoline-3-carboxylate
6-bromo-7-fluoro-1-methyl-3,1-benzoxazine-2,4-dione	Crude product was triturated with ethyl acetate	ethyl-6-bromo-7-fluoro-4-hydroxy-1-methyl-2-oxo-quinoline-3-carboxylate

Table P1A

Product	LC-MS (ESI)	^{1}H NMR
ethyl-4-hydroxy-1-methyl-6-nitro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate	m/z = 294.04 $[M+H]^+$	

ethyl-8-fluoro-4-hydroxy-1-methyl-6-nitro-2-oxo-1,2-dihydroquinoline-3-carboxylate	m/z = 311.21 $[M+H]^+$	
ethyl-6-bromo-7-fluoro-4-hydroxy-1-methyl-2-oxo-quinoline-3-carboxylate	m/z = 343.9 $[M+H]^+$	(400 MHz, DMSO-d6) δ = 8.34 (d, J = 8.0 Hz, 1H), 7.25 (d, J = 11.2 Hz, 1H), 4.34 - 4.24 (m, 2H), 3.53 (s, 3H), 1.24 (t, J = 8.0 Hz, 3H)

Example P2



To stirred solution of (S)-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl)amino)-1-methyl-6-nitro-1,8-naphthyridin-2(1H)-one (Reactant) (4.0 g, 11.29 mmol, 1 *equiv.*) in DCM (40 mL) was added N-bromosuccinimide (2.0 g, 11.29 mmol, 1 *equiv.*) at 0 °C. The reaction mixture was stirred for 5 minutes, followed by the addition of TFA (4.0 mL). The resulting reaction mixture was stirred at 0 °C for 10 minutes. The reaction mixture was diluted with water (100 mL) and extracted with DCM (2 x 200 mL). The combined organic layers were washed with saturated sodium bicarbonate solution (100 mL), brine (100 mL), dried over anhydrous sodium sulphate, and concentrated under reduced pressure to obtain crude product which was triturated with petroleum ether (100 mL) and dried under vacuum to afford (S)-3-bromo-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl)amino)-1-methyl-6-nitro-1,8-naphthyridin-2(1H)-one (4.0 g) as a yellow solid. **LC-MS (ESI):** m/z = 433.27 $[M+H]^+$

The compounds shown in the "**Product**" column of **Table P2** were synthesized using the method of **Example P2**, with variations noted in **Table P2**.

Table P2

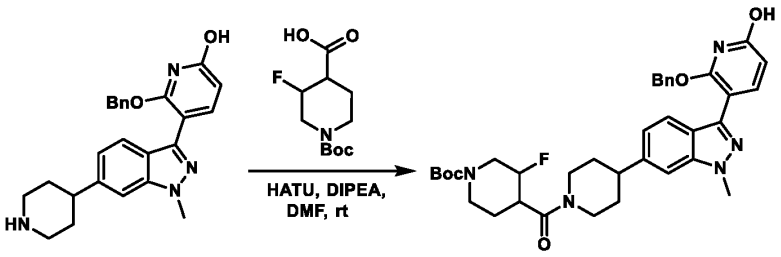
Reactant	Variation from Example P2	Product
(S)-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl)amino)-1-methyl-6-nitro-1,8-naphthyridin-2(1H)-one		(S)-3-bromo-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl)amino)-1-methyl-6-nitro-1,8-naphthyridin-2(1H)-one
(S)-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl)amino)-		(S)-3-bromo-4-((1-cyclopropyl-2,2-difluoro-3-

8-fluoro-1-methyl-6-nitroquinolin-2(1H)-one		hydroxypropyl)amino)-8-fluoro-1-methyl-6-nitroquinolin-2(1H)-one
6-bromo-4-[[(1S)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-7-fluoro-1-methyl-quinolin-2-one	No trifluoracetic acid was added; Crude product was purified by column chromatography instead of trituration	3,6-dibromo-4-[[(1S)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-7-fluoro-1-methyl-quinolin-2-one

Table P2A

Product	LC-MS (ESI)	^{1}H NMR
(S)-3-bromo-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl)amino)-1-methyl-6-nitro-1,8-naphthyridin-2(1H)-one	m/z = 433.27 $[M+H]^+$	
(S)-3-bromo-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl)amino)-8-fluoro-1-methyl-6-nitroquinolin-2(1H)-one	m/z = 451.23 $[M+2H]^+$	
3,6-dibromo-4-[[(1S)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-7-fluoro-1-methyl-quinolin-2-one	m/z = 484.9 $[M+H]^+$	(400 MHz, DMSO-d6) δ = 8.42 (d, J = 7.6 Hz, 1H), 7.64 (d, J = 11.2 Hz, 1H), 5.76 - 5.58 (m, 2H), 3.93 (s, 1H), 3.89 - 3.75 (m, 2H), 3.62 (s, 3H), 1.33 - 1.17 (m, 1H), 0.71 - 0.45 (m, 3H), 0.41 - 0.27 (m, 1H)

Example P3



To a stirred solution of 6-(benzyloxy)-3-(1-methyl-6-(piperidin-4-yl)-1H-indazol-3-yl)pyridin-2-ol (Reactant A) (4.0 g, 9.65 mmol, 1 *equiv.*) and 1-(tert-butoxycarbonyl)-3-fluoropiperidine-4-carboxylic-acid (Reactant B) (2.38 g, 9.65 mmol, 1 *equiv.*) in DMF (40 mL) was added DIPEA (3.11 g, 24.12 mmol, 1 *equiv.*) and HATU (4.4 g, 11.58 mmol, 1.2 *equiv.*) at room temperature. The mixture was stirred at room temperature for 12 hours. The reaction mixture was diluted with ice water, and the solid precipitate was filtered and dried to get crude product. The crude product was then purified by flash chromatography to afford *tert*-butyl-4-(4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidine-1-carbonyl)-3-fluoropiperidine-1-carboxylate (4.0 g) as a pale-yellow solid. **LC-MS (ESI):** m/z = 644.36 $[M+H]^+$

The compounds shown in the "**Product**" column of **Table P3** were synthesized using the method of **Example P3**, with variations noted in **Table P3**.

Table P3

Reactant A	Reactant B	Variation from Example P3	Product
6-(benzyloxy)-3-(1-methyl-6-(piperidin-4-yl)-1H-indazol-3-yl)pyridin-2-ol	1-(tert-butoxycarbonyl)-3-fluoropiperidine-4-carboxylic-acid		*tert*-butyl-4-(4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidine-1-carbonyl)-3-fluoropiperidine-1-carboxylate
6-(benzyloxy)-3-(1-methyl-6-(piperazin-1-yl)-1H-indazol-3-yl)pyridin-2-ol	1-(tert-butoxycarbonyl)-3,3-dimethylpiperidine-4-carboxylic-acid	T3P (1.5 *equiv.*) instead of HATU; reaction time: 2 hours; crude product was used in the next step without further purification	*tert*-butyl-4-(4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperazine-1-carbonyl)-3,3-dimethylpiperidine-1-carboxylate
tert-butyl 3,9-diazaspiro[5.5]undecane-3-carboxylate	1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)-3-methylpiperidine-4-carboxylic-acid	Crude product was used in the next step without further purification	*tert*-butyl-9-(1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)-3-methylpiperidine-4-carbonyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate
3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indazole-hydrochloride	1-(tert-butoxycarbonyl)-3-methylpiperidine-4-carboxylic-acid	T3P (1.5 *equiv.*) instead of HATU; reaction time: 2 hours; work-up A was used	*tert*-butyl-4-(4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)-1,2,3,6-tetrahydropyridine-1-carbonyl)-3-methylpiperidine-1-carboxylate
3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indazole	1-(tert-butoxycarbonyl)-3-methylpiperidine-4-carboxylic-acid	work-up B was used	*tert*-butyl-4-(4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)-1,2,3,6-tetrahydropyridine-1-carbonyl)-3-methylpiperidine-1-carboxylate
3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-6-(piperidin-4-yl)-1H-indazole	1-(tert-butoxycarbonyl)-3,3-dimethylpiperidine-4-carboxylic-acid	Reaction time: 2 hours; crude product was used in the next step without further purification	*tert*-butyl-4-(4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidine-1-carbonyl)-3,3-dimethylpiperidine-1-carboxylate
1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidine-4-carboxylic-acid	*tert*-butyl 3,9-diazaspiro[5.5]undecane-3-carboxylate	Reaction temperature: 0 °C; reaction time: 1 hour	*tert*-butyl-9-(1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidine-4-carbonyl)-3,9-

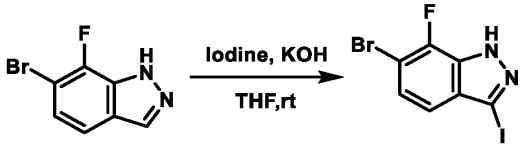
			diazaspiro[5.5]undecane-3-carboxylate
1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidine-4-carboxylic-acid	*tert*-butyl 3,9-diazaspiro[5.5]undecane-3-carboxylate	Reaction temperature: 0 °C; reaction time: 2 hours	*tert*-butyl-9-(1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidine-4-carbonyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate
3-(2,6-dibenzyloxy-3-pyridyl)-6-fluoro-1-methyl-7-piperazin-1-yl-indazole	1-tert-butoxycarbonyl-3-methyl-piperidine-4-carboxylic-acid	work-up A was used	*tert*-butyl-4-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-6-fluoro-1-methyl-indazol-7-yl]piperazine-1-carbonyl]-3-methyl-piperidine-1-carboxylate
3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-6-(piperidin-4-yl)-1H-indazole	1-(tert-butoxycarbonyl)-3-fluoropiperidine-4-carboxylic-acid	Reaction time: 5 hours	*tert*-butyl-4-(4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidine-1-carbonyl)-3-fluoropiperidine-1-carboxylate
6-(benzyloxy)-3-(1-methyl-6-(piperidin-4-yl)-1H-indazol-3-yl)pyridin-2-ol	(3S,4S)-1-(tert-butoxycarbonyl)-3-methylpiperidine-4-carboxylic-acid	Reaction time: 16 hours	*tert*-butyl (3S,4S)-4-(4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidine-1-carbonyl)-3-methylpiperidine-1-carboxylate
6-(benzyloxy)-5-(1-methyl-7-(piperazin-1-yl)-1H-indazol-3-yl)pyridin-2-ol	(3S,4S)-1-(tert-butoxycarbonyl)-3-methylpiperidine-4-carboxylic-acid	Reaction time: 4 hours	*tert*-butyl-(3S,4S)-4-(4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-1-methyl-1H-indazol-7-yl)piperazine-1-carbonyl)-3-methylpiperidine-1-carboxylate
6-(benzyloxy)-3-(1-methyl-6-(piperidin-4-yl)-1H-indazol-3-yl)pyridin-2-ol	(3R,4R)-1-(tert-butoxycarbonyl)-3-methylpiperidine-4-carboxylic-acid	Reaction time: 16 hours	*tert*-butyl (3R,4R)-4-(4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidine-1-carbonyl)-3-methylpiperidine-1-carboxylate
6-(benzyloxy)-5-(1-methyl-7-(piperazin-1-yl)-1H-indazol-3-yl)pyridin-2-ol	(3R,4R)-1-(tert-butoxycarbonyl)-3-methylpiperidine-4-carboxylic-acid	Reaction time: 4 hours	*tert*-butyl-(3R,4R)-4-(4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-1-methyl-1H-indazol-7-yl)piperazine-1-carbonyl)-3-methylpiperidine-1-carboxylate

Table P3A

Product	LC-MS (ESI)
tert-butyl-4-(4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidine-1-carbonyl)-3-fluoropiperidine-1-carboxylate	m/z = 644.36 $[M+H]^+$

tert-butyl-4-(4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperazine-1-carbonyl)-3,3-dimethylpiperidine-1-carboxylate	m/z = 655.70 $[M+H]^+$
tert-butyl-9-(1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)-3-methylpiperidine-4-carbonyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	m/z = 799.52 $[M+H]^+$
tert-butyl-4-(4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)-1,2,3,6-tetrahydropyridine-1-carbonyl)-3-methylpiperidine-1-carboxylate	m/z = 746.38 $[M+H]^+$
tert-butyl-4-(4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)-1,2,3,6-tetrahydropyridine-1-carbonyl)-3-methylpiperidine-1-carboxylate	m/z = 747.93 $[M+H]^+$
tert-butyl-4-(4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidine-1-carbonyl)-3,3-dimethylpiperidine-1-carboxylate	m/z = 744.77 $[M+H]^+$
tert-butyl-9-(1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidine-4-carbonyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	m/z = 817.75 $[M+H]^+$
tert-butyl-9-(1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidine-4-carbonyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	m/z = 817.48 $[M+H]^+$
tert-butyl-4-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-6-fluoro-1-methyl-indazol-7-yl]piperazine-1-carbonyl]-3-methyl-piperidine-1-carboxylate	m/z = 749.4 $[M+H]^+$
tert-butyl-4-(4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidine-1-carbonyl)-3-fluoropiperidine-1-carboxylate	m/z = 734.74 $[M+H]^+$
tert-butyl (3S,4S)-4-(4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidine-1-carbonyl)-3-methylpiperidine-1-carboxylate	m/z = 640.37 $[M+H]^+$
tert-butyl-(3S,4S)-4-(4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-1-methyl-1H-indazol-7-yl)piperazine-1-carbonyl)-3-methylpiperidine-1-carboxylate	m/z = 639.65 $[M-H]^-$
tert-butyl (3R,4R)-4-(4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidine-1-carbonyl)-3-methylpiperidine-1-carboxylate	m/z = 640.74 $[M+H]^+$
tert-butyl-(3R,4R)-4-(4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-1-methyl-1H-indazol-7-yl)piperazine-1-carbonyl)-3-methylpiperidine-1-carboxylate	m/z = 639.61 $[M-H]^-$

Example P4



A solution of 6-bromo-7-fluoro-1H-indazole (Reactant) (16.0 g, 74.41 mmol, 1 *equiv.*) and potassium hydroxide (12.52 g, 223.23 mmol, 1 *equiv.*) in THF (160 mL) was stirred at room temperature for 1 hour. To this mixture was added Iodine (18.88 g, 74.41 mmol, 1 *equiv.*) at 0°C. The resulting reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was quenched with ice-water (200 ml) and extracted with ethyl-acetate (500 ml). The organic layer was concentrated under reduced pressure to get crude compound which was triturated with diethyl-ether (200 mL) to get 6-bromo-7-fluoro-3-iodo-1H-indazole (20.0 g) as a brown solid. **LC-MS (ESI):** m/z = 342.40 $[M+H]^+$

The compounds shown in the "**Product**" column of **Table P4** were synthesized using the method of **Example P4**, with variations noted in **Table P4**.

Table P4

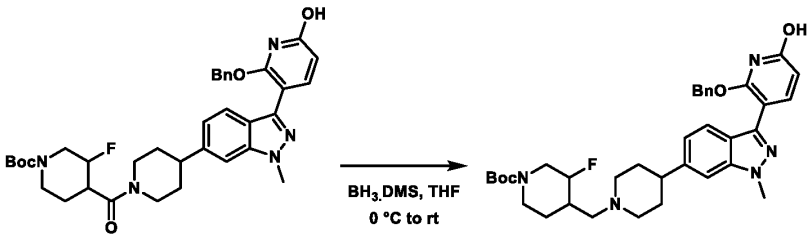
Reactant	Variation from Example P4	Product
6-bromo-7-fluoro-1H-indazole		6-bromo-7-fluoro-3-iodo-1H-indazole
3-bromo-4-(trifluoromethyl)aniline	NIS (1.0 *equiv.*) instead of iodine; reaction time: 2 hours; reaction solvent: acetic acid; crude product was purified by flash column chromatography instead of trituration	5-bromo-2-iodo-4-(trifluoromethyl)aniline
6-bromo-5-(trifluoromethyl)-1H-indazole	Reaction solvent: DMF; reaction time: 1 hour; work-up C was used	6-bromo-3-iodo-5-(trifluoromethyl)-1H-indazole
tert-butyl-(2R)-2-methyl-4-(1-methylindazol-6-yl)piperidine-1-carboxylate	NIS (1.5 *equiv.*) instead of iodine; reaction solvent: DMSO; reaction temperature: 90 °C; reaction time: 2 hours; work-up C was used	*tert*-butyl-(2R)-4-(3-iodo-1-methyl-indazol-6-yl)-2-methyl-piperidine-1-carboxylate
tert-butyl-2,2-dimethyl-4-(1-methylindazol-6-yl)piperidine-1-carboxylate	NIS (1.5 *equiv.*) instead of iodine; reaction solvent: DMSO; reaction temperature: 90 °C; reaction time: 1 hours; work-up A was used	*tert*-butyl-4-(3-iodo-1-methyl-indazol-6-yl)-2,2-dimethyl-piperidine-1-carboxylate
6-bromo-5-fluoro-1H-indazole	Reaction solvent: 1,4 dioxane; reaction time: 2 hour; work-up C was used	6-bromo-5-fluoro-3-iodo-1H-indazole
6-bromo-5-methyl-1H-indazole	Reaction solvent: DMF; reaction time: 12 hours; reaction temperature: 30 °C; work-up A was used	6-bromo-3-iodo-5-methyl-1H-indazole
tert-butyl-3-fluoro-4-(1-methylindazol-6-yl)piperidine-1-carboxylate	NIS (1.5 *equiv.*) instead of iodine; reaction solvent: DMSO; reaction temperature: 90 °C; reaction time: 2 hours; work-up A was used	*tert*-butyl-3-fluoro-4-(3-iodo-1-methyl-indazol-6-yl)piperidine-1-carboxylate
6-bromo-1,7-dimethyl-1H-indazole	NIS (1.5 *equiv.*) instead of iodine; reaction solvent: DMSO; reaction temperature: 90 °C; reaction	6-bromo-3-iodo-1,7-dimethyl-1H-indazole

	time: 3 hours; work-up A was used	
2-fluoro-3-(trifluoromethyl)aniline	NBS (1.1 *equiv.*) instead of iodine; reaction solvent: DCM; work-up U was used	4-bromo-2-fluoro-3-(trifluoromethyl)aniline
6-bromo-7-(trifluoromethyl)-1H-indazole	NIS (1.5 *equiv.*) instead of iodine; reaction solvent: DMSO; reaction temperature: 90 °C; reaction time: 1 hour; work-up Q was used	6-bromo-3-iodo-7-(trifluoromethyl)-1H-indazole
6-bromo-1H-indazole	Reaction time: 3 hours; work-up J was used	6-bromo-3-iodo-1H-indazole
3-bromo-2,4-difluoro-aniline	Reaction solvent: EtOH; Ag_2SO_4 (1.0 *equiv.*) instead of potassium hydroxide; reaction time 3 hours; work-up H was used	3-bromo-2,4-difluoro-6-iodo-aniline
6-bromo-5,7-difluoro-1H-indazole	Reaction solvent: DMF; reaction time: 0.5 hours; work-up D was used	6-bromo-5,7-difluoro-3-iodo-1H-indazole

Table P4A

Product	LC-MS (ESI)	^{1}H NMR
6-bromo-7-fluoro-3-iodo-1H-indazole	m/z = 342.40 $[M+H]^+$	
5-bromo-2-iodo-4-(trifluoromethyl)aniline	m/z = 365.8 $[M+H]^+$	
6-bromo-3-iodo-5-(trifluoromethyl)-1H-indazole	m/z = 390.8 $[M+H]^+$	
tert-butyl-(2R)-4-(3-iodo-1-methyl-indazol-6-yl)-2-methyl-piperidine-1-carboxylate	m/z = 456.0 $[M+H]^+$	
tert-butyl-4-(3-iodo-1-methyl-indazol-6-yl)-2,2-dimethyl-piperidine-1-carboxylate	m/z = 470.1 $[M+H]^+$	
6-bromo-5-fluoro-3-iodo-1H-indazole	m/z = 340.7 $[M+H]^+$	
6-bromo-3-iodo-5-methyl-1H-indazole		
tert-butyl-3-fluoro-4-(3-iodo-1-methyl-indazol-6-yl)piperidine-1-carboxylate	m/z = 460.2 $[M+H]^+$	
6-bromo-3-iodo-1,7-dimethyl-1H-indazole		(400 MHz, DMSO-d6) δ = 7.37 (d, J = 8.8 Hz, 1H), 7.16 (d, J = 8.8 Hz, 1H), 4.29 (s, 3H), 2.81 (s, 3H)
4-bromo-2-fluoro-3-(trifluoromethyl)aniline	m/z = 259.0 $[M+H]^+$	(400 MHz, CHLOROFORM-d) δ = 7.22 - 7.14 (m, 1H), 6.70 (t, J = 8.4 Hz, 1H)
6-bromo-3-iodo-7-(trifluoromethyl)-1H-indazole	m/z = 390.7 $[M+H]^+$	
6-bromo-3-iodo-1H-indazole	m/z = 323.06 $[M+H]^+$	
3-bromo-2,4-difluoro-6-iodo-aniline	m/z = 333.8 $[M+H]^+$	
6-bromo-5,7-difluoro-3-iodo-1H-indazole		

Example P5



To a stirred solution of *tert*-butyl-4-(4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidine-1-carbonyl)-3-fluoropiperidine-1-carboxylate (Reactant) (4.0 g, 6.21 mmol, 1 *equiv.*) in THF (80.0 mL) was added BH_3.DMS (neat) (8.0 mL) at 0 °C. The mixture was stirred at room temperature for 16 hours. The reaction mixture was then quenched with MeOH (30 mL), concentrated and co-distilled with MeOH (30 mL) to get crude. The crude product was refluxed with MeOH (150 mL) for 4 hours, cooled to room temperature, concentrated, and dried to afford *tert*-butyl-4-((4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (2.0 g) as an off white solid. **LC-MS (ESI):** m/z = 630.39 $[M+H]^+$

The compounds shown in the "**Product**" column of **Table P5** were synthesized using the method of **Example P5**, with variations noted in **Table P5**.

Table P5

Reactant	Variation from Example P5	Product
tert-butyl-4-(4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidine-1-carbonyl)-3-fluoropiperidine-1-carboxylate		*tert*-butyl-4-((4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate
tert-butyl-4-(4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperazine-1-carbonyl)-3,3-dimethylpiperidine-1-carboxylate	Crude product was purified by flash column chromatography	*tert*-butyl-4-((4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperazin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate
1-tert-butoxycarbonyl-3-methyl-piperidine-4-carboxylic-acid	Reaction was under N_2 atmosphere; reaction temperature: 60 °C; reaction time: 2.5 hours; No co-distillation step; crude was purified by flash column chromatography	*tert*-butyl-4-(hydroxylmethyl)-3-methyl-piperidine-1-carboxylate
tert-butyl-4-(4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidine-1-carbonyl)-3,3-dimethylpiperidine-1-carboxylate	Reaction time: 6 hours; work-up M was used	*tert*-butyl-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate
tert-butyl-9-(1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-	Reaction time: 18 hours; work-up M was used	*tert*-butyl-9-((1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-

fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidine-4-carbonyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate		fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate
tert-butyl-9-(1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidine-4-carbonyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	work-up M was used	*tert*-butyl-9-((1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate
tert-butyl-4-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-6-fluoro-1-methyl-indazol-7-yl]piperazine-1-carbonyl]-3-methyl-piperidine-1-carboxylate	Reaction temperature: 50 °C; reaction time: 2 hours; work-up P was used	*tert*-butyl-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-6-fluoro-1-methyl-indazol-7-yl]piperazin-1-yl]methyl]-3-methyl-piperidine-1-carboxylate
(3R,4S)-1-tert-butoxycarbonyl-3-methyl-piperidine-4-carboxylic-acid	BH_3THF (4.0 *equiv.*) in THF instead of BH_3.DMS; reaction temperature: 60 °C; reaction time: 2 hours; reaction was quenched with MeOH followed by work-up H	*tert*-butyl-(3R,4S)-4-(hydroxymethyl)-3-methyl-piperidine-1-carboxylate
(3R,4R)-1-tert-butoxycarbonyl-3-methyl-piperidine-4-carboxylic-acid	BH_3THF (4.0 *equiv.*) in THF instead of BH_3.DMS; reaction temperature: 60 °C; reaction time: 2 hours; work-up P was used	*tert*-butyl-(3R,4R)-4-(hydroxymethyl)-3-methyl-piperidine-1-carboxylate
(4R)-1-tert-butoxycarbonyl-3,3-difluoro-piperidine-4-carboxylic-acid	BH_3THF (4.0 *equiv.*) in THF instead of BH_3.DMS; reaction temperature: 60 °C; reaction time: 2 hours; work-up P was used	*tert*-butyl-(4R)-3,3-difluoro-4-(hydroxymethyl)piperidine-1-carboxylate
(4S)-1-tert-butoxycarbonyl-3,3-difluoro-piperidine-4-carboxylic-acid	BH_3THF (4.0 *equiv.*) in THF instead of BH_3.DMS; reaction temperature: 60 °C; reaction time: 2 hours; work-up P was used	*tert*-butyl-(4S)-3,3-difluoro-4-(hydroxymethyl)piperidine-1-carboxylate
tert-butyl-4-(4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidine-1-carbonyl)-3-fluoropiperidine-1-carboxylate	BH_3THF (4.0 *equiv.*) in THF instead of BH_3.DMS; reaction temperature: 70 °C; reaction time: 6 hours	*tert*-butyl-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate
tert-butyl (3S,4S)-4-(4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidine-1-carbonyl)-3-methylpiperidine-1-carboxylate		*tert*-butyl (3S,4S)-4-((4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate
tert-butyl-(3S,4S)-4-(4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-1-methyl-1H-indazol-7-yl)piperazine-1-carbonyl)-3-methylpiperidine-1-carboxylate	Crude was purified by flash column chromatography after reflux with MeOH	*tert*-butyl-(3S,4S)-4-((4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-1-methyl-1H-indazol-7-yl)piperazin-1-yl)methyl)-3-methylpiperidine-1-carboxylate
tert-butyl (3R,4R)-4-(4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidine-1-carbonyl)-3-methylpiperidine-1-carboxylate		*tert*-butyl (3R,4R)-4-((4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate
tert-butyl-(3R,4R)-4-(4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-1-methyl-1H-indazol-7-	Crude was purified by flash column chromatography after reflux with MeOH	*tert*-butyl-(3R,4R)-4-((4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-1-methyl-1H-indazol-7-

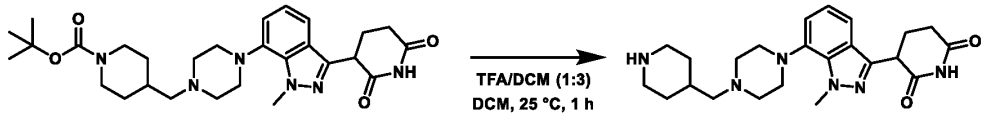
yl)piperazine-1-carbonyl)-3-methylpiperidine-1-carboxylate		yl)piperazin-1-yl)methyl)-3-methylpiperidine-1-carboxylate

Table P5A

Product	LC-MS (ESI)	^{1}H NMR
tert-butyl-4-((4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate	m/z = 630.39 $[M+H]^+$	
tert-butyl-4-((4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperazin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate	m/z = 641.35 $[M+H]^+$	
tert-butyl-4-(hydroxylmethyl)-3-methyl-piperidine-1-carboxylate		(400 MHz, DMSO-d6) δ = 4.37 (t, J = 5.2 Hz, 1H), 3.92 (d, J = 12.8 Hz, 2H), 3.55-3.45 (m, 1H), 3.33 - 3.21 (m, 2H), 2.68 (s, 1H), 1.72-1.60 (m, 1H), 1.39 (s, 9H), 1.33 - 1.26 (m, 1H), 1.22-1.07 (m, 2H), 0.84 (d, J = 6.4 Hz, 3H)
tert-butyl-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate	m/z = 730.48 $[M+H]^+$	
tert-butyl-9-((1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	m/z = 803.92 $[M+H]^+$	
tert-butyl-9-((1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	m/z = 803.76 $[M+H]^+$	
tert-butyl-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-6-fluoro-1-methyl-indazol-7-yl]piperazin-1-yl]methyl]-3-methyl-piperidine-1-carboxylate	m/z = 735.7 $[M+H]^+$	
tert-butyl-(3R,4S)-4-(hydroxymethyl)-3-methyl-piperidine-1-carboxylate		(400 MHz, DMSO-d6) δ = 4.37 (t, J = 5.2 Hz, 1H), 3.92 (br d, J = 12.8 Hz, 1H), 3.79 (br d, J = 2.8 Hz, 1H), 3.48 (ddd, J = 3.2, 5.2, 10.4 Hz, 1H), 3.32 - 3.24 (m, 1H), 1.71 - 1.61 (m, 1H), 1.34 - 1.24 (m, 1H), 1.20 - 1.09 (m, 2H), 0.84 (d, J = 6.4 Hz, 3H)
tert-butyl-(3R,4R)-4-(hydroxymethyl)-3-methyl-piperidine-1-carboxylate	m/z = 603.3 $[M+H]^+$	
tert-butyl-(4R)-3,3-difluoro-4-(hydroxymethyl)piperidine-1-carboxylate		(400 MHz, CHLOROFORM-d) δ = 4.44 - 4.04 (m, 2H), 4.03 - 3.94 (m, 1H), 3.71 - 3.59 (m, 1H), 3.11 - 2.70 (m, 2H), 2.15 - 1.99 (m, 1H), 1.93 - 1.82 (m, 2H), 1.65 - 1.52 (m, 1H), 1.46 (s, 9H)
tert-butyl-(4S)-3,3-difluoro-4-(hydroxymethyl)piperidine-1-carboxylate		(400 MHz, CHLOROFORM-d) δ = 4.40 - 4.06 (m, 2H), 4.04 - 3.94 (m, 1H), 3.72 - 3.58 (m, 1H), 3.09 - 2.70 (m, 2H), 2.18 - 1.99 (m, 1H), 1.93 - 1.83 (m, 2H), 1.66 - 1.52 (m, 2H), 1.46 (s, 9H)
tert-butyl-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate	m/z = 720.7 $[M+H]^+$	

tert-butyl (3S,4S)-4-((4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate	m/z = 626.77 $[M+H]^+$	
tert-butyl-(3S,4S)-4-((4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-1-methyl-1H-indazol-7-yl)piperazin-1-yl)methyl)-3-methylpiperidine-1-carboxylate	m/z = 627.38 $[M+H]^+$	
tert-butyl (3R,4R)-4-((4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate	m/z = 626.69 $[M+H]^+$	
tert-butyl-(3R,4R)-4-((4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-1-methyl-1H-indazol-7-yl)piperazin-1-yl)methyl)-3-methylpiperidine-1-carboxylate	m/z = 627.45 $[M+H]^+$	

Example P6



To a solution of *tert*-butyl-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-7-yl]piperazin-1-yl]methyl]piperidine-1-carboxylate (Reactant) (250 mg, 476.51 μmol, 1 *equiv.*) in DCM (3 mL) was added TFA (1 mL). The mixture was stirred at 25 °C for 1 hour. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to afford 3-[1-methyl-7-[4-(4-piperidylmethyl)piperazin-1-yl]indazol-3-yl]piperidine-2,6-dione (160 mg) as a green solid. **LC-MS (ESI):** m/z = 425.2 $[M+H]^+$

The compounds shown in the "**Product**" column of **Table P6** were synthesized using the method of **Example P6**, with variations noted in **Table P6**.

Table P6

Reactant	Variation from Example P6	Product
tert-butyl-(3S)-4-[(1-benzyloxycarbonyl-4-piperidyl)methyl]-3-methyl-piperazine-1-carboxylate	Reaction time: 5 hours; The residue was used in the next step without further purification	benzyl-4-[[(2S)-2-methylpiperazin-1-yl]methyl]piperidine-1-carboxylate
tert-butyl-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-7-yl]piperazin-1-yl]methyl]piperidine-1-carboxylate		3-[1-methyl-7-[4-(4-piperidylmethyl)piperazin-1-yl]indazol-3-yl]piperidine-2,6-dione
tert-butyl-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-5-	Residue was triturated with DCM	3-[1-methyl-6-(4-piperidyl)-5-(trifluoromethyl)indazol-3-

Reactant	Variation from Example P6	Product
(trifluoromethyl)indazol-6-yl]piperidine-1-carboxylate		yl]piperidine-2,6-dione
tert-butyl-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-5-(trifluoromethyl)indazol-6-yl]-1-piperidyl]methyl]piperidine-1-carboxylate	Reaction time: 5 hours; the residue was used in the next step without further purification	3-[1-methyl-6-[1-(4-piperidylmethyl)-4-piperidyl]-5-(trifluoromethyl)indazol-3-yl]piperidine-2,6-dione
tert-butyl-4-[3-(2,6-dioxo-3-piperidyl)-7-fluoro-1-methyl-indazol-6-yl]piperidine-1-carboxylate	Reaction solvent: HCl/Dioxane (4.0 M) instead of TFA/DCM; The residue was used in the next step without further purification	3-[7-fluoro-1-methyl-6-(4-piperidyl)indazol-3-yl]piperidine-2,6-dione
tert-butyl-(3R,4S)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate	Reaction solvent: HCl/Dioxane (4.0 M) instead of TFA/DCM; reaction time: 12 hours; The residue was used in the next step without further purification	3-(7-fluoro-1-methyl-6-(1-(((3R,4S)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1H-indazol-3-yl)piperidine-2,6-dione
tert-butyl-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-7-yl]piperidine-1-carboxylate	The residue was used in the next step without further purification	3-[1-methyl-7-(4-piperidyl)indazol-3-yl]piperidine-2,6-dione
tert-butyl-(3S,4S)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-7-yl]-1-piperidyl]methyl]-3-methyl-piperidine-1-carboxylate	The residue was used in the next step without further purification	3-[1-methyl-7-[1-[[(3S,4S)-3-methyl-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione
tert-butyl-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidine-1-carboxylate	The residue was triturated with diethyl-ether	6-(benzyloxy)-3-(1-methyl-6-(piperidin-4-yl)-1H-indazol-3-yl)pyridin-2-ol
tert-butyl-(3S,4R)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate	Work-up I was used	3-(6-(1-(((3S,4R)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione
tert-butyl-(3R,4S)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate	Work-up I was used	3-(6-(1-(((3R,4S)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione
tert-butyl-(4R)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperazin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate	Work-up I was used	3-(6-(4-(((R)-3,3-dimethylpiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione
tert-butyl-(4S)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperazin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate	Work-up I was used	3-(6-(4-(((S)-3,3-dimethylpiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione
tert-butyl-9-(((3S,4S)-1-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	Work-up I was used	3-(6-((3S,4S)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione
tert-butyl-9-(((3R,4R)-1-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-	Work-up I was used	3-(6-((3R,4R)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione

Reactant	Variation from Example P6	Product
carboxylate		
tert-butyl-4-(((2S)-4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-7-yl)-2-methylpiperazin-1-yl)methyl)-3,3-difluoropiperidine-1-carboxylate	The residue was used in the next step without further purification	3-(7-((3S)-4-((3,3-difluoropiperidin-4-yl)methyl)-3-methylpiperazin-1-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione
tert-butyl-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)-3,3-difluoro-3,6-dihydropyridine-1(2H)-carboxylate	Reaction solvent: HCl/Dioxane (4.0 M) instead of TFA/DCM; The residue was triturated with diethyl ether and used in the next step without further purification	6-(benzyloxy)-5-(6-(3,3-difluoro-1,2,3,6-tetrahydropyridin-4-yl)-1-methyl-1H-indazol-3-yl)pyridin-2-ol
tert-butyl-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)-3,3-difluoropiperidin-1-yl)methyl)piperidine-1-carboxylate	Reaction solvent: HCl/Dioxane (4.0 M) instead of TFA/DCM; the residue was triturated with diethyl ether	3-(6-(3,3-difluoro-1-(piperidin-4-ylmethyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione
tert-butyl-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate	Reaction solvent: HCl/Dioxane (4.0 M) instead of TFA/DCM; the residue was triturated with diethyl ether and used in the next step without further purification	3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indazole-hydrochloride
tert-butyl-(3S,4S)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate	The residue was triturated with diethyl ether and used in the next step without further purification	3-(7-fluoro-1-methyl-6-(1-(((3S,4S)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1H-indazol-3-yl)piperidine-2,6-dione
tert-butyl-(3R,4R)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate	The residue was triturated with diethyl ether and used in the next step without further purification	3-(7-fluoro-1-methyl-6-(1-(((3R,4R)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1H-indazol-3-yl)piperidine-2,6-dione
tert-butyl-4-acetylpiperidine-1-carboxylate	The residue was triturated with diethyl ether and used in the next step without further purification	1-(piperidin-4-yl)ethan-1-one
tert-butyl-9-((1R)-1-(1-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	Reaction solvent: HCl/Dioxane (4.0 M) instead of TFA/DCM; the residue was triturated with diethyl ether	3-(6-(4-((R)-1-(3,9-diazaspiro[5.5]undecan-3-yl)ethyl)piperidin-1-yl)-7-fluoro-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione
tert-butyl-9-((1R)-1-(1-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	Reaction solvent: HCl/Dioxane (4.0 M) instead of TFA/DCM; the residue was triturated with diethyl ether	3-(6-(4-((R)-1-(3,9-diazaspiro[5.5]undecan-3-yl)ethyl)piperidin-1-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione
tert-butyl-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate	The residue was triturated with diethyl ether	3-(1-methyl-6-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1H-indazol-3-yl)piperidine-2,6-dione
tert-butyl-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate	The residue was triturated with n-pentane	3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indazole
tert-butyl-(3S,4S)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-	The residue was triturated with n-pentane	3-(5-fluoro-1-methyl-6-(1-(((3S,4S)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1H-indazol-3-yl)piperidine-2,6-dione

Reactant	Variation from Example P6	Product
carboxylate		
tert-butyl-(3R,4R)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate	The residue was triturated with n-pentane	3-(5-fluoro-1-methyl-6-(1-(((3R,4R)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1H-indazol-3-yl)piperidine-2,6-dione
tert-butyl-9-((1S)-1-(1-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	The residue was triturated with diethyl ether	3-(6-(4-((S)-1-(3,9-diazaspiro[5.5]undecan-3-yl)ethyl)piperidin-1-yl)-7-fluoro-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione
tert-butyl-9-((1S)-1-(1-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	The residue was triturated with diethyl ether	3-(6-(4-((S)-1-(3,9-diazaspiro[5.5]undecan-3-yl)ethyl)piperidin-1-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione
tert-butyl-(2R)-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-2-methyl-piperidine-1-carboxylate	Reaction solvent: HCl/Dioxane (4.0 M) instead of TFA/DCM; the residue was used in the next step without further purification	6-benzyloxy-3-[1-methyl-6-[(2R)-2-methyl-4-piperidyl]indazol-3-yl]-3H-pyridin-2-one
tert-butyl-4-[[(2R,4R)-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-2-methyl-1-piperidyl]methyl]piperidine-1-carboxylate	Reaction solvent: HCl/Dioxane (4.0 M) instead of TFA/DCM; the residue was used in the next step without further purification	3-(1-methyl-6-((2R,4R)-2-methyl-1-(piperidin-4-ylmethyl)piperidin-4-yl)-1H-indazol-3-yl)piperidine-2,6-dione
tert-butyl-4-[(1R)-1-[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-1-piperidyl]-2,2,2-trifluoro-ethyl]piperidine-1-carboxylate	The residue was used in the next step without further purification	3-[1-methyl-6-[1-[(1R)-2,2,2-trifluoro-1-(4-piperidyl)ethyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione
tert-butyl-4-[(1S)-1-[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-1-piperidyl]-2,2,2-trifluoro-ethyl]piperidine-1-carboxylate	The residue was used in the next step without further purification	3-[1-methyl-6-[1-[(1S)-2,2,2-trifluoro-1-(4-piperidyl)ethyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione
tert-butyl-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperazin-1-yl)methyl)piperidine-1-carboxylate	Reaction solvent: HCl/Dioxane (4.0 M) instead of TFA/DCM; The residue was used in the next step without further purification	3-(1-methyl-6-(4-(piperidin-4-ylmethyl)piperazin-1-yl)-1H-indazol-3-yl)piperidine-2,6-dione
tert-butyl-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-7-(trifluoromethyl)indazol-6-yl]-1-piperidyl]methyl]piperidine-1-carboxylate	Work-up N was used	3-[1-methyl-6-[1-(4-piperidylmethyl)-4-piperidyl]-7-(trifluoromethyl)indazol-3-yl]piperidine-2,6-dione
tert-butyl-(3R,4S)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-7-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate	Reaction solvent: HCl/Dioxane (4.0 M) instead of TFA/DCM; reaction time: 14 hours; the residue was used in the next step without further purification	3-(1-methyl-7-(1-(((3R,4S)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1H-indazol-3-yl)piperidine-2,6-dione
tert-butyl-(3S,4R)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-7-yl)piperidin-1-yl)methyl)-3-methyl-piperidine-1-carboxylate	Reaction solvent: HCl/Dioxane (4.0 M) instead of TFA/DCM; the residue was used in the next step without further purification.	3-(1-methyl-7-(1-(((3S,4R)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1H-indazol-3-yl)piperidine-2,6-dione
tert-butyl-(4R)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-	Work-up I was used	3-(6-(1-(((R)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-1-

Reactant	Variation from Example P6	Product
yl)methyl)-3,3-dimethylpiperidine-1-carboxylate		methyl-1H-indazol-3-yl)piperidine-2,6-dione
tert-butyl-(4S)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate	Work-up I was used	3-(6-(1-(((S)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione
tert-butyl-9-(((3R,4R)-1-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	Work-up I was used	3-(6-((3R,4R)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-7-fluoro-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione
tert-butyl-9-(((3S,4S)-1-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	Work-up I was used	3-(6-((3S,4S)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-7-fluoro-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione
tert-butyl-9-(((3R,4S)-1-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	Work-up I was used	3-(6-((3R,4S)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-7-fluoro-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione
tert-butyl-9-(((3S,4R)-1-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	Work-up I was used	3-(6-((3S,4R)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-7-fluoro-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione
tert-butyl-9-(((3R,4R)-1-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	Work-up I was used	3-(6-((3R,4R)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-5-fluoro-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione
tert-butyl-9-(((3S,4S)-1-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	Work-up I was used	3-(6-((3S,4S)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-5-fluoro-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione
tert-butyl-9-(((3R,4S)-1-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	Work-up I was used	3-(6-((3R,4S)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-5-fluoro-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione
tert-butyl-9-(((3S,4R)-1-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	Work-up I was used	3-(6-((3S,4R)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-5-fluoro-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione
tert-butyl-4-(3-(2,6-dioxopiperidin-3-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)piperidine-1-carboxylate	Reaction time: 2 hours; the residue was triturated with diethyl-ether and the solid was dried under reduced pressure	3-(6-(piperidin-4-yl)-1H-indazol-3-yl)piperidine-2,6-dione

Reactant	Variation from Example P6	Product
tert-butyl-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1H-indazol-6-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate	Reaction time: 2 hours; the residue was triturated with diethyl-ether and the solid was dried under reduced pressure	3-(6-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1H-indazol-3-yl)piperidine-2,6-dione
tert-butyl-(3S,4S)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate	Reaction time: 2 hours; the residue was triturated with *n*-pentane and the solid was dried under reduced pressure	3-(6-(1-(((3S,4S)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione
tert-butyl-(3S,4S)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-6-fluoro-1-methyl-indazol-7-yl]piperazin-1-yl]methyl]-3-methyl-piperidine-1-carboxylate	The residue was used in the next step without further purification	3-[6-fluoro-1-methyl-7-[4-[[(3S,4S)-3-methyl-4-piperidyl]methyl]piperazin-1-yl]indazol-3-yl]piperidine-2,6-dione
tert-butyl-(3R,4R)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-6-fluoro-1-methyl-indazol-7-yl]piperazin-1-yl]methyl]-3-methyl-piperidine-1-carboxylate	The residue was used in the next step without further purification	3-[6-fluoro-1-methyl-7-[4-[[(3R,4R)-3-methyl-4-piperidyl]methyl]piperazin-1-yl]indazol-3-yl]piperidine-2,6-dione
tert-butyl-(4S)-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-2,2-dimethyl-piperidine-1-carboxylate	Reaction solvent: HCl/Dioxane (4.0 M) in DCM instead of TFA/DCM; the residue was used in the next step without further purification	3-[6-[(4S)-2,2-dimethyl-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione
tert-butyl-4-[[(4S)-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-2,2-dimethyl-1-piperidyl]methyl]piperidine-1-carboxylate	Reaction solvent: HCl/Dioxane (4.0 M) in DCM instead of TFA/DCM; the residue was used in the next step without further purification	3-[6-[(4S)-2,2-dimethyl-1-(4-piperidylmethyl)-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione
tert-butyl-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5,7-difluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]piperidine-1-carboxylate	Reaction solvent: HCl/Dioxane (4.0 M) in DCM instead of TFA/DCM; the residue was used in the next step without further purification	3-[5,7-difluoro-1-methyl-6-[1-(4-piperidylmethyl)-4-piperidyl]indazol-3-yl]piperidine-2,6-dione
tert-butyl-(4R)-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-2,2-dimethyl-piperidine-1-carboxylate	Reaction solvent: HCl/Dioxane (4.0 M) in DCM instead of TFA/DCM; the residue was used in the next step without further purification	3-[6-[(4R)-2,2-dimethyl-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione
tert-butyl-4-[[(4R)-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-2,2-dimethyl-1-piperidyl]methyl]piperidine-1-carboxylate	Reaction solvent: HCl/Dioxane (4.0 M) in DCM instead of TFA/DCM; the residue was used in the next step without further purification	3-[6-[(4R)-2,2-dimethyl-1-(4-piperidylmethyl)-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione
tert-butyl-4-[3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate	Work-up N was used	3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)indazole
tert-butyl-4-[(1S)-1-[4-[3-(2,6-dioxo-3-piperidyl)-7-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]ethyl]piperidine-1-carboxylate	Reaction solvent: HCl/Dioxane (4.0 M) in DCM instead of TFA/DCM; the residue was used in the next step without further purification	3-[7-fluoro-1-methyl-6-[1-[(1S)-1-(4-piperidyl)ethyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione
tert-butyl-4-[(1S)-1-[4-[3-(2,6-dioxo-3-piperidyl)-5-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]ethyl]piperidine-1-carboxylate	Reaction solvent: HCl/Dioxane (4.0 M) in DCM instead of TFA/DCM; the residue was used in the next step without further purification	3-[5-fluoro-1-methyl-6-[1-[(1S)-1-(4-piperidyl)ethyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione

Reactant	Variation from Example P6	Product
benzyl-9-[(1S)-1-(1-tert-butoxycarbonyl-4-piperidyl)ethyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate	Reaction solvent: HCl/Dioxane (4.0 M) in DCM instead of TFA/DCM; the residue was used in the next step without further purification	benzyl-9-[(1S)-1-(4-piperidyl)ethyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate
tert-butyl-4-[3-(2,6-dioxo-3-piperidyl)-1-(2,2,2-trifluoroethyl)indazol-6-yl]piperidine-1-carboxylate	Reaction solvent: HCl/Dioxane (4.0 M) in DCM instead of TFA/DCM; the residue was used in the next step without further purification	3-[6-(4-piperidyl)-1-(2,2,2-trifluoroethyl)indazol-3-yl]piperidine-2,6-dione
tert-butyl-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-(2,2,2-trifluoroethyl)indazol-6-yl]-1-piperidyl]methyl]piperidine-1-carboxylate	HCl/Dioxane (4.0 M) instead of TFA/DCM; The residue was used in the next step without further purification	3-[6-[1-(4-piperidylmethyl)-4-piperidyl]-1-(2,2,2-trifluoroethyl)indazol-3-yl]piperidine-2,6-dione
tert-butyl-4-[(1R)-1-[4-[3-(2,6-dioxo-3-piperidyl)-7-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]ethyl]piperidine-1-carboxylate	Reaction solvent: HCl/Dioxane (4.0 M) in DCM instead of TFA/DCM; the residue was used in the next step without further purification	3-[7-fluoro-1-methyl-6-[1-[(1R)-1-(4-piperidyl)ethyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione
tert-butyl-4-[3-(2,6-dioxo-3-piperidyl)-5-fluoro-1-methyl-indazol-6-yl]piperidine-1-carboxylate	Reaction solvent: HCl/Dioxane (4.0 M) in DCM instead of TFA/DCM; the residue was used in the next step without further purification	3-[5-fluoro-1-methyl-6-(4-piperidyl)indazol-3-yl]piperidine-2,6-dione
tert-butyl-(3R,4S)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-methyl-piperidine-1-carboxylate	Reaction solvent: HCl/Dioxane (4.0 M) in DCM instead of TFA/DCM; the residue was used in the next step without further purification	3-[5-fluoro-1-methyl-6-[1-[[(3R,4S)-3-methyl-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione
tert-butyl-4-[3-(2,6-dioxo-3-piperidyl)-1-isopropyl-indazol-6-yl]piperidine-1-carboxylate	Reaction solvent: HCl/Dioxane (4.0 M) in DCM instead of TFA/DCM; the residue was used in the next step without further purification	3-[1-isopropyl-6-(4-piperidyl)indazol-3-yl]piperidine-2,6-dione
tert-butyl-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-isopropyl-indazol-6-yl]-1-piperidyl]methyl]piperidine-1-carboxylate	Reaction solvent: HCl/Dioxane (4.0 M) in DCM instead of TFA/DCM; the residue was used in the next step without further purification	3-[1-isopropyl-6-[1-(4-piperidylmethyl)-4-piperidyl]indazol-3-yl]piperidine-2,6-dione
tert-butyl-(3R,4R)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-7-yl]-1-piperidyl]methyl]-3-methyl-piperidine-1-carboxylate	Reaction solvent: HCl/Dioxane (4.0 M) in DCM instead of TFA/DCM; the residue was used in the next step without further purification	3-[1-methyl-7-[1-[[(3R,4R)-3-methyl-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione
tert-butyl-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-3-fluoro-piperidine-1-carboxylate	Reaction solvent: HCl/Dioxane (4.0 M) in DCM instead of TFA/DCM; the residue was used in the next step without further purification	3-(2,6-dibenzyloxy-3-pyridyl)-6-(3-fluoro-4-piperidyl)-1-methyl-indazole
tert-butyl-4-[[(3S,4S)-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-3-fluoro-1-piperidyl]methyl]piperidine-1-carboxylate	Reaction solvent: HCl/Dioxane (4.0 M) in DCM instead of TFA/DCM; the residue was used in the next step without further purification	3-[6-[(3S,4S)-3-fluoro-1-(4-piperidylmethyl)-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione
tert-butyl-(4R)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3,3-difluoro-piperidine-1-carboxylate	Reaction solvent: HCl/Dioxane (4.0 M) in DCM instead of TFA/DCM; reaction time: 2 hours; the residue was used in	3-[6-[1-[[(4R)-3,3-difluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione

Reactant	Variation from Example P6	Product
	the next step without further purification	
tert-butyl-(4S)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3,3-difluoro-piperidine-1-carboxylate	Reaction solvent: HCl/Dioxane (4.0 M) in DCM instead of TFA/DCM; reaction time: 2 hours; the residue was used in the next step without further purification	3-[6-[1-[[(4S)-3,3-difluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione
benzyl-9-[(1-tert-butoxycarbonyl-4-methyl-4-piperidyl)methyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate	Reaction solvent: HCl/Dioxane (4.0 M) in DCM instead of TFA/DCM; the residue was used in the next step without further purification	benzyl-9-[(4-methyl-4-piperidyl)methyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate
tert-butyl-4-[(1S)-1-[4-[3-(2,6-dioxo-3-piperidyl)-5,7-difluoro-1-methyl-indazol-6-yl]-1-piperidyl]ethyl]piperidine-1-carboxylate	Reaction solvent: HCl/Dioxane (4.0 M) in DCM instead of TFA/DCM; the residue was used in the next step without further purification	3-[5,7-difluoro-1-methyl-6-[1-[(1S)-1-(4-piperidyl)ethyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione
tert-butyl-4-[3-(2,6-dioxo-3-piperidyl)-1,5-dimethyl-indazol-6-yl]piperidine-1-carboxylate	Reaction solvent: HCl/Dioxane (2.0 M) in DCM instead of TFA/DCM; the residue was used in the next step without further purification	3-[1,5-dimethyl-6-(4-piperidyl)indazol-3-yl]piperidine-2,6-dione
tert-butyl-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1,5-dimethyl-indazol-6-yl]-1-piperidyl]methyl]piperidine-1-carboxylate	Reaction solvent: HCl/Dioxane (2.0 M) in DCM instead of TFA/DCM; the residue was used in the next step without further purification	3-[1,5-dimethyl-6-[1-(4-piperidylmethyl)-4-piperidyl]indazol-3-yl]piperidine-2,6-dione
benzyl-9-[(1-tert-butoxycarbonyl-4-piperidyl)methyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate	Reaction solvent: HCl/Dioxane (2.0 M) in DCM instead of TFA/DCM; the residue was used in the next step without further purification	benzyl-9-(4-piperidylmethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate
tert-butyl-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate	Reaction solvent: HCl/Dioxane (2.0 M) in DCM instead of TFA/DCM; the residue was used in the next step without further purification	3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)indazole
tert-butyl-(3S,4S)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-(trifluoromethyl)piperidine-1-carboxylate	Reaction solvent: HCl/Dioxane (2.0 M) in DCM instead of TFA/DCM; the residue was used in the next step without further purification	3-[1-methyl-6-[1-[[(3S,4S)-3-(trifluoromethyl)-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione
tert-butyl-(3S,4R)-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-3-fluoro-piperidine-1-carboxylate	Reaction solvent: HCl/Dioxane (2.0 M) in DCM instead of TFA/DCM; reaction time: 3 hours; the residue was used in the next step without further purification	3-(2,6-dibenzyloxy-3-pyridyl)-6-[(3S,4R)-3-fluoro-4-piperidyl]-1-methyl-indazole
tert-butyl-4-[[(3S,4R)-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-3-fluoro-1-piperidyl]methyl]piperidine-1-carboxylate	Reaction solvent: HCl/Dioxane (2.0 M) in DCM instead of TFA/DCM; reaction time: 3 hours; the residue was used in the next step without further purification	3-[6-[(3S,4R)-3-fluoro-1-(4-piperidylmethyl)-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione
tert-butyl-(3R,4S)-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-3-fluoro-piperidine-1-carboxylate	Reaction solvent: HCl/Dioxane (2.0 M) in DCM instead of TFA/DCM; the residue was used in the next step without further	3-(2,6-dibenzyloxy-3-pyridyl)-6-[(3R,4S)-3-fluoro-4-piperidyl]-1-methyl-indazole

Reactant	Variation from Example P6	Product
	purification	
tert-butyl-4-[[(3R,4S)-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-3-fluoro-1-piperidyl]methyl]piperidine-1-carboxylate	Reaction solvent: HCl/Dioxane (2.0 M) in DCM instead of TFA/DCM; the residue was used in the next step without further purification	3-[6-[(3R,4S)-3-fluoro-1-(4-piperidylmethyl)-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione
tert-butyl-(3S,4R)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-fluoro-piperidine-1-carboxylate	Reaction solvent: HCl/Dioxane (2.0 M) in DCM instead of TFA/DCM; the residue was used in the next step without further purification	3-[6-[1-[[(3S,4R)-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione
tert-butyl-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate	Reaction solvent: HCl/Dioxane (2.0 M) in DCM instead of TFA/DCM; reaction time: 4 hours; the residue was used in the next step without further purification	3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indazole
tert-butyl-(3R,4S)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate	Reaction solvent: HCl/Dioxane (2.0 M) in DCM instead of TFA/DCM; the residue was used in the next step without further purification	3-(6-(1-(((3R,4S)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione
tert-butyl-4-bromo-3,6-dihydro-2H-pyridine-1-carboxylate	Reaction solvent: HCl/Dioxane (2.0 M) in DCM instead of TFA/DCM; reaction time: 12 hours; the residue was used in the next step without further purification	4-bromo-1,2,3,6-tetrahydropyridine
tert-butyl-4-[(1S)-1-[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-7-(trifluoromethyl)indazol-6-yl]-1-piperidyl]ethyl]piperidine-1-carboxylate	Reaction solvent: HCl/Dioxane (2.0 M) in DCM instead of TFA/DCM; reaction time: 4 hours; the residue was used in the next step without further purification	3-[1-methyl-6-[1-[(1S)-1-(4-piperidyl)ethyl]-4-piperidyl]-7-(trifluoromethyl)indazol-3-yl]piperidine-2,6-dione
tert-butyl-(3R,4R)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-(trifluoromethyl)piperidine-1-carboxylate	Reaction solvent: HCl/Dioxane (2.0 M) in DCM instead of TFA/DCM; reaction time: 4 hours; the residue was used in the next step without further purification	3-[1-methyl-6-[1-[[(3R,4R)-3-(trifluoromethyl)-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione
tert-butyl-4-[(1R)-1-[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-7-(trifluoromethyl)indazol-6-yl]-1-piperidyl]ethyl]piperidine-1-carboxylate	Reaction solvent: HCl/Dioxane (2.0 M) in DCM instead of TFA/DCM; reaction time: 4 hours; the residue was used in the next step without further purification	3-[1-methyl-6-[1-[(1R)-1-(4-piperidyl)ethyl]-4-piperidyl]-7-(trifluoromethyl)indazol-3-yl]piperidine-2,6-dione
tert-butyl-(3R,4R)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate	Reaction time: 3 hours; work-up I was used	3-(6-(1-(((3R,4R)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione
tert-butyl-(3S,4S)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate	Reaction time: 3 hours; work-up I was used	3-(1-methyl-6-(1-(((3S,4S)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1H-indazol-3-yl)piperidine-2,6-dione
tert-butyl-(3S,4S)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-7-yl)piperazin-1-	Reaction time: 3 hours; work-up I was used	3-(1-methyl-7-(4-(((3S,4S)-3-methylpiperidin-4-yl)methyl)piperazin-1-yl)-1H-

Reactant	Variation from Example P6	Product
yl)methyl)-3-methylpiperidine-1-carboxylate		indazol-3-yl)piperidine-2,6-dione
tert-butyl-(3R,4R)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate	Reaction time: 3 hours; work-up I was used	3-(1-methyl-6-(1-(((3R,4R)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1H-indazol-3-yl)piperidine-2,6-dione
tert-butyl-(3R,4R)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-7-yl)piperazin-1-yl)methyl)-3-methylpiperidine-1-carboxylate	Reaction time: 3 hours; work-up I was used	3-(1-methyl-7-(4-(((3R,4R)-3-methylpiperidin-4-yl)methyl)piperazin-1-yl)-1H-indazol-3-yl)piperidine-2,6-dione
tert-butyl-4-(3-(2,6-dioxopiperidin-3-yl)-1,7-dimethyl-1H-indazol-6-yl)piperidine-1-carboxylate	Reaction solvent: HCl/Dioxane (2.0 M) in DCM instead of TFA/DCM; reaction time: 4 hours; the residue was used in the next step without further purification	3-(1,7-dimethyl-6-(piperidin-4-yl)-1H-indazol-3-yl)piperidine-2,6-dione
tert-butyl-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1,7-dimethyl-1H-indazol-6-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate	Work-up E was used	3-(1,7-dimethyl-6-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1H-indazol-3-yl)piperidine-2,6-dione
tert-butyl 4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-7-(trifluoromethyl)indazol-6-yl]piperidine-1-carboxylate	Work-up V was used	3-[1-methyl-6-(4-piperidyl)-7-(trifluoromethyl)indazol-3-yl]piperidine-2,6-dione
tert-butyl 9-((1-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	Reaction time: 3 hours; work-up G was used	3-[6-[4-(3,9-diazaspiro[5.5]undecan-3-ylmethyl)-1-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione
tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperazine-1-carboxylate	Work-up I was used	6-(benzyloxy)-3-(1-methyl-6-(piperazin-1-yl)-1H-indazol-3-yl)pyridin-2-ol
tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-7-yl)piperazine-1-carboxylate	Work-up I was used	6-(benzyloxy)-5-(1-methyl-7-(piperazin-1-yl)-1H-indazol-3-yl)pyridin-2-ol
tert-butyl-(3R)-4-[(1-benzyloxycarbonyl-4-piperidyl)methyl]-3-methyl-piperazine-1-carboxylate	Work-up N was used	benzyl-4-[[(2R)-2-methylpiperazin-1-yl]methyl]piperidine-1-carboxylate
benzyl-9-[(1R)-1-(1-tert-butoxycarbonyl-4-piperidyl)ethyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate	Reaction solvent: HCl/Dioxane (2.0 M) in DCM instead of TFA/DCM; reaction time: 4 hours; the residue was used in the next step without further purification	benzyl-9-[(1R)-1-(4-piperidyl)ethyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate
tert-butyl-4-[[(3R,4R)-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-3-fluoro-1-piperidyl]methyl]piperidine-1-carboxylate	Reaction solvent: HCl/Dioxane (2.0 M) in DCM instead of TFA/DCM; reaction time: 4 hours; the residue was used in the next step without further purification	3-[6-[(3R,4R)-3-fluoro-1-(4-piperidylmethyl)-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione

Table P6A

Product	LC-MS (ESI)
benzyl-4-[[(2S)-2-methylpiperazin-1-yl]methyl]piperidine-1-carboxylate	m/z = 332.3 $[M+H]^+$
3-[1-methyl-7-[4-(4-piperidylmethyl)piperazin-1-yl]indazol-3-yl]piperidine-2,6-dione	m/z = 425.2 $[M+H]^+$
3-[1-methyl-6-(4-piperidyl)-5-(trifluoromethyl)indazol-3-yl]piperidine-2,6-dione	m/z = 395.1 $[M+H]^+$
3-[1-methyl-6-[1-(4-piperidylmethyl)-4-piperidyl]-5-(trifluoromethyl)indazol-3-yl]piperidine-2,6-dione	m/z = 492.3 $[M+H]^+$
3-[7-fluoro-1-methyl-6-(4-piperidyl)indazol-3-yl]piperidine-2,6-dione	m/z = 345.1 $[M+H]^+$
3-(7-fluoro-1-methyl-6-(1-(((3R,4S)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1H-indazol-3-yl)piperidine-2,6-dione	m/z = 456.3 $[M+H]^+$
3-[1-methyl-7-(4-piperidyl)indazol-3-yl]piperidine-2,6-dione	
3-[1-methyl-7-[1-[[(3S,4S)-3-methyl-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione	m/z = 438.4 $[M+H]^+$
6-(benzyloxy)-3-(1-methyl-6-(piperidin-4-yl)-1H-indazol-3-yl)pyridin-2-ol	m/z = 415.36 $[M+H]^+$
3-(6-(1-(((3S,4R)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione	m/z = 442.26 $[M+H]^+$
3-(6-(1-(((3R,4S)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione	m/z = 442.26 $[M+H]^+$
3-(6-(4-(((R)-3,3-dimethylpiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione	m/z = 453.56 $[M+H]^+$
3-(6-(4-(((S)-3,3-dimethylpiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione	m/z = 453.60 $[M+H]^+$
3-(6-((3S,4S)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione	m/z = 507.34 $[M+H]^+$
3-(6-((3R,4R)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione	m/z = 507.37 $[M+H]^+$
3-(7-((3S)-4-((3,3-difluoropiperidin-4-yl)methyl)-3-methylpiperazin-1-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione	m/z = 475.24 $[M+H]^+$
6-(benzyloxy)-5-(6-(3,3-difluoro-1,2,3,6-tetrahydropyridin-4-yl)-1-methyl-1H-indazol-3-yl)pyridin-2-ol	m/z = 503.56 $[M+H]^+$
3-(6-(3,3-difluoro-1-(piperidin-4-ylmethyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione	m/z: 460.59 $[M-H]^-$
3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indazole-hydrochloride	m/z = 521.57 $[M+H]^+$
3-(7-fluoro-1-methyl-6-(1-(((3S,4S)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1H-indazol-3-yl)piperidine-2,6-dione	m/z = 456.44 $[M+H]^+$
3-(7-fluoro-1-methyl-6-(1-(((3R,4R)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1H-indazol-3-yl)piperidine-2,6-dione	m/z = 456.48 $[M+H]^+$
1-(piperidin-4-yl)ethan-1-one	m/z = 127.9 $[M+H]^+$

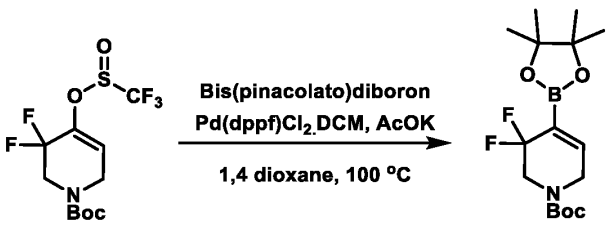
3-(6-(4-((R)-1-(3,9-diazaspiro[5.5]undecan-3-yl)ethyl)piperidin-1-yl)-7-fluoro-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione	m/z = 525.37 $[M+H]^+$
3-(6-(4-((R)-1-(3,9-diazaspiro[5.5]undecan-3-yl)ethyl)piperidin-1-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione	m/z = 525.37 $[M+H]^+$
3-(1-methyl-6-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1H-indazol-3-yl)piperidine-2,6-dione	m/z = 424.26 $[M+H]^+$
3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indazole	m/z = 521.27 $[M+H]^+$
3-(5-fluoro-1-methyl-6-(1-(((3S,4S)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1H-indazol-3-yl)piperidine-2,6-dione	m/z = 456.30 $[M+H]^+$
3-(5-fluoro-1-methyl-6-(1-(((3R,4R)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1H-indazol-3-yl)piperidine-2,6-dione	m/z = 456.52 $[M+H]^+$
3-(6-(4-((S)-1-(3,9-diazaspiro[5.5]undecan-3-yl)ethyl)piperidin-1-yl)-7-fluoro-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione	m/z = 525.3 $[M+H]^+$
3-(6-(4-((S)-1-(3,9-diazaspiro[5.5]undecan-3-yl)ethyl)piperidin-1-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione	m/z = 507.3 $[M+H]^+$
6-benzyloxy-3-[1-methyl-6-[(2R)-2-methyl-4-piperidyl]indazol-3-yl]-3H-pyridin-2-one	m/z = 429.2 [M+H]
3-(1-methyl-6-((2R,4R)-2-methyl-1-(piperidin-4-ylmethyl)piperidin-4-yl)-1H-indazol-3-yl)piperidine-2,6-dione	m/z = 438.3 $[M+H]^+$
3-[1-methyl-6-[1-[(1R)-2,2,2-trifluoro-1-(4-piperidyl)ethyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione	
3-[1-methyl-6-[1-[(1S)-2,2,2-trifluoro-1-(4-piperidyl)ethyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione	
3-(1-methyl-6-(4-(piperidin-4-ylmethyl)piperazin-1-yl)-1H-indazol-3-yl)piperidine-2,6-dione	m/z = 424.3 $[M+H]^+$
3-[1-methyl-6-[1-(4-piperidylmethyl)-4-piperidyl]-7-(trifluoromethyl)indazol-3-yl]piperidine-2,6-dione	
3-(1-methyl-7-(1-(((3R,4S)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1H-indazol-3-yl)piperidine-2,6-dione	m/z = 438.3 $[M+H]^+$
3-(1-methyl-7-(1-(((3S,4R)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1H-indazol-3-yl)piperidine-2,6-dione	m/z = 438.2 $[M+H]^+$
3-(6-(1-(((R)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione	m/z = 452.52 $[M+H]^+$
3-(6-(1-(((S)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione	m/z = 452.52 $[M+H]^+$
3-(6-((3R,4R)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-7-fluoro-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione	m/z = 525.56 $[M+H]^+$
3-(6-((3S,4S)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-7-fluoro-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione	m/z = 525.64 $[M+H]^+$
3-(6-((3R,4S)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-7-fluoro-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione	m/z = 525.33 $[M+H]^+$

3-(6-((3S,4R)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-7-fluoro-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione	m/z = 525.33 $[M+H]^+$
3-(6-((3R,4R)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-5-fluoro-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione	m/z = 525.33 $[M+H]^+$
3-(6-((3S,4S)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-5-fluoro-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione	m/z = 525.64 $[M+H]^+$
3-(6-((3R,4S)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-5-fluoro-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione	m/z = 525.33 $[M+H]^+$
3-(6-((3S,4R)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-5-fluoro-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione	m/z = 525.33 $[M+H]^+$
3-(6-(piperidin-4-yl)-1H-indazol-3-yl)piperidine-2,6-dione	m/z = 313.34 $[M+H]^+$
3-(6-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1H-indazol-3-yl)piperidine-2,6-dione	m/z = 410.42 $[M+H]^+$
3-(6-(1-(((3S,4S)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione	m/z = 442.29 $[M+H]^+$
3-[6-fluoro-1-methyl-7-[4-[[(3S,4S)-3-methyl-4-piperidyl]methyl]piperazin-1-yl]indazol-3-yl]piperidine-2,6-dione	m/z = 457.1 $[M+H]^+$
3-[6-fluoro-1-methyl-7-[4-[[(3R,4R)-3-methyl-4-piperidyl]methyl]piperazin-1-yl]indazol-3-yl]piperidine-2,6-dione	
3-[6-[(4S)-2,2-dimethyl-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione	m/z = 355.2 $[M+H]^+$
3-[6-[(4S)-2,2-dimethyl-1-(4-piperidylmethyl)-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione	m/z = 452.4 $[M+H]^+$
3-[5,7-difluoro-1-methyl-6-[1-(4-piperidylmethyl)-4-piperidyl]indazol-3-yl]piperidine-2,6-dione	m/z = 460.1 $[M+H]^+$
3-[6-[(4R)-2,2-dimethyl-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione	m/z = 355.2 $[M+H]^+$
3-[6-[(4R)-2,2-dimethyl-1-(4-piperidylmethyl)-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione	m/z = 452.3 $[M+H]^+$
3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)indazole	m/z = 521.2 $[M+H]^+$
3-[7-fluoro-1-methyl-6-[1-[(1S)-1-(4-piperidyl)ethyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione	m/z = 456.2 $[M+H]^+$
3-[5-fluoro-1-methyl-6-[1-[(1S)-1-(4-piperidyl)ethyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione	m/z = 456.2 $[M+H]^+$
benzyl-9-[(1S)-1-(4-piperidyl)ethyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate	m/z = 400.1 $[M+H]^+$
3-[6-(4-piperidyl)-1-(2,2,2-trifluoroethyl)indazol-3-yl]piperidine-2,6-dione	m/z = 395.1 $[M+H]^+$
3-[6-[1-(4-piperidylmethyl)-4-piperidyl]-1-(2,2,2-trifluoroethyl)indazol-3-yl]piperidine-2,6-dione	
3-[7-fluoro-1-methyl-6-[1-[(1R)-1-(4-piperidyl)ethyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione	m/z = 456.2 $[M+H]^+$
3-[5-fluoro-1-methyl-6-(4-piperidyl)indazol-3-yl]piperidine-2,6-dione	m/z = 345.0 $[M+H]^+$
3-[5-fluoro-1-methyl-6-[1-[[(3R,4S)-3-methyl-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione	m/z = 456.2 $[M+H]^+$
3-[1-isopropyl-6-(4-piperidyl)indazol-3-yl]piperidine-	

2,6-dione	
3-[1-isopropyl-6-[1-(4-piperidylmethyl)-4-piperidyl]indazol-3-yl]piperidine-2,6-dione	
3-[1-methyl-7-[1-[[(3R,4R)-3-methyl-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione	
3-(2,6-dibenzyloxy-3-pyridyl)-6-(3-fluoro-4-piperidyl)-1-methyl-indazole	m/z = 523.3 $[M+H]^+$
3-[6-[(3S,4S)-3-fluoro-1-(4-piperidylmethyl)-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione	m/z = 442.2 $[M+H]^+$
3-[6-[1-[[(4R)-3,3-difluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione	m/z = 460.2 $[M+H]^+$
3-[6-[1-[[(4S)-3,3-difluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione	m/z = 460.0 $[M+H]^+$
benzyl-9-[(4-methyl-4-piperidyl)methyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate	
3-[5,7-difluoro-1-methyl-6-[1-[(1S)-1-(4-piperidyl)ethyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione	m/z = 474.1 $[M+H]^+$
3-[1,5-dimethyl-6-(4-piperidyl)indazol-3-yl]piperidine-2,6-dione	
3-[1,5-dimethyl-6-[1-(4-piperidylmethyl)-4-piperidyl]indazol-3-yl]piperidine-2,6-dione	
benzyl-9-(4-piperidylmethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	
3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)indazole	m/z = 503.4 $[M+H]^+$
3-[1-methyl-6-[1-[[(3S,4S)-3-(trifluoromethyl)-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione	
3-(2,6-dibenzyloxy-3-pyridyl)-6-[(3S,4R)-3-fluoro-4-piperidyl]-1-methyl-indazole	m/z = 523.2 $[M+H]^+$
3-[6-[(3S,4R)-3-fluoro-1-(4-piperidylmethyl)-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione	m/z = 442.2 $[M+H]^+$
3-(2,6-dibenzyloxy-3-pyridyl)-6-[(3R,4S)-3-fluoro-4-piperidyl]-1-methyl-indazole	m/z = 523.1 $[M+H]^+$
3-[6-[(3R,4S)-3-fluoro-1-(4-piperidylmethyl)-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione	m/z = 442.2 $[M+H]^+$
3-[6-[1-[[(3S,4R)-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione	m/z = 442.2 $[M+H]^+$
3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indazole	m/z = 503.2 $[M+H]^+$
3-(6-(1-(((3R,4S)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione	m/z = 442.2 $[M+H]^+$
4-bromo-1,2,3,6-tetrahydropyridine	
3-[1-methyl-6-[1-[(1S)-1-(4-piperidyl)ethyl]-4-piperidyl]-7-(trifluoromethyl)indazol-3-yl]piperidine-2,6-dione	m/z = 506.2 $[M+H]^+$
3-[1-methyl-6-[1-[[(3R,4R)-3-(trifluoromethyl)-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione	m/z = 492.2 $[M+H]^+$
3-[1-methyl-6-[1-[(1R)-1-(4-piperidyl)ethyl]-4-piperidyl]-7-(trifluoromethyl)indazol-3-yl]piperidine-2,6-dione	m/z = 506.2 $[M+H]^+$
3-(6-(1-(((3R,4R)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione	m/z = 442.45 $[M+H]^+$
3-(1-methyl-6-(1-(((3S,4S)-3-methylpiperidin-4-	m/z = 438.61 $[M+H]^+$

yl)methyl)piperidin-4-yl)-1H-indazol-3-yl)piperidine-2,6-dione	
3-(1-methyl-7-(4-(((3S,4S)-3-methylpiperidin-4-yl)methyl)piperazin-1-yl)-1H-indazol-3-yl)piperidine-2,6-dione	m/z = 439.28 $[M+H]^+$
3-(1-methyl-6-(1-(((3R,4R)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1H-indazol-3-yl)piperidine-2,6-dione	m/z = 438.46 $[M+H]^+$
3-(1-methyl-7-(4-(((3R,4R)-3-methylpiperidin-4-yl)methyl)piperazin-1-yl)-1H-indazol-3-yl)piperidine-2,6-dione	m/z = 439.49 $[M+H]^+$
3-(1,7-dimethyl-6-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1H-indazol-3-yl)piperidine-2,6-dione	
3-(1,7-dimethyl-6-(piperidin-4-yl)-1H-indazol-3-yl)piperidine-2,6-dione	
3-[1-methyl-6-(4-piperidyl)-7-(trifluoromethyl)indazol-3-yl]piperidine-2,6-dione	m/z = 395.1 $[M+H]^+$
3-[6-[4-(3,9-diazaspiro[5.5]undecan-3-ylmethyl)-1-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione	m/z = 493.37 $[M+H]^+$
6-(benzyloxy)-3-(1-methyl-6-(piperazin-1-yl)-1H-indazol-3-yl)pyridin-2-ol	m/z = 416.39 $[M+H]^+$
6-(benzyloxy)-5-(1-methyl-7-(piperazin-1-yl)-1H-indazol-3-yl)pyridin-2-ol	m/z = 416.39 $[M+H]^+$
benzyl-4-[[(2R)-2-methylpiperazin-1-yl]methyl]piperidine-1-carboxylate	m/z = 332.2 $[M+H]^+$
benzyl-9-[(1R)-1-(4-piperidyl)ethyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate	m/z = 400.1 $[M+H]^+$
3-[6-[(3R,4R)-3-fluoro-1-(4-piperidylmethyl)-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione	m/z = 442.2 $[M+H]^+$

Example P7



To a stirred solution of *tert*-butyl-3,3-difluoro-4-(((trifluoromethyl)sulfinyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (Reactant) (4.0 g, 11.38 mmol, 1 *equiv.*) in 1,4-dioxane (120.0 mL) was added bis(pinacolato)diboron (4.33 g, 17.08 mmol, 1 *equiv.*) and potassium acetate (3.35 g, 34.16 mmol, 1 *equiv.*). The mixture was degassed with argon for five minutes followed by the addition of $Pd(dppf)Cl_2$.DCM (0.83 g, 1.13 mmol, 1 *equiv.*). The resulting reaction mixture was heated to 100°C for 16 hours. The reaction mixture was cooled to room temperature, diluted with ethyl-acetate (50 mL), filtered through a celite bed, and washed with 100 mL of 10% MeOH in DCM. The filtrate was concentrated to get the crude product which was purified by flash chromatography to afford *tert*-butyl-3,3-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (1.3 g) as an off white solid.

The compounds shown in the "**Product**" column of **Table P7** were synthesized using the method of **Example P7**, with variations noted in **Table P7**.

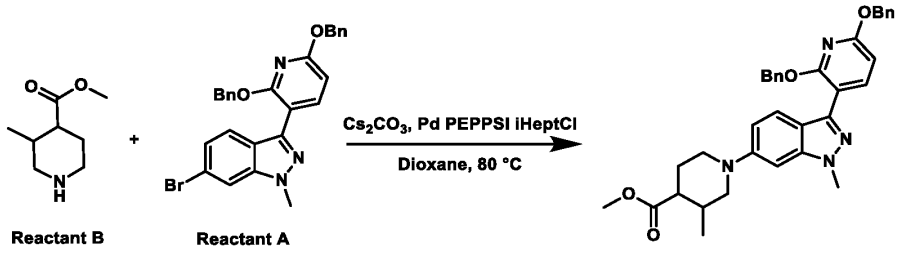
Table P7

Reactant	Variation from Example P7	Product
tert-butyl-3,3-difluoro-4-(((trifluoromethyl)sulfinyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate		*tert*-butyl-3,3-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate
tert-butyl-4-[(4-bromo-3,6-dihydro-2H-pyridin-1-yl)methyl]piperidine-1-carboxylate	Reaction solvent: toluene; $Pd(dppf)Cl_2$ (0.1 *equiv.*) instead of $Pd(dppf)Cl_2$.DCM; reaction temperature: 70 °C; reaction time: 2 hours; work-up D was used	*tert*-butyl-4-[[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridin-1-yl]methyl]piperidine-1-carboxylate
tert-butyl-4-[1-(4-bromo-3,6-dihydro-2H-pyridin-1-yl)ethyl]piperidine-1-carboxylate	Reaction solvent: toluene; $Pd(dppf)Cl_2$ (0.1 *equiv.*) instead of $Pd(dppf)Cl_2$.DCM; reaction temperature: 70 °C; reaction time: 2 hours; work-up Q was used	*tert*-butyl-4-[1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridin-1-yl]ethyl]piperidine-1-carboxylate

Table P7A

Product	LC-MS (ESI)
tert-butyl-3,3-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate	
tert-butyl-4-[[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridin-1-yl]methyl]piperidine-1-carboxylate	m/z = 407.1 $[M+H]^+$
tert-butyl-4-[1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridin-1-yl]ethyl]piperidine-1-carboxylate	m/z = 3421.3 $[M+H]^+$

Example P8



A stirred solution of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-1-methyl-1H-indazole (prepared using published methods, e.g., in International Application Publication No. WO 2021/127586) (Reactant A) (2.0 g, 4.01 mmol, 1 *equiv.*), methyl-3-methylpiperidine-4-carboxylate (Reactant B) (3.10 g, 20.0 mmol, 1 *equiv.*), and cesium carbonate (7.82 g,

24.00 mmol, 1 *equiv.*) in 1,4-dioxane (40 mL) was degassed with argon for 10 minutes. To this mixture was added Pd-PEPPSI-iHeptCl (0.97 g, 1.00 mmol, 1 *equiv.*) and degassed for an additional 5 minutes. The resulting reaction mixture was stirred at 80 °C for 6 hours. The reaction mixture was then filtered through a celite bed and concentrated under vacuum to obtain crude product which was purified by column chromatography to afford methyl-1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)-3-methylpiperidine-4-carboxylate (2.60 g) as yellow solid. **LC-MS (ESI):** m/z = 577.51 $[M+H]^+$

The compounds shown in the "**Product**" column of **Table P8** were synthesized using the method of **Example P8**, with variations noted in **Table P8**.

Table P8

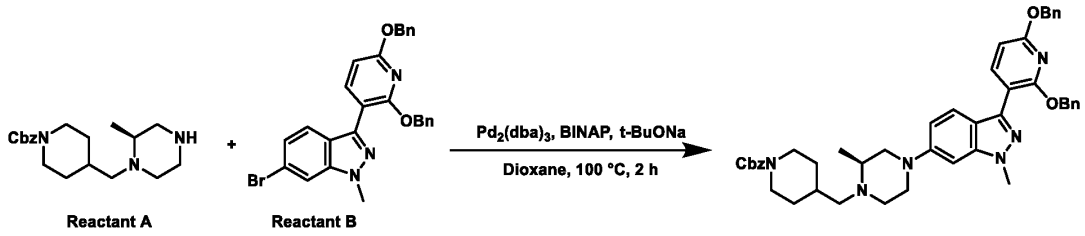
Reactant A	Reactant B	Variation from Example P8	Product
3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-1-methyl-1H-indazole	methyl-3-methylpiperidine-4-carboxylate		methyl-1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)-3-methylpiperidine-4-carboxylate
3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-bromo-1-methyl-1H-indazole	*tert*-butyl-3,3-difluoro-4-(((S)-2-methylpiperazin-1-yl)methyl)piperidine-1-carboxylate	Sodium *tert*-butoxide (1.0 *equiv.*) instead of cesium carbonate	*tert*-butyl-4-(((S)-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-7-yl)-2-methylpiperazin-1-yl)methyl)-3,3-difluoropiperidine-1-carboxylate
3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-7-fluoro-1-methyl-1H-indazole	*tert*-butyl-9-(1-(piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	Sodium *tert*-butoxide (1.0 *equiv.*) instead of cesium carbonate	*tert*-butyl-9-(1-(1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate
6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazole	methyl-3-methylpiperidine-4-carboxylate	Reaction temperature: 100 °C; reaction time: 10 hours	methyl-1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidine-4-carboxylate
3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-7-fluoro-1-methyl-1H-indazole	methyl-3-methylpiperidine-4-carboxylate	Reaction time: 10 hours	methyl-1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidine-4-carboxylate
3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-bromo-1-methyl-1H-indazole	*tert*-butyl piperazine-1-carboxylate	Reaction temperature: 100 °C; reaction time: 16 hours	*tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-7-yl)piperazine-1-carboxylate

Table P8A

Product	LC-MS (ESI)

methyl-1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)-3-methylpiperidine-4-carboxylate	m/z = 577.51 $[M+H]^+$
tert-butyl-4-(((S)-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-7-yl)-2-methylpiperazin-1-yl)methyl)-3,3-difluoropiperidine-1-carboxylate	m/z = 753.85 $[M+H]^+$
tert-butyl-9-(1-(1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	m/z: 437.15 $[M-H]^-$
methyl-1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidine-4-carboxylate	m/z = 595.61 $[M+H]^+$
methyl-1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidine-4-carboxylate	m/z = 595.70 $[M+H]^+$
tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-7-yl)piperazine-1-carboxylate	m/z = 606.55 $[M+H]^+$

Example P9



Reactant A Reactant B

A mixture of benzyl-4-[[(2S)-2-methylpiperazin-1-yl]methyl]piperidine-1-carboxylate (Reactant A) (4.7 g, 14.18 mmol, 1 *equiv.*), 6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazole (Reactant B) (7.10 g, 14.18 mmol, 1 *equiv.*), t-BuONa (2.86 g, 29.78 mmol, 2.1 *equiv.*), BINAP (1.77 g, 2.84 mmol, 0.2 *equiv.*) and $Pd_2(dba)_3$ (1.30 g, 1.42 mmol, 0.1 *equiv.*) in dioxane (50 mL) was degassed and purged with N_2 three times. The mixture was stirred at 100 °C for 2 hours under N_2 atmosphere. The reaction mixture was diluted with H_2O (50 mL) and extracted with DCM (210 mL). The combined organic layers were washed with brine (210 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue which was purified by prep-HPLC to afford benzyl-4-[[(2S)-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-2-methyl-piperazin-1-yl]methyl]piperidine-1-carboxylate (770 mg) as a brown oil. **LC-MS (ESI):** m/z = 751.4 $[M+H]^+$

The compounds shown in the "**Product**" column of **Table P9** were synthesized using the method of **Example P9**, with variations noted in **Table P9**.

Table P9

Reactant A	Reactant B	Variation from	Product

		Example P9	
benzyl-4-[[(2S)-2-methylpiperazin-1-yl]methyl]piperidine-1-carboxylate	6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazole		benzyl-4-[[(2S)-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-2-methyl-piperazin-1-yl]methyl]piperidine-1-carboxylate
tert-butyl-4-(piperazin-1-ylmethyl)piperidine-1-carboxylate	7-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazole	Reaction time: 12 hours	*tert*-butyl-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-7-yl]piperazin-1-yl]methyl]piperidine-1-carboxylate
piperazine	7-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-6-fluoro-1-methyl-indazole	Reaction solvent: toluene; reaction time: 12 hours; crude was purified by flash column chromatography	3-(2,6-dibenzyloxy-3-pyridyl)-6-fluoro-1-methyl-7-piperazin-1-yl-indazole
benzyl-9-[(1S)-1-(4-piperidyl)ethyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate	6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazole	Reaction temperature: 95 °C; reaction time: 3 hours; RuPhos Pd G3 (0.1 *equiv.*) instead of $Pd_2(dba)_3$; no BINAP; crude was purified by flash column chromatography	benzyl-9-[(1S)-1-[1-[3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazol-6-yl]-4-piperidyl]ethyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate
benzyl-9-[(4-methyl-4-piperidyl)methyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate	6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazole	Reaction temperature: 95 °C; reaction time: 4 hours; RuPhos Pd G3 (0.1 *equiv.*) instead of $Pd_2(dba)_3$; no BINAP; crude was purified by flash column chromatography	benzyl-9-[[1-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-4-methyl-4-piperidyl]methyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate
benzyl-9-(4-piperidylmethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-1,5-dimethyl-indazole	Reaction temperature: 95 °C; reaction time: 3 hours; RuPhos Pd G3 (0.1 *equiv.*) instead of $Pd_2(dba)_3$; no BINAP; crude was purified by flash column chromatography	benzyl-9-[[1-[3-(2,6-dibenzyloxy-3-pyridyl)-1,5-dimethyl-indazol-6-yl]-4-piperidyl]methyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate
benzyl-9-(4-piperidylmethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-1,7-dimethyl-1H-indazole	Reaction temperature: 95 °C; reaction time: 3 hours; RuPhos Pd G3 (0.1 *equiv.*) instead of $Pd_2(dba)_3$; no BINAP; crude was purified by flash column chromatography	benzyl-9-[[1-[3-(2,6-dibenzyloxy-3-pyridyl)-1,7-dimethyl-indazol-6-yl]-4-piperidyl]methyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate
benzyl-4-[[(2R)-2-methylpiperazin-1-yl]methyl]piperidine-1-carboxylate	6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazole	Reaction temperature: 95 °C; reaction time: 3 hours; Xphos-Pd-G3 (0.1 equiv.) instead of Pd2(dba)3; no BINAP; Cs_2CO_3 (3.0 *equiv.*) instead of t-BuONa; crude was purified by flash column	benzyl-4-[[(2R)-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-2-methyl-piperazin-1-yl]methyl]piperidine-1-carboxylate

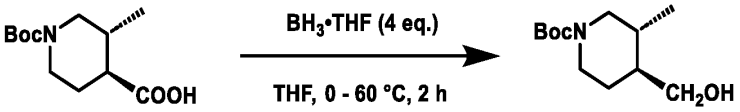
		chromatography	
benzyl-9-[(1R)-1-(4-piperidyl)ethyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate	6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazole	Reaction temperature: 95 °C; reaction time: 3 hours; RuPhos Pd G3 (0.1 *equiv.*) instead of $Pd_2(dba)_3$; no BINAP; crude was purified by flash column chromatography	benzyl-9-[(1R)-1-[1-[3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazol-6-yl]-4-piperidyl]ethyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate

Table P9A

Product	LC-MS (ESI)	^{1}H NMR
benzyl-4-[[(2S)-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-2-methyl-piperazin-1-yl]methyl]piperidine-1-carboxylate	m/z = 751.4 $[M+H]^+$	
tert-butyl-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-7-yl]piperazin-1-yl]methyl]piperidine-1-carboxylate	m/z = 703.5 $[M+H]^+$	(400 MHz, CHLOROFORM-d) δ = 7.85 (d, J = 8.0 Hz, 1H), 7.47 - 7.27 (m, 2H), 7.47 - 7.27 (m, 7H), 7.28 (s, 1H), 7.26 (s, 1H), 7.04 - 7.00 (m, 1H), 6.99 - 6.94 (m, 1H), 6.51 (d, J = 8.0 Hz, 1H), 5.47 (s, 2H), 5.40 (s, 2H), 4.42 (s, 3H), 3.29 - 3.11 (m, 2H), 3.09 - 2.83 (m, 4H), 2.73 (t, J = 12.0 Hz, 2H), 2.48 - 2.33 (m, 2H), 2.29 (d, J = 6.8 Hz, 2H), 1.85 - 1.64 (m, 3H), 1.58 (s, 4H), 1.48 (s, 9H)
3-(2,6-dibenzyloxy-3-pyridyl)-6-fluoro-1-methyl-7-piperazin-1-yl-indazole	m/z = 524.2 $[M+H]^+$	
benzyl-9-[(1S)-1-[1-[3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazol-6-yl]-4-piperidyl]ethyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate	m/z = 837.3 $[M+H]^+$	
benzyl-9-[[1-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-4-methyl-4-piperidyl]methyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate	m/z = 819.6 $[M+H]^+$	
benzyl-9-[[1-[3-(2,6-dibenzyloxy-3-pyridyl)-1,5-dimethyl-indazol-6-yl]-4-piperidyl]methyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate	m/z = 819.8 $[M+H]^+$	
benzyl-9-[[1-[3-(2,6-dibenzyloxy-3-pyridyl)-1,7-dimethyl-indazol-6-yl]-4-piperidyl]methyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate		(400 MHz, DMSO-d6) δ = 7.85 (d, J = 8.0 Hz, 1H), 7.52 - 7.23 (m, 16H), 6.90 (d, J = 8.8 Hz, 1H), 6.51 (d, J = 8.0 Hz, 1H), 5.57 - 5.29 (m, 4H), 5.15 (s, 2H), 4.36 (s, 3H), 3.56 - 3.42 (m, 4H), 3.09 (d, J = 11.6 Hz, 2H), 2.81 - 2.66 (m, 5H), 2.41 (s, 4H), 2.29 (d, J = 7.2 Hz, 2H), 1.87 (d, J = 12.4 Hz, 2H), 1.59 - 1.53 (m, 4H), 1.51 - 1.37 (m, 7H)
benzyl-4-[[(2R)-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-2-methyl-piperazin-1-yl]methyl]piperidine-1-carboxylate	m/z = 751.5 $[M+H]^+$	(400 MHz, DMSO-d6) δ = 7.88 (d, J = 8.0 Hz, 1H), 7.53 -7.43 (m, 3H), 7.42 -7.26 (m, 13H), 6.87 -6.76 (m, 2H), 6.56 (d, J = 8.0 Hz, 1H), 5.76 (s, 1H), 5.43 (d, J = 16.0 Hz, 4H), 5.07 (s, 2H), 4.03 (d, J = 7.2 Hz, 1H), 3.99 (d, J = 2.8 Hz, 1H), 3.96 (s, 3H), 3.49 (d, J = 11.6 Hz, 2H), 2.96 -2.76 (m, 4H), 2.63 -2.53 (m, 2H), 2.35 -

		2.22 (m, 1H), 2.00 -1.94 (m, 1H), 1.82 (d, J = 12.4 Hz, 1H), 1.73 -1.59 (m, 2H), 1.06 (d, J = 6.0 Hz, 3H), 1.03 -0.88 (m, 2H)
benzyl-9-[(1R)-1-[1-[3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazol-6-yl]-4-piperidyl]ethyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate	m/z = 837.3 $[M+H]^+$	

Example P10



A mixture of (3*R*,4*S*)-1-(tert-butoxycarbonyl)-3-methylpiperidine-4-carboxylic-acid (Reactant) (1.1 g, 4.52 mmol, 1.0 *equiv.*) in THF (10 mL) was degassed and purged with N_2 three times. To this mixture was added BH_3•THF (1 M, 18.08 mL, 4.0 *equiv.*) at 0 °C. The mixture was stirred at 60 °C for 2 hours under N_2 atmosphere. The reaction mixture was quenched by the addition of MeOH at 0°C, followed by the addition of H_2O (20 mL). This mixture was extracted with ethyl acetate (60 mL) and the combined organic layers were washed with brine (40 mL), dried over sodium sulfate, and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography to give *tert*-butyl-(3*R*,4*S*)-4-(hydroxymethyl)-3-methylpiperidine-1-carboxylate (810 mg) as a colorless oil. **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 4.36 (t, J = 5.2 Hz, 1H), 3.95 – 3.72 (m, 2H), 3.47 (m, 1H), 3.32 – 3.26 (m, 2H), 1.68 – 1.61 (m, 1H), 1.38 (s, 9H), 1.33 – 1.25 (m, 1H), 1.19 – 1.07 (m, 2H), 0.83 (d, J = 6.4 Hz, 3H)

The compounds shown in the "**Product**" column of **Table P10** were synthesized using the method of **Example P10**, with variations noted in **Table P10**.

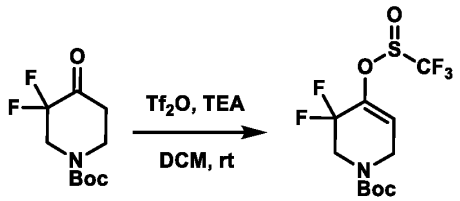
Table P10

Reactant	Variation from Example P10	Product
(3R,4S)-1-(tert-butoxycarbonyl)-3-methylpiperidine-4-carboxylic-acid		*tert*-butyl-(3R,4S)-4-(hydroxymethyl)-3-methylpiperidine-1-carboxylate
(3S,4S)-1-tert-butoxycarbonyl-3-methyl-piperidine-4-carboxylic-acid		*tert*-butyl-(3S,4S)-4-(hydroxymethyl)-3-methyl-piperidine-1-carboxylate

Table 10A

Product	^{1}H NMR
tert-butyl-(3R,4S)-4-(hydroxymethyl)-3-methylpiperidine-1-carboxylate	(400 MHz, DMSO-d6) δ = 4.36 (t, J = 5.2 Hz, 1H), 3.95 – 3.72 (m, 2H), 3.47 (m, 1H), 3.32 – 3.26 (m, 2H), 1.68 – 1.61 (m, 1H), 1.38 (s, 9H), 1.33 – 1.25 (m, 1H), 1.19 – 1.07 (m, 2H), 0.83 (d, J = 6.4 Hz, 3H)
tert-butyl-(3S,4S)-4-(hydroxymethyl)-3-methyl-piperidine-1-carboxylate	(400 MHz, DMSO-d6) δ = 4.40 (t, J = 4.8 Hz, 1H), 4.00 - 3.80 (m, 1H), 3.74 - 3.66 (m, 1H), 3.26 – 3.23 (m, 2H), 2.94 - 2.58 (m, 2H), 1.88 – 1.86 (m, 1H), 1.69 – 1.64 (m, 1H), 1.40 - 1.30 (m, 10H), 1.26 - 1.15 (m, 1H), 0.74 (d, J = 7.2 Hz, 3H)

Example P11



To a stirred solution of *tert*-butyl-3,3-difluoro-4-oxopiperidine-1-carboxylate (Reactant) (7.0 g, 29.75 mmol, 1 *equiv.*) in DCM (280.0 mL) was added TEA (21 mL, 148.79 mmol, 1 *equiv.*) and trifluoromethanesulfonic-anhydride (15.0 mL, 89.275 mmol, 1 *equiv.*) at 0 °C. The reaction mixture was stirred at room temperature for 6 hours. The reaction mixture was concentrated under reduced pressure, diluted with water (100 mL) and extracted with DCM (2 x 200mL). The combined organic layers were washed with brine solution (100 mL), dried over anhydrous sodium sulfate, filtered, and dried under vacuum to get crude product which was purified by column chromatography to afford *tert*-butyl-3,3-difluoro-4-(((trifluoromethyl)sulfinyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (4.5 g) as a yellow solid.

The compounds shown in the "**Product**" column of **Table P11** were synthesized using the method of **Example P11**, with variations noted in **Table P11**.

Table P11

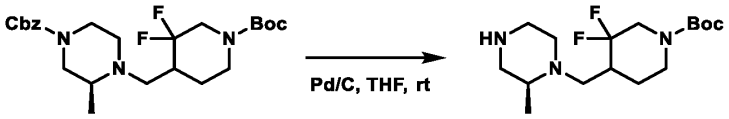
Reactant	Variation from Example P11	Product
tert-butyl-3,3-difluoro-4-oxopiperidine-1-carboxylate		*tert*-butyl-3,3-difluoro-4-(((trifluoromethyl)sulfinyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate
tert-butyl-(2R)-2-methyl-4-oxo-piperidine-1-carboxylate	1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (1.3 *equiv.*) instead of trifluoromethanesulfonic-anhydride;	*tert*-butyl-(2R)-2-methyl-4-(trifluoromethylsulfonyloxy)-3,6-dihydro-2H-pyridine-1-carboxylate

	LiHMDS (1.2 *equiv.*) instead of TEA; reactants were added at -78 °C	
tert-butyl-4-[2,2,2-trifluoro-1-(4-oxo-1-piperidyl)ethyl]piperidine-1-carboxylate	1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (1.3 *equiv.*) instead of trifluoromethanesulfonic-anhydride; LiHMDS (1.2 *equiv.*) instead of TEA; reactants were added at -78 °C	*tert*-butyl-4-[2,2,2-trifluoro-1-[4-(trifluoromethylsulfonyloxy)-3,6-dihydro-2H-pyridin-1-yl]ethyl]piperidine-1-carboxylate
tert-butyl-2,2-dimethyl-4-oxo-piperidine-1-carboxylate	1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (1.3 *equiv.*) instead of trifluoromethanesulfonic-anhydride; LiHMDS (1.2 *equiv.*) instead of TEA; reactants were added at -78 °C; reaction time: 12 hours	*tert*-butyl-6,6-dimethyl-4-(trifluoromethylsulfonyloxy)-2,3-dihydropyridine-1-carboxylate

Table P11A

Product	LC-MS (ESI)	^{1}H NMR
tert-butyl-3,3-difluoro-4-(((trifluoromethyl)sulfinyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate		
tert-butyl-(2R)-2-methyl-4-(trifluoromethylsulfonyloxy)-3,6-dihydro-2H-pyridine-1-carboxylate	m/z = 289.8 $[M+H]^+$	
tert-butyl-4-[2,2,2-trifluoro-1-[4-(trifluoromethylsulfonyloxy)-3,6-dihydro-2H-pyridin-1-yl]ethyl]piperidine-1-carboxylate	m/z = 440.8 $[M+H]^+$	
tert-butyl-6,6-dimethyl-4-(trifluoromethylsulfonyloxy)-2,3-dihydropyridine-1-carboxylate		(400 MHz, DMSO-d6) δ = 7.40 - 7.29 (m, 2H), 7.25 - 7.17 (m, 2H), 5.95 (s, 1H), 3.99 - 3.85 (m, 2H), 2.43 (td, J = 1.6, 4.0 Hz, 1H), 2.35 (d, J = 0.8 Hz, 1H), 2.38 - 2.31 (m, 1H), 1.36 - 1.27 (m, 16H)

Example P12



To a stirred solution of benzyl-(3S)-4-((1-(tert-butoxycarbonyl)-3,3-difluoropiperidin-4-yl)methyl)-3-methylpiperazine-1-carboxylate (Reactant) (0.8 g, 1.71 mmol, 1 *equiv.*) in THF (8.0 ml) was added Pd on carbon (10 wt%) (100% w/w) (0.8 g). The heterogeneous mixture was stirred under hydrogen pressure (40 psi) at room temperature for 12 hours. The reaction mixture was then filtered through celite and the filtrate was concentrated under reduced pressure to afford *tert*-butyl-3,3-difluoro-4-(((S)-2-methylpiperazin-1-yl)methyl)piperidine-1-carboxylate (0.7 g, crude) as a brown gum which was used in the next step without further purification. **LC-MS (ESI):** m/z = 334.23 $[M+H]^+$

The compounds shown in the "**Product**" column of **Table P12** were synthesized using the method of **Example P12**, with variations noted in **Table P12**.

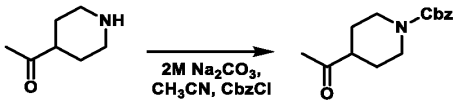
Table P12

Reactant	Variation from Example P12	Product
benzyl-(3S)-4-((1-(tert-butoxycarbonyl)-3,3-difluoropiperidin-4-yl)methyl)-3-methylpiperazine-1-carboxylate		*tert*-butyl-3,3-difluoro-4-(((S)-2-methylpiperazin-1-yl)methyl)piperidine-1-carboxylate
tert-butyl-9-(1-(1-((benzyloxy)carbonyl)piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	$Pd(OH)_2$ on carbon (20 wt%) (2.0 g, 100% w/w) instead of Pd on carbon (10 wt%)	*tert*-butyl-9-(1-(piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate
benzyl-4-[[(2S)-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-2-methyl-piperazin-1-yl]methyl]piperidine-1-carboxylate	Pd on carbon (10 wt%) (0.2 *equiv.*) and $Pd(OH)_2$ (0.3 *equiv.*); reaction solvent: CF_3CH_2OH as solvent	3-[1-methyl-6-[(3S)-3-methyl-4-(4-piperidylmethyl)piperazin-1-yl]indazol-3-yl]piperidine-2,6-dione

Table P12A

Product	LC-MS (ESI)
tert-butyl-3,3-difluoro-4-(((S)-2-methylpiperazin-1-yl)methyl)piperidine-1-carboxylate	m/z = 334.23 $[M+H]^+$
tert-butyl-9-(1-(piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	m/z = 366.51 $[M+H]^+$
3-[1-methyl-6-[(3S)-3-methyl-4-(4-piperidylmethyl)piperazin-1-yl]indazol-3-yl]piperidine-2,6-dione	m/z = 439.2 $[M+H]^+$

Example P13



To a stirred solution of 1-(piperidin-4-yl)ethan-1-one (Reactant) (7.0 g, 55.03 mmol, 1 *equiv.*) in CH_3CN (70.0 mL) was added 2M aqueous sodium carbonate (85. mL, 170.6 mmol, 1 *equiv.*) and benzyl-chloroformate (10.2 mL, 66.04 mmol, 1 *equiv.*) at 0°C. The reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was then concentrated under reduced pressure to obtain crude product which was triturated with diethyl ether (50 ml) and dried under vacuum to afford benzyl-4-acetylpiperidine-1-carboxylate (6.0 g) as an off solid. **LC-MS (ESI):** m/z = 262.0 $[M+H]^+$

The compounds shown in the "**Product**" column of **Table P13** were synthesized using the method of **Example P13**, with variations noted in **Table P13**.

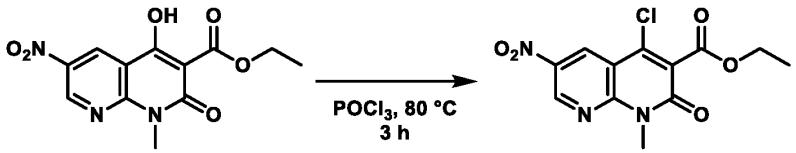
Table P13

Reactant	Variation from Example P13	Product
1-(piperidin-4-yl)ethan-1-one		benzyl-4-acetylpiperidine-1-carboxylate

Table P13A

Product	LC-MS (ESI)
benzyl-4-acetylpiperidine-1-carboxylate	m/z = 262.0 $[M+H]^+$

Example P14



A solution of ethyl-4-hydroxy-1-methyl-6-nitro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate (Reactant) (15.0 g, 61.04 mmol, 1 *equiv.*) in $POCl_3$ (50 mL) was stirred at 80 °C for 3 hours. The reaction mixture was quenched with sodium bicarbonate solution (150 mL) and extracted with ethyl-acetate (3 x100 mL). The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was washed with n-pentane and dried under reduced pressure to afford ethyl-4-chloro-1-methyl-6-nitro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate (8 g) as a brown solid. **LC-MS (ESI):** m/z = 312.0 $[M+H]^+$

The compounds shown in the "**Product**" column of **Table P14** were synthesized using the method of **Example P14**, with variations noted in **Table P14**.

Table P14

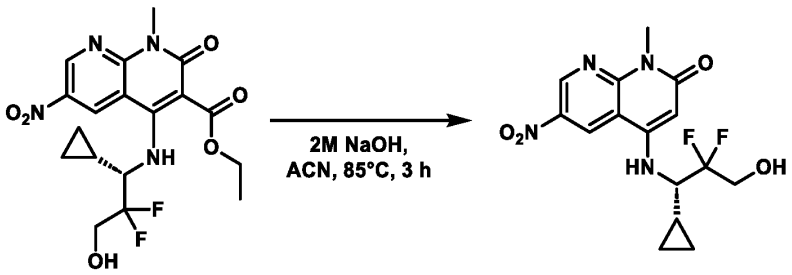
Reactant	Variation from Example P14	Product
ethyl-4-hydroxy-1-methyl-6-nitro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate		ethyl-4-chloro-1-methyl-6-nitro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate
ethyl-8-fluoro-4-hydroxy-1-methyl-6-nitro-2-oxo-1,2-dihydroquinoline-3-carboxylate	Work-up O was used	ethyl-4-chloro-8-fluoro-1-methyl-6-nitro-2-oxo-1,2-dihydroquinoline-3-carboxylate

ethyl-6-bromo-7-fluoro-4-hydroxy-1-methyl-2-oxo-quinoline-3-carboxylate	$(COCl)_2$ (3.0 *equiv.*) instead of $POCl_3$; reaction solvent: DMF; reaction temperature: 70°C; reaction time: 30 minutes; work-up G was used	ethyl-6-bromo-4-chloro-7-fluoro-1-methyl-2-oxo-quinoline-3-carboxylate

Table P14A

Product	LC-MS (ESI)	^{1}H NMR
ethyl-4-chloro-1-methyl-6-nitro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate	m/z = 312.00 $[M+H]^+$	
ethyl-4-chloro-8-fluoro-1-methyl-6-nitro-2-oxo-1,2-dihydroquinoline-3-carboxylate	m/z = 329.04 $[M+H]^+$	
ethyl-6-bromo-4-chloro-7-fluoro-1-methyl-2-oxo-quinoline-3-carboxylate	m/z = 362.0 $[M+H]^+$	(400 MHz, DMSO-d6) δ = 8.23 (d, J = 7.2 Hz, 1H), 7.81 (d, J = 10.8 Hz, 1H), 4.39 - 4.33 (m, 2H), 3.60 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H)

Example P15



To a stirred solution of ethyl-(S)-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl)amino)-1-methyl-6-nitro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate (Reactant) (8.0 g, 18.81 mmol, 1 *equiv.*) in acetonitrile (40 mL) was added 2M NaOH solution (40 mL). The mixture was stirred at 85 °C for 3 hours. The reaction mixture was diluted with ice-water (200 mL) and acidified with 1N HCl to pH~6. The resulting solid was filtered off, washed with water (100 mL), n-pentane (100 mL), and dried under vacuum to afford (S)-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl)amino)-1-methyl-6-nitro-1,8-naphthyridin-2(1H)-one (4.0 g) as a yellow solid. **LC-MS (ESI):** m/z = 355.36 $[M+H]^+$

The compounds shown in the "**Product**" column of **Table P15** were synthesized using the method of **Example P15**, with variations noted in **Table P15**.

Table P15

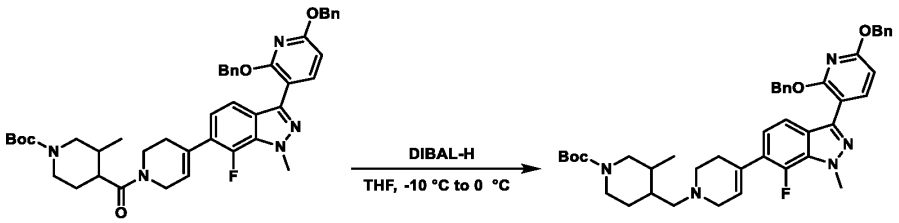
Reactant	Variation from Example P15	Product

ethyl-(S)-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl)amino)-1-methyl-6-nitro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate		(S)-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl)amino)-1-methyl-6-nitro-1,8-naphthyridin-2(1H)-one
ethyl-(S)-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl)amino)-8-fluoro-1-methyl-6-nitro-2-oxo-1,2-dihydroquinoline-3-carboxylate		(S)-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl)amino)-8-fluoro-1-methyl-6-nitroquinolin-2(1H)-one

Table P15A

Product	LC-MS (ESI)
(S)-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl)amino)-1-methyl-6-nitro-1,8-naphthyridin-2(1H)-one	m/z = 355.36 $[M+H]^+$
(S)-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl)amino)-8-fluoro-1-methyl-6-nitroquinolin-2(1H)-one	m/z = 372.18 $[M+H]^+$

Example P16



To a stirred solution of *tert*-butyl-4-(4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)-1,2,3,6-tetrahydropyridine-1-carbonyl)-3-methylpiperidine-1-carboxylate (Reactant) (0.9 g, 1.20 mmol, 1 *equiv.*) in THF (18.0 mL) was added DIBAL-H (1.0 M in toluene) (2.7 mL) dropwise at -10 °C. The mixture was stirred at 0 °C for 1 hour. The reaction mixture was then quenched with a saturated solution of ammonium chloride (3.0 mL) then diluted with water and extracted with ethyl acetate (3 x 60 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to obtain crude product which was purified by flash chromatography to afford *tert*-butyl-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)-3,6-dihydropyridin-1(2H)-yl)methyl)-3-methylpiperidine-1-carboxylate (0.53 g) as an off-white solid. **LC-MS (ESI):** m/z = 732.44 $[M+H]^+$

The compounds shown in the "**Product**" column of **Table P16** were synthesized using the method of **Example P16**, with variations noted in **Table P16**.

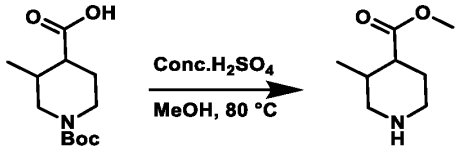
Table P16

Reactant	Variation from Example P16	Product
tert-butyl-4-(4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)-1,2,3,6-tetrahydropyridine-1-carbonyl)-3-methylpiperidine-1-carboxylate		*tert*-butyl-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)-3,6-dihydropyridin-1(2H)-yl)methyl)-3-methylpiperidine-1-carboxylate

Table P16A

Product	LC-MS (ESI)
tert-butyl-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)-3,6-dihydropyridin-1(2H)-yl)methyl)-3-methylpiperidine-1-carboxylate	m/z = 732.44 [M+H]+

Example P17



To a stirred solution of 1-(tert-butoxycarbonyl)-3-methylpiperidine-4-carboxylic-acid (Reactant) (4.0 g, 16.45 mmol, 1 *equiv.*) in MeOH (80 mL) was added conc. H_2SO_4 (4.0 mL) dropwise at 0 °C. The mixture was stirred at 80 °C for 3 hours. The reaction mixture was then concentrated under reduced pressure, diluted with ethyl-acetate (200 mL), and washed with a solution of saturated sodium bicarbonate (300 mL) and brine solution (200 mL). The separated organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford methyl-3-methylpiperidine-4-carboxylate (3.10 g, crude) as brown liquid which was used in the next step without further purification. **LC-MS (ESI):** m/z = 158.03 $[M+H]^+$

The compounds shown in the "**Product**" column of **Table P17** were synthesized using the method of **Example P17**, with variations noted in **Table P17**.

Table P17

Reactant	Variation from Example P17	Product
1-(tert-butoxycarbonyl)-3-methylpiperidine-4-carboxylic-acid		methyl-3-methylpiperidine-4-carboxylate
2-chloro-5-(trifluoromethyl)pyridine-4-carboxylic-acid	$(COCl)_2$ (2.0 *equiv.*) instead of H_2SO_4; reaction temperature: 20 °C; reaction time: 1 hour; work-up H was used	methyl-2-chloro-5-(trifluoromethyl)pyridine-4-carboxylate

Table P17A

Product	LC-MS (ESI)	^{1}H NMR
methyl-3-methylpiperidine-4-carboxylate	m/z = 158.03 $[M+H]^+$	
methyl-2-chloro-5-(trifluoromethyl)pyridine-4-carboxylate		(400 MHz, DMSO-d6) δ = 8.98 (s, 1H), 8.04 (s, 1H), 3.92 (s, 3H)

Example P18



To a stirred solution of 2-(methylamino)-5-nitronicotinic-acid (Reactant) (20.0 g, 101.50 mmol, 1 *equiv.*) in DMF (200 mL) was added HATU (57.89 g, 152.25 mmol, 1 *equiv.*), and DIPEA (53 mL, 304.50 mmol, 1 *equiv.*) at 0 °C. The mixture was stirred at room temperature for 3 hours. The reaction mixture was then quenched with ice cold water (1000 mL), and the precipitated solid was filtered, washed with n-pentane, and dried under vacuum to afford 3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl-2-(methylamino)-5-nitronicotinate (15 g) as a brown solid. **LC-MS (ESI):** m/z = 316.09 $[M+H]^+$

The compounds shown in the "**Product**" column of **Table P18** were synthesized using the method of **Example P18**, with variations noted in **Table P18**.

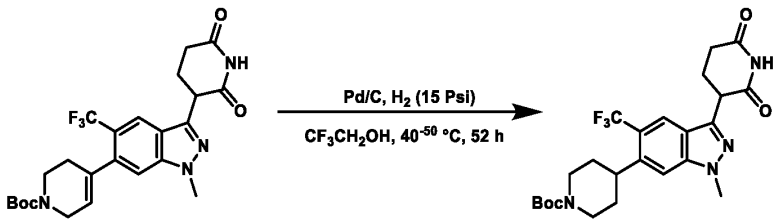
Table P18

Reactant	Variation from Example P18	Product
2-(methylamino)-5-nitronicotinic-acid		3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl-2-(methylamino)-5-nitronicotinate

Table P18A

Product	LC-MS (ESI)
3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl-2-(methylamino)-5-nitronicotinate	m/z = 316.09 [M+H]+

Example P19



To a solution of *tert*-butyl-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-5-(trifluoromethyl)indazol-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (Reactant) (1.7 g, 3.45 mmol, 1 *equiv.*) in CF_3CH_2OH (20 mL) was added Pd on carbon (10 wt%) (1.03 g, 966.52 μmol, 10% purity, 0.28 *equiv.*) under N_2 atmosphere. The suspension was degassed and purged with H_2 three times. The mixture was stirred under H_2 (15 psi) at 40 °C for 48 hours. The mixture was then stirred at 50 °C for 4 hours. The reaction mixture was then filtered and concentrated under reduced pressure to give *tert*-butyl-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-5-(trifluoromethyl)indazol-6-yl]piperidine-1-carboxylate (1.6 g, crude) as a white solid which was used in the next step without further purification. **LC-MS (ESI):** m/z = 495.2 $[M+H]^+$

The compounds shown in the "**Product**" column of **Table P19** were synthesized using the method of **Example P19**, with variations noted in **Table P19**.

Table P19

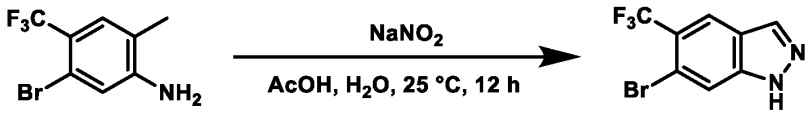
Reactant	Variation from Example P19	Product
tert-butyl-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-5-(trifluoromethyl)indazol-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate		*tert*-butyl-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-5-(trifluoromethyl)indazol-6-yl]piperidine-1-carboxylate
tert-butyl-(2R)-2-methyl-4-(1-methylindazol-6-yl)-3,6-dihydro-2H-pyridine-1-carboxylate	Reaction temperature: 25 °C; reaction time: 12 hours; crude product was purified by flash column chromatography	*tert*-butyl-(2R)-2-methyl-4-(1-methylindazol-6-yl)piperidine-1-carboxylate
tert-butyl-6,6-dimethyl-4-(1-methylindazol-6-yl)-2,3-dihydropyridine-1-carboxylate	Reaction temperature: 25 °C; reaction time: 12 hours; reaction solvent: MeOH; crude product was purified by flash column chromatography	*tert*-butyl-2,2-dimethyl-4-(1-methylindazol-6-yl)piperidine-1-carboxylate
tert-butyl-3-fluoro-4-(1-methylindazol-6-yl)-3,6-dihydro-2H-pyridine-1-carboxylate	Reaction temperature: 45 °C; reaction time: 1 hour; reaction solvent: ethyl acetate; crude product was purified by flash column chromatography	*tert*-butyl-3-fluoro-4-(1-methylindazol-6-yl)piperidine-1-carboxylate
1,7-dimethyl-6-nitro-1H-indazole	Reaction temperature: 25 °C; reaction time: 12 hours; reaction solvent: MeOH	1,7-dimethyl-1H-indazol-6-amine

Table P19A

Product	LC-MS (ESI)	^{1}H NMR

tert-butyl-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-5-(trifluoromethyl)indazol-6-yl]piperidine-1-carboxylate	m/z = 495.2 $[M+H]^+$	
tert-butyl-(2R)-2-methyl-4-(1-methylindazol-6-yl)piperidine-1-carboxylate	m/z = 330.0 $[M+H]^+$	
tert-butyl-2,2-dimethyl-4-(1-methylindazol-6-yl)piperidine-1-carboxylate	m/z = 344.3 $[M+H]^+$	
tert-butyl-3-fluoro-4-(1-methylindazol-6-yl)piperidine-1-carboxylate	m/z = 334.1 $[M+H]^+$	
1,7-dimethyl-1H-indazol-6-amine		(400 MHz, DMSO-d6) δ = 7.64 (s, 1H), 7.20 (d, J = 8.4 Hz, 1H), 6.56 (d, J = 8.4 Hz, 1H), 5.00 (s, 2H), 4.13 (s, 3H), 2.38 (s, 3H)

Example P20



To a solution of 5-bromo-2-methyl-4-(trifluoromethyl)aniline (Reactant) (3 g, 11.81 mmol, 1 *equiv.*) in AcOH (30 mL) was added $NaNO_2$ (814.75 mg, 11.81 mmol, 1 *equiv.*) in H_2O (1.5 mL) at 0°C. The mixture was stirred at 25 °C for 12 hours. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with H_2O (20 mL), filtered, and concentrated under reduced pressure to give crude product which was triturated with petroleum ether at 25 °C for 30 min to afford 6-bromo-5-(trifluoromethyl)-1H-indazole (2.3 g) as a red solid. **LC-MS (ESI):** m/z = 264.8 $[M+H]^+$

The compounds shown in the "**Product**" column of **Table P20** were synthesized using the method of **Example P20**, with variations noted in **Table P20**.

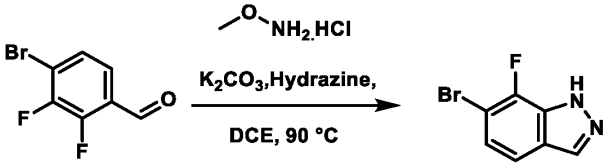
Table P20

Reactant	Variation from Example P20	Product
5-bromo-2-methyl-4-(trifluoromethyl)aniline		6-bromo-5-(trifluoromethyl)-1H-indazole

Table P20A

Product	LC-MS (ESI)
6-bromo-5-(trifluoromethyl)-1H-indazole	m/z = 264.8 $[M+H]^+$

Example P21



A solution of 4-bromo-2,3-difluorobenzaldehyde (Reactant) (25 g, 113.12 mmol, 1 *equiv.*), O-methylhydroxylamine (28.34 g, 339.36 mmol, 1 *equiv.*) and potassium carbonate (23.45 g, 169.68 mmol, 1 *equiv.*) in DCE (250 mL) was stirred at room temperature for 8 hours. To this mixture was added hydrazine (125.0 mL) at 0 °C. The reaction mixture was heated at 100 °C and stirred for 40 hours. The reaction mixture was quenched with ice cold water (300 mL) and extracted with ethyl-acetate (500 mL). The separated organic layers were washed with brine solution (50 mL), dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure to get crude product which was triturated with diethyl-ether (200 mL) to afford 6-bromo-7-fluoro-1H-indazole (16.0 g) as an off white solid. **LC-MS (ESI):** m/z = 212.95 $[M-H]^-$

The compounds shown in the "**Product**" column of **Table P21** were synthesized using the method of **Example P21**, with variations noted in **Table P21**.

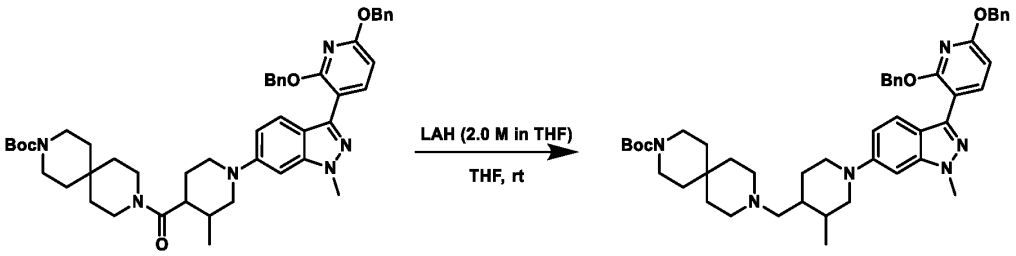
Table P21

Reactant	Variation from Example P21	Product
4-bromo-2,3-difluorobenzaldehyde		6-bromo-7-fluoro-1H-indazole
(E)-1-(4-bromo-2,5-difluoro-phenyl)-N-methoxy-methanimine	No O-methylhydroxylamine was added; reaction temperature: 90 °C; reaction time: 16 hours; work-up A was used	6-bromo-5-fluoro-1H-indazole
(E)-1-[4-bromo-2-fluoro-3-(trifluoromethyl)phenyl]-N-methoxy-methanimine	No O-methylhydroxylamine was added; reaction temperature: 90 °C; reaction time: 2 hours; work-up H was used	6-bromo-7-(trifluoromethyl)-1H-indazole

Table P21A

Product	LC-MS (ESI)
6-bromo-7-fluoro-1H-indazole	m/z = 212.95 $[M-H]^-$
6-bromo-5-fluoro-1H-indazole	m/z = 250.0 $[M+H]^+$
6-bromo-7-(trifluoromethyl)-1H-indazole	m/z = 266.9 $[M+H]^+$

Example P22



To a stirred solution of *tert*-butyl-9-(1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)-3-methylpiperidine-4-carbonyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (Reactant) (3.50 g, 4.38 mmol, 1 *equiv.*) in THF (105 mL), was added 2.0M LAH in THF (7.0 mL) at 0 °C. The resulting reaction mixture was stirred at the same temperature for 1 hour. The reaction mixture was then diluted with DCM (600 mL) and quenched with saturated NH_4Cl solution (400 mL). The organic layer was washed with brine solution (300 mL), dried over anhydrous sodium sulfate, filtered, and dried under vacuum to afford crude product which was purified by column chromatography to afford *tert*-butyl-9-((1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (3.50 g) as a yellow solid. **LC-MS (ESI):** m/z = 785.45 $[M+H]^+$

The compounds shown in the "**Product**" column of **Table P22** were synthesized using the method of **Example P22**, with variations noted in **Table P22**.

Table P22

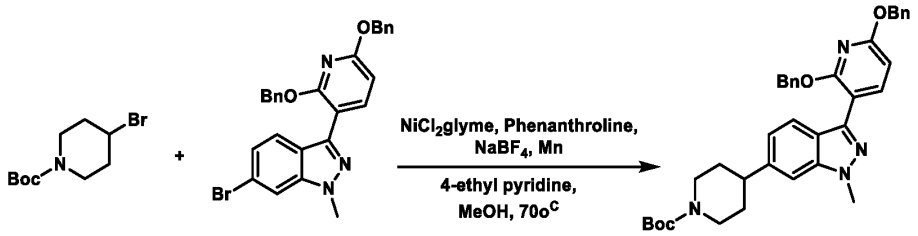
Reactant	Variation from Example P22	Product
tert-butyl-9-(1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)-3-methylpiperidine-4-carbonyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate		*tert*-butyl-9-((1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate
tert-butyl-4-(4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)-1,2,3,6-tetrahydropyridine-1-carbonyl)-3-methylpiperidine-1-carboxylate		*tert*-butyl-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)-3,6-dihydropyridin-1(2H)-yl)methyl)-3-methylpiperidine-1-carboxylate
1-(tert-butyl) 4-methyl 3-(trifluoromethyl)piperidine-1,4-dicarboxylate	Work-up R was used	*tert*-butyl-4-(hydroxymethyl)-3-(trifluoromethyl)piperidine-1-carboxylate

Table P22A

Product	LC-MS (ESI)

tert-butyl-9-((1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	m/z = 785.45 $[M+H]^+$
tert-butyl-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)-3,6-dihydropyridin-1(2H)-yl)methyl)-3-methylpiperidine-1-carboxylate	m/z = 732.75 $[M+H]^+$
tert-butyl-4-(hydroxymethyl)-3-(trifluoromethyl)piperidine-1-carboxylate	m/z = 282.1 $[M+H]^+$

Example P23



To a stirred solution of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-1-methyl-1H-indazole (prepared using published methods, e.g., in International Application Publication No. WO 2021/127586) (Reactant A) (12.0 g, 23.98 mmol, 1 *equiv.*) and *tert*-butyl-4-bromopiperidine-1-carboxylate (Reactant B) (12.6 g, 47.96 mmol, 1 *equiv.*) in MeOH (180 mL) was added nickel(II)chloride ethylene glycol dimethyl-ether complex (0.52 g , 2.39 mmol, 1 *equiv.*), 1,10-phenanthroline (0.86 g , 4.79 mmol, 1 *equiv.*), manganese (2.63 g , 47.96 mmol, 1 *equiv.*) and sodium tetrafluoroborate (1.31 g , 11.99 mmol, 1 *equiv.*). The reaction mixture was stirred for 10 minutes followed by the addition of 4-ethyl-pyridine (1.28 g, 11.99 mmol, 1 *equiv.*) at room temperature. The resulting mixture was stirred at 70°C for 16 hours. The reaction mixture was then concentrated under reduced pressure, quenched with water (1000 mL) and extracted with ethyl acetate (3 x 300 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to obtain crude product which was purified by flash chromatography to afford *tert*-butyl-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidine-1-carboxylate (7.0 g) as a pale-yellow solid. **LC-MS (ESI):** m/z = 605.36 $[M+H]^+$

The compounds shown in the "**Product**" column of **Table P23** were synthesized using the method of **Example P23**, with variations noted in **Table P23**.

Table P23

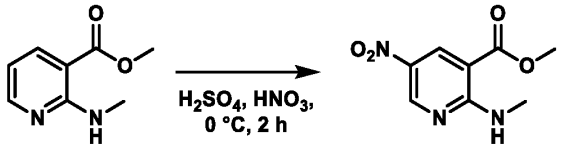
Reactant A	Reactant B	Variation from Example P23	Product

3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-1-methyl-1H-indazole	*tert*-butyl-4-bromopiperidine-1-carboxylate		*tert*-butyl-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidine-1-carboxylate

Table P23A

Product	LC-MS (ESI)
tert-butyl-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidine-1-carboxylate	m/z = 605.36 $[M+H]^+$

Example P24



To a stirred solution of methyl-2-(methylamino)nicotinate (Reactant) (40.0 g, 264.65 mmol, 1 *equiv.*) in sulfuric-acid (100 mL) was drop wise added nitric-acid (40 mL) at 0 °C. The reaction mixture was allowed to stir at room temperature for 2 hours. The reaction mixture was then poured into a crushed ice solution (2000 mL) and the solid precipitate was filtered and dried under vacuum to afford the methyl-2-(methylamino)-5-nitronicotinate (30 g) as a yellow solid. **LC-MS (ESI):** m/z = 212.21 $[M+H]^+$

The compounds shown in the "**Product**" column of **Table P24** were synthesized using the method of **Example P24**, with variations noted in **Table P24**.

Table P24

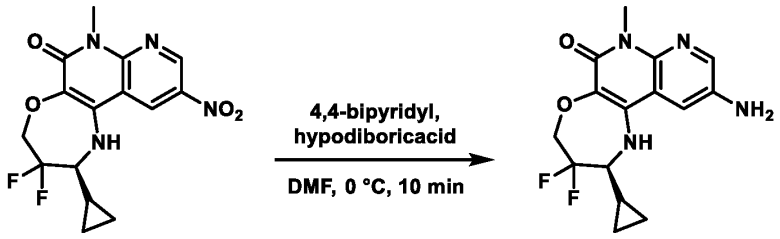
Reactant	Variation from Example P24	Product
methyl-2-(methylamino)nicotinate		methyl-2-(methylamino)-5-nitronicotinate
8-fluoro-2H-benzo[d][1,3]oxazine-2,4(1H)-dione	KNO_3 (1.0 *equiv.*) instead of nitric-acid	8-fluoro-6-nitro-2H-benzo[d][1,3]oxazine-2,4(1H)-dione
4-bromo-2-fluoro-3-(trifluoromethyl)aniline	Reaction solvent: H_2O (200 mL) and H_2SO_4 (200 mL) in MeCN (100mL); $NaNO_2$ (1.8 *equiv.*) instead of nitric-acid; KI (2.5 *equiv.*) was added; reaction temperature: 0 °C; work-up J was used	1-bromo-3-fluoro-4-iodo-2-(trifluoromethyl)benzene

Table P24A

Product	LC-MS (ESI)
methyl-2-(methylamino)-5-nitronicotinate	m/z = 212.21 $[M+H]^+$

8-fluoro-6-nitro-2H-benzo[d][1,3]oxazine-2,4(1H)-dione	m/z = 225.13 $[M-H]^-$
1-bromo-3-fluoro-4-iodo-2-(trifluoromethyl)benzene	m/z = 367.9 $[M+H]^+$

Example P25



To a stirred solution of (S)-2-cyclopropyl-3,3-difluoro-7-methyl-10-nitro-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-6(7H)-one (Reactant) (2.0 g, 5.68 mmol, 1 *equiv.*) in DMF (20 mL) was added 4,4'-dipyridyl (0.044 g, 0.28 mmol, 1 *equiv.*) followed by hypodiboric-acid (1.52 g, 17.01 mmol, 1 *equiv.*) portion wise at 0 °C. The mixture was stirred at 0 °C for 10 minutes. The reaction mixture was then diluted with water (50 mL) and the resulting solid was filtered, washed with water (100 mL), n-pentane (100 mL) and dried under vacuum to afford (S)-10-amino-2-cyclopropyl-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-6(7H)-one (1.5 g) as a yellow solid. **^{1}H NMR 400 MHz, DMSO-*d*$_6$**: δ 8.02 (d, *J* = 2.00 Hz, 1H), 7.59 (d, *J* = 2.40 Hz, 1H), 6.21 (d, *J* = 2.40 Hz, 1H), 5.19 (s, 2H), 4.49-4.30 (m, 2H), 3.53 (s, 3H), 3.26-3.18 (m, 1H), 1.30 (t, *J* = 4.40 Hz, 1H), 0.71-0.68 (m, 1H), 0.52-0.49 (m, 2H), 0.34-0.32 (m, 1H) **LC-MS (ESI):** m/z = 323.36 $[M+H]^+$

The compounds shown in the "**Product**" column of **Table P25** were synthesized using the method of **Example P25**, with variations noted in **Table P25**.

Table P25

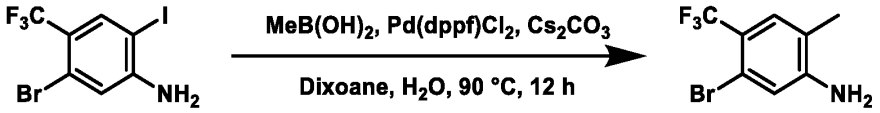
Reactant	Variation from Example P25	Product
(S)-2-cyclopropyl-3,3-difluoro-7-methyl-10-nitro-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-6(7H)-one		(S)-10-amino-2-cyclopropyl-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-6(7H)-one
(S)-2-cyclopropyl-3,3,8-trifluoro-7-methyl-10-nitro-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7H)-one		(S)-10-amino-2-cyclopropyl-3,3,8-trifluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7H)-one

Table P25A

Product	LC-MS (ESI)	^{1}H NMR
(S)-10-amino-2-cyclopropyl-3,3-difluoro-7-methyl-1,2,3,4-	m/z = 323.36 $[M+H]^+$	400 MHz, DMSO-d6: δ 8.02 (d, J = 2.00 Hz, 1H), 7.59 (d, J = 2.40 Hz, 1H), 6.21 (d, J = 2.40 Hz,

tetrahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-6(7H)-one		1H), 5.19 (s, 2H), 4.49-4.30 (m, 2H), 3.53 (s, 3H), 3.26-3.18 (m, 1H), 1.30 (t, J = 4.40 Hz, 1H), 0.71-0.68 (m, 1H), 0.52-0.49 (m, 2H), 0.34-0.32 (m, 1H)
(S)-10-amino-2-cyclopropyl-3,3,8-trifluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7H)-one	m/z = 340.36 $[M+H]^+$	

Example P26



A mixture of 5-bromo-2-iodo-4-(trifluoromethyl)aniline (Reactant) (13.98 g, 38.21 mmol, 1 *equiv.*), methylboronic-acid (2.74 g, 45.85 mmol, 1.2 *equiv.*), Cs_2CO_3 (49.79 g, 152.82 mmol, 4 *equiv.*) and $Pd(dppf)Cl_2$ (2.80 g, 3.82 mmol, 0.1 *equiv.*) in dioxane (90 mL) and H_2O (30 mL) was degassed and purged with N_2 three times. The mixture was stirred at 90 °C for 12 hours under N_2 atmosphere. The reaction mixture was diluted with H_2O (90 mL) and extracted with ethyl acetate (360 mL). The combined organic layers were washed with brine (360 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to afford 5-bromo-2-methyl-4-(trifluoromethyl)aniline (3.58 g) as a yellow solid. **LC-MS (ESI):** m/z = 253.9 $[M+H]^+$

The compounds shown in the "**Product**" column of **Table P26** were synthesized using the method of **Example P26**, with variations noted in **Table P26**.

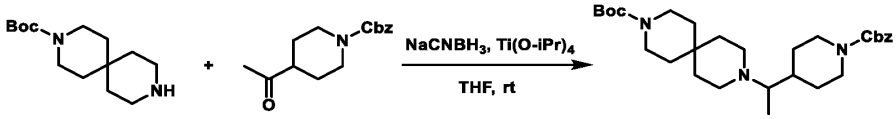
Table P26

Reactant	Variation from Example P26	Product
5-bromo-2-iodo-4-(trifluoromethyl)aniline		5-bromo-2-methyl-4-(trifluoromethyl)aniline

Table P26A

Product	LC-MS (ESI)
5-bromo-2-methyl-4-(trifluoromethyl)aniline	m/z = 253.9 $[M+H]^+$

Example P27



To a stirred solution of *tert*-butyl 3,9-diazaspiro[5.5]undecane-3-carboxylate (Reactant A) (5.0 g, 19.6 mmol, 1 *equiv.*) and benzyl-4-acetylpiperidine-1-carboxylate (Reactant B) (4.1 g, 15.7 mmol, 1 *equiv.*) in THF (20 mL) was added titanium(IV)isopropoxide (5.0 mL). The mixture was stirred for 1 hour at room temperature followed by the addition of sodium cyanoborohydride (3.7 g, 58.96 mmol, 3.8 *equiv.*) at 0°C. The reaction medium was stirred at room temperature for 6 hours. The reaction mixture was quenched with water (30.0 mL) and extracted with DCM (50.0 mL). The organic layer was separated and washed with brine solution (30.0 mL), dried over anhydrous sodium sulfate, filtered, and dried under vacuum to get crude product which was purified by flash column chromatography to afford *tert*-butyl-9-(1-(1-((benzyloxy)carbonyl)piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (2.1 g) as a white solid. **LC-MS (ESI):** m/z = 500.6 $[M+H]^+$

The compounds shown in the "**Product**" column of **Table P27** were synthesized using the method of **Example P27**, with variations noted in **Table P27**.

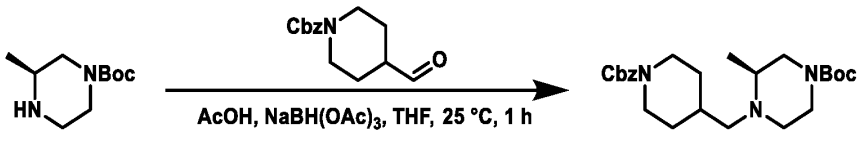
Table P27

Reactant A	Reactant B	Variation from Example P27	Product
tert-butyl-3,9-diazaspiro[5.5]undecane-3-carboxylate	benzyl-4-acetylpiperidine-1-carboxylate		*tert*-butyl-9-(1-(1-((benzyloxy)carbonyl)piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate

Table P27A

Product	LC-MS (ESI)
tert-butyl-9-(1-(1-((benzyloxy)carbonyl)piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	m/z = 500.6 $[M+H]^+$

Example P28



To a solution of *tert*-butyl-(3S)-3-methylpiperazine-1-carboxylate (Reactant A) (2 g, 9.99 mmol, 1 *equiv.*) and benzyl-4-formylpiperidine-1-carboxylate (Reactant B) (2.72 g, 10.98 mmol, 1.1 *equiv.*) in THF (20 mL) was added dropwise AcOH (59.97 mg, 998.62 µmol, 57.17 µL, 0.1 *equiv.*). After addition, the mixture was stirred at this room temperature for 30 min, followed by the addition of $NaBH(OAc)_3$ (3.17 g, 14.98 mmol, 1.5 *equiv.*) dropwise. The resulting mixture was stirred at 25 °C for 1 hour. The reaction mixture was quenched by

aqueous sodium bicarbonate, and then extracted with DCM (60 mL). The combined organic layers were washed with brine (90 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to afford *tert*-butyl-(3S)-4-[(1-benzyloxycarbonyl-4-piperidyl)methyl]-3-methyl-piperazine-1-carboxylate (3.9 g) as a yellow oil. **LC-MS (ESI):** m/z = 432.4 $[M+H]^+$

The compounds shown in the "**Product**" column of **Table P28** were synthesized using the method of **Example P28**, with variations noted in **Table P28**.

Table P28

Reactant A	Reactant B	Variation from Example P28	Product
tert-butyl-(3S)-3-methylpiperazine-1-carboxylate	benzyl-4-formylpiperidine-1-carboxylate		*tert*-butyl-(3S)-4-[(1-benzyloxycarbonyl-4-piperidyl)methyl]-3-methyl-piperazine-1-carboxylate
3-[1-methyl-6-(4-piperidyl)-5-(trifluoromethyl)indazol-3-yl]piperidine-2,6-dione	*tert*-butyl-4-formylpiperidine-1-carboxylate		*tert*-butyl-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-5-(trifluoromethyl)indazol-6-yl]-1-piperidyl]methyl]piperidine-1-carboxylate
3-[7-fluoro-1-methyl-6-(4-piperidyl)indazol-3-yl]piperidine-2,6-dione	*tert*-butyl-(3R,4S)-4-formyl-3-methylpiperidine-1-carboxylate	Reaction conditions did not contain acetic acid; work-up J was used	*tert*-butyl-(3R,4S)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate
3-[1-methyl-7-(4-piperidyl)indazol-3-yl]piperidine-2,6-dione	*tert*-butyl-(3S,4S)-4-formyl-3-methyl-piperidine-1-carboxylate	Reaction conditions did not contain acetic acid; reaction was quenched with H_2O (instead of sodium bicarbonate)	*tert*-butyl-(3S,4S)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-7-yl]-1-piperidyl]methyl]-3-methyl-piperidine-1-carboxylate
6-(benzyloxy)-5-(6-(3,3-difluoro-1,2,3,6-tetrahydropyridin-4-yl)-1-methyl-1H-indazol-3-yl)pyridin-2-ol	*tert*-butyl-4-formylpiperidine-1-carboxylate		*tert*-butyl-4-((4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-1-methyl-1H-indazol-6-yl)-3,3-difluoro-3,6-dihydropyridin-1(2H)-yl)methyl)piperidine-1-carboxylate
6-(benzyloxy)-3-(1-methyl-6-(piperidin-4-yl)-1H-indazol-3-yl)pyridin-2-ol	*tert*-butyl-4-formylpiperidine-1-carboxylate	Sodium acetate (1.0 *equiv.*) instead of AcOH; $NaCNBH_3$ (2.0 *equiv.*) instead of $NaBH(OAc)_3$; work-up K was used	*tert*-butyl-4-((4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate
6-benzyloxy-3-[1-methyl-6-[(2R)-2-methyl-4-piperidyl]indazol-3-yl]-3H-pyridin-2-one	*tert*-butyl-4-formylpiperidine-1-carboxylate	Reaction solvent: DCM; reaction time: 12 hours	*tert*-butyl-4-[[(2R)-4-[3-(6-benzyloxy-2-oxo-3H-pyridin-3-yl)-1-methyl-indazol-6-yl]-2-methyl-1-piperidyl]methyl]piperidine-1-carboxylate
3-(1-methyl-6-(piperazin-1-yl)-1H-indazol-3-yl)piperidine-	*tert*-butyl-4-formylpiperidine-1-carboxylate	Reaction solvent: DCM	*tert*-butyl-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperazin-1-

2,6-dione			yl)methyl)piperidine-1-carboxylate
3-[1-methyl-6-(4-piperidyl)-7-(trifluoromethyl)indazol-3-yl]piperidine-2,6-dione	*tert*-butyl-4-formylpiperidine-1-carboxylate	Reaction solvent: DCM; work-up J was used	*tert*-butyl-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-7-(trifluoromethyl)indazol-6-yl]-1-piperidyl]methyl]piperidine-1-carboxylate
3-[1-methyl-7-(4-piperidyl)indazol-3-yl]piperidine-2,6-dione	*tert*-butyl-(3R,4S)-4-formyl-3-methylpiperidine-1-carboxylate	Reaction solvent: DCM; reaction time: 16 hours; residue was purified by prep-TLC	*tert*-butyl-(3R,4S)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-7-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate
3-[1-methyl-7-(4-piperidyl)indazol-3-yl]piperidine-2,6-dione	*tert*-butyl-(3S,4R)-4-formyl-3-methyl-piperidine-1-carboxylate	DIPEA (1.0 *equiv.*) instead of AcOH; reaction solvent: DCM; reaction time: 16 hours	*tert*-butyl-(3S,4R)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-7-yl)piperidin-1-yl)methyl)-3-methyl-piperidine-1-carboxylate
3-(6-(piperidin-4-yl)-1H-indazol-3-yl)piperidine-2,6-dione	*tert*-butyl-4-formylpiperidine-1-carboxylate	Sodium acetate (1.0 *equiv.*) instead of AcOH; reaction time: 16 hours; purified by reverse phase column chromatography	*tert*-butyl-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1H-indazol-6-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate
3-[6-[(4S)-2,2-dimethyl-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione	*tert*-butyl-4-formylpiperidine-1-carboxylate	Reaction solvent: DCM; reaction time: 12 hours; work-up A was used	*tert*-butyl-4-[[(4S)-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-2,2-dimethyl-1-piperidyl]methyl]piperidine-1-carboxylate
4-bromo-1,2,3,6-tetrahydropyridine	*tert*-butyl-4-formylpiperidine-1-carboxylate	Reaction solvent: DCM; work-up H was used	*tert*-butyl-4-[(4-bromo-3,6-dihydro-2H-pyridin-1-yl)methyl]piperidine-1-carboxylate
3-[6-[(4R)-2,2-dimethyl-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione	*tert*-butyl-4-formylpiperidine-1-carboxylate	Reaction solvent: DCM; reaction time: 12 hours; work-up A was used	*tert*-butyl-4-[[(4R)-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-2,2-dimethyl-1-piperidyl]methyl]piperidine-1-carboxylate
3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)indazole	*tert*-butyl-4-acetylpiperidine-1-carboxylate	Reaction solvent: DCM; $Ti(i\text{-}PrO)_4$ (3.0 *equiv.*) instead of AcOH; reaction time: 12 hours; work-up S was used	*tert*-butyl-4-[1-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridin-1-yl]ethyl]piperidine-1-carboxylate
3-[6-(4-piperidyl)-1-(2,2,2-trifluoroethyl)indazol-3-yl]piperidine-2,6-dione	*tert*-butyl-4-formylpiperidine-1-carboxylate	Work-up S was used	*tert*-butyl-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-(2,2,2-trifluoroethyl)indazol-6-yl]-1-piperidyl]methyl]piperidine-1-carboxylate
3-[5-fluoro-1-methyl-6-(4-piperidyl)indazol-3-yl]piperidine-2,6-dione	*tert*-butyl-(3R,4S)-4-formyl-3-methyl-piperidine-1-carboxylate	Reaction solvent: DCM; reaction time: 12 hours; work-up S was used	*tert*-butyl-(3R,4S)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-methyl-piperidine-1-carboxylate
3-[1-isopropyl-6-(4-piperidyl)indazol-3-yl]piperidine-2,6-dione	*tert*-butyl-4-formylpiperidine-1-carboxylate	Reaction solvent: DCM; work-up A was used	*tert*-butyl-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-isopropyl-indazol-6-yl]-1-piperidyl]methyl]piperidine-1-carboxylate
3-[1-methyl-7-(4-piperidyl)indazol-3-	*tert*-butyl-(3R,4R)-4-formyl-3-methyl-	Reaction solvent: DCM; reaction time: 12 hours;	*tert*-butyl-(3R,4R)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-

yl]piperidine-2,6-dione	piperidine-1-carboxylate	work-up A was used	methyl-indazol-7-yl]-1-piperidyl]methyl]-3-methyl-piperidine-1-carboxylate
3-(2,6-dibenzyloxy-3-pyridyl)-6-(3-fluoro-4-piperidyl)-1-methyl-indazole	*tert*-butyl-4-formylpiperidine-1-carboxylate	Reaction solvent: DCM; reaction time: 12 hours; work-up H was used	*tert*-butyl-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-3-fluoro-1-piperidyl]methyl]piperidine-1-carboxylate
3-[1-methyl-6-(4-piperidyl)indazol-3-yl]piperidine-2,6-dione	*tert*-butyl-(4R)-3,3-difluoro-4-formyl-piperidine-1-carboxylate	Reaction solvent: DMSO; reaction time: 12 hours; work-up H was used	*tert*-butyl-(4R)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3,3-difluoro-piperidine-1-carboxylate
3-[1-methyl-6-(4-piperidyl)indazol-3-yl]piperidine-2,6-dione	*tert*-butyl-(4S)-3,3-difluoro-4-formyl-piperidine-1-carboxylate	Reaction solvent: DMSO; reaction time: 12 hours; work-up H was used	*tert*-butyl-(4S)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3,3-difluoro-piperidine-1-carboxylate
benzyl 3,9-diazaspiro[5.5]undecane-3-carboxylate	*tert*-butyl-4-formyl-4-methyl-piperidine-1-carboxylate	$Ti(Oi\text{-}Pr)_4$ (3.0 *equiv.*) instead of AcOH; work-up S was used (extracted with 10% MeOH in DCM instead of 100% DCM)	benzyl-9-[(1-tert-butoxycarbonyl-4-methyl-4-piperidyl)methyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate
3-[1,5-dimethyl-6-(4-piperidyl)indazol-3-yl]piperidine-2,6-dione	*tert*-butyl-4-formylpiperidine-1-carboxylate	Reaction solvent: THF:DMSO (2:1); KOAc (2.0 *equiv.*) was added with AcOH; reaction temperature: 40 °C; reaction time: 6 hours; work-up T was used	*tert*-butyl-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1,5-dimethyl-indazol-6-yl]-1-piperidyl]methyl]piperidine-1-carboxylate
benzyl 3,9-diazaspiro[5.5]undecane-3-carboxylate	*tert*-butyl-4-formylpiperidine-1-carboxylate	Reaction solvent: DCM; $Ti(i\text{-}PrO)_4$ (3.0 *equiv.*) instead of AcOH; reaction time: 12 hours; work-up A was used	benzyl-9-[(1-tert-butoxycarbonyl-4-piperidyl)methyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate
3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)indazole	*tert*-butyl-4-formyl-3-(trifluoromethyl)piperidine-1-carboxylate	Work-up T was used	*tert*-butyl-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridin-1-yl]methyl]-3-(trifluoromethyl)piperidine-1-carboxylate
3-(2,6-dibenzyloxy-3-pyridyl)-6-[(3S,4R)-3-fluoro-4-piperidyl]-1-methyl-indazole	*tert*-butyl-4-formylpiperidine-1-carboxylate	Reaction time: 12 hours; work-up H was used	*tert*-butyl-4-[[(3S,4R)-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-3-fluoro-1-piperidyl]methyl]piperidine-1-carboxylate
3-(2,6-dibenzyloxy-3-pyridyl)-6-[(3R,4S)-3-fluoro-4-piperidyl]-1-methyl-indazole	*tert*-butyl-4-formylpiperidine-1-carboxylate	Reaction time: 12 hours; work-up A was used	*tert*-butyl-4-[[(3R,4S)-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-3-fluoro-1-piperidyl]methyl]piperidine-1-carboxylate
3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)indazole	*tert*-butyl-(3S,4R)-3-fluoro-4-formyl-piperidine-1-carboxylate	Reaction solvent: DMSO; work-up A was used	*tert*-butyl-(3S,4R)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridin-1-yl]methyl]-3-fluoro-piperidine-1-carboxylate

3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indazole	*tert*-butyl-(3R,4S)-3-fluoro-4-formylpiperidine-1-carboxylate	Reaction solvent: DMSO; work-up A was used	*tert*-butyl-(3R,4S)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)-3,6-dihydropyridin-1(2H)-yl)methyl)-3-fluoropiperidine-1-carboxylate
4-bromo-1,2,3,6-tetrahydropyridine	*tert*-butyl-4-acetylpiperidine-1-carboxylate	Reaction solvent: DCM; $Ti(i\text{-}PrO)_4$ (3.0 *equiv.*) instead of AcOH; reaction time: 16 hours; work-up S was used	*tert*-butyl-4-[1-(4-bromo-3,6-dihydro-2H-pyridin-1-yl)ethyl]piperidine-1-carboxylate
3-(1,7-dimethyl-6-(piperidin-4-yl)-1H-indazol-3-yl)piperidine-2,6-dione	*tert*-butyl 4-formylpiperidine-1-carboxylate	Reaction solvent: DC; reaction time: 12 hours; work-up H was used	*tert*-butyl-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1,7-dimethyl-1H-indazol-6-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate
tert-butyl-(3R)-3-methylpiperazine-1-carboxylate	benzyl-4-formylpiperidine-1-carboxylate	Reaction temperature: 20 °C; reaction time: 2hours	*tert*-butyl-(3R)-4-[(1-benzyloxycarbonyl-4-piperidyl)methyl]-3-methyl-piperazine-1-carboxylate

Table P28A

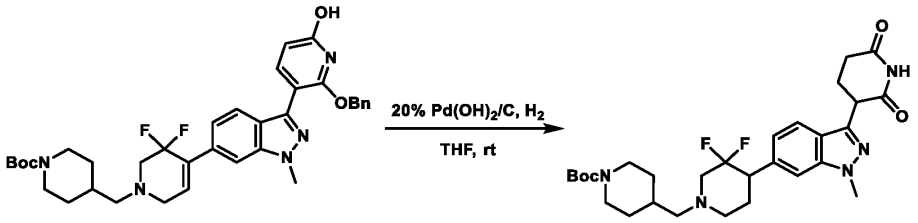
Product	LC-MS (ESI)	^{1}H NMR
tert-butyl-(3S)-4-[(1-benzyloxycarbonyl-4-piperidyl)methyl]-3-methyl-piperazine-1-carboxylate	m/z = 432.4 $[M+H]^+$	
tert-butyl-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-5-(trifluoromethyl)indazol-6-yl]-1-piperidyl]methyl]piperidine-1-carboxylate	m/z = 592.2 $[M+H]^+$	
tert-butyl-(3R,4S)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate	m/z = 556.3 $[M+H]^+$	
tert-butyl-(3S,4S)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-7-yl]-1-piperidyl]methyl]-3-methyl-piperidine-1-carboxylate	m/z = 538.5 $[M+H]^+$	
tert-butyl-4-((4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-1-methyl-1H-indazol-6-yl)-3,3-difluoro-3,6-dihydropyridin-1(2H)-yl)methyl)piperidine-1-carboxylate	m/z: 437.15 $[M-H]^-$	
tert-butyl-4-((4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate	m/z = 612.63 $[M+H]^+$	
tert-butyl-4-[[(2R)-4-[3-(6-benzyloxy-2-oxo-3H-pyridin-3-yl)-1-methyl-indazol-6-yl]-2-methyl-1-piperidyl]methyl]piperidine-1-carboxylate	m/z = 626.4 $[M+H]^+$	
tert-butyl-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-	m/z = 524.3 $[M+H]^+$	

indazol-6-yl)piperazin-1-yl)methyl)piperidine-1-carboxylate		
tert-butyl-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-7-(trifluoromethyl)indazol-6-yl]-1-piperidyl]methyl]piperidine-1-carboxylate	m/z = 592.2 $[M+H]^+$	
tert-butyl-(3R,4S)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-7-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate	m/z = 538.3 $[M+H]^+$	
tert-butyl-(3S,4R)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-7-yl)piperidin-1-yl)methyl)-3-methyl-piperidine-1-carboxylate	m/z = 538.3 $[M+H]^+$	
tert-butyl-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1H-indazol-6-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate	m/z = 510.64 $[M+H]^+$	
tert-butyl-4-[[(4S)-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-2,2-dimethyl-1-piperidyl]methyl]piperidine-1-carboxylate	m/z = 468.2 $[M+H]^+$	
tert-butyl-4-[(4-bromo-3,6-dihydro-2H-pyridin-1-yl)methyl]piperidine-1-carboxylate	m/z = 361.0 $[M+H]^+$	
tert-butyl-4-[[(4R)-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-2,2-dimethyl-1-piperidyl]methyl]piperidine-1-carboxylate	m/z = 552.5 $[M+H]^+$	
tert-butyl-4-[1-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridin-1-yl]ethyl]piperidine-1-carboxylate		
tert-butyl-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-(2,2,2-trifluoroethyl)indazol-6-yl]-1-piperidyl]methyl]piperidine-1-carboxylate	m/z = 592.2 $[M+H]^+$	
tert-butyl-(3R,4S)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-methyl-piperidine-1-carboxylate	m/z = 556.1 $[M+H]^+$	
tert-butyl-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-isopropyl-indazol-6-yl]-1-piperidyl]methyl]piperidine-1-carboxylate	m/z = 552.2 $[M+H]^+$	(400 MHz, DMSO-d6) δ = 10.86 (s, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.48 (s, 1H), 7.01 (d, J = 7.6 Hz, 1H), 5.01 - 4.88(m, 1H), 4.32 (dd, J = 5.2, 10.0 Hz, 1H), 4.03 (q, J = 7.2 Hz, 2H), 3.98 - 3.85 (m, 2H), 2.95 (br d, J = 11.2 Hz, 2H), 2.67 (td, J =2.0, 3.6 Hz, 3H), 2.35 - 2.31 (m, 3H), 2.16 (br d, J = 7.2 Hz, 3H), 1.89 (s, 1H), 1.77 (br d, J = 6.0 Hz, 7H), 1.43 (dd, J = 2.0, 6.4 Hz, 6H), 1.41 - 1.36 (m, 10H)
tert-butyl-(3R,4R)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-	m/z = 538.2 $[M+H]^+$	

indazol-7-yl]-1-piperidyl]methyl]-3-methyl-piperidine-1-carboxylate		
tert-butyl-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-3-fluoro-1-piperidyl]methyl]piperidine-1-carboxylate	m/z = 720.3 $[M+H]^+$	
tert-butyl-(4R)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3,3-difluoro-piperidine-1-carboxylate	m/z = 560.3 $[M+H]^+$	
tert-butyl-(4S)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3,3-difluoro-piperidine-1-carboxylate	m/z = 560.3 $[M+H]^+$	
benzyl-9-[(1-tert-butoxycarbonyl-4-methyl-4-piperidyl)methyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate	m/z = 500.2 $[M+H]^+$	
tert-butyl-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1,5-dimethyl-indazol-6-yl]-1-piperidyl]methyl]piperidine-1-carboxylate		
benzyl-9-[(1-tert-butoxycarbonyl-4-piperidyl)methyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate	m/z = 486.3 $[M+H]^+$	
tert-butyl-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridin-1-yl]methyl]-3-(trifluoromethyl)piperidine-1-carboxylate	m/z = 768.3 $[M+H]^+$	
tert-butyl-4-[[(3S,4R)-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-3-fluoro-1-piperidyl]methyl]piperidine-1-carboxylate	m/z = 720.1 $[M+H]^+$	(400 MHz, DMSO-d6) δ = 7.94 - 7.87 (m, 1H), 7.66 - 7.56 (m, 1H), 7.46 (d, J = 6.8 Hz, 3H), 7.42 - 7.23 (m, 8H), 7.06 - 6.98 (m, 1H), 6.58 (d, J = 8.0 Hz, 1H), 5.48 - 5.37 (m, 4H), 4.92 - 4.71 (m, 1H), 4.07 - 4.00 (m, 5H), 3.98 - 3.88 (m, 2H), 3.22 - 3.11 (m, 1H), 3.04 - 2.83 (m, 2H), 2.80 - 2.62 (m, 2H), 2.35 - 2.07 (m, 5H), 2.01 - 1.96 (m, 3H), 1.77 - 1.64 (m, 4H), 1.43 - 1.37 (m, 9H)
tert-butyl-4-[[(3R,4S)-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-3-fluoro-1-piperidyl]methyl]piperidine-1-carboxylate	m/z = 630.2 $[M+H]^+$	
tert-butyl-(3S,4R)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridin-1-yl]methyl]-3-fluoro-piperidine-1-carboxylate	m/z = 718.3 $[M+H]^+$	
tert-butyl-(3R,4S)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)-3,6-dihydropyridin-1(2H)-yl)methyl)-3-fluoropiperidine-1-carboxylate	m/z = 718.3 $[M+H]^+$	
tert-butyl-4-[1-(4-bromo-3,6-dihydro-2H-pyridin-1-yl)ethyl]piperidine-1-carboxylate	m/z = 374.9 $[M+H]^+$	

tert-butyl-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1,7-dimethyl-1H-indazol-6-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate		(400 MHz, DMSO-d6) δ = 10.86 (s, 1H), 7.45 (d, J = 8.4 Hz, 1H), 7.02 (d, J = 8.8 Hz, 1H), 4.23 (s, 3H), 3.99 - 3.88 (m, 3H), 3.16 (s, 1H), 3.04 - 2.91 (m, 2H), 2.68 (s, 3H), 2.66 - 2.54 (m, 3H), 2.35 - 2.26 (m, 2H), 2.18 - 2.05 (m, 3H), 1.84 - 1.51 (m, 8H), 1.39 (s, 9H), 1.38 (s, 1H), 1.03 - 0.91 (m, 2H)
tert-butyl-(3R)-4-[(1-benzyloxycarbonyl-4-piperidyl)methyl]-3-methyl-piperazine-1-carboxylate	m/z = 432.3 $[M+H]^+$	

Example P29



To a stirred solution of *tert*-butyl-4-((4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-1-methyl-1H-indazol-6-yl)-3,3-difluoro-3,6-dihydropyridin-1(2H)-yl)methyl)piperidine-1-carboxylate (Reactant) (0.2 g, 0.31 mmol, 1 *equiv.*) in THF (0.4 mL) was added $Pd(OH)_2$ on carbon (20 wt%) (0.2 g, 100% w/w). The mixture was stirred under hydrogen atmosphere (80 psi) at room temperature for 5 hours. The reaction mixture was diluted with THF (12.0 mL), filtered through a pad of celite, and washed with an excess of 20% THF in DCM. The filtrate was collected and concentrated to afford *tert*-butyl-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)-3,3-difluoropiperidin-1-yl)methyl)piperidine-1-carboxylate (0.15 g). **LC-MS (ESI): m/z** = 457.17 $[M+H]^+$

The compounds shown in the "**Product**" column of **Table P29** were synthesized using the method of **Example P29**, with variations noted in **Table P29**.

Table P29

Reactant	Variation from Example P29	Product
tert-butyl-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-7-yl]piperazin-1-yl]methyl]piperidine-1-carboxylate	Reaction catalyst system: Pd on carbon (10 wt%) (1.0 *equiv.*) and $Pd(OH)_2$ on carbon (20 wt%) (1.0 *equiv.*); reaction solvent: CF_3CH_2OH; work-up D was used	*tert*-butyl-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-7-yl]piperazin-1-yl]methyl]piperidine-1-carboxylate
tert-butyl-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-5-(trifluoromethyl)indazol-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate	Reaction catalyst system: Pd on carbon (10 wt%) (1.0 *equiv.*) and $Pd(OH)_2$ on carbon (20 wt%) (1.0 *equiv.*); reaction solvent: CF_3CH_2OH; work-up D was used	*tert*-butyl-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-5-(trifluoromethyl)indazol-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate

tert-butyl-4-[3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate	Reaction catalyst system: Pd on carbon (10 wt%) (1.0 *equiv.*), $Pd(OH)_2$ on carbon (20 wt%) (1.0 *equiv.*), and acetic acid (0.1 *equiv.*); reaction solvent: CF_3CH_2OH; work-up D was used	*tert*-butyl-4-[3-(2,6-dioxo-3-piperidyl)-7-fluoro-1-methyl-indazol-6-yl]piperidine-1-carboxylate
tert-butyl-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-7-yl]-3,6-dihydro-2H-pyridine-1-carboxylate	Reaction catalyst system: Pd on carbon (10 wt%) (1.0 *equiv.*) and $Pd(OH)_2$ on carbon (20 wt%) (1.0 *equiv.*); reaction solvent: CF_3CH_2OH; work-up D was used	*tert*-butyl-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-7-yl]piperidine-1-carboxylate
tert-butyl-(3S,4R)-4-((4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate	Reaction time: 16 hours; residue was triturated with diethyl ether	*tert*-butyl-(3S,4R)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate
tert-butyl-(R)-4-((4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperazin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate	Reaction time: 12 hours; residue was triturated with diethyl ether	*tert*-butyl-(4R)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperazin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate
tert-butyl-(S)-4-((4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperazin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate	Reaction time: 12 hours; residue was triturated with diethyl ether	*tert*-butyl-(4S)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperazin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate
tert-butyl-9-(((3S,4S)-1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	Reaction time: 16 hours	*tert*-butyl-9-(((3S,4S)-1-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate
tert-butyl-9-(((3R,4R)-1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	Reaction time: 16 hours	*tert*-butyl-9-(((3R,4R)-1-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate
tert-butyl-4-(((S)-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-7-yl)-2-methylpiperazin-1-yl)methyl)-3,3-difluoropiperidine-1-carboxylate	Reaction time: 12 hours	*tert*-butyl-4-(((2S)-4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-7-yl)-2-methylpiperazin-1-yl)methyl)-3,3-difluoropiperidine-1-carboxylate
tert-butyl-4-((4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-1-methyl-1H-indazol-6-yl)-3,3-difluoro-3,6-dihydropyridin-1(2H)-yl)methyl)piperidine-1-carboxylate		*tert*-butyl-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)-3,3-difluoropiperidin-1-yl)methyl)piperidine-1-carboxylate
tert-butyl-(3S,4S)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)-3,6-dihydropyridin-1(2H)-yl)methyl)-3-methylpiperidine-1-carboxylate		*tert*-butyl-(3S,4S)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate
tert-butyl-(3R,4R)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)-3,6-dihydropyridin-1(2H)-		*tert*-butyl-(3R,4R)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)piperidin-

yl)methyl)-3-methyl-piperidine-1-carboxylate		1-yl)methyl)-3-methylpiperidine-1-carboxylate
tert-butyl-(R)-9-(1-(1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate		*tert*-butyl-9-((1R)-1-(1-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate
tert-butyl-(S)-9-(1-(1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate		*tert*-butyl-9-((1S)-1-(1-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate
tert-butyl-(R)-9-(1-(1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate		*tert*-butyl-9-((1R)-1-(1-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate
tert-butyl-(S)-9-(1-(1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate		*tert*-butyl-9-((1S)-1-(1-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate
tert-butyl-4-((4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate	Reaction time: 16 hours	*tert*-butyl-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate
tert-butyl-(3S,4S)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)-3,6-dihydropyridin-1(2H)-yl)methyl)-3-methylpiperidine-1-carboxylate	Residue was triturated with n-pentane	*tert*-butyl-(3S,4S)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate
tert-butyl-(3R,4R)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)-3,6-dihydropyridin-1(2H)-yl)methyl)-3-methylpiperidine-1-carboxylate	Residue was triturated with n-pentane	*tert*-butyl-(3R,4R)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate
tert-butyl (3R,4S)-4-((4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate	Residue was triturated with diethyl ether	*tert*-butyl-(3R,4S)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate
tert-butyl-4-(((2R,4R)-4-(3-(6-(benzyloxy)-2-oxo-1,2-dihydropyridin-3-yl)-1-methyl-1H-indazol-6-yl)-2-methylpiperidin-1-yl)methyl)piperidine-1-carboxylate	Pd on carbon (10 wt%) (1.0 *equiv.*) with $Pd(OH)_2$ on carbon (20 wt%) (1.0 *equiv.*); reaction solvent: CF_3CH_2OH; reaction time: 12 hours; work-up D was used	*tert*-butyl-4-[[(2R,4R)-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-2-methyl-1-piperidyl]methyl]piperidine-1-carboxylate
tert-butyl-4-[(1R)-1-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridin-1-yl]-2,2,2-trifluoro-ethyl]piperidine-1-carboxylate	Pd on carbon (10 wt%) (1.0 *equiv.*) with $Pd(OH)_2$ on carbon (20 wt%) (1.0 *equiv.*); reaction solvent: CF_3CH_2OH; reaction time: 12 hours; work-up D was used	*tert*-butyl-4-[(1R)-1-[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-1-piperidyl]-2,2,2-trifluoro-ethyl]piperidine-1-carboxylate

tert-butyl-4-[(1S)-1-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridin-1-yl]-2,2,2-trifluoro-ethyl]piperidine-1-carboxylate	Pd on carbon (10 wt%) (1.0 *equiv.*) with $Pd(OH)_2$ on carbon (20 wt%) (1.0 *equiv.*); reaction solvent: CF_3CH_2OH; reaction time: 12 hours; work-up D was used	*tert*-butyl-4-[(1S)-1-[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-1-piperidyl]-2,2,2-trifluoro-ethyl]piperidine-1-carboxylate
tert-butyl-(R)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate	Reaction time: 12 hours; crude product was triturated with diethyl ether	*tert*-butyl-(4R)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate
tert-butyl-(S)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate	Reaction time: 12 hours; crude product was triturated with diethyl ether	*tert*-butyl-(4S)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate
tert-butyl-9-(((3R,4R)-1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	Reaction time: 18 hours	*tert*-butyl-9-(((3R,4R)-1-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate
tert-butyl-9-(((3S,4S)-1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	Reaction time: 18 hours	*tert*-butyl-9-(((3S,4S)-1-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate
tert-butyl-9-(((3R,4S)-1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	Reaction time: 16 hours	*tert*-butyl-9-(((3R,4S)-1-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate
tert-butyl-9-(((3S,4R)-1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	Reaction time: 16 hours	*tert*-butyl-9-(((3S,4R)-1-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate
tert-butyl-9-(((3R,4R)-1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	Reaction time: 16 hours	*tert*-butyl-9-(((3R,4R)-1-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate
tert-butyl-9-(((3S,4S)-1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	Reaction time: 16 hours	*tert*-butyl-9-(((3S,4S)-1-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate
tert-butyl-9-(((3R,4S)-1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	Reaction time: 16 hours	*tert*-butyl-9-(((3R,4S)-1-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate
tert-butyl-9-(((3S,4R)-1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-	Reaction time: 24 hours	*tert*-butyl-9-(((3S,4R)-1-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-

fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate		methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate
tert-butyl-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate	Pd on carbon (10 wt%) instead of $Pd(OH)_2$ on carbon (20 wt%); reaction solvent: THF:MeOH (1:1)	*tert*-butyl-4-(3-(2,6-dioxopiperidin-3-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)piperidine-1-carboxylate
tert-butyl-(3S,4S)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate	Reaction time: 16 hours; crude product was triturated with n-pentane	*tert*-butyl-(3S,4S)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate
tert-butyl-(3S,4S)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-6-fluoro-1-methyl-indazol-7-yl]piperazin-1-yl]methyl]-3-methyl-piperidine-1-carboxylate	Pd on carbon (10 wt%) (0.5 *equiv.*) with $Pd(OH)_2$ on carbon (20 wt%) (0.5 *equiv.*) instead of $Pd(OH)_2$ on carbon (20 wt%) (100% w/w); AcOH (0.1 *equiv.*) was added to the reaction; reaction solvent: CF_3CH_2OH; reaction time: 16 hours; work-up D was used	*tert*-butyl-(3S,4S)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-6-fluoro-1-methyl-indazol-7-yl]piperazin-1-yl]methyl]-3-methyl-piperidine-1-carboxylate
tert-butyl-(3R,4R)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-6-fluoro-1-methyl-indazol-7-yl]piperazin-1-yl]methyl]-3-methyl-piperidine-1-carboxylate	Pd on carbon (10 wt%) (0.5 *equiv.*) with $Pd(OH)_2$ on carbon (20 wt%) (0.5 *equiv.*) instead of $Pd(OH)_2$ on carbon (20 wt%) (100% w/w); AcOH (0.1 *equiv.*) was added to the reaction; reaction solvent: CF_3CH_2OH; reaction time: 16 hours; work-up D was used	*tert*-butyl-(3R,4R)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-6-fluoro-1-methyl-indazol-7-yl]piperazin-1-yl]methyl]-3-methyl-piperidine-1-carboxylate
tert-butyl-(4S)-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-2,2-dimethyl-piperidine-1-carboxylate	Pd on carbon (10 wt%) (0.2 *equiv.*) with $Pd(OH)_2$ on carbon (20 wt%) (0.2 *equiv.*) instead of $Pd(OH)_2$ on carbon (20 wt%) (100% w/w); reaction solvent: CF_3CH_2OH; reaction time: 12 hours; work-up D was used	*tert*-butyl-(4S)-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-2,2-dimethyl-piperidine-1-carboxylate
tert-butyl-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridin-1-yl]methyl]piperidine-1-carboxylate	Pd on carbon (10 wt%) (0.2 *equiv.*) with $Pd(OH)_2$ on carbon (20 wt%) (0.2 *equiv.*) instead of $Pd(OH)_2$ on carbon (20 wt%) (100% w/w); reaction solvent: CF_3CH_2OH; reaction time: 12 hours; work-up H was used	*tert*-butyl-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5,7-difluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]piperidine-1-carboxylate
tert-butyl-(4R)-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-2,2-dimethyl-piperidine-1-carboxylate	Pd on carbon (10 wt%) (0.2 *equiv.*) with $Pd(OH)_2$ on carbon (20 wt%) (0.2 *equiv.*) instead of $Pd(OH)_2$ on carbon (20 wt%) (100% w/w); reaction solvent: CF_3CH_2OH; reaction time: 12 hours; work-up D was used	*tert*-butyl-(4R)-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-2,2-dimethyl-piperidine-1-carboxylate
tert-butyl-4-[(1S)-1-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridin-1-yl]ethyl]piperidine-1-carboxylate	Pd on carbon (10 wt%) (0.2 *equiv.*) with $Pd(OH)_2$ on carbon (20 wt%) (0.2 *equiv.*) instead of $Pd(OH)_2$ on carbon (20 wt%) (100% w/w); reaction solvent: CF_3CH_2OH; reaction time: 12 hours; work-up D was used	*tert*-butyl-4-[(1S)-1-[4-[3-(2,6-dioxo-3-piperidyl)-7-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]ethyl]piperidine-1-carboxylate

tert-butyl-4-[(1S)-1-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridin-1-yl]ethyl]piperidine-1-carboxylate	Pd on carbon (10 wt%) (0.2 *equiv.*) with $Pd(OH)_2$ on carbon (20 wt%) (0.2 *equiv.*) instead of $Pd(OH)_2$ on carbon (20 wt%) (100% w/w); reaction solvent: CF_3CH_2OH; reaction time: 12 hours; work-up D was used	*tert*-butyl-4-[(1S)-1-[4-[3-(2,6-dioxo-3-piperidyl)-5-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]ethyl]piperidine-1-carboxylate
benzyl-9-[(1S)-1-[1-[3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazol-6-yl]-4-piperidyl]ethyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate	Pd on carbon (10 wt%) (0.5 *equiv.*) with $Pd(OH)_2$ on carbon (20 wt%) (0.5 *equiv.*) instead of $Pd(OH)_2$ on carbon (20 wt%) (100% w/w); reaction solvent: CF_3CH_2OH; reaction time: 16 hours; work-up D was used	3-[6-[4-[(1S)-1-(3,9-diazaspiro[5.5]undecan-3-yl)ethyl]-1-piperidyl]-5-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione
tert-butyl-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-(2,2,2-trifluoroethyl)indazol-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate	Pd on carbon (10 wt%) (0.3 *equiv.*) with $Pd(OH)_2$ on carbon (20 wt%) (0.3 *equiv.*) instead of $Pd(OH)_2$ on carbon (20 wt%) (100% w/w); reaction solvent: CF_3CH_2OH; reaction time: 16 hours; work-up H was used	*tert*-butyl-4-[3-(2,6-dioxo-3-piperidyl)-1-(2,2,2-trifluoroethyl)indazol-6-yl]piperidine-1-carboxylate
tert-butyl-4-[(1R)-1-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridin-1-yl]ethyl]piperidine-1-carboxylate	Pd on carbon (10 wt%) (0.2 *equiv.*) with $Pd(OH)_2$ on carbon (20 wt%) (0.2 *equiv.*) instead of $Pd(OH)_2$ on carbon (20 wt%) (100% w/w); reaction solvent: CF_3CH_2OH; reaction time: 6 hours; work-up D was used	*tert*-butyl-4-[(1R)-1-[4-[3-(2,6-dioxo-3-piperidyl)-7-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]ethyl]piperidine-1-carboxylate
tert-butyl-4-[3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate	Pd on carbon (10 wt%) (0.2 *equiv.*) with $Pd(OH)_2$ on carbon (20 wt%) (0.2 *equiv.*) instead of $Pd(OH)_2$ on carbon (20 wt%) (100% w/w); reaction solvent: CF_3CH_2OH; reaction time: 12 hours; work-up D was used	*tert*-butyl-4-[3-(2,6-dioxo-3-piperidyl)-5-fluoro-1-methyl-indazol-6-yl]piperidine-1-carboxylate
tert-butyl-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-isopropyl-indazol-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate	Pd on carbon (10 wt%) (0.5 *equiv.*) with $Pd(OH)_2$ on carbon (20 wt%) (0.5 *equiv.*) instead of $Pd(OH)_2$ on carbon (20 wt%) (100% w/w); reaction solvent: CF_3CH_2OH; reaction time: 12 hours; work-up D was used	*tert*-butyl-4-[3-(2,6-dioxo-3-piperidyl)-1-isopropyl-indazol-6-yl]piperidine-1-carboxylate
tert-butyl-4-[[(3S,4S)-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-3-fluoro-1-piperidyl]methyl]piperidine-1-carboxylate	Pd on carbon (10 wt%) (0.5 *equiv.*) with $Pd(OH)_2$ on carbon (20 wt%) (0.5 *equiv.*) instead of $Pd(OH)_2$ on carbon (20 wt%) (100% w/w); reaction solvent: CF_3CH_2OH; reaction time: 12 hours; work-up D was used	*tert*-butyl-4-[[(3S,4S)-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-3-fluoro-1-piperidyl]methyl]piperidine-1-carboxylate
benzyl-9-[[1-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-4-methyl-4-piperidyl]methyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate	Pd on carbon (10 wt%) (0.3 *equiv.*) with $Pd(OH)_2$ on carbon (20 wt%) (0.3 *equiv.*) instead of $Pd(OH)_2$ on carbon (20 wt%) (100% w/w); AcOH (0.1 *equiv.*) was added to the reaction; reaction solvent: CF_3CH_2OH; reaction time: 16 hours; work-up T was used	3-[6-[4-(3,9-diazaspiro[5.5]undecan-3-ylmethyl)-4-methyl-1-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione
tert-butyl-4-[(1S)-1-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-	Pd on carbon (10 wt%) (0.3 *equiv.*) with $Pd(OH)_2$ on carbon	*tert*-butyl-4-[(1S)-1-[4-[3-(2,6-dioxo-3-piperidyl)-5,7-difluoro-1-

difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridin-1-yl]ethyl]piperidine-1-carboxylate	(20 wt%) (0.3 *equiv.*) instead of $Pd(OH)_2$ on carbon (20 wt%) (100% w/w); reaction solvent: CF_3CH_2OH; reaction time: 2 days; work-up H was used	methyl-indazol-6-yl]-1-piperidyl]ethyl]piperidine-1-carboxylate
tert-butyl-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1,5-dimethyl-indazol-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate	Pd on carbon (10 wt%) (0.1 *equiv.*) with $Pd(OH)_2$ on carbon (20 wt%) (0.1 *equiv.*) instead of $Pd(OH)_2$ on carbon (20 wt%) (100% w/w); AcOH (0.1 *equiv.*) was added to the reaction; reaction solvent: 2,2,2-trifluoroethanol; reaction time: 16 hours; work-up D was used	*tert*-butyl-4-[3-(2,6-dioxo-3-piperidyl)-1,5-dimethyl-indazol-6-yl]piperidine-1-carboxylate
benzyl-9-[[1-[3-(2,6-dibenzyloxy-3-pyridyl)-1,5-dimethyl-indazol-6-yl]-4-piperidyl]methyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate	Pd on carbon (10 wt%) (0.2 *equiv.*) with $Pd(OH)_2$ on carbon (20 wt%) (0.2 *equiv.*) instead of $Pd(OH)_2$ on carbon (20 wt%) (100% w/w); reaction solvent: CF_3CH_2OH; reaction time: 12 hours; work-up D was used	3-[6-[4-(3,9-diazaspiro[5.5]undecan-3-ylmethyl)-1-piperidyl]-1,5-dimethyl-indazol-3-yl]piperidine-2,6-dione
tert-butyl-(3S,4S)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridin-1-yl]methyl]-3-(trifluoromethyl)piperidine-1-carboxylate	Pd on carbon (10 wt%) (0.5 *equiv.*) instead of $Pd(OH)_2$ on carbon (20 wt%) (100% w/w); reaction time: 16 hours; work-up D was used	*tert*-butyl-(3S,4S)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-(trifluoromethyl)piperidine-1-carboxylate
tert-butyl-4-[[(3S,4R)-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-3-fluoro-1-piperidyl]methyl]piperidine-1-carboxylate	Pd on carbon (10 wt%) (0.5 *equiv.*) with $Pd(OH)_2$ on carbon (20 wt%) (0.5 *equiv.*) instead of $Pd(OH)_2$ on carbon (20 wt%) (100% w/w); reaction solvent: CF_3CH_2OH; reaction time: 16 hours; work-up D was used	*tert*-butyl-4-[[(3S,4R)-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-3-fluoro-1-piperidyl]methyl]piperidine-1-carboxylate
tert-butyl-4-[[(3R,4S)-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-3-fluoro-1-piperidyl]methyl]piperidine-1-carboxylate	Pd on carbon (10 wt%) (0.2 *equiv.*) with $Pd(OH)_2$ on carbon (20 wt%) (0.2 *equiv.*) instead of $Pd(OH)_2$ on carbon (20 wt%) (100% w/w); reaction solvent: CF_3CH_2OH; reaction time: 16 hours; work-up D was used	*tert*-butyl-4-[[(3R,4S)-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-3-fluoro-1-piperidyl]methyl]piperidine-1-carboxylate
tert-butyl-(3S,4R)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridin-1-yl]methyl]-3-fluoro-piperidine-1-carboxylate	Pd on carbon (10 wt%) (0.5 *equiv.*) with $Pd(OH)_2$ on carbon (20 wt%) (0.5 *equiv.*) instead of $Pd(OH)_2$ on carbon (20 wt%) (100% w/w); reaction solvent: CF_3CH_2OH; reaction time: 36 hours; work-up D was used	*tert*-butyl-(3S,4R)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-fluoro-piperidine-1-carboxylate
tert-butyl-(3R,4S)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)-3,6-dihydropyridin-1(2H)-yl)methyl)-3-fluoropiperidine-1-carboxylate	Pd on carbon (10 wt%) (0.7 *equiv.*) with $Pd(OH)_2$ on carbon (20 wt%) (1.0 *equiv.*) instead of $Pd(OH)_2$ on carbon (20 wt%) (100% w/w); reaction solvent: CF_3CH_2OH; reaction time: 12 hours; work-up T was used (purified by prep-TLC instead of prep-HPLC)	*tert*-butyl-(3R,4S)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate
benzyl-9-[[1-[3-(2,6-dibenzyloxy-3-pyridyl)-1,7-dimethyl-indazol-6-yl]-4-piperidyl]methyl]-3,9-	Pd on carbon (10 wt%) (0.3 *equiv.*) with $Pd(OH)_2$ on carbon (20 wt%) (0.3 *equiv.*) instead of	3-[6-[4-(3,9-diazaspiro[5.5]undecan-3-ylmethyl)-1-piperidyl]-1,7-

diazaspiro[5.5]undecane-3-carboxylate	$Pd(OH)_2$ on carbon (20 wt%) (100% w/w); reaction solvent: CF_3CH_2OH; reaction time: 12 hours; work-up D was used	dimethyl-indazol-3-yl]piperidine-2,6-dione
tert-butyl-4-[(1S)-1-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-7-(trifluoromethyl)indazol-6-yl]-3,6-dihydro-2H-pyridin-1-yl]ethyl]piperidine-1-carboxylate	Pd on carbon (10 wt%) (0.5 *equiv.*) with $Pd(OH)_2$ on carbon (20 wt%) (0.5 *equiv.*) instead of $Pd(OH)_2$ on carbon (20 wt%) (100% w/w); reaction solvent: CF_3CH_2OH; reaction time: 12 hours; work-up H was used	*tert*-butyl-4-[(1S)-1-[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-7-(trifluoromethyl)indazol-6-yl]-1-piperidyl]ethyl]piperidine-1-carboxylate
tert-butyl-(3R,4R)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridin-1-yl]methyl]-3-(trifluoromethyl)piperidine-1-carboxylate	Pd on carbon (10 wt%) (0.5 *equiv.*) instead of $Pd(OH)_2$ on carbon (20 wt%) (100% w/w); reaction time: 16 hours; work-up D was used	*tert*-butyl-(3R,4R)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-(trifluoromethyl)piperidine-1-carboxylate
tert-butyl-4-[(1R)-1-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-7-(trifluoromethyl)indazol-6-yl]-3,6-dihydro-2H-pyridin-1-yl]ethyl]piperidine-1-carboxylate	Pd on carbon (10 wt%) (0.5 *equiv.*) with $Pd(OH)_2$ on carbon (20 wt%) (0.5 *equiv.*) instead of $Pd(OH)_2$ on carbon (20 wt%) (100% w/w); reaction solvent: CF_3CH_2OH; reaction time: 12 hours; work-up H was used	*tert*-butyl-4-[(1R)-1-[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-7-(trifluoromethyl)indazol-6-yl]-1-piperidyl]ethyl]piperidine-1-carboxylate
tert-butyl-(3R,4R)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate	$Pd(OH)_2$ on carbon (20 wt%) (200% w/w) instead of $Pd(OH)_2$ on carbon (20 wt%) (100% w/w); reaction time: 16 hours; 50% THF in DCM instead of 20% THF in DCM	*tert*-butyl-(3R,4R)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate
tert-butyl (3S,4S)-4-((4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate	$Pd(OH)_2$ on carbon (20 wt%) (200% w/w) instead of $Pd(OH)_2$ on carbon (20 wt%) (100% w/w); reaction time: 16 hours; 50% THF in DCM instead of 20% THF in DCM	*tert*-butyl-(3S,4S)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate
tert-butyl-(3S,4S)-4-((4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-1-methyl-1H-indazol-7-yl)piperazin-1-yl)methyl)-3-methylpiperidine-1-carboxylate	$Pd(OH)_2$ on carbon (20 wt%) (150% w/w) instead of $Pd(OH)_2$ on carbon (20 wt%) (100% w/w); reaction time: 16 hours; 50% THF in DCM instead of 20% THF in DCM	*tert*-butyl-(3S,4S)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-7-yl)piperazin-1-yl)methyl)-3-methylpiperidine-1-carboxylate
tert-butyl (3R,4R)-4-((4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate	$Pd(OH)_2$ on carbon (20 wt%) (200% w/w) instead of $Pd(OH)_2$ on carbon (20 wt%) (100% w/w); reaction time: 16 hours; 50% THF in DCM instead of 20% THF in DCM	*tert*-butyl-(3R,4R)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate
tert-butyl-(3R,4R)-4-((4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-1-methyl-1H-indazol-7-yl)piperazin-1-yl)methyl)-3-methylpiperidine-1-carboxylate	$Pd(OH)_2$ on carbon (20 wt%) (150% w/w) instead of $Pd(OH)_2$ on carbon (20 wt%) (100% w/w); reaction time: 16 hours; 50% THF in DCM instead of 20% THF in DCM	*tert*-butyl-(3R,4R)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-7-yl)piperazin-1-yl)methyl)-3-methylpiperidine-1-carboxylate
tert-butyl-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1,7-dimethyl-1H-indazol-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate	Pd on carbon (10 wt%) (0.1 *equiv.*) with $Pd(OH)_2$ on carbon (20 wt%) (0.1 *equiv.*) instead of $Pd(OH)_2$ on carbon (20 wt%) (100% w/w); AcOH (0.1 *equiv.*) was added to the reaction;	*tert*-butyl-4-(3-(2,6-dioxopiperidin-3-yl)-1,7-dimethyl-1H-indazol-6-yl)piperidine-1-carboxylate

	reaction solvent: CF_3CH_2OH; reaction time: 16 hours; work-up D was used (filtered through celite)	
tert-butyl 4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-7-(trifluoromethyl)indazol-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate	Pd on carbon (10 wt%) (0.1 *equiv.*) with $Pd(OH)_2$ on carbon (20 wt%) (0.1 *equiv.*) instead of $Pd(OH)_2$ on carbon (20 wt%) (100% w/w); AcOH (0.1 *equiv.*) was added to the reaction; reaction solvent: CF_3CH_2OH; reaction temperature: 40 °C; reaction time: 12 hours; work-up H was used	*tert*-butyl 4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-7-(trifluoromethyl)indazol-6-yl]piperidine-1-carboxylate
tert-butyl 9-((1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	Reaction time: 8 hours; residue was washed with n-pentane after work-up	*tert*-butyl 9-((1-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate
benzyl-4-[[(2R)-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-2-methyl-piperazin-1-yl]methyl]piperidine-1-carboxylate	Pd on carbon (10 wt%) (0.5 *equiv.*) with $Pd(OH)_2$ on carbon (20 wt%) (0.5 *equiv.*) instead of $Pd(OH)_2$ on carbon (20 wt%) (100% w/w); reaction solvent: CF_3CH_2OH; reaction time: 16 hours; work-up K was used	3-[1-methyl-6-[(3R)-3-methyl-4-(4-piperidylmethyl)piperazin-1-yl]indazol-3-yl]piperidine-2,6-dione
benzyl-9-[(1R)-1-[1-[3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazol-6-yl]-4-piperidyl]ethyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate	Pd on carbon (10 wt%) (0.5 *equiv.*) with $Pd(OH)_2$ on carbon (20 wt%) (0.5 *equiv.*) instead of $Pd(OH)_2$ on carbon (20 wt%) (100% w/w); reaction solvent: CF_3CH_2OH; reaction time: 16 hours; work-up D was used	3-[6-[4-[(1R)-1-(3,9-diazaspiro[5.5]undecan-3-yl)ethyl]-1-piperidyl]-5-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione
tert-butyl-4-[[(3R,4R)-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-3-fluoro-1-piperidyl]methyl]piperidine-1-carboxylate	Pd on carbon (10 wt%) (0.5 *equiv.*) with $Pd(OH)_2$ on carbon (20 wt%) (0.5 *equiv.*) instead of $Pd(OH)_2$ on carbon (20 wt%) (100% w/w); reaction solvent: CF_3CH_2OH; reaction time: 12 hours; work-up D was used	*tert*-butyl-4-[[(3R,4R)-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-3-fluoro-1-piperidyl]methyl]piperidine-1-carboxylate

Table P29A

Product	LC-MS (ESI)	^{1}H NMR
tert-butyl-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-7-yl]piperazin-1-yl]methyl]piperidine-1-carboxylate	m/z = 525.2 $[M+H]^+$	
tert-butyl-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-5-(trifluoromethyl)indazol-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate	m/z = 493.2 $[M+H]^+$	
tert-butyl-4-[3-(2,6-dioxo-3-piperidyl)-7-fluoro-1-methyl-indazol-6-yl]piperidine-1-carboxylate	m/z = 445.2 $[M+H]^+$	
tert-butyl-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-7-yl]piperidine-1-carboxylate	m/z = 427.2 $[M+H]^+$	

tert-butyl-(3S,4R)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate	m/z = 542.51 $[M+H]^+$	
tert-butyl-(4R)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperazin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate	m/z = 553.74 $[M+H]^+$	
tert-butyl-(4S)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperazin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate	m/z = 553.70 $[M+H]^+$	
tert-butyl-9-(((3S,4S)-1-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	m/z = 607.76 $[M+H]^+$	
tert-butyl-9-(((3R,4R)-1-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	m/z = 607.65 $[M+H]^+$	
tert-butyl-4-(((2S)-4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-7-yl)-2-methylpiperazin-1-yl)methyl)-3,3-difluoropiperidine-1-carboxylate	m/z = 575.54 $[M+H]^+$	
tert-butyl-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)-3,3-difluoropiperidin-1-yl)methyl)piperidine-1-carboxylate	m/z = 457.17 $[M+H]^+$	
tert-butyl-(3S,4S)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate	m/z = 556.62 $[M+H]^+$	
tert-butyl-(3R,4R)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate	m/z = 556.72 $[M+H]^+$	
tert-butyl-9-((1R)-1-(1-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	m/z = 625.42 $[M+H]^+$	
tert-butyl-9-((1S)-1-(1-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	m/z = 625.39 $[M+H]^+$	
tert-butyl-9-((1R)-1-(1-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	m/z = 625.42 $[M+H]^+$	
tert-butyl-9-((1S)-1-(1-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	m/z = 625.39 $[M+H]^+$	
tert-butyl-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate	m/z = 524.32 $[M+H]^+$	

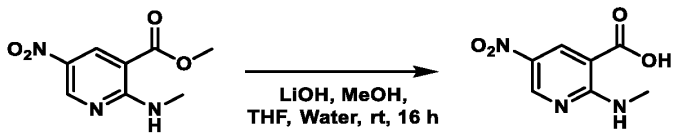
tert-butyl-(3S,4S)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate	m/z = 556.60 $[M+H]^+$	
tert-butyl-(3R,4R)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate	m/z = 556.38 $[M+H]^+$	
tert-butyl (3R,4S)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate	m/z = 540.37 $[M+H]^+$	
tert-butyl-4-[[(2R,4R)-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-2-methyl-1-piperidyl]methyl]piperidine-1-carboxylate	m/z = 538.4 $[M+H]^+$	
tert-butyl-4-[(1R)-1-[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-1-piperidyl]-2,2,2-trifluoro-ethyl]piperidine-1-carboxylate		
tert-butyl-4-[(1S)-1-[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-1-piperidyl]-2,2,2-trifluoro-ethyl]piperidine-1-carboxylate		
tert-butyl-(4R)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate	m/z = 553.70 $[M+H]^+$	
tert-butyl-(4S)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate	m/z = 552.43 $[M+H]^+$	
tert-butyl-9-(((3R,4R)-1-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	m/z = 625.42 $[M+H]^+$	
tert-butyl-9-(((3S,4S)-1-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	m/z = 625.42 $[M+H]^+$	
tert-butyl-9-(((3R,4S)-1-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	m/z = 625.46 $[M+H]^+$	
tert-butyl-9-(((3S,4R)-1-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	m/z = 625.46 $[M+H]^+$	
tert-butyl-9-(((3R,4R)-1-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	m/z = 625.39 $[M+H]^+$	
tert-butyl-9-(((3S,4S)-1-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-	m/z = 625.82 $[M+H]^+$	

1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate		
tert-butyl-9-(((3R,4S)-1-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	m/z = 625.39 $[M+H]^+$	
tert-butyl-9-(((3S,4R)-1-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	m/z = 625.58 $[M+2H]^+$	
tert-butyl-4-(3-(2,6-dioxopiperidin-3-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)piperidine-1-carboxylate	m/z = 497.55 $[M+H]^+$	
tert-butyl-(3S,4S)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate	m/z = 542.31 $[M+H]^+$	
tert-butyl-(3S,4S)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-6-fluoro-1-methyl-indazol-7-yl]piperazin-1-yl]methyl]-3-methyl-piperidine-1-carboxylate	m/z = 557.1 $[M+H]^+$	
tert-butyl-(3R,4R)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-6-fluoro-1-methyl-indazol-7-yl]piperazin-1-yl]methyl]-3-methyl-piperidine-1-carboxylate	m/z = 557.4 $[M+H]^+$	
tert-butyl-(4S)-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-2,2-dimethyl-piperidine-1-carboxylate	m/z = 455.4 $[M+H]^+$	
tert-butyl-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5,7-difluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]piperidine-1-carboxylate	m/z = 560.1 $[M+H]^+$	
tert-butyl-(4R)-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-2,2-dimethyl-piperidine-1-carboxylate	m/z = 455.2 $[M+H]^+$	
tert-butyl-4-[(1S)-1-[4-[3-(2,6-dioxo-3-piperidyl)-7-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]ethyl]piperidine-1-carboxylate	m/z = 556.2 $[M+H]^+$	
tert-butyl-4-[(1S)-1-[4-[3-(2,6-dioxo-3-piperidyl)-5-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]ethyl]piperidine-1-carboxylate	m/z = 455.2 $[M+H]^+$	
3-[6-[4-[(1S)-1-(3,9-diazaspiro[5.5]undecan-3-yl)ethyl]-1-piperidyl]-5-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione	m/z = 525.2 $[M+H]^+$	
tert-butyl-4-[3-(2,6-dioxo-3-piperidyl)-1-(2,2,2-trifluoroethyl)indazol-6-yl]piperidine-1-carboxylate	m/z: 439.0 $[M-56]^+$	
tert-butyl-4-[(1R)-1-[4-[3-(2,6-dioxo-3-piperidyl)-7-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]ethyl]piperidine-1-carboxylate	m/z = 556.2 $[M+H]^+$	

tert-butyl-4-[3-(2,6-dioxo-3-piperidyl)-5-fluoro-1-methyl-indazol-6-yl]piperidine-1-carboxylate	m/z = 445.1 $[M+H]^+$	
tert-butyl-4-[3-(2,6-dioxo-3-piperidyl)-1-isopropyl-indazol-6-yl]piperidine-1-carboxylate		
tert-butyl-4-[[(3S,4S)-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-3-fluoro-1-piperidyl]methyl]piperidine-1-carboxylate	m/z = 542.4 $[M+H]^+$	
3-[6-[4-(3,9-diazaspiro[5.5]undecan-3-ylmethyl)-4-methyl-1-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione	m/z = 507.3 $[M+H]^+$	
tert-butyl-4-[(1S)-1-[4-[3-(2,6-dioxo-3-piperidyl)-5,7-difluoro-1-methyl-indazol-6-yl]-1-piperidyl]ethyl]piperidine-1-carboxylate	m/z = 574.1 $[M+H]^+$	
tert-butyl-4-[3-(2,6-dioxo-3-piperidyl)-1,5-dimethyl-indazol-6-yl]piperidine-1-carboxylate		
3-[6-[4-(3,9-diazaspiro[5.5]undecan-3-ylmethyl)-1-piperidyl]-1,5-dimethyl-indazol-3-yl]piperidine-2,6-dione	m/z = 507.4 $[M+H]^+$	
tert-butyl-(3S,4S)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-(trifluoromethyl)piperidine-1-carboxylate	m/z = 592.3 $[M+H]^+$	
tert-butyl-4-[[(3S,4R)-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-3-fluoro-1-piperidyl]methyl]piperidine-1-carboxylate	m/z = 542.3 $[M+H]^+$	
tert-butyl-4-[[(3R,4S)-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-3-fluoro-1-piperidyl]methyl]piperidine-1-carboxylate	m/z = 542.4 $[M+H]^+$	
tert-butyl-(3S,4R)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-fluoro-piperidine-1-carboxylate	m/z = 542.3 $[M+H]^+$	
tert-butyl-(3R,4S)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate	m/z = 542.3 $[M+H]^+$	
3-[6-[4-(3,9-diazaspiro[5.5]undecan-3-ylmethyl)-1-piperidyl]-1,7-dimethyl-indazol-3-yl]piperidine-2,6-dione		
tert-butyl-4-[(1S)-1-[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-7-(trifluoromethyl)indazol-6-yl]-1-piperidyl]ethyl]piperidine-1-carboxylate	m/z = 606.6 $[M+H]^+$	
tert-butyl-(3R,4R)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-(trifluoromethyl)piperidine-1-carboxylate	m/z = 592.3 $[M+H]^+$	
tert-butyl-4-[(1R)-1-[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-7-(trifluoromethyl)indazol-6-yl]-1-piperidyl]ethyl]piperidine-1-carboxylate	m/z = 606.5 $[M+H]^+$	

tert-butyl-(3R,4R)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate	m/z = 542.35 $[M+H]^+$	
tert-butyl-(3S,4S)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate	m/z = 538.39 $[M+H]^+$	
tert-butyl-(3S,4S)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-7-yl)piperazin-1-yl)methyl)-3-methylpiperidine-1-carboxylate	m/z = 539.41 $[M+H]^+$	
tert-butyl-(3R,4R)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate	m/z = 538.70 $[M+H]^+$	
tert-butyl-(3R,4R)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-7-yl)piperazin-1-yl)methyl)-3-methylpiperidine-1-carboxylate	m/z = 539.41 $[M+H]^+$	
tert-butyl-4-(3-(2,6-dioxopiperidin-3-yl)-1,7-dimethyl-1H-indazol-6-yl)piperidine-1-carboxylate		(400 MHz, DMSO-d6) δ = 10.85 (s, 1H), 7.44 (d, J = 8.4 Hz, 1H), 6.99 (d, J = 8.8 Hz, 1H), 4.24 (s, 3H), 4.14 - 4.03 (m, 2H), 3.18 - 3.07 (m, 2H), 2.98 - 2.81 (m, 2H), 2.70 (s, 3H), 2.66 - 2.55 (m, 2H), 2.34 - 2.28 (m, 1H), 2.18 - 2.08 (m, 1H), 1.67 - 1.53 (m, 4H), 1.43 (s, 9H)
tert-butyl 4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-7-(trifluoromethyl)indazol-6-yl]piperidine-1-carboxylate	m/z = 495.2 $[M+H]^+$	
tert-butyl 9-((1-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	m/z = 593.67 [M+H]+	
3-[1-methyl-6-[(3R)-3-methyl-4-(4-piperidylmethyl)piperazin-1-yl]indazol-3-yl]piperidine-2,6-dione	m/z = 439.3 $[M+H]^+$	
3-[6-[4-[(1R)-1-(3,9-diazaspiro[5.5]undecan-3-yl)ethyl]-1-piperidyl]-5-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione	m/z = 525.2 $[M+H]^+$	
tert-butyl-4-[[(3R,4R)-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-3-fluoro-1-piperidyl]methyl]piperidine-1-carboxylate	m/z = 542.3 $[M+H]^+$	

Example P30



To stirred solution of methyl-2-(methylamino)-5-nitronicotinate (Reactant) (30.0 g, 142.13 mmol, 1 *equiv.*) in THF (300 mL), MeOH (300 mL) and water (60 mL) was added lithium

hydroxide monohydrate (17.89 g, 426.41 mmol, 1 *equiv.*) at 0 °C. The resulting reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was then concentrated under vacuum. The crude product was acidified to pH = 2 with 1N HCl solution and the resulting solid was filtered and dried under vacuum to afford 2-(methylamino)-5-nitronicotinic-acid (20.0 g) as an off-white solid. **LC-MS (ESI):** m/z = 198.10 $[M+H]^+$

The compounds shown in the "**Product**" column of **Table P30** were synthesized using the method of **Example P30**, with variations noted in **Table P30**.

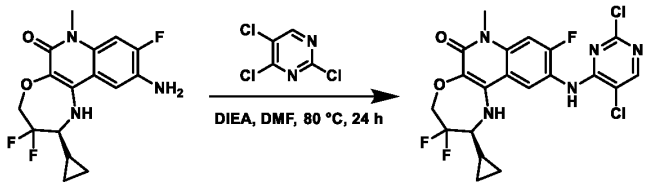
Table P30

Reactant	Variation from Example P30	Product
methyl-2-(methylamino)-5-nitronicotinate		2-(methylamino)-5-nitronicotinic-acid
methyl-1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)-3-methylpiperidine-4-carboxylate	Reaction did not contain MeOH; reaction was extracted with petroleum ether before acidification	1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)-3-methylpiperidine-4-carboxylic-acid
methyl-1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidine-4-carboxylate	Reaction did not contain MeOH	1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidine-4-carboxylic-acid
methyl-1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidine-4-carboxylate	Reaction did not contain MeOH; reaction temperature: 50 °C; reaction time: 20 hours	1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidine-4-carboxylic-acid

Table P30A

Product	LC-MS (ESI)
2-(methylamino)-5-nitronicotinic-acid	m/z = 198.10 $[M+H]^+$
1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)-3-methylpiperidine-4-carboxylic-acid	m/z = 563.61 $[M+H]^+$
1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidine-4-carboxylic-acid	m/z = 581.81 $[M+H]^+$
1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidine-4-carboxylic-acid	m/z = 581.28 $[M+H]^+$

Example P31



To a solution of (2S)-10-amino-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1H-[1,4]oxazepino[2,3-c]quinolin-6-one (Reactant A) (206 mg, 607.11 μmol, 1 *equiv.*) in DMF (3

mL) was added DIPEA (235.39 mg, 1.82 mmol, 317.24 µL, 3 *equiv.*) and 2,4,5-trichloropyrimidine (Reactant B) (133.63 mg, 728.53 µmol, 1.2 *equiv.*). The mixture was stirred at 80 °C for 24 hours. The reaction mixture was diluted with H_2O (5 mL) and extracted with ethyl acetate (15 mL). The combined organic layers were washed with brine (30 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to afford (2S)-2-cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3,9-trifluoro-7-methyl-2,4-dihydro-1H-[1,4]oxazepino[2,3-c]quinolin-6-one (315 mg) as a white solid. **LC-MS (ESI): m/z** = 486.0 $[M+H]^+$

The compounds shown in the "**Product**" column of **Table P31** were synthesized using the method of **Example P31**, with variations noted in **Table P31**.

Table P31

Reactant A	Reactant B	Variation from Example P31	Product
(2S)-10-amino-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1H-[1,4]oxazepino[2,3-c]quinolin-6-one	2,4,5-trichloropyrimidine		(2S)-2-cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3,9-trifluoro-7-methyl-2,4-dihydro-1H-[1,4]oxazepino[2,3-c]quinolin-6-one
methyl-2-chloronicotinate	methylamine (2M, in THF)	Reaction solvent: THF; reaction temperature: 70 °C; reaction time: 16 hours; work-up E was used	methyl-2-(methylamino)nicotinate
ethyl-4-chloro-1-methyl-6-nitro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate	(S)-3-amino-3-cyclopropyl-2,2-difluoropropan-1-ol	Reaction solvent: CH_3CN; reaction temperature: 130 °C; reaction time: 48 hours; work-up F was used	ethyl-(S)-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl)amino)-1-methyl-6-nitro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate
(S)-3-bromo-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl)amino)-1-methyl-6-nitro-1,8-naphthyridin-2(1H)-one		Reaction solvent: THF; reaction temperature: 60 °C; reaction time: 4 hours; the crude material was triturated with petroleum ether	(S)-2-cyclopropyl-3,3-difluoro-7-methyl-10-nitro-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-6(7H)-one
(S)-10-amino-2-cyclopropyl-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-6(7H)-one	2,4,5-trichloropyrimidine	Reaction solvent: DMSO; reaction temperature: 25 °C; reaction time: 4 hours; work-up L was used	(S)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-6(7H)-one
ethyl-4-chloro-8-fluoro-1-methyl-6-nitro-2-oxo-1,2-dihydroquinoline-3-	(S)-3-amino-3-cyclopropyl-2,2-difluoropropan-1-ol	Reaction solvent: CH_3CN; reaction temperature: 130 °C; reaction time: 36 hours;	ethyl-(S)-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl)amino)-

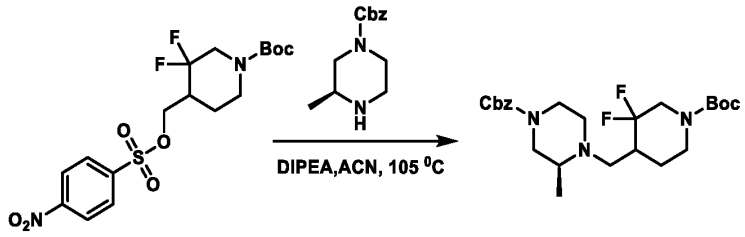
carboxylate		work-up H was used	8-fluoro-1-methyl-6-nitro-2-oxo-1,2-dihydroquinoline-3-carboxylate
(S)-3-bromo-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl)amino)-8-fluoro-1-methyl-6-nitroquinolin-2(1H)-one		Reaction solvent: THF; reaction temperature: 60 °C; reaction time: 12 hours	(S)-2-cyclopropyl-3,3,8-trifluoro-7-methyl-10-nitro-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7H)-one
(S)-10-amino-2-cyclopropyl-3,3,8-trifluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7H)-one	2,4,5-trichloropyrimidine	Reaction solvent: DMSO; reaction temperature: 25 °C; reaction time: 8 hours; work-up F was used	(S)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3,8-trifluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7H)-one
ethyl-6-bromo-4-chloro-7-fluoro-1-methyl-2-oxo-quinoline-3-carboxylate	(3S)-3-amino-3-cyclopropyl-2,2-difluoro-propan-1-ol	Reaction solvent: N-Methyl-2-pyrrolidone; reaction temperature: 200°C in a microwave reactor; reaction time: 2 hours	6-bromo-4-[[(1S)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-7-fluoro-1-methyl-quinolin-2-one
3,6-dibromo-4-[[(1S)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-7-fluoro-1-methyl-quinolin-2-one		Reaction solvent: THF; reaction temperature: 60 °C; reaction time: 2 hours; t-BuOK (1.0 *equiv.*) instead of DIPEA; work-up H was used	(2S)-10-bromo-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1H-[1,4]oxazepino[2,3-c]quinolin-6-one

Table P31A

Product	LC-MS (ESI)	^{1}H NMR
(2S)-2-cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3,9-trifluoro-7-methyl-2,4-dihydro-1H-[1,4]oxazepino[2,3-c]quinolin-6-one	m/z = 486.0 $[M+H]^+$	
methyl-2-(methylamino)nicotinate	m/z = 167.00 $[M+H]^+$	
ethyl-(S)-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl)amino)-1-methyl-6-nitro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate	m/z = 427.33 $[M+H]^+$	
(S)-2-cyclopropyl-3,3-difluoro-7-methyl-10-nitro-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-6(7H)-one	m/z = 353.31 $[M+H]^+$	
(S)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-6(7H)-one	m/z = 469.32 $[M+H]^+$	
ethyl-(S)-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl)amino)-8-fluoro-1-methyl-6-nitro-2-oxo-1,2-dihydroquinoline-3-carboxylate	m/z = 444.15 $[M+H]^+$	
(S)-2-cyclopropyl-3,3,8-trifluoro-7-methyl-10-nitro-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7H)-one	m/z = 370.07 $[M+H]^+$	

(S)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3,8-trifluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7H)-one	m/z = 486.05 $[M+H]^+$	
6-bromo-4-[[(1S)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-7-fluoro-1-methyl-quinolin-2-one	m/z = 404.9 $[M+H]^+$	(400 MHz, DMSO-d6) δ = 8.70 (d, J = 7.6 Hz, 1H), 7.47 (d, J = 11.6 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 5.63 - 5.48 (m, 2H), 3.90 - 3.65 (m, 2H), 3.55 - 3.46 (m, 1H), 1.30 – 1.23 (m, 1H), 0.73 - 0.62 (m, 1H), 0.61 - 0.54 (m, 1H), 0.51 – 0.47 (m, 1H), 0.26- 0.20 (m, 1H)
(2S)-10-bromo-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1H-[1,4]oxazepino[2,3-c]quinolin-6-one	m/z = 402.9 $[M+H]^+$	(400 MHz, DMSO-d6) δ = 8.52 (d, J = 7.6 Hz, 1H), 7.51 (d, J = 11.6 Hz, 1H), 6.55 (s, 1H), 4.53 - 4.30 (m, 2H), 3.51 (s, 3H), 3.28 - 3.19 (m, 1H), 1.35 - 1.22 (m, 1H), 0.78 - 0.67 (m, 1H), 0.60 - 0.48 (m, 2H), 0.38 - 0.26 (m, 1H)

Example P32



To a stirred solution of *tert*-butyl-3,3-difluoro-4-((((4-nitrophenyl)sulfonyl)oxy)methyl)piperidine-1-carboxylate (Reactant B) (1.0 g, 2.29 mmol, 1 *equiv.*) and benzyl-(S)-3-methylpiperazine-1-carboxylate (Reactant A) (537 mg, 2.3 mmol, 1.0 *equiv.*) in CH_3CN (10.0 mL) was added DIPEA (2.87 mL, 16.03 mmol, 1 *equiv.*) at room temperature. The reaction mixture was stirred at 105 °C for 18 hours. The reaction mixture was then quenched with water (20 mL) and extracted with ethyl-acetate (50 mL). The organic layer was separated and washed with brine solution (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to get crude product which was purified by flash column chromatography to afford benzyl-(3S)-4-((1-(tert-butoxycarbonyl)-3,3-difluoropiperidin-4-yl)methyl)-3-methylpiperazine-1-carboxylate (0.8 g) as colorless gum. **LC-MS (ESI):** m/z = 468.27 $[M+H]^+$

The compounds shown in the "**Product**" column of **Table P32** were synthesized using the method of **Example P32**, with variations noted in **Table P32**.

Table P32

Reactant A	Reactant B	Variation from Example P32	Product

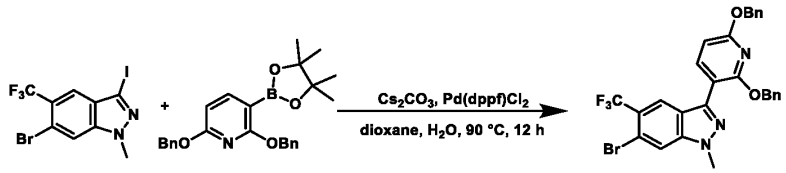
6-bromo-3-iodo-5-(trifluoromethyl)-1H-indazole	Iodomethane	Reaction solvent: THF; reaction temperature: 25 °C; reaction time: 2 hours; t-BuOK (1.4 *equiv.*) instead of DIPEA	6-bromo-3-iodo-1-methyl-5-(trifluoromethyl)indazole
benzyl-(S)-3-methylpiperazine-1-carboxylate	*tert*-butyl-3,3-difluoro-4-((((4-nitrophenyl)sulfonyl)oxy)methyl)piperidine-1-carboxylate		benzyl-(3S)-4-((1-(tert-butoxycarbonyl)-3,3-difluoropiperidin-4-yl)methyl)-3-methylpiperazine-1-carboxylate
6-bromo-7-fluoro-3-iodo-1H-indazole	Iodomethane	Reaction solvent: THF; reaction temperature: 25 °C; reaction time: 3 hours; t-BuOK (1.0 *equiv.*) instead of DIPEA	6-bromo-7-fluoro-3-iodo-1-methyl-1H-indazole
6-bromo-7-fluoro-1H-3,1-benzoxazine-2,4-dione	Iodomethane	Reaction solvent: dimethylacetamide; reaction temperature: 25 °C; reaction time: 2 hours	6-bromo-7-fluoro-1-methyl-3,1-benzoxazine-2,4-dione
tert-butyl-4-(1-amino-2,2,2-trifluoro-ethyl)piperidine-1-carboxylate	1,5-dichloropentan-3-one	Reaction solvent: MeOH; reaction temperature: 70 °C; reaction time: 4 hours	*tert*-butyl-4-[2,2,2-trifluoro-1-(4-oxo-1-piperidyl)ethyl]piperidine-1-carboxylate
6-bromo-5-fluoro-3-iodo-1H-indazole	Iodomethane	Reaction solvent: DMF; NaH (1.5 *equiv.*) instead of DIPEA; reaction temperature: 25 °C; reaction time: 1 hour; work-up A was used (dilute with NH_4Cl (aq) instead of H_2O)	6-bromo-5-fluoro-3-iodo-1-methyl-indazole
6-bromo-3-iodo-5-methyl-1H-indazole	Iodomethane	Reaction solvent: DMF; K_2CO_3 (3.0 *equiv.*) instead of DIPEA; reaction temperature: 40 °C; reaction time: 16 hours; work-up A was used	6-bromo-3-iodo-1,5-dimethyl-indazole
7-methyl-6-nitro-1H-indazole	Iodomethane	Reaction solvent: DMF; K_2CO_3 (3.0 *equiv.*) instead of DIPEA; reaction temperature: 40 °C; reaction time: 2 hours	1,7-dimethyl-6-nitro-1H-indazole
6-bromo-3-iodo-7-(trifluoromethyl)-1H-indazole	Iodomethane	Reaction solvent: DMF; Cs_2CO_3 (3.0 *equiv.*) instead of DIPEA; reaction temperature: 0 °C; reaction time: 2 hours	6-bromo-3-iodo-1-methyl-7-(trifluoromethyl)indazole
6-bromo-3-iodo-1H-indazole	3,4-dihydro-2H-pyran	p-Toluenesulfonicacid monohydrate (0.2 *equiv.*) instead of DIPEA; reaction solvent: THF; reaction temperature: 70 °C; reaction time: 7 hours	6-bromo-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole
6-bromo-5,7-difluoro-3-iodo-1H-indazole	Iodomethane	Reaction temperature: 25 °C; reaction time: 2 hours	6-bromo-5,7-difluoro-3-iodo-1-methyl-indazole
6-bromo-3-iodo-1H-indazole	1,1,1-trifluoro-2-iodo-ethane	Reaction temperature: 90 °C; reaction time: 3 hours; reaction solvent: DMF	6-bromo-3-iodo-1-(2,2,2-trifluoroethyl)indazole

Table P32A

Product	LC-MS (ESI)	^{1}H NMR
6-bromo-3-iodo-1-methyl-5-(trifluoromethyl)indazole	m/z = 404.8 $[M+H]^+$	
benzyl-(3S)-4-((1-(tert-butoxycarbonyl)-3,3-difluoropiperidin-4-yl)methyl)-3-methylpiperazine-1-carboxylate	m/z = 468.27 $[M+H]^+$	

6-bromo-7-fluoro-3-iodo-1-methyl-1H-indazole	m/z = 354.84 $[M+H]^+$	
6-bromo-7-fluoro-1-methyl-3,1-benzoxazine-2,4-dione	m/z : 273.9 $[M+H]^+$	(400 MHz, DMSO-d6) δ = 8.25 (d, J = 7.2 Hz, 1H), 7.61 (d, J = 10.8 Hz, 1H), 3.44 (s, 3H)
tert-butyl-4-[2,2,2-trifluoro-1-(4-oxo-1-piperidyl)ethyl]piperidine-1-carboxylate	m/z = 309.2 $[M+H]^+$	
6-bromo-5-fluoro-3-iodo-1-methyl-indazole	m/z = 356.6 $[M+H]^+$	
6-bromo-3-iodo-1,5-dimethyl-indazole		
1,7-dimethyl-6-nitro-1H-indazole		(400 MHz, $CDCl_3$-d) δ = 8.01 (s, 1H), 7.64 - 7.60 (m, 1H), 7.53 - 7.50 (m, 1H), 4.42 (s, 3H), 2.90 (s, 3H).
6-bromo-3-iodo-1-methyl-7-(trifluoromethyl)indazole	m/z = 404.8 $[M+H]^+$	
6-bromo-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole	m/z = 406.90 $[M+H]^+$	
6-bromo-5,7-difluoro-3-iodo-1-methyl-indazole	m/z = 372.8 $[M+H]^+$	
6-bromo-3-iodo-1-(2,2,2-trifluoroethyl)indazole	m/z: 404.7/406.7 $[M+H]^+$	

Example P33



A mixture of 6-bromo-3-iodo-1-methyl-5-(trifluoromethyl)indazole (Reactant A) (3 g, 7.41 mmol, 1 *equiv.*), 2,6-dibenzyloxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (Reactant B) (2.94 g, 7.04 mmol, 0.95 *equiv.*), $Pd(dppf)Cl_2$ (542.07 mg, 740.83 μmol, 0.1 *equiv.*) and Cs_2CO_3 (7.24 g, 22.22 mmol, 3 *equiv.*) in dioxane (30 mL) and H_2O (10 mL) was degassed and purged with N_2 three times. The mixture was stirred at 90 °C for 12 hours under N_2 atmosphere. The reaction mixture was diluted with H_2O (20 mL) and extracted with ethyl acetate (90 mL). The combined organic layers were washed with brine (90 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography to afford 6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-5-(trifluoromethyl)indazole (2.1 g) as a yellow oil. **LC-MS (ESI):** m/z = 568.1 $[M+H]^+$

The compounds shown in the "**Product**" column of **Table P33** were synthesized using the method of **Example P33**, with variations noted in **Table P33**.

Table P33

Reactant A	Reactant B	Variation from Example P33	Product
6-bromo-3-iodo-1-methyl-5-	2,6-dibenzyloxy-3-		6-bromo-3-(2,6-

(trifluoromethyl)indazole	(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine		dibenzyloxy-3-pyridyl)-1-methyl-5-(trifluoromethyl)indazole
6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-5-(trifluoromethyl)indazole	*tert*-butyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate	Reaction time: 1 hour	*tert*-butyl-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-5-(trifluoromethyl)indazol-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate
3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-7-fluoro-1-methyl-1H-indazole	*tert*-butyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate	Reaction temperature: 100 °C; reaction time: 20 hours; K_3PO_4 (3.0 *equiv.*) instead of Cs_2CO_3; work-up H was used	*tert*-butyl-4-[3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate
7-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazole	*tert*-butyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate	Reaction temperature: 100 °C; reaction time: 1 hour	*tert*-butyl-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-7-yl]-3,6-dihydro-2H-pyridine-1-carboxylate
tert-butyl-(2R)-4-(3-iodo-1-methyl-indazol-6-yl)-2-methyl-piperidine-1-carboxylate	(2,6-dibenzyloxy-3-pyridyl)boronic-acid	Reaction temperature: 100 °C; reaction time: 5 hours	*tert*-butyl-(2R)-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-2-methyl-piperidine-1-carboxylate
tert-butyl-(2R)-2-methyl-4-(trifluoromethylsulfonyloxy)-3,6-dihydro-2H-pyridine-1-carboxylate	(1-methylindazol-6-yl)boronic-acid	Reaction temperature: 95 °C; reaction time: 5 hours	*tert*-butyl-(2R)-2-methyl-4-(1-methylindazol-6-yl)-3,6-dihydro-2H-pyridine-1-carboxylate
tert-butyl-4-[2,2,2-trifluoro-1-[4-(trifluoromethylsulfonyloxy)-3,6-dihydro-2H-pyridin-1-yl]ethyl]piperidine-1-carboxylate	3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazole	Reaction temperature: 95 °C; reaction time: 5 hours	*tert*-butyl-4-(1-(4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)-3,6-dihydropyridin-1(2H)-yl)-2,2,2-trifluoroethyl)piperidine-1-carboxylate
6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazole	*tert*-butyl-4-[[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridin-1-yl]methyl]piperidine-1-carboxylate	K_2CO_3 (3.0 *equiv.*) instead of $CsCO_3$; reaction temperature: 100 °C; work-up H was used	*tert*-butyl-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridin-1-yl]methyl]piperidine-1-carboxylate
tert-butyl-4-(3-iodo-1-methyl-indazol-6-yl)-2,2-dimethyl-piperidine-1-carboxylate	2,6-dibenzyloxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine	Reaction temperature: 100 °C; reaction time: 5 hours	*tert*-butyl-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-2,2-dimethyl-piperidine-1-carboxylate
3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-7-fluoro-1-methyl-1H-indazole	*tert*-butyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate		*tert*-butyl-4-[3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate
6-bromo-5-fluoro-3-iodo-1-methyl-indazole	2,6-dibenzyloxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine	Reaction time: 16 hours	6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazole
6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-1-(2,2,2-	*tert*-butyl-4-(4,4,5,5-tetramethyl-1,3,2-	Reaction temperature: 100	*tert*-butyl-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-

trifluoroethyl)indazole	dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate	°C; reaction time: 2 hours	(2,2,2-trifluoroethyl)indazol-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate
6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazole	*tert*-butyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate		*tert*-butyl-4-[3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate
6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-1-isopropyl-indazole	*tert*-butyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate	Reaction temperature: 100 °C; reaction time: 2 hours	*tert*-butyl-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-isopropyl-indazol-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate
6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazole	*tert*-butyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate	Reaction temperature: 100 °C; reaction time: 2 hours	*tert*-butyl-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate
6-bromo-3-iodo-1,5-dimethyl-indazole	2,6-dibenzyloxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine	Reaction solvent; THF; reaction temperature: 16 hours	6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-1,5-dimethyl-indazole
6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-1,5-dimethyl-indazole	*tert*-butyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate	Reaction temperature: 100 °C; reaction time: 2 hours	*tert*-butyl-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1,5-dimethyl-indazol-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate
6-bromo-1-methyl-indazole	*tert*-butyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate	Reaction temperature: 100 °C; reaction time: 2 hours	*tert*-butyl-4-(1-methylindazol-6-yl)-3,6-dihydro-2H-pyridine-1-carboxylate
tert-butyl-3-fluoro-4-(3-iodo-1-methyl-indazol-6-yl)piperidine-1-carboxylate	2,6-dibenzyloxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine	Reaction temperature: 100 °C; reaction time: 2 hours	*tert*-butyl-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-3-fluoro-piperidine-1-carboxylate
3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-1-methyl-1H-indazole	*tert*-butyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate	Reaction temperature: 100 °C; reaction time: 1 hour	*tert*-butyl-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate
6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-7-(trifluoromethyl)indazole	*tert*-butyl-4-[1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridin-1-yl]ethyl]piperidine-1-carboxylate	Reaction temperature: 95 °C; reaction time: 16 hours	*tert*-butyl-4-[1-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-7-(trifluoromethyl)indazol-6-yl]-3,6-dihydro-2H-pyridin-1-yl]ethyl]piperidine-1-carboxylate
tert-butyl-6,6-dimethyl-4-(trifluoromethylsulfonyloxy)-2,3-dihydropyridine-1-carboxylate	(1-methylindazol-6-yl)boronic-acid	Na_2CO_3 (3.0 *equiv.*) instead of Cs_2CO_3; reaction temperature: 95 °C; reaction time: 5 hours	*tert*-butyl-6,6-dimethyl-4-(1-methylindazol-6-yl)-2,3-dihydropyridine-1-carboxylate
6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazole	*tert*-butyl-4-[1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-	Reaction time: 5 hours; residue was purified by prep-	*tert*-butyl-4-[1-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazol-

	yl)-3,6-dihydro-2H-pyridin-1-yl]ethyl]piperidine-1-carboxylate	HPLC	6-yl]-3,6-dihydro-2H-pyridin-1-yl]ethyl]piperidine-1-carboxylate
6-bromo-3-iodo-1,7-dimethyl-1H-indazole	2,6-bis(benzyloxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine	Reaction solvent: THF:H_2O (10:1); reaction temperature: 60 °C; reaction time: 16 hours	3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-1,7-dimethyl-1H-indazole
3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-1,7-dimethyl-1H-indazole	*tert*-butyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate	Reaction temperature: 100 °C; reaction time: 2 hours	*tert*-butyl-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1,7-dimethyl-1H-indazol-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate
6-bromo-3-iodo-1-methyl-7-(trifluoromethyl)indazole	2,6-dibenzyloxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine		6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-7-(trifluoromethyl)indazole
6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-7-(trifluoromethyl)indazole	*tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate	K_2CO_3 (2.5 *equiv.*) instead of Cs_2CO_3; reaction temperature: 80 °C; reaction time: 2 hours	*tert*-butyl 4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-7-(trifluoromethyl)indazol-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate
6-bromo-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole	(2,6-bis(benzyloxy)pyridin-3-yl) boronic acid	Na_2CO_3 (3.0 *equiv.*) instead of Cs_2CO_3; reaction temperature: 100 °C; reaction time: 16 hours; reaction filtered through celite before work-up	3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole
6-bromo-5,7-difluoro-3-iodo-1-methyl-indazole	2,6-dibenzyloxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine	Reaction temperature: 100 °C; reaction time: 1 hour	6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazole
6-bromo-3-iodo-1-(2,2,2-trifluoroethyl)indazole	2,6-dibenzyloxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine	Reaction temperature: 90 °C; reaction time: 16 hour	6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-1-(2,2,2-trifluoroethyl)indazole

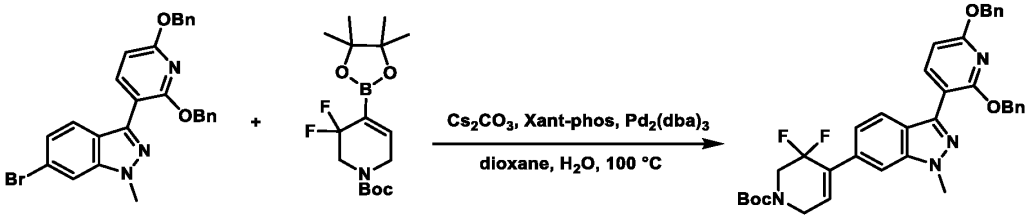
Table P33A

Product	LC-MS (ESI)	^{1}H NMR
6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-5-(trifluoromethyl)indazole	m/z = 568.1 $[M+H]^+$	
tert-butyl-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-5-(trifluoromethyl)indazol-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate	m/z = 671.3 $[M+H]^+$	
tert-butyl-4-[3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate	m/z = 621.3 $[M+H]^+$	
tert-butyl-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-7-yl]-3,6-	m/z = 603.4 $[M+H]^+$	

dihydro-2H-pyridine-1-carboxylate		
tert-butyl-(2R)-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-2-methyl-piperidine-1-carboxylate	m/z = 619.6 $[M+H]^+$	
tert-butyl-(2R)-2-methyl-4-(1-methylindazol-6-yl)-3,6-dihydro-2H-pyridine-1-carboxylate	m/z = 328.3 $[M+H]^+$	
tert-butyl-4-(1-(4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)-3,6-dihydropyridin-1(2H)-yl)-2,2,2-trifluoroethyl)piperidine-1-carboxylate	m/z = 768.3 $[M+H]^+$	
tert-butyl-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridin-1-yl]methyl]piperidine-1-carboxylate	m/z = 736.3 $[M+H]^+$	
tert-butyl-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-2,2-dimethyl-piperidine-1-carboxylate	m/z = 633.3 $[M+H]^+$	
tert-butyl-4-[3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate	m/z = 621.2 $[M+H]^+$	
6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazole	m/z = 519.9 $[M+H]^+$	
tert-butyl-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-(2,2,2-trifluoroethyl)indazol-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate	m/z = 671.2 $[M+H]^+$	
tert-butyl-4-[3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate	m/z = 621.3 $[M+H]^+$	
tert-butyl-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-isopropyl-indazol-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate	m/z = 631.4 $[M+H]^+$	
tert-butyl-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate	m/z = 603.4 $[M+H]^+$	
6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-1,5-dimethyl-indazole		
tert-butyl-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1,5-dimethyl-indazol-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate		
tert-butyl-4-(1-methylindazol-6-yl)-3,6-dihydro-2H-pyridine-1-carboxylate	m/z = 314.0 $[M+H]^+$	
tert-butyl-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-3-fluoro-piperidine-1-carboxylate	m/z = 623.1 $[M+H]^+$	
tert-butyl-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate	m/z = 603.3 $[M+H]^+$	
tert-butyl-4-[1-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-7-(trifluoromethyl)indazol-6-yl]-3,6-dihydro-2H-pyridin-1-yl]ethyl]piperidine-1-carboxylate	m/z = 782.3 $[M+H]^+$	
tert-butyl-6,6-dimethyl-4-(1-	m/z = 342.2	

methylindazol-6-yl)-2,3-dihydropyridine-1-carboxylate	$[M+H]^+$	
tert-butyl-4-[1-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridin-1-yl]ethyl]piperidine-1-carboxylate	m/z = 732.5 $[M+H]^+$	
3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-1,7-dimethyl-1H-indazole		(400 MHz, $CDCl_3$-d) δ = 7.83 (d, J = 8.0 Hz, 1H), 7.47 - 7.43 (m, 2H), 7.39 (t, J = 7.2 Hz, 2H), 7.32 (dd, J = 9.2, 14.0 Hz, 6H), 7.27 - 7.24 (m, 1H), 7.18 (d, J = 8.4 Hz, 1H), 6.52 (d, J = 8.0 Hz, 1H), 5.43 (d, J = 15.2 Hz, 4H), 4.36 (s, 3H), 2.87 (s, 3H)
tert-butyl-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1,7-dimethyl-1H-indazol-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate		(400 MHz, DMSO-d6) δ = 7.83 (d, J = 8.0 Hz, 1H), 7.48 - 7.45 (m, 2H), 7.42 - 7.37 (m, 3H), 7.37 - 7.33 (m, 3H), 7.32 - 7.25 (m, 4H), 6.76 (d, J = 8.4 Hz, 1H), 6.58 (d, J = 8.0 Hz, 1H), 5.42 (d, J = 2.4 Hz, 4H), 4.30 (s, 3H), 4.01 - 3.97 (m, 2H), 3.58 (t, J = 5.2 Hz, 2H), 2.64 (s, 3H), 2.27 (d, J = 1.2 Hz, 2H), 1.45 (s, 9H)
6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-7-(trifluoromethyl)indazole	m/z = 568.0 $[M+H]^+$	
tert-butyl 4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-7-(trifluoromethyl)indazol-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate	m/z = 671.2 $[M+H]^+$	
3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole	m/z = 570.20 $[M+H]^+$	
6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazole	m/z = 536.0 $[M+H]^+$	
6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-1-(2,2,2-trifluoroethyl)indazole	m/z = 568.2/570.2 $[M+H]^+$	

Example P34



To a stirred solution of *tert*-butyl-3,3-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (Reactant B) (1.0 g, 2.89 mmol, 1 *equiv.*) and 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-1-methyl-1H-indazole (prepared using published methods, e.g., in International Application Publication No. WO 2021/127586) (Reactant A) (1.015 g, 2.02 mmol, 1 *equiv.*) in dioxane: water (30mL:10mL) was added Cs_2CO_3 (2.83 g, 8.69 mmol, 1 *equiv.*). The resulting mixture was purged with N_2 gas for 15 min followed by the addition of $Pd_2(dba)_3$ (0.133 g, 0.14 mmol, 0.05 *equiv.*) and XantPhos (0.168 g, 0.29 mmol, 0.1 *equiv.*). The reaction mixture was heated to 100°C and stirred for 6 hours. The reaction

mixture was then diluted with water (50 mL) and extracted with ethyl acetate (3 x 50mL). The combined organic layers were washed with brine solution (20 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure to obtain crude product which was purified by flash column chromatography to afford *tert*-butyl-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)-3,3-difluoro-3,6-dihydropyridine-1(2H)-carboxylate (0.4 g) as a white solid. **LC-MS (ESI):** m/z = 639.2 $[M+H]^+$

The compounds shown in the "**Product**" column of **Table P34** were synthesized using the method of **Example P34**, with variations noted in **Table P34**.

Table P34

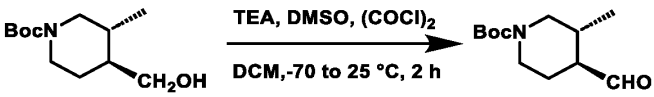
Reactant A	Reactant B	Variation from Example P34	Product
3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-1-methyl-1H-indazole	*tert*-butyl-3,3-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate		*tert*-butyl-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)-3,3-difluoro-3,6-dihydropyridine-1(2H)-carboxylate
6-bromo-7-fluoro-3-iodo-1-methyl-1H-indazole	(2,6-bis(benzyloxy)pyridin-3-yl)boronic-acid	Reaction time: 16 hours	3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-7-fluoro-1-methyl-1H-indazole
3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-7-fluoro-1-methyl-1H-indazole	*tert*-butyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate	Reaction time: 18 hours	*tert*-butyl-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate
6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazole	*tert*-butyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate		*tert*-butyl-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate
(2S)-10-bromo-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1H-[1,4]oxazepino[2,3-c]quinolin-6-one	diphenylmethanimine	Reaction solvent: toluene; reaction time: 12 hours	(2S)-10-(benzhydrylideneamino)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1H-[1,4]oxazepino[2,3-c]quinolin-6-one
3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole	*tert*-butyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate	Potassium phosphate (3.0 *equiv.*) instead of Cs_2CO_3; Tetrakis(triphenylphosphine)-palladium(0) (10 wt%) instead of $Pd_2(dba)_3$; no XantPhos was added; reaction was filtered through celite before work-up	*tert*-butyl-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate
3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-1-methyl-1H-indazole	*tert*-butyl 9-(piperidin-4-ylmethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	RuPhos (0.1 *equiv.*) instead of XantPhos; RuPhos-PdG3 (0.05 *equiv.*) instead of $Pd_2(dba)_3$; reaction	*tert*-butyl 9-((1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-

		temperature: 80 °C; reaction time: 3 hours; work-up K was used	4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate
3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-1-methyl-1H-indazole	tert-butyl piperazine-1-carboxylate	RuPhos (0.1 *equiv.*) instead of XantPhos; RuPhos-PdG3 (0.05 *equiv.*) instead of $Pd_2(dba)_3$; reaction temperature: 100 °C; reaction time: 8 hours; work-up K was used	*tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperazine-1-carboxylate

Table P34A

Product	LC-MS (ESI	^{1}H NMR
tert-butyl-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)-3,3-difluoro-3,6-dihydropyridine-1(2H)-carboxylate	m/z = 639.25 $[M+H]^+$	
3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-7-fluoro-1-methyl-1H-indazole	m/z = 520.36 $[M+H]^+$	
tert-butyl-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate	m/z = 622.10 $[M+H]^+$	
tert-butyl-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate	m/z = 621.26 $[M+H]^+$	
(2S)-10-(benzhydrylideneamino)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1H-[1,4]oxazepino[2,3-c]quinolin-6-one	m/z = 504.1 $[M+H]^+$	(400 MHz, DMSO-d6) δ = 7.73 - 7.68 (m, 3H), 7.58 (t, J = 6.8 Hz, 1H), 7.53 - 7.48 (m, 2H), 7.38 - 7.33 (m, 3H), 7.22 - 7.16 (m, 3H), 6.17 (s, 1H), 4.48 - 4.25 (m, 2H), 3.43 (s, 3H), 3.24 - 3.11 (m, 1H), 1.30 - 1.21 (m, 1H), 0.73 - 0.64 (m, 1H), 0.60 - 0.44 (m, 2H), 0.30 - 0.19 (m, 1H)
tert-butyl-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate	m/z = 673.59 $[M+H]^+$	
tert-butyl 9-((1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	m/z = 771.83 $[M+H]^+$	
tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperazine-1-carboxylate	m/z = 606.67 $[M+H]^+$	

Example P35



To A mixture of $(COCl)_2$ (442.80 mg, 3.49 mmol, 305.38 µL, 2.0 *equiv.*) in DCM (10 mL) at -70 °C was added DMSO (545.16 mg, 6.98 mmol, 545.16 µL, 4.0 *equiv.*). The mixture was

stirred for 0.5 hours followed by the addition of *tert*-butyl-(3*R*,4*S*)-4-(hydroxymethyl)-3-methylpiperidine-1-carboxylate (Reactant) (400 mg, 1.74 mmol, 1 *equiv.*) in DCM (10 mL). The resulting reaction mixture was stirred at -70 °C for 1 hour. To this mixture was added TEA (1.06 g, 10.47 mmol, 1.46 mL, 6.0 *equiv.*). The resulting reaction mixture was warmed to 25 °C and stirred for 0.5 hours under N_2 atmosphere. The reaction mixture was then concentrated under reduced pressure to remove DCM. The residue was diluted with H_2O (50 mL) and extracted with ethyl acetate (100 mL). The combined organic layers were washed with brine (90 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give *tert*-butyl-(3*R*,4*S*)-4-formyl-3-methylpiperidine-1-carboxylate (200 mg, 879.90 μmol) as a colorless oil. **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 9.58 (d, J = 2.8 Hz, 1H), 3.90 - 3.75 (m, 2H), 2.80 (t, J = 11.2 Hz, 1H), 2.19 - 2.10 (m, 1H), 1.77 - 1.67 (m, 2H), 1.39 (s, 9H), 1.38 - 1.30 (m, 2H), 0.88 (d, J = 6.4 Hz, 3H)

The compounds shown in the "**Product**" column of **Table P35** were synthesized using the method of **Example P35**, with variations noted in **Table P35**.

Table P35

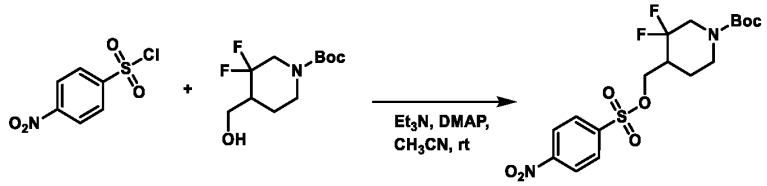
Reactant	Variation from Example P35	Product
tert-butyl-(3R,4S)-4-(hydroxymethyl)-3-methylpiperidine-1-carboxylate		*tert*-butyl-(3R,4S)-4-formyl-3-methylpiperidine-1-carboxylate
tert-butyl-(3S,4S)-4-(hydroxymethyl)-3-methyl-piperidine-1-carboxylate		*tert*-butyl-(3S,4S)-4-formyl-3-methyl-piperidine-1-carboxylate
tert-butyl-(3S,4R)-4-(hydroxylmethyl)-3-methyl-piperidine-1-carboxylate		*tert*-butyl-(3S,4R)-4-formyl-3-methyl-piperidine-1-carboxylate
tert-butyl-(3R,4S)-4-(hydroxymethyl)-3-methyl-piperidine-1-carboxylate	Work-up S was used	*tert*-butyl-(3R,4S)-4-formyl-3-methyl-piperidine-1-carboxylate
tert-butyl-(3R,4R)-4-(hydroxymethyl)-3-methyl-piperidine-1-carboxylate	Reaction temperature: -70 °C; reaction time: 1 hour	*tert*-butyl-(3R,4R)-4-formyl-3-methyl-piperidine-1-carboxylate
tert-butyl-4-(hydroxymethyl)-3-(trifluoromethyl)piperidine-1-carboxylate	Reaction temperature: -70 °C; reaction time: 1.5 hour	*tert*-butyl-4-formyl-3-(trifluoromethyl)piperidine-1-carboxylate

Table P35A

Product	^{1}H NMR
tert-butyl-(3R,4S)-4-formyl-3-methylpiperidine-1-carboxylate	(400 MHz, DMSO-d6) δ = 9.58 (d, J = 2.8 Hz, 1H), 3.90 - 3.75 (m, 2H), 2.80 (t, J = 11.2 Hz, 1H), 2.19 - 2.10 (m, 1H), 1.77 - 1.67 (m, 2H), 1.39 (s, 9H), 1.38 - 1.30 (m, 2H), 0.88 (d, J = 6.4 Hz, 3H)
tert-butyl-(3S,4S)-4-formyl-3-methyl-piperidine-1-carboxylate	(400 MHz, DMSO-d6) δ = 9.60 (s, 1H), 3.95 - 3.75 (m, 1H), 3.70 - 3.61 (m, 1H), 3.11 - 2.98 (m, 1H), 2.93 - 2.74 (m, 1H), 2.65 – 2.61 (m, 1H), 2.38 - 2.25 (m, 1H), 1.60 - 1.52 (m, 2H), 1.38 (s, 9H), 0.78 (d, J = 7.2 Hz, 3H)

tert-butyl-(3S,4R)-4-formyl-3-methyl-piperidine-1-carboxylate	(400 MHz, DMSO-d6) δ = 9.58 (s, 1H), 3.96 - 3.74 (m, 2H), 2.80 (t, J = 10.4 Hz, 1H), 2.49 - 2.31 (m, 1H), 2.21 - 2.09 (m, 1H), 1.78 - 1.65 (m, 2H), 1.39 (s, 10H), 0.88 (d, J = 6.4 Hz, 3H)
tert-butyl-(3R,4S)-4-formyl-3-methyl-piperidine-1-carboxylate	(400 MHz, DMSO-d6) δ = 9.59 (d, J = 2.4 Hz, 1H), 3.94 - 3.76 (m, 2H), 2.81 (br t, J = 11.2 Hz, 1H), 2.23 - 2.12 (m, 1H), 1.85 - 1.67 (m, 2H), 1.44 - 1.33 (m, 11H), 0.88 (d, J = 6.4 Hz, 3H)
tert-butyl-(3R,4R)-4-formyl-3-methyl-piperidine-1-carboxylate	(400 MHz, DMSO-d6) δ = 7.90 (d, J = 8.0 Hz, 1H), 7.66 (s, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.52 - 7.44 (m, 2H), 7.41 - 7.33 (m, 5H), 7.32 - 7.25 (m, 3H), 7.20 (d, J = 1.2 Hz, 1H), 6.58 (d, J = 8.0 Hz, 1H), 5.44 (d, J = 16.4 Hz, 4H), 5.20 (s, 1H), 4.10 - 4.00 (m, 3H), 3.89 (d, J = 6.4 Hz, 2H), 3.27 - 3.06 (m, 2H), 1.97 - 1.84 (m, 2H), 1.64 (d, J = 12.4 Hz, 2H), 1.43 (s, 8H)
tert-butyl-4-formyl-3-(trifluoromethyl)piperidine-1-carboxylate	

Example P36



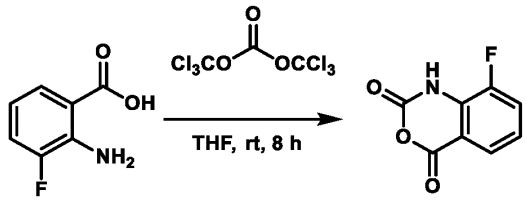
To a stirred solution of *tert*-butyl-3,3-difluoro-4-(hydroxymethyl)piperidine-1-carboxylate (Reactant) (1.0 g, 3.98 mmol, 1 *equiv.*) and 4-nitrobenzenesulfonyl chloride (1.76 g, 7.96 mmol, 1 *equiv.*) in CH_3CN (20.0 ml) was added TEA (1.6 mL, 11.95 mmol, 1 *equiv.*) and DMAP (0.048 g, 0.39 mmol, 1 *equiv.*) at 0 °C. The resultant mixture was stirred at room temperature for 1.5 hours. The reaction mixture was quenched with water (20 mL) and extracted with ethyl-acetate (50 mL x 3). The organic layer was separated and washed with brine solution (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give a crude product which was purified by flash column chromatography to afford *tert*-butyl-3,3-difluoro-4-((((4-nitrophenyl)sulfonyl)oxy)methyl)piperidine-1-carboxylate (1.0 g) as off white solid. **LC-MS (ESI):** m/z = 459.10 $[M+Na]^+$

The compounds shown in the "**Product**" column of **Table P36** were synthesized using the method of **Example P36**, with variations noted in **Table P36**.

Table P36

Reactant	Variation from Example P36	Product
tert-butyl-3,3-difluoro-4-(hydroxymethyl)piperidine-1-carboxylate		*tert*-butyl-3,3-difluoro-4-((((4-nitrophenyl)sulfonyl)oxy)methyl)piperidine-1-carboxylate

Example P37



To a stirred solution of 2-amino-3-fluorobenzoic-acid (Reactant) (15 g, 96.69 mmol, 1 *equiv.*) in THF (300 mL) at 0 °C was added bis(trichloromethyl) carbonate (11.47 g, 38.67 mmol, 1 *equiv.*). The reaction mixture was stirred at room temperature for 8 hours. The reaction mixture was poured into ice water and the solid was filtered, washed with water then petroleum ether, and dried under vacuum to afford 8-fluoro-2H-benzo[d][1,3]oxazine-2,4(1H)-dione (14.0 g) as a light brown solid. **LC-MS (ESI):** m/z = 180.13 $[M-H]^-$.

The compounds shown in the "**Product**" column of **Table P37** were synthesized using the method of **Example P37**, with variations noted in **Table P37**.

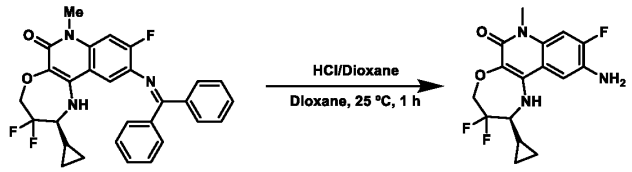
Table P37

Reactant	Variation from Example P37	Product
2-amino-3-fluorobenzoic-acid		8-fluoro-2H-benzo[d][1,3]oxazine-2,4(1H)-dione
2-amino-5-bromo-4-fluoro-benzoic acid	Reaction temperature: 70°C; reaction time: 2 hours	6-bromo-7-fluoro-1H-3,1-benzoxazine-2,4-dione

Table P37A

Product	LC-MS (ESI)	^{1}H NMR
8-fluoro-2H-benzo[d][1,3]oxazine-2,4(1H)-dione	m/z = 180.13 $[M-H]^-$	
6-bromo-7-fluoro-1H-3,1-benzoxazine-2,4-dione		(400 MHz, DMSO-d6) δ = 11.98 (s, 1H), 8.19 (d, J = 7.6 Hz, 1H), 7.03 (d, J = 9.2 Hz, 1H)

Example P38



To a solution of (2S)-10-(benzhydrylideneamino)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1H-[1,4]oxazepino[2,3-c]quinolin-6-one (Reactant) (2.07 g, 4.12 mmol, 1 *equiv.*) in dioxane (7 mL) was added HCl/dioxane (14 mL). The mixture was stirred at 25 °C for 1 hour.

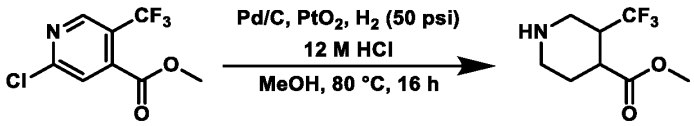
The reaction mixture was concentrated under reduced pressure to give a residue which was purified by prep-HPLC to afford (2S)-10-amino-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1H-[1,4]oxazepino[2,3-c]quinolin-6-one (931 mg) as a pink solid. **LC-MS (ESI):** m/z = 8340.1 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 7.40 - 7.27 (m, 1H), 7.25 - 7.15 (m, 1H), 6.04 (d, J = 3.2 Hz, 1H), 5.02 (s, 2H), 4.48 - 4.24 (m, 2H), 3.46 (s, 3H), 3.26 - 3.13 (m, 1H), 1.37 - 1.24 (m, 1H), 0.75 - 0.64 (m, 1H), 0.56 - 0.46 (m, 2H), 0.37 - 0.27 (m, 1H)

The compounds shown in the "**Product**" column of **Table P38** were synthesized using the method of **Example P38**, with variations noted in **Table P38**.

Table P38

Reactant	Variation from Example P38	Product
(2S)-10-(benzhydrylideneamino)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1H-[1,4]oxazepino[2,3-c]quinolin-6-one		(2S)-10-amino-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1H-[1,4]oxazepino[2,3-c]quinolin-6-one

Example P39



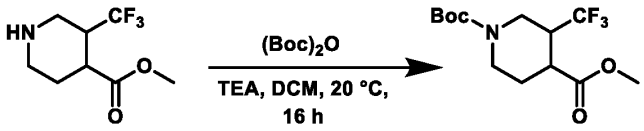
To a solution of PtO_2 (1.52 g, 6.68 mmol, 0.04 *equiv.*) and Pd on carbon (10 wt%) (7.11 g, 6.68 mmol, 0.04 *equiv.*) in AcOH (1000 mL) was added methyl-2-chloro-5-(trifluoromethyl)pyridine-4-carboxylate (40 g, 166.96 mmol, 1 *equiv.*) and HCl (12 M, 6.96 mL, 0.5 *equiv.*) under N_2 atmosphere. The solution was degassed and purged with H_2 (50 Psi) three times. The mixture was then stirred at 80 °C for 16 hours under H_2 (50 Psi) atmosphere. The reaction mixture was then filtered and concentrated under reduced pressure to afford methyl-3-(trifluoromethyl)piperidine-4-carboxylate (70 g) as a colorless oil which was used in the next step without further purification.

The compounds shown in the "**Product**" column of **Table P39** were synthesized using the method of **Example P39**, with variations noted in **Table P39**.

Table P39

Reactant	Variation from Example P39	Product
methyl-2-chloro-5-(trifluoromethyl)pyridine-4-carboxylate		methyl-3-(trifluoromethyl)piperidine-4-carboxylate

Example P40



To a solution of methyl-3-(trifluoromethyl)piperidine-4-carboxylate (25 g, 118.38 mmol, 1 *equiv.*) in DCM (500 mL) was added $(Boc)_2O$ (51.67 g, 236.76 mmol, 54.39 mL, 2 *equiv.*) and TEA (59.90 g, 591.91 mmol, 82.39 mL, 5 *equiv.*). The mixture was stirred at 20 °C for 16 hours. The reaction mixture was filtered and concentrated under reduced pressure to give 1-(tert-butyl) 4-methyl 3-(trifluoromethyl)piperidine-1,4-dicarboxylate (11 g) as a colorless oil. **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 4.19 - 3.86 (m, 2H), 3.84 (s, 3H), 3.05 (td, J = 4.8, 9.2 Hz, 2H), 3.00 - 2.81 (m, 2H), 1.70 (d, J = 4.4 Hz, 2H), 1.38 (s, 9H)

The compounds shown in the "**Product**" column of **Table P40** were synthesized using the method of **Example P40**, with variations noted in **Table P40**.

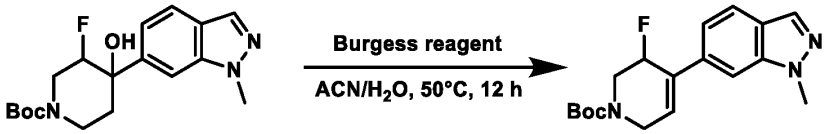
Table P40

Reactant	Variation from Example P40	Product
methyl-3-(trifluoromethyl)piperidine-4-carboxylate		1-(tert-butyl) 4-methyl 3-(trifluoromethyl)piperidine-1,4-dicarboxylate

Table P40A

Product	^{1}H NMR
1-(tert-butyl) 4-methyl 3-(trifluoromethyl)piperidine-1,4-dicarboxylate	(400 MHz, DMSO-d6) δ = 4.19 - 3.86 (m, 2H), 3.84 (s, 3H), 3.05 (td, J = 4.8, 9.2 Hz, 2H), 3.00 - 2.81 (m, 2H), 1.70 (d, J = 4.4 Hz, 2H), 1.38 (s, 9H)

Example P41



To a solution of *tert*-butyl-3-fluoro-4-hydroxy-4-(1-methylindazol-6-yl)piperidine-1-carboxylate (16.00 g, 45.79 mmol, 1 *equiv.*) in toluene (50 mL) was added methoxycarbonyl-(triethylammonio)sulfonyl-azanide (54.56 g, 228.96 mmol, 5 *equiv.*). The mixture was stirred at 50 °C for 12 hr. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with water and extracted with ethyl acetate. The combined

organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to afford *tert*-butyl-3-fluoro-4-(1-methylindazol-6-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (6 g) as a white solid. **LC-MS (ESI):** m/z = 332.1 $[M+H]^+$

The compounds shown in the "**Product**" column of **Table P41** were synthesized using the method of **Example P41**, with variations noted in **Table P41**.

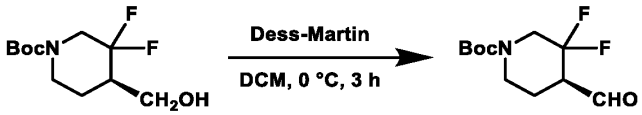
Table P41

Reactant	Variation from Example P41	Product
tert-butyl-3-fluoro-4-hydroxy-4-(1-methylindazol-6-yl)piperidine-1-carboxylate		*tert*-butyl-3-fluoro-4-(1-methylindazol-6-yl)-3,6-dihydro-2H-pyridine-1-carboxylate

Table P41A

Product	LC-MS (ESI)
tert-butyl-3-fluoro-4-(1-methylindazol-6-yl)-3,6-dihydro-2H-pyridine-1-carboxylate	m/z = 332.1 $[M+H]^+$

Example P42



To a solution of *tert*-butyl-(4*R*)-3,3-difluoro-4-(hydroxymethyl)piperidine-1-carboxylate (300 mg, 1.19 mmol, 1 *equiv.*) in DCM (5 mL) was dropwise added DMP (1.01 g, 2.39 mmol, 739.80 µL, 2 *equiv.*) at 0 °C. The resulting mixture was stirred at 0 °C for 3 hours. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to afford *tert*-butyl-(4*R*)-3,3-difluoro-4-formyl-piperidine-1-carboxylate (140 mg) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$-d) δ = 9.85 (s, 1H), 4.27 - 3.83 (m, 2H), 3.28 - 3.09 (m, 1H), 2.91 (br t, J = 10.0 Hz, 1H), 2.82 - 2.67 (m, 1H), 1.93 - 1.80 (m, 2H), 1.40 (s, 9H)

The compounds shown in the "**Product**" column of **Table P42** were synthesized using the method of **Example P42**, with variations noted in **Table P42**.

Table P42

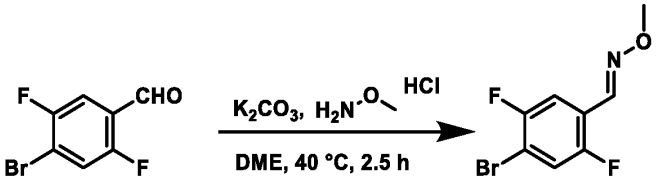
Reactant	Variation from Example P42	Product

tert-butyl-(4R)-3,3-difluoro-4-(hydroxymethyl)piperidine-1-carboxylate		*tert*-butyl-(4R)-3,3-difluoro-4-formyl-piperidine-1-carboxylate
tert-butyl-(4S)-3,3-difluoro-4-(hydroxymethyl)piperidine-1-carboxylate		*tert*-butyl-(4S)-3,3-difluoro-4-formyl-piperidine-1-carboxylate
tert-butyl-(3S,4R)-3-fluoro-4-(hydroxymethyl)piperidine-1-carboxylate		*tert*-butyl-(3S,4R)-3-fluoro-4-formyl-piperidine-1-carboxylate
tert-butyl-(3R,4S)-3-fluoro-4-(hydroxymethyl)piperidine-1-carboxylate		*tert*-butyl-(3R,4S)-3-fluoro-4-formylpiperidine-1-carboxylate

Table P42A

Product	^{1}H NMR
tert-butyl-(4R)-3,3-difluoro-4-formyl-piperidine-1-carboxylate	(400 MHz, $CDCl_3$-d) δ = 9.85 (s, 1H), 4.27 - 3.83 (m, 2H), 3.28 - 3.09 (m, 1H), 2.91 (br t, J = 10.0 Hz, 1H), 2.82 - 2.67 (m, 1H), 1.93 - 1.80 (m, 2H), 1.40 (s, 9H)
tert-butyl-(4S)-3,3-difluoro-4-formyl-piperidine-1-carboxylate	(400 MHz, $CDCl_3$-d) δ = 4.40 - 4.06 (m, 2H), 4.04 - 3.94 (m, 1H), 3.72 - 3.58 (m, 1H), 3.09 - 2.70 (m, 2H), 2.18 - 1.99 (m, 1H), 1.93 - 1.83 (m, 2H), 1.66 - 1.52 (m, 2H), 1.46 (s, 9H)
tert-butyl-(3S,4R)-3-fluoro-4-formyl-piperidine-1-carboxylate	(400 MHz, DMSO-d6) δ = 9.66 (s, 1H), 5.49 - 5.18 (m, 1H), 4.35 - 3.93 (m, 2H), 2.91 - 2.69 (m, 2H), 1.76 - 1.67 (m, 1H), 1.64 - 1.51 (m, 1H), 1.42 - 1.36 (m, 10H)
tert-butyl-(3R,4S)-3-fluoro-4-formylpiperidine-1-carboxylate	(400 MHz, $CDCl_3$-d) δ = 9.76 (s, 1H), 5.31 - 5.01 (m, 1H), 4.60 - 4.10 (m, 2H), 3.18 - 2.64 (m, 2H), 2.59 - 2.31 (m, 1H), 2.00 (dq, J = 4.4, 12.8 Hz, 1H), 1.84 (br d, J = 12.0 Hz, 1H), 1.47 (s, 9H)

Example P43



To a solution of 4-bromo-2,5-difluoro-benzaldehyde (95 g, 429.87 mmol, 1 *equiv.*) in DME (950 mL) was added O-methylhydroxylamine (43.08 g, 515.84 mmol, 1.2 *equiv.*) and K_2CO_3 (178.23 g, 1.29 mol, 3 *equiv.*). The reaction mixture was stirred at 45 °C for 2.5 hours. The reaction mixture was filtered and concentrated under reduced pressure to afford (E)-1-(4-bromo-2,5-difluoro-phenyl)-N-methoxy-methanimine (95 g, crude) as a yellow oil. **LC-MS (ESI):** m/z = 249.9 $[M+H]^+$

The compounds shown in the "**Product**" column of **Table P43** were synthesized using the method of **Example P43**, with variations noted in **Table P43**.

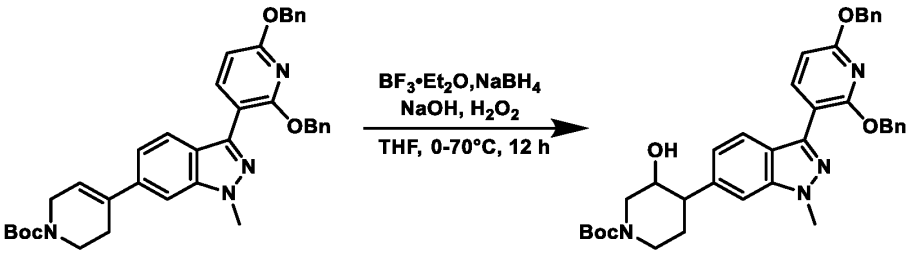
Table P43

Reactant	Variation from Example P43	Product
4-bromo-2,5-difluoro-benzaldehyde		(E)-1-(4-bromo-2,5-difluoro-phenyl)-N-methoxy-methanimine
4-bromo-2-fluoro-3-(trifluoromethyl)benzaldehyde		(E)-1-[4-bromo-2-fluoro-3-(trifluoromethyl)phenyl]-N-methoxy-methanimine

Table P43A

Product	LC-MS (ESI)
(E)-1-(4-bromo-2,5-difluoro-phenyl)-N-methoxy-methanimine	m/z = 249.9 $[M+H]^+$
(E)-1-[4-bromo-2-fluoro-3-(trifluoromethyl)phenyl]-N-methoxy-methanimine	m/z = 265.1 $[M+H]^+$

Example P44



To a cooled (0 °C) solution of $NaBH_4$ (1.88 g, 49.77 mmol, 3 *equiv.*) in anhydrous THF (150 mL) was added $BF_3.Et_2O$ (7.06 g, 49.77 mmol, 6.12 mL, 3 *equiv.*). The reaction mixture was allowed to warm to 25°C and stirred for 30 min. A solution of *tert*-butyl-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (10 g, 16.59 mmol, 1 *equiv.*) in anhydrous THF (7 mL) was added over a period of 30 min. The mixture was stirred at 25°C for 2 hours. The reaction mixture was quenched by the slow addition of H_2O (15 mL) followed by EtOH (15 mL). NaOH (3.32 g, 82.96 mmol, 30.16 mL, 5 *equiv.*) and then H_2O_2 (3.76 g, 33.18 mmol, 3.19 mL, 30% purity, 2 *equiv.*) were added, and the reaction mixture was heated to 70 °C for 12 hours. The reaction mixture was cooled to room temperature before the addition of CH_2Cl_2 (150 mL). The pH of the mixture was adjusted to pH ~ 6-7 using 3 N HCl (30 mL), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL), and the organic layers were combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to afford *tert*-butyl-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-3-hydroxy-piperidine-1-carboxylate (9.7 g) as a yellow solid. **LC-MS (ESI):** m/z = 621.3 $[M+H]^+$

The compounds shown in the "**Product**" column of **Table P44** were synthesized using the method of **Example P44**, with variations noted in **Table P44**.

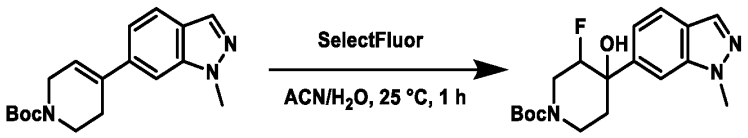
Table P44

Reactant	Variation from Example P44	Product
tert-butyl-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate		*tert*-butyl-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-3-hydroxy-piperidine-1-carboxylate

Table P44A

Product	LC-MS (ESI)
tert-butyl-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-3-hydroxy-piperidine-1-carboxylate	m/z = 621.3 [M+H]+

Example P45



To a solution of *tert*-butyl-4-(1-methylindazol-6-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (24 g, 76.58 mmol, 1 *equiv.*) in MeCN (224 mL) and H_2O (56 mL) was added SelectFluor (48.83 g, 137.85 mmol, 1.8 *equiv.*). The mixture was stirred at 25 °C for 1 hour. The reaction mixture was quenched by addition sodium bicarbonate and then extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to afford *tert*-butyl-3-fluoro-4-hydroxy-4-(1-methylindazol-6-yl)piperidine-1-carboxylate (16 g) as a white solid. **LC-MS (ESI):** m/z = 350.0 $[M+H]^+$

The compounds shown in the "**Product**" column of **Table P45** were synthesized using the method of **Example P45**, with variations noted in **Table P45**.

Table P45

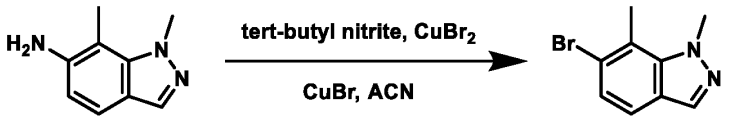
Reactant	Variation from Example P45	Product
tert-butyl-4-(1-methylindazol-6-yl)-3,6-dihydro-2H-pyridine-1-carboxylate		*tert*-butyl-3-fluoro-4-hydroxy-4-(1-methylindazol-6-yl)piperidine-1-carboxylate

Table P45A

Product	LC-MS (ESI)

tert-butyl-3-fluoro-4-hydroxy-4-(1-methylindazol-6-yl)piperidine-1-carboxylate	m/z = 350.0 [M+H]+

Example P46



To a solution of 1,7-dimethyl-1*H*-indazol-6-amine (6.3 g, 39.08 mmol, 1 *equiv.*) in MeCN (65 mL) was added tert-butyl nitrite (8.06 g, 78.16 mmol, 9.30 mL, 2.0 *equiv.*). The mixture was stirred at 0 °C for 0.5 hours. To this mixture was added $CuBr_2$ (13.09 g, 58.62 mmol, 2.74 mL, 1.5 *equiv.*) and CuBr (2.80 g, 19.54 mmol, 595.14 µL, 0.5 *equiv.*). The resulting mixture was stirred at 60 °C for 1 hour. The reaction mixture was added into ethyl acetate, then washed with cold ammonia (60 mL) and H_2O (150 mL). The mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give 6-bromo-1,7-dimethyl-1*H*-indazole (7.2 g) as a yellow solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 7.99 (s, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 4.28 (s, 3H), 2.82 (s, 3H).

The compounds shown in the "**Product**" column of **Table P46** were synthesized using the method of **Example P46**, with variations noted in **Table P46**.

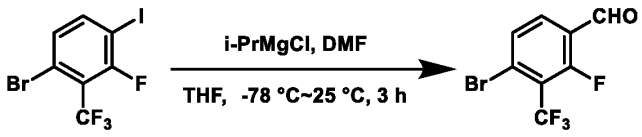
Table P46

Reactant	Variation from Example P46	Product
1,7-dimethyl-1H-indazol-6-amine		6-bromo-1,7-dimethyl-1H-indazole

Table P46A

Product	^{1}H NMR
6-bromo-1,7-dimethyl-1H-indazole	(400 MHz, DMSO-d6) δ = 7.99 (s, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 4.28 (s, 3H), 2.82 (s, 3H)

Example P47



To a solution of 1-bromo-3-fluoro-4-iodo-2-(trifluoromethyl)benzene (47.6 g, 129.03 mmol, 1 *equiv.*) in THF (500 mL) was added dropwise chloro(isopropyl)magnesium (2 M, 67.74 mL,

1.05 *equiv.*) at -78 °C. After addition, the mixture was stirred at this temperature for 1 hour. To this mixture was added DMF (10.37 g, 141.94 mmol, 10.92 mL, 1.1 *equiv.*) dropwise at -78 °C. The resulting mixture was stirred at 25°C for 2 hours. The reaction was quenched by addition of NH_4Cl (100 mL) at 0 °C. Then the mixture was diluted with H_2O (200 mL) and extracted with ethyl acetate (300 mL ×3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue which was purified by column chromatography to afford 4-bromo-2-fluoro-3-(trifluoromethyl)benzaldehyde (28 g) as a brown solid. **GCMS** m/z = 271.1 [M]

The compounds shown in the "**Product**" column of **Table P47** were synthesized using the method of **Example P47**, with variations noted in **Table P47**.

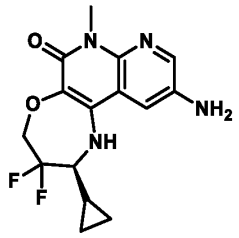
Table P47

Reactant	Variation from Example P47	Product
1-bromo-3-fluoro-4-iodo-2-(trifluoromethyl)benzene		4-bromo-2-fluoro-3-(trifluoromethyl)benzaldehyde

Table P47A

Product	GCMS (EI)
4-bromo-2-fluoro-3-(trifluoromethyl)benzaldehyde	m/z = 271.1 [M]

Example P48. (*S*)-10-amino-2-cyclopropyl-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-6(7*H*)-one



Preparation of methyl 2-(methylamino) nicotinate

A mixture of methyl 2-chloronicotinate (50 g, 292.80 mmol) and methylamine (2M in THF) (500 mL) was heated at 70 °C and stirred for 16 hours. The reaction mixture was concentrated and dried under vacuum to afford methyl 2-(methylamino) nicotinate (40.0 g) as a brown solid. The crude product was used in the next step without further purification.

LC-MS (ESI): m/z = 167.00 $[M+H]^+$

Preparation of methyl 2-(methylamino)-5-nitronicotinate

To a stirred solution of methyl 2-(methylamino) nicotinate (40.0 g, 264.65 mmol) in sulfuric acid (100 mL) was drop wise added nitric acid (40 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was poured into crushed ice (2000 mL) and the solid was filtered and dried under vacuum to afford the methyl 2-(methylamino)-5-nitronicotinate (30 g) as a yellow solid.

LC-MS (ESI): m/z = 212.21 $[M+H]^+$

Preparation of 2-(methylamino)-5-nitronicotinic acid

To a stirred solution of methyl 2-(methylamino)-5-nitronicotinate (30.0 g, 142.13 mmol) in THF (300 mL), methanol (300 mL), and water (60 mL) was added lithium hydroxide monohydrate (17.89 g, 426.41 mmol) at 0 °C. The resulting reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was concentrated under vacuum and the crude product was acidified to pH ~ 2 with 1N HCl solution. The resulting solid was filtered and dried under reduced pressure to afford 2-(methylamino)-5-nitronicotinic acid (20.0 g) as an off-white solid.

LC-MS (ESI): m/z = 198.10 $[M+H]^+$

Preparation of 3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl 2-(methylamino)-5-nitronicotinate

To a stirred solution of 2-(methylamino)-5-nitronicotinic acid (20.0 g, 101.50 mmol) in DMF (200 mL) was added HATU (57.89 g, 152.25 mmol), and DIPEA (53 mL, 304.50 mmol) at 0 °C. The mixture was stirred at room temperature for 3 hours. The reaction mixture was quenched with ice cold water (1000 mL) and the precipitated solid was filtered, washed with n-pentane and dried under vacuum to afford 3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl 2-(methylamino)-5-nitronicotinate (15 g) as a brown solid.

LC-MS (ESI): m/z = 316.09 $[M+H]^+$

Preparation of ethyl 4-hydroxy-1-methyl-6-nitro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate

To a suspension of NaH (11.43 g, 476.08 mmol) in DMF (150 mL) was added diethyl malonate (76.25 g, 476.08 mmol) at 0 °C. The mixture was stirred at room temperature for 2 hours. The reaction mixture was then cooled to 0 °C and 3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl 2-(methylamino)-5-nitronicotinate (15.0 g, 47.60 mmol) was added portion wise at 0 °C. The mixture was stirred at room temperature for 2 hours followed by the addition of potassium

carbonate (2.84 g, 20.61 mmol). The resulting reaction mixture was stirred at 100 °C for 16 hours. The reaction mixture was quenched with ice cold water (500 mL) and the precipitated solid was filtered, washed with n-pentane, and dried under vacuum to afford ethyl 4-hydroxy-1-methyl-6-nitro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate (10 g) as a brown solid.

LC-MS (ESI): m/z = 294.04 $[M+H]^+$

Preparation of ethyl 4-chloro-1-methyl-6-nitro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate

A stirred suspension of ethyl 4-hydroxy-1-methyl-6-nitro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate (15.0 g, 61.04 mmol) in $POCl_3$ (50 mL) was stirred at 80 °C for 3 hours. The reaction mixture was quenched with sodium bicarbonate solution (150 mL) and extracted with ethyl acetate (3 x100 mL). The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was washed with n-pentane and dried under reduced pressure to afford ethyl 4-chloro-1-methyl-6-nitro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate (8 g) as a brown solid**.**

LC-MS (ESI): m/z = 312.00 $[M+H]^+$

Preparation of ethyl (*S*)-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl) amino)-1-methyl-6-nitro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate

To a stirred solution of ethyl 4-chloro-1-methyl-6-nitro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate (8.0 g, 25.72 mmol) and (*S*)-3-amino-3-cyclopropyl-2,2-difluoropropan-1-ol (7.77 g, 51.44 mmol) in MeCN (80 mL) was added DIPEA (13.30 mL, 70.78 mmol). The mixture was stirred at 130 °C in an autoclave for 48 hours. The reaction mixture was quenched with ice cold water (150 mL) and the precipitated solid was filtered, washed with n-pentane (100 mL) and dried under vacuum to afford ethyl (*S*)-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl) amino)-1-methyl-6-nitro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate (8 g) as a yellow solid.

LC-MS (ESI): m/z = 427.33 $[M+H]^+$

Preparation of (*S*)-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl) amino)-1-methyl-6-nitro-1,8-naphthyridin-2(1H)-one

To a stirred solution of ethyl (*S*)-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl) amino)-1-methyl-6-nitro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate (8.0 g, 18.81 mmol) in MeCN (40 mL) was added a 2M NaOH solution (40 mL). The resulting mixture was

stirred at 85 °C for 3 hours. The reaction mixture was diluted with ice-water (200 mL) and acidified with 1N HCl to pH~6. The resulting solid was filtered off, washed with water (100 mL), n-pentane (100 mL) and dried under vacuum to afford (*S*)-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl) amino)-1-methyl-6-nitro-1,8-naphthyridin-2(1H)-one (4.0 g) as a yellow solid.

LC-MS (ESI): m/z = 355.36 $[M+H]^+$

Preparation of (*S*)-3-bromo-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl) amino)-1-methyl-6-nitro-1,8-naphthyridin-2(1H)-one

To a stirred solution of (*S*)-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl) amino)-1-methyl-6-nitro-1,8-naphthyridin-2(1H)-one (4.0 g, 11.29 mmol) in DCM (40 mL) was added NBS (2.0 g, 11.29 mmol) at 0 °C. The mixture was stirred for 5 minutes, followed by the addition of TFA (4.0 mL). The resulting reaction mixture was stirred at 0 °C for 10 minutes. The reaction mixture was diluted with water (100 mL) and extracted with DCM (2 x 200 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (100 mL), brine (100 mL), dried over anhydrous sodium sulphate, and concentrated under reduced pressure to obtain crude product. The crude product was triturated with petroleum ether (100 mL) and dried under vacuum to afford (*S*)-3-bromo-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl) amino)-1-methyl-6-nitro-1,8-naphthyridin-2(1H)-one (4.0 g) as a yellow solid.

LC-MS (ESI): m/z = 433.27 $[M+H]^+$

Preparation of (*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-10-nitro-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-6(7*H*)-one

To a stirred solution (*S*)-3-bromo-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl) amino)-1-methyl-6-nitro-1,8-naphthyridin-2(1H)-one (4.0 g, 9.25 mmol) in THF (40 mL) was added LiOtBu (1M in THF) (13.8 mL). The reaction was stirred at 60 °C for 4 hours. The reaction mixture was diluted with water (100 mL) and extracted with DCM (2 x 200 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulphate, and concentrated under reduced pressure to obtain crude product which was triturated with petroleum ether (100 mL) and dried under vacuum to afford (*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-10-nitro-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-6(7*H*)-one (2.0 g) as a yellow solid.

LC-MS (ESI): m/z = 353.31 $[M+H]^+$

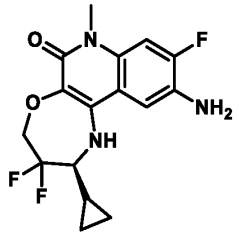
Preparation of (*S*)-10-amino-2-cyclopropyl-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-6(7*H*)-one

To a stirred solution of 3(*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-10-nitro-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-6(7*H*)-one (2.0 g, 5.68 mmol) in DMF (20 mL) were added 4,4'-dipyridyl (0.044 g, 0.28 mmol) and hypodiboric acid (1.52 g, 17.01 mmol) portion wise at 0 °C. The mixture was stirred at 0 °C for 10 minutes. The crude was diluted with water (50 mL), and the resulting solid was filtered off, washed with water (100 mL), n-pentane (100 mL), and dried under vacuum to afford (*S*)-10-amino-2-cyclopropyl-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-6(7*H*)-one (1.5 g) as a yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 (d, J = 2.00 Hz, 1H), 7.59 (d, J = 2.40 Hz, 1H), 6.21 (d, J = 2.40 Hz, 1H), 5.19 (s, 2H), 4.49-4.30 (m, 2H), 3.53 (s, 3H), 3.26-3.18 (m, 1H), 1.30 (t, J = 4.40 Hz, 1H), 0.71-0.68 (m, 1H), 0.52-0.49 (m, 2H), 0.34-0.32 (m, 1H).

LC-MS (ESI): m/z = 323.36 $[M+H]^+$

Example P49. (2*S*)-10-amino-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one



Preparation of 6-bromo-7-fluoro-1*H*-3,1-benzoxazine-2,4-dione

To a solution of 2-amino-5-bromo-4-fluoro-benzoic acid (90 g, 384.58 mmol, 1 *equiv.*) in THF (900 mL) was added bis (trichloromethyl) carbonate (39.94 g, 134.60 mmol, 0.35 *equiv.*) at 0 °C under N_2. The mixture was stirred at 70 °C for 2 hours. The reaction mixture was filtered and washed with THF. The filtrate was concentrated under reduced pressure to give 6-bromo-7-fluoro-1*H*-3,1-benzoxazine-2,4-dione (81.2 g) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.98 (s, 1H), 8.19 (d, J = 7.6 Hz, 1H), 7.03 (d, J = 9.2 Hz, 1H).

Preparation of 6-bromo-7-fluoro-1-methyl-3,1-benzoxazine-2,4-dione

To a solution of 6-bromo-7-fluoro-1*H*-3,1-benzoxazine-2,4-dione (81.2 g, 312.29

mmol, 1 *equiv.*) in dimethylacetamide (90 mL) was added iodomethane (132.98 g, 936.86 mmol, 58.32 mL, 3 *equiv.*) and DIPEA (80.72 g, 624.58 mmol, 108.79 mL, 2 *equiv.*). The mixture was stirred at 25 °C for 2 hours. The reaction mixture was diluted with H_2O (100 mL) and filtered to obtain 6-bromo-7-fluoro-1-methyl-3,1-benzoxazine-2,4-dione (80 g) as a white solid.

LC-MS (ESI): m/z = 273.9 $[M+H]^+$

Preparation of ethyl 6-bromo-7-fluoro-4-hydroxy-1-methyl-2-oxo-quinoline-3-carboxylate

A mixture of 6-bromo-7-fluoro-1-methyl-3,1-benzoxazine-2,4-dione (80 g, 291.92 mmol, 1 *equiv.*), diethyl propanedioate (140.27 g, 875.77 mmol, 132.96 mL, 3 *equiv.*), and NaH (23.35 g, 583.85 mmol, 60% purity, 2 *equiv.*) in DMF (1000 mL) was degassed and purged with N_2 three times. The mixture was stirred at 25 °C for 2 hours under N_2 atmosphere. The reaction mixture was diluted with saturated ammonium chloride (1500 mL), filtered, and concentrated under reduced pressure to give a residue, which was triturated with ethyl acetate at 25 °C for 30 minutes to obtain ethyl 6-bromo-7-fluoro-4-hydroxy-1-methyl-2-oxo-quinoline-3-carboxylate (37 g) as a white solid.

LC-MS (ESI): m/z = 343.9 $[M+H]^+$

Preparation of ethyl 6-bromo-4-chloro-7-fluoro-1-methyl-2-oxo-quinoline-3-carboxylate

To a solution of ethyl 6-bromo-7-fluoro-4-hydroxy-1-methyl-2-oxo-quinoline-3-carboxylate (15 g, 43.59 mmol, 1 *equiv.*) in DMF (150 mL) was added dropwise $(COCl)_2$ (16.60 g, 130.76 mmol, 11.45 mL, 3 *equiv.*). The mixture was stirred at 70 °C for 0.5 hours. The reaction mixture was quenched by H_2O (500 mL), filtered, and concentrated under reduced pressure to give a residue, which was triturated with petroleum ether at 25 °C for 10 minutes to obtain ethyl 6-bromo-4-chloro-7-fluoro-1-methyl-2-oxo-quinoline-3-carboxylate (11.2 g) as a white solid.

LC-MS (ESI): m/z = 362.0 $[M+H]^+$

Preparation of 6-bromo-4-[[(1*S*)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-7-fluoro-1-methyl-quinolin-2-one

Ethyl 6-bromo-4-chloro-7-fluoro-1-methyl-2-oxo-quinoline-3-carboxylate (700 mg,

1.93 mmol, 1 *equiv.*), (3*S*)-3-amino-3-cyclopropyl-2,2-difluoro-propan-1-ol (398.43 mg, 2.12 mmol, 1.1 *equiv.*, HCl) and DIPEA (748.56 mg, 5.79 mmol, 1.01 mL, 3 *equiv.*) were taken up into a microwave tube with NMP (15 mL). The sealed tube was heated at 200 °C for 2 hours in a microwave reactor. The reaction mixture was diluted with H_2O (120 mL) and extracted with ethyl acetate (360 mL). The combined organic layers were washed with brine (2400 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (60% ethyl acetate/petroleum ether) to afford 6-bromo-4-[[(1*S*)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-7-fluoro-1-methyl-quinolin-2-one as a yellow solid.

LC-MS (ESI): m/z = 404.9 $[M+H]^+$

Preparation of 3,6-dibromo-4-[[(1*S*)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-7-fluoro-1-methyl-quinolin-2-one

To a solution of 6-bromo-4-[[(1*S*)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-7-fluoro-1-methyl-quinolin-2-one (3.6 g, 8.47 mmol, 1 *equiv.*) in DMF (36 mL) was added NBS (1.36 g, 7.62 mmol, 0.9 *equiv.*) at 0 °C. The mixture was stirred at 0 °C for 20 minutes. The reaction mixture was diluted with H_2O (40 mL) and extracted with ethyl acetate (150 mL). The combined organic layers were washed with brine 150 mL (50 mL × 3), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography (25% ethyl acetate/petroleum ether) to afford 3,6-dibromo-4-[[(1*S*)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-7-fluoro-1-methyl-quinolin-2-one (2.7 g) as a yellow solid.

LC-MS (ESI): m/z = 484.9 $[M+H]^+$

Preparation of (2*S*)-10-bromo-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one

To a solution of 3,6-dibromo-4-[[(1*S*)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-7-fluoro-1-methyl-quinolin-2-one (2.7 g, 5.58 mmol, 1 *equiv.*) in THF (10 mL) was added t-BuOK (1 M, 2.79 mL, 0.5 *equiv.*). The mixture was stirred at 60 °C for 1 hour followed by the addition of t-BuOK (1 M, 2.79 mL, 0.5 *equiv.*). The resulting mixture was stirred at 60 °C for 0.1 hours. The reaction mixture was concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography (40% ethyl acetate/petroleum ether) to afford (2*S*)-10-bromo-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (2.2 g) as a white solid.

LC-MS (ESI): m/z = 402.9 $[M+H]^+$

Preparation of (2*S*)-10-(benzhydrylideneamino)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one

A mixture of (2*S*)-10-bromo-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (2.2 g, 5.46 mmol, 1 *equiv.*), diphenylmethanimine (1.19 g, 6.55 mmol, 1.10 mL, 1.2 *equiv.*), $Pd_2(dba)_3$ (499.66 mg, 545.64 μmol, 0.1 *equiv.*), XantPhos (631.44 mg, 1.09 mmol, 0.2 *equiv.*), and cesium carbonate (4.44 g, 13.64 mmol, 2.5 *equiv.*) in toluene (25 mL) was degassed and purged with N_2 three times. The mixture was stirred at 100 °C for 12 hours under N_2 atmosphere. The reaction mixture was diluted with H_2O (30 mL) and extracted with ethyl acetate (90 mL). The combined organic layers were washed with brine (90 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography (50% ethyl acetate/petroleum ether) to afford (2*S*)-10-(benzhydrylideneamino)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (2.07 g) as a yellow solid.

LC-MS (ESI): m/z = 504.1 $[M+H]^+$

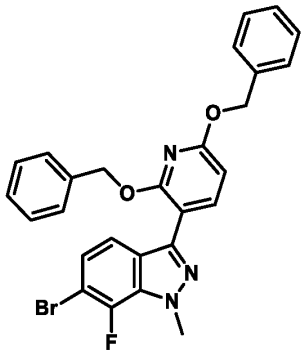
Preparation of (2*S*)-10-amino-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one

To a solution of (2*S*)-10-(benzhydrylideneamino)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (2.07 g, 4.12 mmol, 1 *equiv.*) in 1,4-dioxane (7 mL) was added HCl in 1,4-dioxane (14 mL). The mixture was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give a residue which was purified by prep-HPLC to afford (2*S*)-10-amino-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (931 mg) as a pink solid.

LC-MS (ESI): m/z = 340.1 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.40 - 7.27 (m, 1H), 7.25 - 7.15 (m, 1H), 6.04 (d, J = 3.2 Hz, 1H), 5.02 (s, 2H), 4.48 - 4.24 (m, 2H), 3.46 (s, 3H), 3.26 - 3.13 (m, 1H), 1.37 - 1.24 (m, 1H), 0.75 - 0.64 (m, 1H), 0.56 - 0.46 (m, 2H), 0.37 - 0.27 (m, 1H).

Example P50. 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-7-fluoro-1-methyl-1*H*-indazole



Preparation of 6-bromo-7-fluoro-1*H*-indazole

A solution of 4-bromo-2,3-difluorobenzaldehyde (25 g, 113.12 mmol), O-methylhydroxylamine (28.34 g, 339.36 mmol) and potassium carbonate (23.45 g, 169.68 mmol) in DCE (250 mL) was stirred at room temperature for 8 hours. To this solution was added hydrazine (125.0 mL) at 0 °C. The reaction mixture was heated at 100 °C for 40 hours. The reaction mixture was quenched with ice cold water (300 mL) and extracted with ethyl-acetate (500 mL). The separated organic layer was washed with brine solution (50 mL), dried over anhydrous sodium sulphate, filtered, and concentrated to get crude product which was purified by trituration with diethyl-ether (200 mL) to afford 6-bromo-7-fluoro-1*H*-indazole (16.0 g) as an off white solid.

LC-MS (ESI): m/z = 212.95 $[M-H]^-$

Preparation of 6-bromo-7-fluoro-3-iodo-1*H*-indazole

A solution of 6-bromo-7-fluoro-1*H*-indazole (16.0 g, 74.41 mmol) and potassium hydroxide (12.52 g, 223.23 mmol) in THF (160 mL) was stirred at room temperature for 1 hour. To this solution was added iodine (18.88 g, 74.41 mmol) at 0°C. The reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was quenched by ice-water (200 ml) and extracted with ethyl-acetate (500 ml). The organic layer was concentrated under reduced pressure to get crude product which was purified by trituration with diethyl-ether (200 mL) to get 6-bromo-7-fluoro-3-iodo-1*H*-indazole (20.0 g) as a brown solid.

LC-MS (ESI): m/z = 342.40 $[M+H]^+$

Preparation of 6-bromo-7-fluoro-3-iodo-1-methyl-1*H*-indazole

A solution of 6-bromo-7-fluoro-3-iodo-1*H*-indazole (20.0 g, 58.66 mmol) and t-BuOK (19.75 g, 175.99 mmol) in THF (200 mL) was stirred for 10 minutes at room temperature. To this solution was added iodomethane (8.32 g, 58.66 mmol) at 0°C. The reaction mixture was

stirred at room temperature for 3 hours. The reaction mixture was quenched by ice-water (200 ml) and extracted with ethyl-acetate (200 mL). The organic layer was concentrated under reduced pressure to get crude product which was purified by flash column chromatography (5-10 % ethyl-acetate in petroleum ether) to afford 6-bromo-7-fluoro-3-iodo-1-methyl-1*H*-indazole (9.0 g).

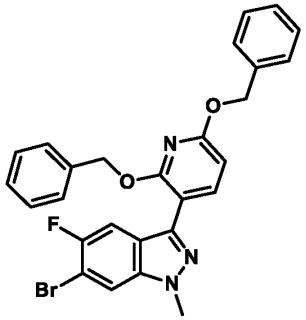
LC-MS (ESI): m/z = 354.84 $[M+H]^+$

Preparation of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-7-fluoro-1-methyl-1*H*-indazole

To a stirred solution of 6-bromo-7-fluoro-3-iodo-1-methyl-1*H*-indazole (5.0 g, 14.08 mmol), 2,6-bis(benzyloxy)pyridin-3-yl)boronic-acid (4.72 g, 14.08 mmol) and cesium carbonate (11.47 g, 35.21 mmol) in 1,4-dioxane (50 mL) under nitrogen gas was added XantPhos (1.63 g, 2.81 mmol) and $Pd_2(dba)_3$ (1.29 g, 1.40 mmol). The mixture was heated at 100 °C and stirred for 16 hours. The reaction mixture was filtered through a celite pad and the reaction mixture was quenched by ice-water (50 ml) and extracted with ethyl-acetate (200 mL). The organic layer was concentrated under reduced pressure to get crude product which was purified by flash column chromatography (0-20% ethyl-acetate in petroleum ether) to afford 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-7-fluoro-1-methyl-1*H*-indazole (3 g) as a white solid.

LC-MS (ESI): m/z = 520.36 $[M+H]^+$

Example P51. 6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazole



Preparation of (E)-1-(4-bromo-2,5-difluoro-phenyl)-N-methoxy-methanimine

To a solution of 4-bromo-2,5-difluoro-benzaldehyde (95 g, 429.87 mmol, 1 *equiv.*) in DME (950 mL) was added O-methylhydroxylamine (43.08 g, 515.84 mmol, 1.2 *equiv.*, HCl) and potassium carbonate (178.23 g, 1.29 mol, 3 *equiv.*). The reaction mixture was stirred at 45 °C for 2.5 hours. The reaction mixture was then filtered and concentrated under reduced

pressure to afford (E)-1-(4-bromo-2,5-difluoro-phenyl)-N-methoxy-methanimine (95 g) as a yellow oil.

LC-MS (ESI): m/z = 249.9 $[M+H]^+$

Preparation of 6-bromo-5-fluoro-1*H*-indazole

To a solution of (E)-1-(4-bromo-2,5-difluoro-phenyl)-N-methoxy-methanimine (90 g, 359.94 mmol, 1 *equiv.*) in DME (1000 mL) was added $NH_2NH_2.H_2O$ (90.09 g, 1.80 mol, 87.30 mL, 5 *equiv.*). The reaction mixture was stirred at 90 °C for 16 hours. To this mixture was added H_2O and extracted with ethyl acetate (1500 mL). The organic phase was washed with brine (500 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (petroleum ether/ethyl-acetate=1/0 to 5/1) to afford 6-bromo-5-fluoro-1*H*-indazole (8 g).

LC-MS (ESI): m/z = 250.0 $[M+H]^+$

Preparation of 6-bromo-5-fluoro-3-iodo-1*H*-indazole

To a solution of 6-bromo-5-fluoro-1*H*-indazole (7.6 g, 35.35 mmol, 1 *equiv.*) in dioxane (76 mL) and H_2O (19 mL) was added KOH (2.97 g, 53.02 mmol, 1.5 *equiv.*) and I_2 (13.46 g, 53.02 mmol, 10.68 mL, 1.5 *equiv.*) at 0 °C. The reaction mixture was stirred at 25 °C for 2 hours. To the mixture was added aqueous sodium sulfite (50 mL) and extracted with ethyl acetate (200 mL). The organic phase was washed with brine (100 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl-acetate=20/1 to 5/1) to afford 6-bromo-5-fluoro-3-iodo-1*H*-indazole (10 g) as a yellow solid.

LC-MS (ESI): m/z = 340.7 $[M+H]^+$

Preparation of 6-bromo-5-fluoro-3-iodo-1-methyl-indazole

To a solution of 6-bromo-5-fluoro-3-iodo-1*H*-indazole (10 g, 29.33 mmol, 1 *equiv.*) in DMF (100 mL) was added NaH (1.76 g, 44.00 mmol, 60% purity, 1.5 *equiv.*) at 0 °C. The reaction mixture was stirred at 0°C for 0.5 hours. To this mixture was added iodomethane (8.33 g, 58.67 mmol, 3.65 mL, 2 *equiv.*). The reaction mixture was stirred at 25 °C for 1 hour. To this mixture was added aqueous ammonium chloride (50 mL) and then extracted with ethyl acetate (200 mL). The organic phase was washed with brine (150 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue which was purified by column chromatography (petroleum ether/ethyl-acetate=1/0 to 5/1) to afford 6-bromo-5-

fluoro-3-iodo-1-methyl-indazole (6 g) as a yellow solid.

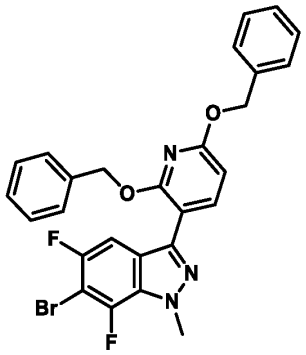
LC-MS (ESI): m/z = 356.6 $[M+H]^+$

Preparation of 6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazole

A mixture of 6-bromo-5-fluoro-3-iodo-1-methyl-indazole (6 g, 16.90 mmol, 1 *equiv.*), 2,6-dibenzyloxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (7.05 g, 16.90 mmol, 1 *equiv.*), $Pd(dppf)Cl_2$ (1.24 g, 1.69 mmol, 0.1 *equiv.*), and cesium carbonate (11.02 g, 33.81 mmol, 2 *equiv.*) in dioxane (100 mL) and H_2O (30 mL) was degassed and purged with N_2 three times. The mixture was stirred at 90 °C for 16 hours under N_2 atmosphere. To this mixture was added H_2O (20 mL) and extracted with ethyl acetate (200 mL). The organic phase was washed with brine (150 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether: ethyl acetate =1:0 to 20:1) to afford 6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazole (6.3 g) as a yellow solid.

LC-MS (ESI): m/z = 519.9 $[M+H]^+$

Example P52. 6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazole



Preparation of 3-bromo-2,4-difluoro-6-iodo-aniline

To a solution of 3-bromo-2,4-difluoro-aniline (250 g, 1.20 mol, 1 *equiv.*) in EtOH (2500 mL) was added Ag_2SO_4 (374.75 g, 1.20 mol, 203.67 mL, 1 *equiv.*) and I_2 (335.56 g, 1.32 mol, 266.32 mL, 1.1 *equiv.*). The reaction mixture was stirred at 25 °C for 2.5 hours. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 1/0 to 10/1) to afford 3-bromo-2,4-difluoro-6-iodo-aniline (290 g) as a red oil.

LC-MS (ESI): m/z = 333.8 $[M+H]^+$

Preparation of 3-bromo-2,4-difluoro-6-methyl-aniline

A mixture of 3-bromo-2,4-difluoro-6-iodo-aniline (30 g, 89.85 mmol, 1 *equiv.*), 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (33.84 g, 134.77 mmol, 37.68 mL, 1.5 *equiv.*), $PdCl_2$(dtbpf) (4.10 g, 6.29 mmol, 0.07 *equiv.*), and potassium phosphate (1.5 M in water, 179.69 mL, 3 *equiv.*) in dioxane (300 mL) was degassed and purged with N_2 three times. The resulting mixture was stirred at 100 °C for 5 hours under N_2 atmosphere. The reaction mixture was diluted with H_2O (300 mL) and extracted with ethyl acetate (900 mL). The combined organic layers were washed with brine (900 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by reverse-phase HPLC to afford 3-bromo-2,4-difluoro-6-methyl-aniline (5.4 g) as a yellow solid.

LC-MS (ESI): m/z = 221.9 $[M+H]^+$

Preparation of (*E*)-1-(3-bromo-2,4-difluoro-6-methylphenyl)-2-(*tert*-butylthio)diazene

To a solution of 3-bromo-2,4-difluoro-6-methyl-aniline (18 g, 81.07 mmol, 1 *equiv.*) in HCl (8 M, 179.98 mL, 17.76 *equiv.*) was added dropwise sodium nitrite (6.15 g, 89.18 mmol, 1.1 *equiv.*) in H_2O (20 mL) at 0 °C. After addition, the resulting mixture was stirred at 0 °C for 0.5 hours. To this mixture, 2-methylpropane-2-thiol (8.04 g, 89.18 mmol, 10.04 mL, 1.1 *equiv.*) in EtOH (40 mL) was added dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 1 hour. The reaction mixture was diluted with H_2O (200 mL) and extracted with ethyl acetate (600 mL). The combined organic layers were washed with brine (900 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (0% ethyl acetate/petroleum ether) to afford (*E*)-1-(3-bromo-2,4-difluoro-6-methylphenyl)-2-(*tert*-butylthio)diazene (14 g) as a yellow solid.

LC-MS (ESI): m/z = 323.0 $[M+H]^+$

Preparation of 6-bromo-5,7-difluoro-1*H*-indazole

To a solution of (*E*)-1-(3-bromo-2,4-difluoro-6-methylphenyl)-2-(*tert*-butylthio)diazene (42.11 g, 130.29 mmol, 1 *equiv.*) in THF (420 mL) was added *t*-BuOK (1 M, 130.29 mL, 1 *equiv.*). The mixture was stirred at 25 °C for 0.5 hours. The reaction mixture was diluted with H_2O (500 mL), and the mixture was acidified using formic acid to pH = 2~3. The reaction mixture was extracted with ethyl acetate (1500 mL). The combined organic layers

were washed with brine (1500 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (5-10% ethyl acetate/petroleum ether) to afford 6-bromo-5,7-difluoro-1*H*-indazole (15.3 g) as a white solid.

LC-MS (ESI): m/z = 232.9 $[M+H]^+$

Preparation of 6-bromo-5,7-difluoro-3-iodo-1*H*-indazole

To a solution of 6-bromo-5,7-difluoro-1*H*-indazole (15.3 g, 65.66 mmol, 1 *equiv.*) in DMF (153 mL) was added KOH (5.53 g, 98.49 mmol, 1.5 *equiv.*) and I_2 (25.00 g, 98.49 mmol, 19.84 mL, 1.5 *equiv.*). The mixture was stirred at 25 °C for 0.5 hours. The mixture was used in the next step without further work up as crude 6-bromo-5,7-difluoro-3-iodo-1*H*-indazole (23.5 g).

Preparation of 6-bromo-5,7-difluoro-3-iodo-1-methyl-indazole

To a stirred solution of 6-bromo-5,7-difluoro-3-iodo-1*H*-indazole (23.5 g, 65.48 mmol, 1 *equiv.*) was added iodomethane (27.88 g, 196.43 mmol, 12.23 mL, 3 *equiv.*). The mixture was stirred at 25 °C for 2 hours. The reaction mixture was diluted with H_2O (200 mL) and extracted with ethyl acetate (600 mL). The combined organic layers were washed with brine (900 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (0~5% ethyl acetate/petroleum ether) to afford 6-bromo-5,7-difluoro-3-iodo-1-methyl-indazole (3.8 g) as a black solid.

LC-MS (ESI): m/z = 372.8 $[M+H]^+$

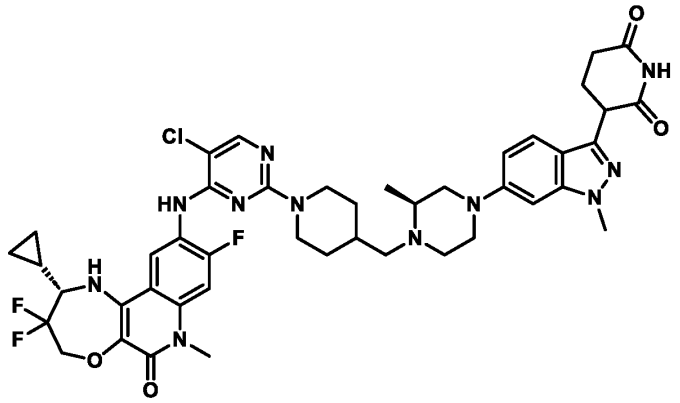
Preparation of 6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazole

A mixture of 6-bromo-5,7-difluoro-3-iodo-1-methyl-indazole (9.5 g, 25.47 mmol, 1 *equiv.*), 2,6-dibenzyloxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (9.57 g, 22.93 mmol, 0.9 *equiv.*), $Pd(dppf)Cl_2$ (1.86 g, 2.55 mmol, 0.1 *equiv.*), and cesium carbonate (20.75 g, 63.68 mmol, 2.5 *equiv.*) in 1,4 dioxane (30 mL) and H_2O (10 mL) was degassed and purged with N_2 three times. The mixture was stirred at 100 °C for 1 hour under N_2 atmosphere. The reaction mixture was diluted with H_2O (20 mL) and extracted with ethyl acetate (90 mL). The combined organic layers were washed with brine (90 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by flash

silica gel chromatography (5% ethyl acetate/petroleum ether) to afford 6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazole (6.3 g) as a white solid.

LC-MS (ESI): m/z = 536.0 $[M+H]^+$

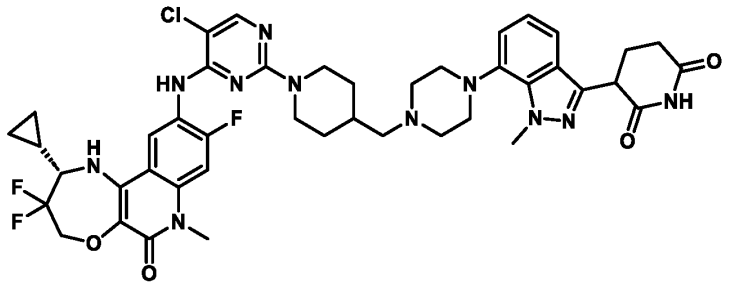
Example 1. 3-[6-[(3*S*)-4-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-3-methyl-piperazin-1-yl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (Compound 102a)



To a solution of (2*S*)-2-cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (See Table P31) (100 mg, 205.65 μmol, 1 *equiv.*) and 3-[1-methyl-6-[(3*S*)-3-methyl-4-(4-piperidylmethyl)piperazin-1-yl]indazol-3-yl]piperidine-2,6-dione (See Table P12) (124.85 mg, 246.77 μmol, 1.2 *equiv.*) in DMSO (1 mL) was added TEA (114.49 μL, 822.58 μmol, 4 *equiv.*). The mixture was stirred at 100 °C for 1 hour. The reaction mixture was filtered to give a residue which was purified by prep-HPLC to afford 3-[6-[(3*S*)-4-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-3-methyl-piperazin-1-yl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (52.78 mg) as an off-white solid.

LC-MS (ESI): m/z = 445.0 $[M+H]^+$

Example 2. 3-[7-[4-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]piperazin-1-yl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (Compound 156a)

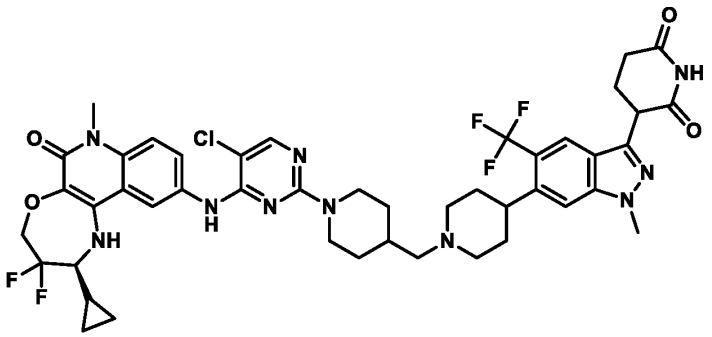


To a solution of 3-[1-methyl-7-[4-(4-piperidylmethyl)piperazin-1-yl]indazol-3-yl]piperidine-2,6-dione (See Table P6) (103.67 mg, 244.20 μmol, 1 *equiv.*) and (2*S*)-2-cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (See Table P31) (95 mg, 195.36 μmol, 0.8 *equiv.*) in DMSO (1 mL) was added TEA (135.96 μL, 976.82 μmol, 4 *equiv.*). The mixture was stirred at 100 °C for 6 hours. The reaction mixture was diluted with H_2O (6 mL) and extracted with ethyl acetate (9 mL). The combined organic layers were washed with aqueous sodium chloride (30 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue which was purified by prep-HPLC to afford 3-[7-[4-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]piperazin-1-yl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (40.93 mg) as a red solid.

LC-MS (ESI): m/z = 874.4 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.87 (s, 1H), 8.81 (s, 1H), 8.19 (d, J = 8.0 Hz, 1H), 8.13 (s, 1H), 8.01 (s, 1H), 7.45 - 7.35(m, 2H), 7.06 - 6.96 (m, 2H), 6.44 (s, 1H), 4.51 - 4.38 (m, 2H), 4.37 - 4.27 (m, 3H), 4.23 (s, 3H), 3.55 (s, 3H), 3.28 - 3.00 (m,3H), 2.99 - 2.77 (m, 3H), 2.75 - 2.55 (m, 5H), 2.38 - 2.27 (m, 2H), 2.25 - 2.12 (m, 3H), 1.82 - 1.62 (m, 3H), 1.37 - 1.21 (m, 1H),0.96 (q, J = 10.4 Hz, 2H), 0.75 - 0.65 (m, 1H), 0.51 (t, J = 6.0 Hz, 2H), 0.37 - 0.27 (m, 1H)

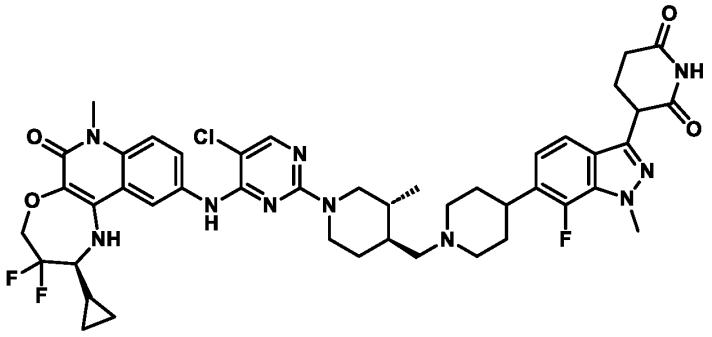
Example 3. 3-(6-(1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-5-(trifluoromethyl)-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 106a)



To a solution of 3-[1-methyl-6-[1-(4-piperidylmethyl)-4-piperidyl]-5-(trifluoromethyl)indazol-3-yl]piperidine-2,6-dione (See Table P6) (150 mg, 305.16 μmol, 1 *equiv.*) in DMSO (5 mL) was added TEA (169.90 μL, 1.22 mmol, 4 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (prepared using published methods, e.g., in International Application Publication Nos. WO 2019/197842 or WO 2021/074620) (142.90 mg, 305.16 μmol, 1 *equiv.*). The mixture was stirred at 100 °C for 1 hour. The reaction mixture was filtered to give a residue which was purified by prep-HPLC to afford 3-(6-(1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-5-(trifluoromethyl)-1*H*-indazol-3-yl)piperidine-2,6-dione (126.84 mg) as a white solid.

LC-MS (ESI): m/z = 923.3 $[M+H]^+$

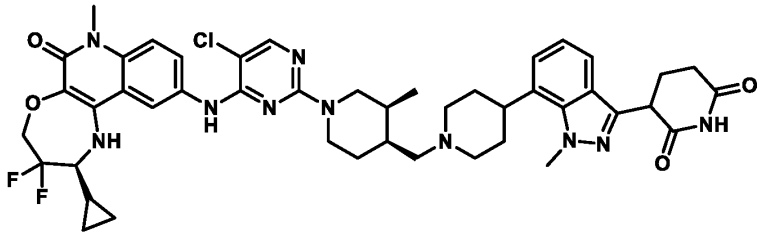
Example 4. 3-(6-(1-(((3*R*,4*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 130e)



A mixture of 3-(7-fluoro-1-methyl-6-(1-(((3*R*,4*S*)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (See Table P6) (430 mg, 943.88 μmol, 1.0 equiv.), (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (574.60 mg, 1.23 mmol, 1.3 equiv.), and TEA (525.50 μL, 3.78 mmol, 4.0 equiv.) in DMSO (3 mL) was stirred at 100 °C for 3 hours. The reaction mixture was concentrated under reduced pressure to give a residue which was purified by prep-HPLC to give 3-(6-(1-(((3*R*,4*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (120.8 mg) as a yellow solid.

LC-MS (ESI): m/z = 887.3 $[M+H]^+$

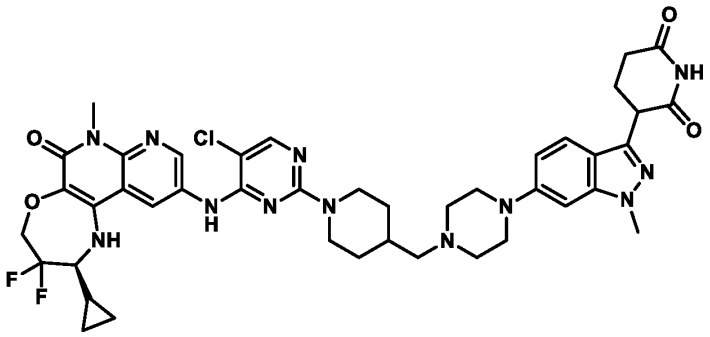
Example 5. 3-[7-[1-[[(3S,4S)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (Compound 101c)



To a solution of 3-[1-methyl-7-[1-[[(3S,4S)-3-methyl-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione (See Table P6) (100 mg, 210.95 μmol, 1 *equiv.* HCl) in DMSO (1 mL) was added TEA (117.45 μL, 843.82 μmol, 4 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (118.54 mg, 253.14 μmol, 1.2 *equiv.*). The mixture was stirred at 100 °C for 1 hour. The reaction mixture was filtered to give a residue which was purified by prep-HPLC to afford 3-[7-[1-[[(3S,4S)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (50.71 mg) as a pink solid.

LC-MS (ESI): m/z = 869.5 $[M+H]^+$

Example 6. 3-(6-(4-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 164a)



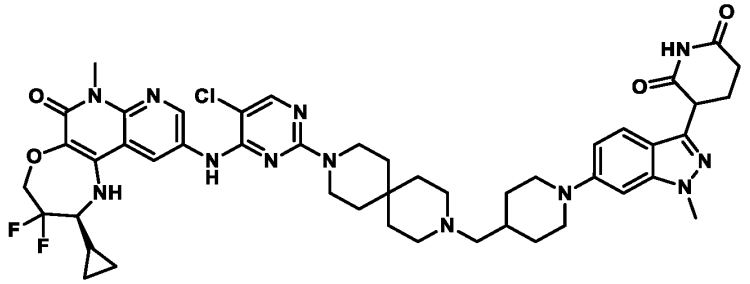
To a stirred solution of (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-6(7*H*)-one (See Table P31) (0.1 g, 0.21 mmol, 1 *equiv.*) in DMSO (1.0 mL) was added 3-(1-methyl-6-(4-(piperidin-4-ylmethyl)piperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (See Table P6) (0.27 g, 0.63 mmol, 1 *equiv.*) and DIPEA (0.18 mL, 1.06 mmol, 1 *equiv.*). The mixture was stirred at 120 °C for 2 hours in a microwave reactor. The reaction mixture was quenched with ice-cold water, and the solid was filtered to get crude product which was purified by prep-HPLC to afford 3-(6-(4-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.059 g) as an off-white solid.

LC-MS (ESI): m/z = 857.50 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.84 (s, 1H), 9.35 (br s, 1H), 9.31 (s, 1H), 8.66 (dd, J = 2.40, 19.00Hz, 2H), 8.18 (s, 1H), 7.50 (d, J = 9.20Hz, 1H), 6.93 (d, J = 8.80Hz, 1H), 6.86 (s, 1H), 6.46 (s, 1H), 4.47-4.38 (m, 4H), 4.27-4.24 (m, 1H), 3.89 (s, 3H), 3.82-3.77 (m, 2H), 3.62 (s, 3H), 3.53-3.51 (m, 1H), 3.26-3.23 (m, 3H), 3.05-3.00 (m, 4H), 2.79-2.76 (m, 2H), 2.63-2.60 (m, 2H), 2.31-2.29 (m, 1H), 2.20-2.16 (m, 1H), 2.00 (br s, 1H), 1.86-1.83 (m, 2H), 1.40-130 (m, 4H), 0.73-0.70 (m, 1H), 0.58-0.51 (m, 2H), 0.36-0.34 (m, 1H).

Example 7. 3-(6-(4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-10-

yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)piperidin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 144a)



Preparation of *tert*-butyl 9-((1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate

To a stirred solution of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-1-methyl-1*H*-indazole (1.0 g, 2.0 mmol) and *tert*-butyl 9-(piperidin-4-ylmethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (1.40 g, 4.0 mmol, prepared using published methods, *e.g.*, International Application No. WO 2022/228547) in 1,4-dioxane (20 mL), cesium carbonate (1.95 g, 6.0 mmol) was added. The reaction was degassed with argon for 10 minutes. t-BuONa (0.09 g, 0.20 mmol) and RuPhos-Pd G3 (0.08 g, 0.10 mmol) were added. The resulting reaction was degassed for 5 minutes. The reaction mixture was stirred at 80 °C for 3 hours. The reaction mixture was cooled to room temperature and filtered through celite. The filtrate was concentrated to isolate a crude product. The crude product was purified by flash column chromatography (30% ethyl acetate in petroleum ether) to afford *tert*-butyl 9-((1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (0.7 g) as an off-white solid.

LC-MS (ESI): m/z = 771.83 $[M+H]^+$

Preparation of *tert*-butyl 9-((1-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate

To a stirred solution of *tert*-butyl 9-((1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (0.7 g, 0.90 mmol) in THF (28 mL), $Pd(OH)_2$ on carbon (0.7 g, 20 wt%) was added at room temperature. The reaction was put under hydrogen pressure (60 psi) and stirred for 8 hours at room temperature. The reaction mixture was filtered through celite. The celite was washed with ethyl acetate and concentrated under reduced pressure to isolate a crude product. The crude product was washed with n-pentane and dried to afford *tert*-butyl 9-((1-(3-(2,6-dioxopiperidin-

3-yl)-1-methyl-1*H*-indazol-6-yl)piperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (0.60 g) as a brown solid.

LC-MS (ESI): m/z = 593.67 $[M+H]^+$

Preparation of 3-(6-(4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)piperidin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

A stirred solution of *tert*-butyl 9-((1-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (0.6 g, 1.01 mmol) in DCM (12 mL) was cooled to 0 °C. TFA (6 mL) was added and the reaction mixture was warmed and stirred room temperature over 3 hours. The reaction mixture was concentrated under reduced pressure to isolate a crude product. The crude product was triturated with diethyl ether (20 mL) to afford 3-(6-(4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)piperidin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.44 g) as a brown solid.

LC-MS (ESI): m/z = 493.37 $[M+H]^+$

Preparation of 3-(6-(4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)piperidin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

To a stirred solution (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-6(7*H*)-one (See Table P31) (0.07 g, 0.15 mmol, 1 *equiv.*) in DMSO (1.5 mL) was added 3-(6-(4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)piperidin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.15 g, 0.30 mmol, 1 *equiv.*) and DIPEA (0.19 mL, 1.5 mmol, 1 *equiv.*). The mixture was stirred at 120 °C for 3 hours in a microwave reactor. The reaction mixture was quenched with ice-cold water, and the solid was filtered to get crude product which was purified by prep HPLC to get 3-(6-(4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)piperidin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.049 g) as an off-white solid.

LC-MS (ESI): m/z = 925.54 $[M+H]^+$.

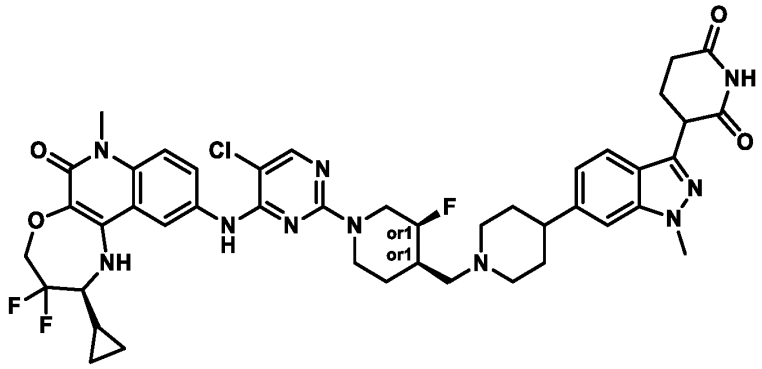
^{1}H NMR (400 MHz, DMSO-d_6): δ 10.84 (s, 1H), 9.14 (s, 1H), 8.79 (br s, 1H), 8.67 (d, J = 12.0Hz, 2H), 8.08 (s, 1H), 7.51 (d, J = 8.80Hz, 1H), 6.93(d, J = 9.20Hz, 1H), 6.87 (s, 1H), 6.46 (s, 1H), 4.51-4.46 (m, 2H), 4.27-4.24 (m, 1H), 3.89-3.80 (m, 5H), 3.62-3.50 (m, 5H), 3.37-

3.34 (m, 3H), 3.03-3.01 (m, 4H), 2.79 (t, J = 12.0Hz, 2H), 2.61 (t, J = 6.0Hz, 3H), 2.30-2.29 (m, 1H), 2.19-2.16 (m, 1H), 2.00 (br s, 1H), 1.84-1.78 (m, 4H), 1.61-1.55 (m, 4H), 1.37-1.87 (m, 6H), 0.72-0.71 (m, 1H), 0.52 (t, J = 6.0Hz, 2H), 0.35-0.34 (m, 1H).

Example 8. 3-(6-(1-(((3*S*,4*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

[3-(6-(1-(((3*S,4*R**)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]**

(Compound 110c)



To a stirred solution of 3-(6-(1-(((3*S*,4*R*)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (See Table P6) (0.20 g, 0.45 mmol, 1 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.085 g, 0.18 mmol, 1 *equiv.*) in DMSO (2.0 mL) was added DIPEA (2.0 mL). The mixture was stirred at 100 °C for 6 hours. The reaction mixture was cooled to room temperature and was added ice water. The precipitated solid was filtered and dried to obtain crude product which was purified by prep HPLC to afford 3-(6-(1-(((3*S*,4*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-(1-(((3*S**,4*R**)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-

fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (0.016 g) as an off white solid.

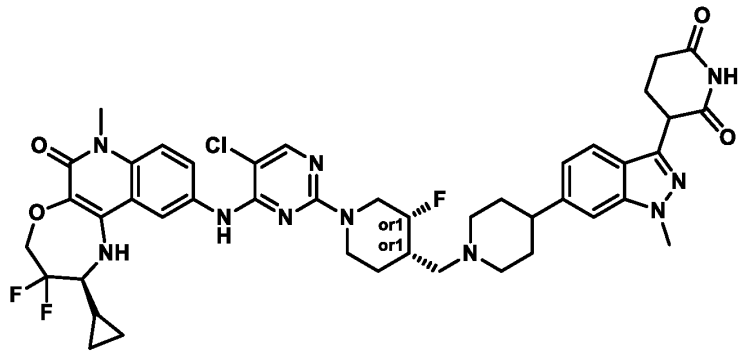
LC-MS (ESI): m/z = 873.52 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.87 (s, 1H), 8.8 (s, 1H), 8.18 (s, 2H), 8.03 (s, 1H), 7.7 (d, *J* = 8.4 Hz, 1H), 7.6 (d, *J* = 8.4 Hz, 1H), 7.48-7.40 (m, 2H), 7.03 (d, *J* = 8.4 Hz, 1H), 6.15 (br s, 1H), 4.92-4.75 (m, 2H), 4.55-4.3 (m, 4H), 3.95 (s, 3H), 3.55 (s, 3H), 3.10-2.92 (m, 3H), 2.85-2.75 (m, 1H), 2.70-2.60 (m, 3H), 2.41-2.30 (m, 2H), 2.21-2.15 (m, 2H), 2.15-2.0 (m, 3H), 1.85-1.65 (br s, 4H), 1.60-1.51 (m, 1H),1.40-1.30 (m, 2H), 0.75-0.65 (m, 1H), 0.61-0.50 (m, 2H), 0.41-0.32 (m, 1H)

Example 9. 3-(6-(1-(((3*R*,4*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

[3-(6-(1-(((3*R,4*S**)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]**

(Compound 110e)



To a stirred solution of 3-(6-(1-(((3*R*,4*S*)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (See Table P6) (0.13 g, 0.29 mmol, 1 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.054 g, 0.11 mmol, 1 *equiv.*) in DMSO (2.0 mL) was added DIPEA (2.0 mL). The mixture was stirred at 100 °C for 6 hours. The reaction mixture was cooled to room temperature and added to ice water. The precipitated solid was filtered and dried to obtain crude product which was purified by perp HPLC to afford

3-(6-(1-(((3*R*,4*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.008 g) as an off white solid.

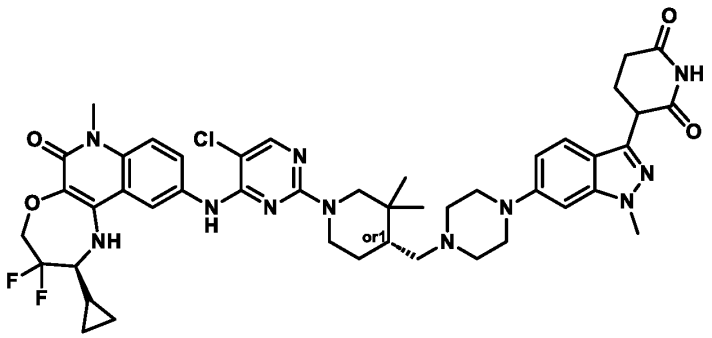
LC-MS (ESI): m/z = 873.52 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.87 (s, 1H), 8.8 (s, 1H), 8.16 (s, 1H), 8.03 (s, 1H), 7.7 (d, *J* = 8.4 Hz, 1H), 7.6 (d, *J* = 8.4 Hz, 1H), 7.47-7.42 (m, 2H), 7.03 (d, *J* = 8.4 Hz, 1H), 6.15 (br s, 1H), 4.92-4.75 (m, 2H), 4.44 - 4.39 (m, 1H), 4.55-4.31 (m, 3H), 3.95 (s, 3H), 3.55 (s, 3H), 3.2-3.14 (m, 1H), 2.85-2.75 (m, 5H), 2.70-2.60 (m, 3H), 2.41-2.30 (m, 1H), 2.21-2.15 (m, 2H), 2.15-2.0-1.95 (m, 3H), 1.85-1.65(br s, 4H), 1.60-1.51 (m, 1H),1.40-1.30 (m, 2H), 0.75-0.65 (m, 1H), 0.61-0.50 (m, 2H), 0.41-0.33 (m, 1H).

Example 10. 3-(6-(4-(((*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

[3-(6-(4-(((*R)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]**

(Compound 131b)



To a stirred solution of 3-(6-(4-(((*R*)-3,3-dimethylpiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (See Table P6) (0.12 g, 0.26 mmol, 1 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.045 g, 0.10 mmol, 1 *equiv.*) in DMSO (2.5 mL) was added DIPEA (0.4 mL, 2.60 mmol, 1 *equiv.*). The resulting reaction

mixture was stirred at 110 °C for 6 hours. The reaction mixture was poured into ice cold water (20 mL) and the precipitated solid was filtered and dried to get crude product which was purified by prep-HPLC to afford 3-(6-(4-(((*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-(4-(((*R**)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (0.008 g) as an off-white solid.

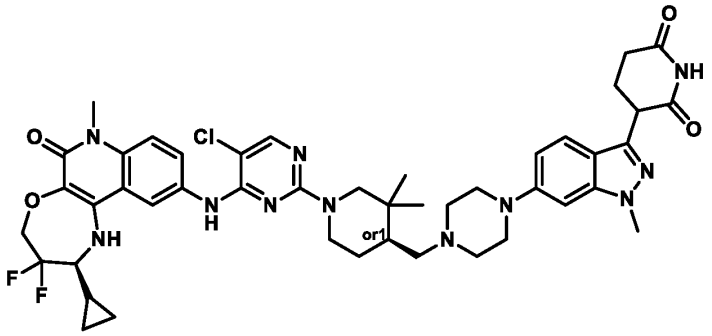
LC-MS (ESI): m/z = 884.45 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.90 (s, 1H), 8.74 (s, 1H), 8.15 (s, 1H), 8.00 (s, 1H), 7.76 (d, *J* = 8.80 Hz, 1H), 7.47 (q, *J* = 9.20 Hz, 2H), 6.91 (d, *J* = 9.20 Hz, 1H), 6.83 (s, 1H), 6.18 (s, 1H), 4.50-4.30 (m, 3H), 4.25-4.24 (m, 1H), 4.15 (brs, 1H), 3.89 (s, 3H), 3.56 (s, 3H), 3.20 (brs, 4H), 2.74-2.50 (m, 5H), 2.50-2.42 (m, 2H), 2.30-2.20 (m, 2H), 2.20-2.00 (m, 3H), 1.76 (d, *J* = 4.00 Hz 1H), 1.51 (s, 1H), 1.41-1.21 (m, 3H), 0.92 (s, 3H), 0.70 (s, 4H), 0.51 (t, *J* = 5.20 Hz, 2H), 0.35 (d, *J* = 4.80 Hz, 1H).

Example 11. 3-(6-(4-(((*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

[3-(6-(4-(((*S)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]**

(Compound 131a)



To a stirred solution of 3-(6-(4-(((*S*)-3,3-dimethylpiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (See Table P6) (0.11 g, 0.24 mmol, 1 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.045 g, 0.09 mmol, 1 *equiv.*) in DMSO (2.5 mL) was added DIPEA (0.4 mL, 2.40 mmol, 1 *equiv.*). The resulting reaction mixture was stirred at 110 °C for 6 hours. The reaction mixture was poured into ice cold water (20 mL) and the solid precipitated was filtered and dried to get crude product which was purified by Prep-HPLC to afford 3-(6-(4-(((*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-(4-(((*S**)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (0.011 g) as an off-white solid.

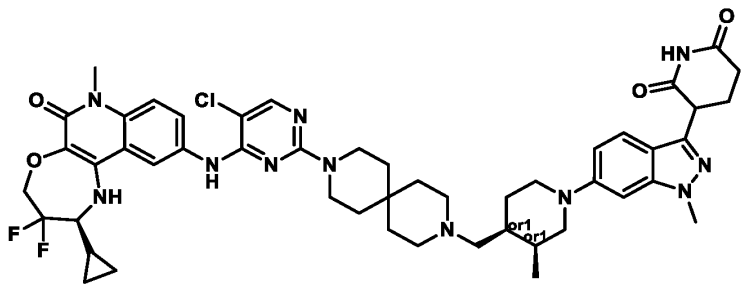
LC-MS (ESI): m/z = 884.94 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.90 (s, 1H), 8.75 (s, 1H), 8.15 (s, 1H), 8.00 (s, 3H), 7.75 (dd, *J* = 1.60, 9.00 Hz, 1H), 7.47 (q, *J* = 9.20 Hz, 2H), 6.91 (d, *J* = 8.80 Hz, 1H), 6.83 (s, 1H), 6.16 (s, 1H), 4.50-4.30 (m, 3H), 4.25-4.24 (m, 1H), 4.15 (brs, 1H), 3.89 (s, 3H), 3.56 (s, 3H), 3.25 (brs, 4 H), 2.80-2.51 (s, 4H), 2.50-2.40 (m, 2H), 2.45-2.30 (m, 2H), 2.20-2.0 (m, 2H), 1.76 (d, *J* = 4.00 Hz 1H), 1.53 (brs, 1H), 1.32-1.24 (m, 3H), 0.93 (s, 3H), 0.70 (s, 4H), 0.52 (t, *J* = 5.60 Hz, 2H), 0.35 (d, *J* = 5.20 Hz, 1H).

Example 12. 3-(6-((3S,4S)-4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

[3-(6-((3S*,4S*)-4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]

(Compound 104a)



To a stirred solution of 3-(6-((3S,4S)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (See Table P6) (0.55 g, 1.09 mmol, 1 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.20 g, 0.43 mmol, 1 *equiv.*) in DMSO (6.0 mL) was added DIPEA (1.5 mL, 8.70 mmol, 1 *equiv.*). The mixture was heated to 100 °C for 10 hours. The reaction mixture was poured into ice cold water (100 mL) and the precipitated solid was filtered and dried under vacuum to afford crude product which was purified by Prep-HPLC to afford 3-(6-((3S,4S)-4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-((3S*,4S*)-4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (0.99 g) as an off-white solid.

LC-MS (ESI): m/z = 938.57 $[M+H]^+$.

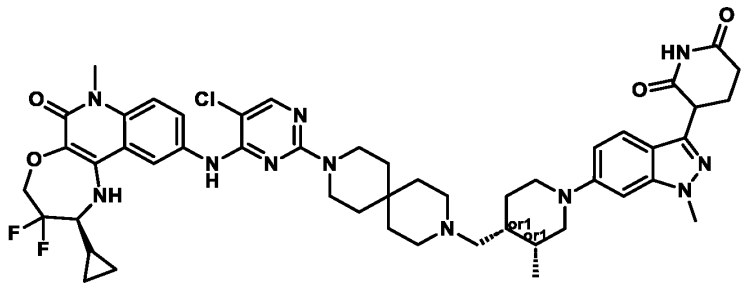
^{1}H NMR (400 MHz, DMSO-d_6): δ 10.84 (s, 1H), 8.76 (s, 1H), 8.19 (d, *J* = 2.00 Hz, 1H), 8.02 (s, 1H), 7.72 (dd, *J* = 2.00, 9.20 Hz, 1H), 7.45-7.43 (m, 2H), 6.87 (d, *J* = 9.20 Hz, 1H), 6.79 (s, 1H), 6.18 (br, 1H), 4.45-4.41 (m, 2H), 4.26-4.25 (m, 1H), 3.87 (s, 3H), 3.57-3.50 (m, 9H), 3.25-3.23 (m, 1H), 2.88 (d, *J* = 9.60 Hz, 1H), 2.63-2.61 (m, 1H), 2.60-2.51 (m, 2H), 2.50-2.33 (m, 5H), 2.33-2.32 (m, 3H), 1.97-1.96 (m, 1H), 1.82-1.75 (m, 1H), 1.54-1.31 (m, 11H), 0.93 (d, *J* = 6.80 Hz, 3H), 0.79-0.69 (m, 1H), 0.53-0.50 (m, 2H), 0.35-0.34 (m, 1H).

Example 13. 3-(6-((3*R*,4*R*)-4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-

yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

[3-(6-((3*R,4*R**)-4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]**

(Compound 104b)



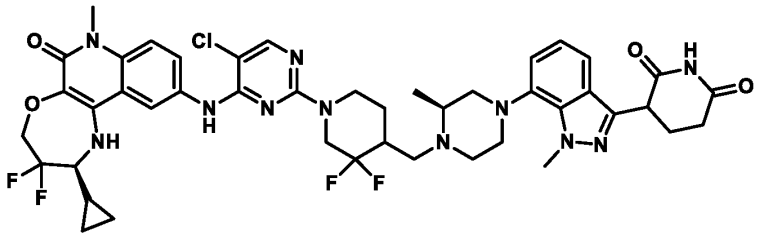
To a stirred solution of 3-(6-((3*R*,4*R*)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (See Table P6) (0.66 g, 1.30 mmol, 1 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.24 g, 0.52 mmol, 1 *equiv.*) in DMSO (6 mL) was added DIPEA (1.8 mL, 10.4 mmol, 1 *equiv.*). The reaction mixture was heated at 100 °C and stirred for 10 hours. The reaction mixture was poured into ice cold water (300 mL) and the precipitated solid was filtered and dried under vacuum to afford crude product which was purified by reverse phase column chromatography to afford 3-(6-((3*R*,4*R*)-4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-((3*R**,4*R**)-4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (0.15 g) as an off-white solid.

LC-MS (ESI): m/z = 938.90 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.84 (s, 1H), 8.77 (s, 1H), 8.19 (d, *J* = 1.60 Hz, 1H), 8.02 (s, 1H), 7.72 (dd, *J* = 2.00, 9.20 Hz, 1H), 7.45 (t, *J* = 8.80 Hz, 2H), 6.87 (d, *J* = 9.20 Hz, 1H), 6.79 (s, 1H), 6.19 (br, 1H), 4.46-4.41 (m, 2H), 4.23-4.22 (m, 1H), 3.88 (s, 3H), 3.75-

3.55 (m, 8H), 3.53-3.50 (m, 1H), 3.21-3.19 (m, 1H), 2.88 (d, *J* = 9.60 Hz, 1H), 2.79-2.70 (m, 1H), 2.61-2.60 (m, 2H), 2.48-2.38 (m, 4H), 2.35-2.12 (m, 4H), 2.18-2.16 (m, 1H), 1.90-1.80 (m, 1H), 1.55-1.54 (m, 6H), 1.47-1.31 (m, 5H), 0.94 (d, *J* = 6.80 Hz, 3H), 0.75-0.65 (m, 1H), 0.53-0.50 (m, 2H), 0.35-0.34 (m, 1H).

Example 14. 3-(7-((3*S*)-4-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-difluoropiperidin-4-yl)methyl)-3-methylpiperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 134a)

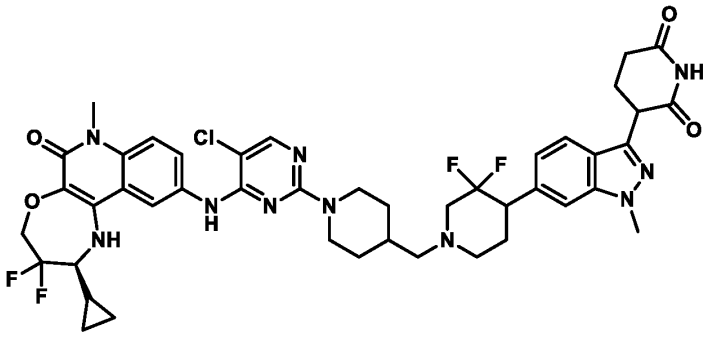


To a stirred solution of 3-(7-((3*S*)-4-((3,3-difluoropiperidin-4-yl)methyl)-3-methylpiperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (See Table P6) (0.2 g, 0.42 mmol, 1 *equiv.*) in dry DMSO (1.0 mL) at room temperature were added DIPEA (1.0 mL) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.098 g, 0.21 mmol, 1 *equiv.*). The mixture was heated at 120 °C and stirred for 4 hours. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure to obtain crude product which was purified by prep HPLC to afford 3-(7-((3*S*)-4-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-difluoropiperidin-4-yl)methyl)-3-methylpiperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.045 g) as off white solid.

LC-MS (ESI): m/z = 906.46, $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.88 (s, 1H), 8.93 (d, *J* = 3.20 Hz, 1H), 8.18 (d, *J* = 5.20 Hz, 1H), 8.07 (d, *J* = 2.80 Hz, 1H), 7.71 (dd, *J* = 1.60, 11.60 Hz, 1H), 7.43 (dd, *J* = 2.00, 14.60 Hz, 2H), 7.03-7.01 (m, 2H), 6.25 (s, 1H), 4.65 (br s, 1H), 4.34-4.31 (m, 4H), 4.24 (s, 3H), 3.57 (s, 3H), 3.02-2.98 (m, 8H), 2.63-2.61 (m, 4H), 2.50-2.45 (m, 2H), 2.38-2.34 (m, 2H), 2.33-2.31 (m, 1H), 2.17-2.09 (m, 1H), 1.33-1.29 (m, 2H), 1.07-1.03 (m, 3H), 0.70 - 0.68 (m, 1H), 0.55-0.49 (m, 2H), 0.36-0.34 (m, 1H)

Example 15. 3-(6-(1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 145a)

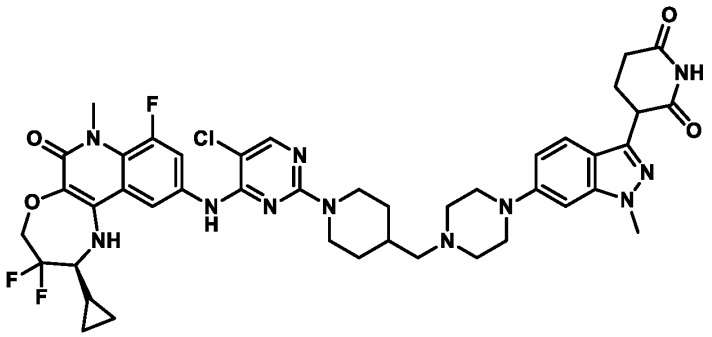


To a stirred solution 3-(6-(3,3-difluoro-1-(piperidin-4-ylmethyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (See Table P6) (0.03 g, 0.065 mmol, 1 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.015 g, 0.033 mmol, 1 *equiv.*) in DMSO (0.9 mL) was added DIPEA (0.11 mL, 0.65 mmol, 1 *equiv.*). The mixture was heated at 100 °C and stirred for 4 hours. The reaction mixture was quenched with ice-cold water, and the solid was filtered to get crude product which was purified by prep HPLC to afford 3-(6-(1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)-3,3-difluoropiperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.005 g).

LC-MS (ESI): m/z = 891.4 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.89 (s, 1H), 8.83 (s, 1H), 8.17 (s, 1H), 8.04 (s, 1H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.64 (bs, 1H), 7.52 (s, 1H), 7.46 (d, *J* = 9.2 Hz, 1H), 7.25-6.90 (m, 3H), 6.20 (s, 1H), 4.44-4.34 (m, 4H), 3.99 (s, 3H), 3.57-3.50 (m, 3H), 3.37-2.81 (m, 5H), 2.67-2.50 (m, 4H), 2.32-2.21 (m, 4H), 2.19-1.60 (m, 6H), 1.50-1.40 (m, 2H), 0.80-0.70 (m, 1H), 0.55-0.45 (m, 2H), 0.35 (br s, 1H).

Example 16. 3-(6-(4-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,8-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 168a)

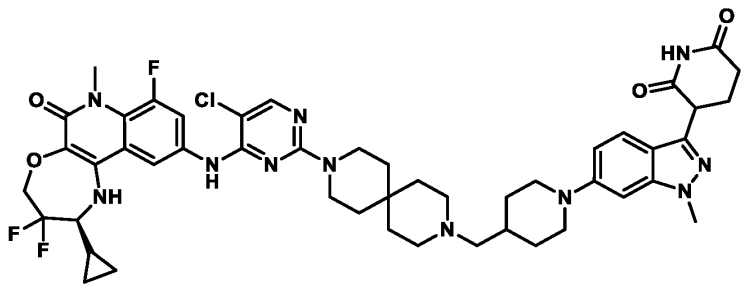


To a stirred solution of (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3,8-trifluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (See Table P31) (0.05 g, 0.103 mmol, 1 *equiv.*) and 3-(1-methyl-6-(4-(piperidin-4-ylmethyl)piperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (See Table P6) (0.088 g, 0.206 mmol, 1 *equiv.*) in DMSO (0.5 mL) was added DIPEA (0.1 mL, 0.514 mmol, 1 *equiv.*). The resulting reaction mixture was stirred at 120 °C for 2 hours in a microwave reactor. The reaction mixture was concentrated under reduced pressure get crude product which was purified by Prep-HPLC to afford 3-(6-(4-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,8-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.017 g) as an off-white solid.

LC-MS (ESI): m/z = 874.53 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.86 (s, 1H), 9.22 (s, 1H), 8.92 (s, 1H), 8.10 (s, 1H), 7.98 (s, 1H), 7.78 (dd, *J* = 2.0 Hz, 16.8 Hz, 1H), 7.57 (d, *J* = 9.20 Hz, 1H), 6.98-6.95 (m, 1H), 6.18 (s, 1H), 4.47-4.43 (m, 3H), 4.30-4.26 (m, 1H), 3.92 (s, 5H), 3.70 (d, *J* = 9.20 Hz, 3H), 3.63-3.60 (m, 2H), 3.26-3.10 (m, 8H), 2.94-2.88 (m, 2H), 2.63-2.60 (m, 1H), 2.29-2.28 (m, 1H), 2.18-2.13 (m, 2H), 1.79-1.77 (m, 2H), 1.23-1.14 (m, 4H), 0.73-0.71 (m, 1H), 0.54-0.52 (m, 2H), 0.35-0.34 (m, 1H).

Example 17. 3-(6-(4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,8-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)piperidin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 150a)



To a stirred solution of (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3,8-trifluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (See Table P31) (0.05 g, 0.103 mmol, 1 *equiv.*) and 3-(6-(4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)piperidin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.101 g, 0.203 mmol, 1 *equiv.*) in DMSO (0.5 mL) was added DIPEA (0.1 mL, 0.514 mmol, 1 *equiv.*). The resulting reaction mixture was stirred at 120 °C for 2 hours in a microwave reactor. The reaction mixture was concentrated under reduced pressure to get crude product which was purified by Prep-HPLC to afford 3-(6-(4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,8-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)piperidin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.013 g) as an off-white solid.

LC-MS (ESI): m/z = 942.53 $[M+H]^+$.

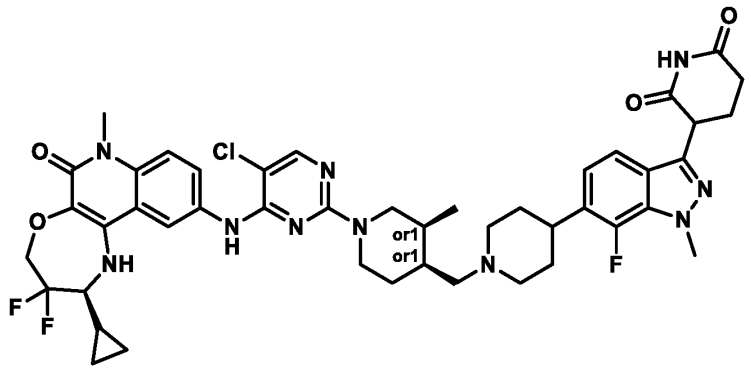
^{1}H NMR (400 MHz, DMSO-d_6): δ 10.84 (s, 1H), 8.84 (s, 1H), 8.05 (d, *J* = 3.60 Hz, 2H), 7.71 (dd, *J* =1.6 Hz, 16.4 Hz, 1H), 7.47 (d, *J* = 9.2 Hz, 1H), 6.89 (d, *J* = 8.80 Hz, 1H), 6.81 (s, 1H), 6.16 (s, 1H), 4.44-4.42 (m, 2H), 4.26-4.22 (m, 1H), 3.88 (s, 3H), 3.78-3.71 (m, 2H), 3.70 (d, *J* = 8.80 Hz, 3H), 3.61(br s, 4H), 3.34-3.24 (m, 1H) 2.74-2.67 (m, 2H), 2.64-2.59 (m, 2H), 2.54-2.49 (m, 3H), 2.28 (br s, 4H), 2.18-2.16 (m, 3H), 1.79 (d, *J* = 12.0 Hz, 2H), 1.70 (br s, 1H), 1.47-1.40 (m, 8H), 1.30-1.21 (m, 1H), 0.72-0.70 (m, 1H), 0.53-0.50 (m, 2H), 0.35-0.34 (m, 1H).

Example 18. 3-(6-(1-(((3S,4S)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

[3-(6-(1-(((3S*,4S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-

methylpiperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]

(Compound 130a)



To a stirred solution of 3-(7-fluoro-1-methyl-6-(1-(((3S,4S)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (See Table P6) (0.11 g, 0.24 mmol, 1 *equiv.*) in DMSO (3.3 mL) was added DIPEA (0.22 mL, 1.2 mmol, 1 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.56 g, 0.12 mmol, 1 *equiv.*). The reaction mixture was heated at 100 °C and stirred for 5 hours. The reaction mixture was quenched with ice cold water, and the resulting precipitate was filtered and dried under reduced pressure to get crude product which was purified by prep HPLC to afford 3-(6-(1-(((3S,4S)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-(1-(((3S*,4S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (38.33 mg) as a white solid.

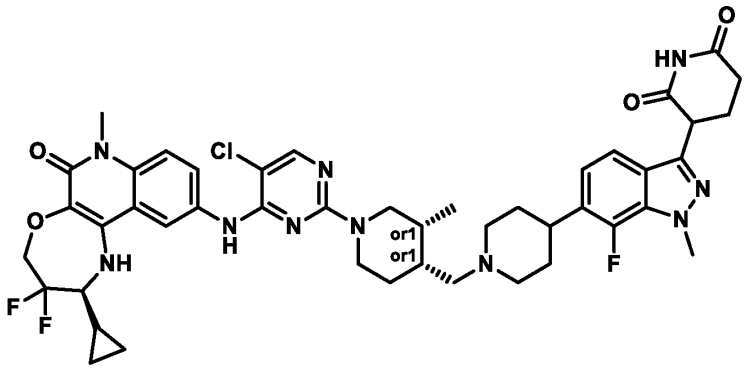
LC-MS (ESI): m/z = 887.54 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.92 (s, 1H), 8.88 (s 1H), 8.14 (d, J = 1.6 Hz, 1H), 8.03 (s, 1H), 7.74-7.71 (m, 1H), 7.53 (d, J = 8.8 Hz, 1H), 7.43 (d, J =9.2 Hz, 1H), 6.99-6.96 (m, 1H), 6.25 (bs, 1H), 4.38-4.34 (m, 4H), 4.12 (s, 3H), 3.66-3.57 (m, 5H), 3.28-3.03 (m, 2H), 2.62-2.58 (m, 1H), 2.59-2.58 (m, 2H), 2.37 (bs, 1H), 2.17-2.13 (m, 4H), 1.97-1.90 (m, 3H), 1.42-1.58 (m, 4H), 1.33-1.16 (m, 4H), 0.79-0.80 (m, 4H), 0.71-0.67 (m, 1H), 0.54-0.51 (m, 2H), 0.34-0.33 (m, 1H).

Example 19. 3-(6-(1-(((3*R*,4*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methyl-piperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

[3-(6-(1-(((3*R,4*R**)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]**

(Compound 130d)



To a stirred solution of 3-(7-fluoro-1-methyl-6-(1-(((3*R*,4*R*)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (See Table P6) (0.15 g, 0.33 mmol, 1 *equiv.*) in DMSO (3.0 mL) was added (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.74 g, 0.16 mmol, 1 *equiv.*) and DIPEA (0.30 mL, 1.64 mmol, 1 *equiv.*). The reaction mixture was heated at 100 °C and stirred for 5 hours. The reaction mixture was quenched with ice cold water and the resulting precipitate was filtered and dried under reduced pressure to get crude product which was purified by Prep HPLC to afford 3-(6-(1-(((3*R*,4*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methyl-piperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-(1-(((3*R**,4*R**)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (47.26 mg) as white solid.

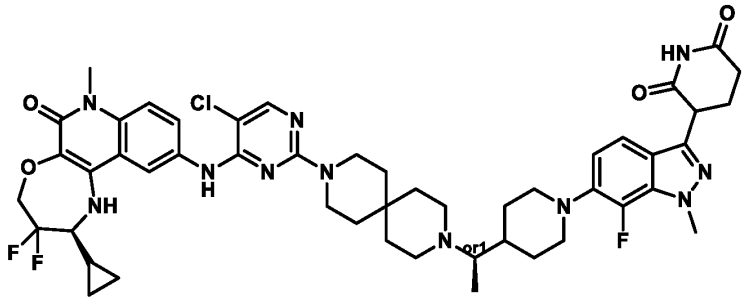
LC-MS (ESI): m/z = 887.58 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.92 (s, 1H), 8.85 (s 1H), 8.14 (d, J = 1.6 Hz, 1H), 8.03 (s, 1H), 7.74 (dd, J = 8.8, 2.0 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.43 (d, J =9.2 Hz, 1H), 6.99-6.96 (m, 1H), 6.24 (bs, 1H), 4.50-4.28 (m, 4H), 4.13 (s, 3H), 3.66-3.63 (m, 2H), 3.57 (s, 3H), 3.28-3.04 (m, 2H), 2.62-2.61 (m, 1H), 2.59-2.58 (m, 2H), 2.37 (bs, 1H), 2.17-2.13 (m, 4H), 1.97-1.90 (m, 3H), 1.42-1.58 (m, 4H), 1.33-1.16 (m, 4H), 0.79-0.80 (m, 4H), 0.71-0.67 (m, 1H), 0.54-0.51 (m, 2H), 0.34-0.33 (m, 1H).

Example 20. 3-(6-(4-((*R*)-1-(9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)piperidin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

[3-(6-(4-((*R)-1-(9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)piperidin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]**

(Compound 142b)



Preparation of 1-(piperidin-4-yl)ethan-1-one

To a stirred solution of *tert*-butyl 4-acetylpiperidine-1-carboxylate (18.0 g, 79.19 mmol) in DCM (180 mL) was added 4M HCl in 1,4-dioxane (18.0 mL) at 0 °C. The resulting reaction mixture was stirred at room temperature for 6 hours. The reaction mixture was concentrated under reduced pressure to obtain crude product which was triturated with diethylether (20.0 mL) and dried under reduced pressure to get 1-(piperidin-4-yl)ethan-1-one (8.0 g) as an off-white solid.

LC-MS (ESI): m/z = 127.9 $[M+H]^+$

Preparation of benzyl 4-acetylpiperidine-1-carboxylate

To a stirred solution of 1-(piperidin-4-yl)ethan-1-one (7.0 g, 55.03 mmol) in MeCN (70.0 mL) was added 2M aqueous sodium carbonate (85. mL, 170.6 mmol) and benzyl chloroformate (10.2 mL, 66.04 mmol) at 0°C. The resultant reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure to obtain crude product which was triturated with diethylether (50.0 ml) and dried under vacuum to afford benzyl 4-acetylpiperidine-1-carboxylate (6.0 g) as an off solid.

LC-MS (ESI): m/z = 262.0 $[M+H]^+$

Preparation of *tert*-butyl 9-(1-(1-((benzyloxy)carbonyl)piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate

To a stirred solution of *tert*-butyl 3,9-diazaspiro[5.5]undecane-3-carboxylate (5.0 g, 19.6 mmol) and benzyl 4-acetylpiperidine-1-carboxylate (4.1 g, 15.7 mmol) in THF (20 mL) was added titanium(IV)isopropoxide (5.0 mL). The mixture was stirred for 1 hour at room temperature. Sodium cyanoborohydride (3.7 g, 58.96 mmol,) was added at 0°C and the reaction mixture was stirred at room temperature for 6 hours. The reaction mixture was quenched with water (30.0 mL) and extracted with DCM (50.0 mL). The organic layer was separated and washed with brine solution (30.0 mL), dried over anhydrous sodium sulfate, filtered and dried under vacuum to get crude product was purified by flash column chromatography (230-400 mesh; 80 % ethyl acetate in petroleum ether) to afford *tert*-butyl 9-(1-(1-((benzyloxy)carbonyl)piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (2.1 g) as a white solid.

LC-MS (ESI): m/z = 500.6 $[M+H]^+$

Preparation of *tert*-butyl 9-(1-(piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate

To a stirred solution of *tert*-butyl 9-(1-(1-((benzyloxy)carbonyl)piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (2.0 g, 2.71 mmol) in THF (80.0 mL) was added $Pd(OH)_2$ on carbon (2.0 g, 100 wt%). The mixture was stirred under hydrogen atmosphere (80 psi) at room temperature for 5 hours. The reaction mixture was diluted with THF (20.0 mL) and filtered through a pad of celite and washed with excess of 20% THF in DCM. The filtrate was collected and concentrated to afford *tert*-butyl 9-(1-(piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate as white solid (1.5 g).

LC-MS (ESI): m/z = 366.51 $[M+H]^+$

Preparation of *tert*-butyl 9-(1-(1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate

To a solution of *tert*-butyl 9-(1-(piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (1.5 g, 4.1 mmol), 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-7-fluoro-1-methyl-1*H*-indazole (1.7 g, 3.2 mmol) in 1,4-dioxane (60 mL) was added t-BuONa (1.3 g, 14.3 mmol). The mixture was degassed with argon for 5 minutes. To this mixture was added Pd-PEPPSI-IHeptCl (0.2 g, 0.2 mmol) and the resultant reaction mixture was heated to 85°C for 6 hours. The reaction mixture was filtered through a celite bed and concentrated under reduced pressure to get crude product which was adsorbed onto silica gel and purified by flash column chromatography (12% ethyl acetate in petroleum ether) to afford *tert*-butyl 9-(1-(1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (1.3 g) as white solid.

LC-MS (ESI): m/z: 437.15 $[M-H]^-$

Preparation of *tert*-butyl (*R*)-9-(1-(1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate and *tert*-butyl (*S*)-9-(1-(1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate

Isomers of *tert*-butyl 9-(1-(1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate were purified by preparative SFC purification to afford *tert*-butyl (*R*)-9-(1-(1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (Isomer-1, 0.4 g) and *tert*-butyl (*S*)-9-(1-(1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (Isomer-2, 0.4 g) as an off white solid.

Preparation of *tert*-butyl 9-((1*R*)-1-(1-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate

To a stirred solution *tert*-butyl (*R*)-9-(1-(1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (0.4 g, 0.49 mmol) in THF (16.0 mL) was added $Pd(OH)_2$ on carbon (0.4 g, 20 wt%). The mixture was stirred under hydrogen atmosphere (15 psi) at room temperature for 5 hours. The reaction mixture was diluted with THF (20.0 mL) and filtered through a pad of celite and washed with excess of 20% THF in DCM. The filtrate was collected and concentrated

to afford *tert*-butyl 9-((1*R*)-1-(1-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate.

LC-MS (ESI): m/z = 625.42 $[M+H]^+$

Preparation of 3-(6-(4-((*R*)-1-(3,9-diazaspiro[5.5]undecan-3-yl)ethyl)piperidin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

To a stirred solution of *tert*-butyl 9-((1*R*)-1-(1-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (0.3 g, 0.48 mmol) in 1,4-Dioxane (3.0 mL) and 4 M HCl in 1,4-dioxane (1.5 mL) at 0 °C. The mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure to obtain crude product which was triturated with diethyl ether (20.0 mL) and dried under reduced pressure to afford 3-(6-(4-((*R*)-1-(3,9-diazaspiro[5.5]undecan-3-yl)ethyl)piperidin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione.

LC-MS (ESI): m/z = 525.37 $[M+H]^+$

Preparation of 3-(6-(4-((*R*)-1-(9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)piperidin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-(4-((*R)-1-(9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)piperidin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]**

To a stirred solution of 3-(6-(4-((*R*)-1-(3,9-diazaspiro[5.5]undecan-3-yl)ethyl)piperidin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.15 g, 0.28 mmol, 1 *equiv.*) in DMSO (4.5 mL) was added DIPEA (0.499 mL, 2.85 mmol, 1 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.067 g, 0.14 mmol, 1 *equiv.*). The resulting mixture was heated at 100 °C and stirred for 4 hours. The reaction mixture was quenched with ice-cold water, and the resulting precipitate was filtered to get crude product which was purified by prep HPLC to afford 3-(6-(4-((*R*)-1-(9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)piperidin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-(4-((*R**)-1-(9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-

c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)piperidin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (0.038 g).

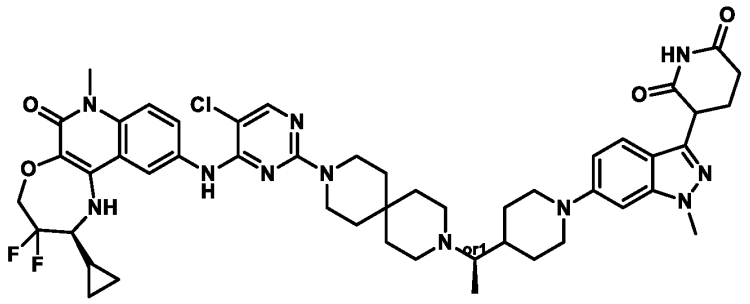
LC-MS (ESI): m/z = 956.66 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.89 (s, 1H), 8.77 (s, 1H), 8.20 (br s, 1H), 8.02 (s, 1H), 7.72 (br d, J = 9.3 Hz, 1H), 7.48 - 7.32 (m, 2H), 6.91 (br t, J = 7.4 Hz, 1H), 6.18 (br s, 1H), 4.53 - 4.24 (m, 3H), 4.06 (s, 3H), 3.56 (br s, 8H), 3.26 - 3.14 (m, 3H), 2.80 - 2.53 (m, 5H), 2.39 - 2.21 (m, 4H), 2.20 - 2.10 (m, 1H), 2.04 (br d, J = 11.1 Hz, 1H), 1.75 (br d, J = 11.5 Hz, 1H), 1.57 - 1.17 (m, 12H), 0.91 (br d, J = 5.9 Hz, 3H), 0.71 (br d, J = 6.4 Hz, 1H), 0.51 (br s, 2H), 0.35 (br s, 1H)

Example 21. 3-(6-(4-((*R*)-1-(9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)piperidin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

[3-(6-(4-((*R)-1-(9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)piperidin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]**

(Compound 114b)



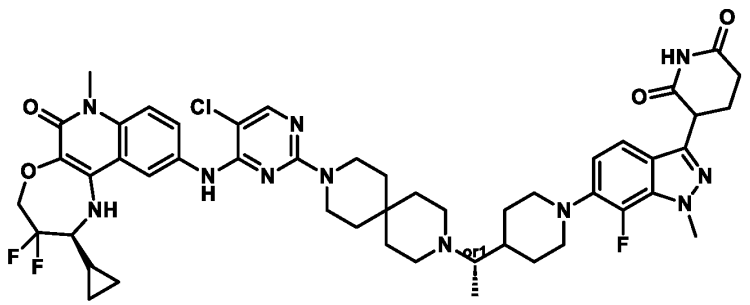
To a stirred solution of 3-(6-(4-((*R*)-1-(3,9-diazaspiro[5.5]undecan-3-yl)ethyl)piperidin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (See Table P6) (0.15 g, 0.28 mmol, 1 *equiv.*) in DMSO (4.5 mL) was added DIPEA (0.499 mL, 2.85 mmol, 1 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.067 g, 0.14 mmol, 1 *equiv.*). The resulting mixture was heated at 100 °C and stirred for 4 hours. The reaction mixture was quenched with ice-cold water, and the resulting precipitate was filtered to get crude product which was purified by prep

HPLC to afford 3-(6-(4-((*R*)-1-(9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)piperidin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-(4-((*R**)-1-(9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)piperidin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (0.0023 g).

LC-MS (ESI): m/z = 938.57 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.83 (s, 1H), 8.76 (s, 1H), 8.29 (s, 1H), 8.21 (s, 1H), 8.02 (s, 1H), 7.73 (d, *J* = 1.6 Hz, 1H), 7.47 (t, *J* = 9.2 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 1H), 6.80 (s, 1H), 6.17 (s, 1H), 4.45-4.32 (m, 2H), 4.25-4.22 (m, 1H), 3.87 (s, 3H), 3.79 (s, 2H), 3.59-3.56 (m, 7H), 2.67-2.60 (m, 4H), 2.50-2.49 (m, 4H), 2.26-2.12 (m, 2H), 2.04-2.01(m, 1H), 1.76-1.73 (m, 1H), 1.43-1.23 (m, 12H), 0.91 (m, 4H), 0.85-0.71 (m, 1H), 0.52-0.51 (m, 2H), 0.35-0.30 (m, 1H)

Example 22. 3-(6-(4-((*S*)-1-(9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)piperidin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-(4-((*S)-1-(9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)piperidin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (Compound 142a)**



Preparation of *tert*-butyl 9-((1*S*)-1-(1-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate

To a stirred solution of *tert*-butyl (*S*)-9-(1-(1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (0.4 g, 0.49 mmol) in THF (16.0 mL) was added $Pd(OH)_2$ on carbon (0.4 g, 20 wt%). The mixture was stirred under hydrogen atmosphere (15 psi) at room temperature for 5 hours. The reaction mixture was diluted with THF (20.0 mL) and filtered through a pad of celite and washed with excess of 20% THF in DCM. The filtrate was collected and concentrated to afford *tert*-butyl 9-((1*S*)-1-(1-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate.

LC-MS (ESI): m/z = 625.39 $[M+H]^+$

Preparation of 3-(6-(4-((*S*)-1-(3,9-diazaspiro[5.5]undecan-3-yl)ethyl)piperidin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

To a stirred solution of *tert*-butyl 9-((1*S*)-1-(1-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (0.3 g, 0.48 mmol,) in 1,4-dioxane (3.0 mL) was added 4 M HCl in 1,4-dioxane (1.5mL) at 0 °C. The mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure to obtain crude product which was triturated with diethyl ether (20.0 ml) and dried under reduced pressure to get 3-(6-(4-((*S*)-1-(3,9-diazaspiro[5.5]undecan-3-yl)ethyl)piperidin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione.

LC-MS (ESI): m/z = 525.3 $[M+H]^+$

Preparation of 3-(6-(4-((*S*)-1-(9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)piperidin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-(4-((*S)-1-(9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)piperidin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]**

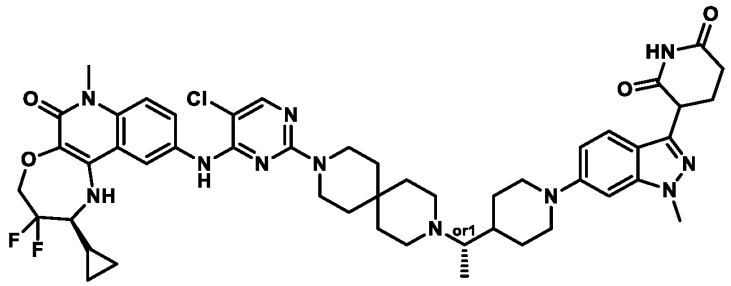
To a stirred solution 3-(6-(4-((*S*)-1-(3,9-diazaspiro[5.5]undecan-3-yl)ethyl)piperidin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.15 g, 0.28 mmol, 1 *equiv.*) and

(*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.067 g, 0.14 mmol, 1 *equiv.*) in DMSO (4.5 mL) was added DIPEA (0.5 mL, 2.85 mmol, 1 *equiv.*). The reaction mixture was heated at 100 °C and stirred for 4 hours. The reaction mixture was quenched with ice-cold water, and the precipitate was filtered to get crude product which was purified by prep HPLC to afford 3-(6-(4-((*S*)-1-(9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)piperidin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-(4-((*S**)-1-(9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)piperidin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (0.040 g).

LC-MS (ESI): m/z = 956.66 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.88 (s, 1H), 8.76 (s, 1H), 8.20 (d, *J* = 1.6 Hz, 1H), 8.02 (s, 1H), 7.73 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.45 (d, *J* = 9.2 Hz, 1H), 7.39 (d, *J* = 8.8 Hz, 1H), 6.93 (t, *J* = 8.0 Hz, 1H), 6.17 (s, 1H), 4.40-4.29 (m, 3H), 4.06 (s, 3H), 3.58 (s, 7H), 3.42-3.37 (m, 2H), 3.22-3.20 (m, 1H), 2.73-2.64 (m, 6H), 2.60-2.57 (m, 4H), 2.50-2.49 (m, 1H), 2.32-2.28 (m, 1H), 2.15 (m, 1H), 1.44-1.32 (m, 12H), 0.95-0.90 (m, 3H), 0.75-0.70 (m, 1H), 0.52-0.49 (m, 2H), 0.35-0.30 (m, 1H).

Example 23. 3-(6-(4-((*S*)-1-(9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)piperidin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-(4-((*S)-1-(9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)piperidin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (Compound 114a)**

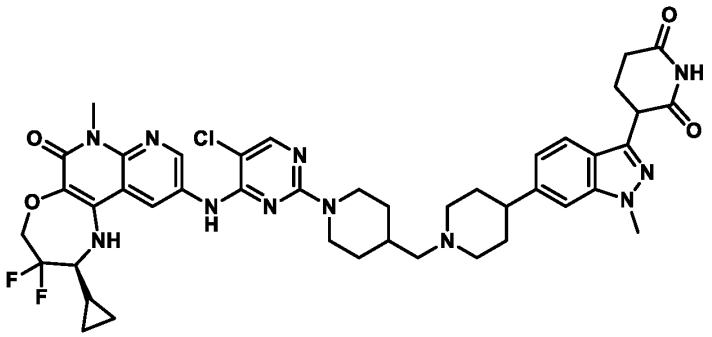


To a stirred solution 3-(6-(4-((*S*)-1-(3,9-diazaspiro[5.5]undecan-3-yl)ethyl)piperidin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (See Table P6) (0.15 g, 0.28 mmol, 1 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.067 g, 0.14 mmol, 1 *equiv.*) in DMSO (4.5 mL) was added DIPEA (0.5 mL, 2.85 mmol, 1 *equiv.*). The reaction mixture was heated at 100 °C and stirred for 4 hours. The reaction mixture was quenched with ice-cold water, and the precipitate was filtered to get crude product which was purified by prep-HPLC to afford 3-(6-(4-((*S*)-1-(9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)piperidin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-(4-((*S**)-1-(9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)piperidin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (0.011 g).

LC-MS (ESI): m/z = 938.54 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.83 (s, 1H), 8.76 (s, 1H), 8.25 (s, 1H), 8.20 (d, *J* = 1.6 Hz, 1H), 8.02 (s, 1H), 7.72 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.47 (t, *J* = 9.2 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 1H), 6.80 (s, 1H), 6.17 (s, 1H), 4.45-4.40 (m, 2H), 4.25-4.22 (m, 1H), 3.87 (s, 3H), 3.79 (bs, 2H), 3.56-3.50 (m, 7H), 2.67-2.58 (m, 4H), 2.50-2.49 (m, 6H), 2.27-2.14 (m, 1H), 2.04-2.01(m, 1H), 1.76-1.23 (m, 13H), 0.91-0.90 (m, 3H), 0.71-0.70 (m, 1H), 0.52-0.49 (m, 2H), 0.35-0.30 (m, 1H).

Example 24: 3-(6-(1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 141a)

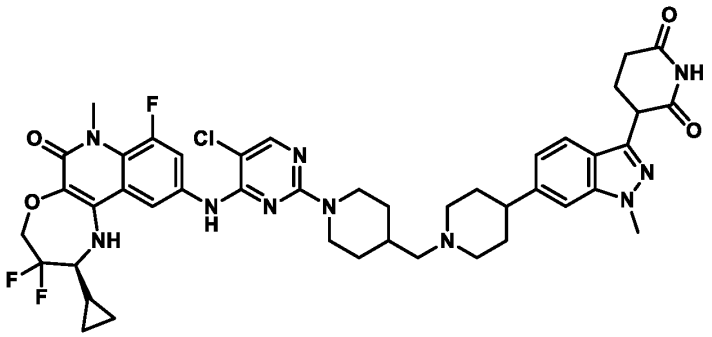


To a stirred solution of 3-(1-methyl-6-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (See Table P6) (0.15 g, 0.35 mmol, 1 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-6(7*H*)-one (See Table P31) (0.066 g, 0.142 mmol, 1 *equiv.*) in DMSO (1.5 mL) was added DIPEA (0.309 mL, 1.771 mmol, 1 *equiv.*). The reaction mixture was stirred at 120° C for 2 hours in a microwave reactor. The reaction mixture was concentrated under reduced pressure to get crude product which was purified by Prep-HPLC to afford 3-(6-(1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.021 g) as an off-white solid.

LC-MS (ESI): m/z = 856.47 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.88 (s, 1H), 9.07 (s, 1H), 8.67 (d, *J* = 6.0 Hz, 2H), 8.07 (s, 1H), 7.63 (d, *J* =8.4 Hz, 1H), 7.41 (s, 1H), 7.03 (d, *J* = 8.40 Hz, 1H), 6.43 (br s, 1H), 4.45 -4.31(m, 5H), 3.97 (s, 3H), 3.62 (s, 3H), 3.20-3.10 (m, 3H), 2.84-2.78 (m, 3H), 2.63-2.57 (m, 3H) 2.40-2.36 (m, 1H), 2.18-2.14 (m, 1H), 1.90-1.71 (m, 7H), 1.25-1.22 (m, 4H), 1.07-1.05 (m, 2H), 0.80-0.79 (m, 1H), 0.55-0.52 (m, 2H), 0.38-0.35 (m, 1H)

Example 25. 3-(6-(1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,8-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 178a)



To a stirred solution of 3-(1-methyl-6-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (See Table P6) (0.15 g, 0.354 mmol, 1 *equiv.*), (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3,8-trifluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (See Table P31) (0.069 g, 0.142 mmol, 1 *equiv.*) in DMSO (1.5 mL) was added DIPEA (0.309 mL, 1.771 mmol, 1 *equiv.*). The reaction mixture was stirred at 120 °C for 2 hours in a microwave reactor. The reaction mixture was concentrated under reduced pressure to get crude product which was purified by Prep-HPLC to afford 3-(6-(1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,8-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.030 g) as an off-white solid.

LC-MS (ESI): m/z = 873.50 $[M+H]^+$.

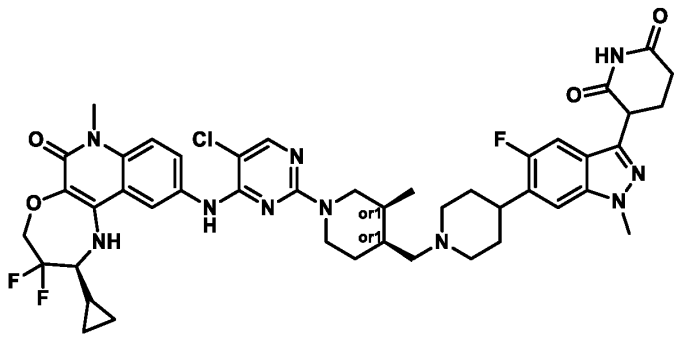
^{1}H NMR (400 MHz, DMSO-d_6): δ 10.87 (s, 1H), 8.84 (s, 1H), 8.06 (s, 1H), 8.03 (s,1H), 7.75 (dd, J = 1.60 Hz, 18.4 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.43 (s, 1H), 7.04 (d, J = 8.80 Hz, 1H), 6.13 (br s, 1H), 4.47-4.30 (m, 5H), 3.96 (s, 3H), 3.70 (d, J = 9.20 Hz, 3H), 3.26-3.24 (m, 1H), 2.98 (br s, 2H), 2.84 (t, J = 12.8 Hz, 2H), 2.65-2.60 (m, 2H), 2.40-2.35 (m, 1H), 2.20-2.15 (m, 2H), 2.00 (br s, 1H), 1.81-1.74 (m, 7H), 1.35 (s, 3H), 1.23 (s, 1H), 1.05-1.03(m, 2H), 0.71-0.70 (m, 1H) ,0.54-0.51(m, 2H), 0.36-0.35 (m, 1H).

Example 26. 3-(6-(1-(((3S,4S)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

[3-(6-(1-(((3S*,4S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-

methylpiperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]

(Compound 121a)



To a stirred solution of 3-(5-fluoro-1-methyl-6-(1-(((3S,4S)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (See Table P6) (0.12 g, 0.26 mmol, 1 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.03 g, 0.09 mmol, 1 *equiv.*) in DMSO (1.2 mL) was added DIPEA (1.2 mL). The reaction mixture was heated at 100 °C and stirred for 18 hours. The reaction mixture was quenched with ice cold water (50 mL) and the precipitated solid was filtered and dried under vacuum to afford crude product which was purified by prep-HPLC to afford 3-(6-(1-(((3S,4S)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-(1-(((3S*,4S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (0.013 g) as an off white solid.

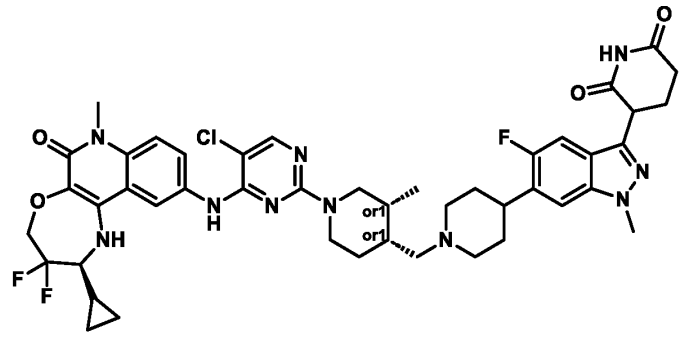
LC-MS (ESI): m/z = 887.50 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.90 (s, 1H), 8.74 (s, 1H), 8.15 (d, *J* = 6.80 Hz, 1H), 8.00 (s, 1H), 7.76 (d, *J* = 9.20 Hz, 1H), 7.56 (d, *J* = 6.00 Hz, 1H), 7.48-7.45 (m, 2H), 6.17 (s, 1H), 4.41-4.29 (m, 4H), 4.00 (s, 3H), 3.57 (s, 3H), 3.01 (brs, 1H), 2.92 (d, *J* = 12.0 Hz, 3H), 2.73 (t, *J* = 17.6 Hz, 2H), 2.59-2.56 (m, 2H), 2.46-2.1.98 (m, 1H), 2.18-2.11 (m, 8H), 1.79 (brs, 4H), 1.36-1.32 (m, 4H), 1.24 (s, 1H), 0.72 (m, 2H), 0.53 (t, *J* = 6.00 Hz, 2H), 0.35 (m, 1H).

Example 27. 3-(6-(1-(((3*R*,4*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

[3-(6-(1-(((3*R,4*R**)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]**

(Compound 121d)



Preparation of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate

To a stirred solution of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-5-fluoro-1-methyl-1*H*-indazole (4.0 g, 7.72 mmol) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (2.98 g, 9.64 mmol) in 1,4-dioxane (32 mL): water (8 mL) was added cesium carbonate (7.54 g, 23.15 mmol). The mixture was purged with N_2 for 15 minutes followed by the addition of $Pd_2(dba)_3$ (0.35 g, 0.39 mmol) and XantPhos (0.45 g, 0.77 mmol). The resulting reaction mixture was heated at 100 °C for 6 hours. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (200 mL), filtered through a celite bed and washed with DCM (300 mL). The filtrate was concentrated to get crude product which was purified by flash chromatography (10-15% of ethyl acetate in petroleum ether) to obtain *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (3.05 g).

LC-MS (ESI): m/z = 621.26 $[M+H]^+$

Preparation of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indazole

To a stirred solution of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (2.00 g, 3.22 mmol) in DCM (40 mL) was added 4M HCl in dioxane (40 mL) and stirred at 0 °C for 2 hours. The reaction mixture was concentrated under reduced pressure to get crude product which was triturated with *n*-pentane to afford 3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indazole (2.30 g) as pale yellow solid.

LC-MS (ESI): m/z = 521.27 $[M+H]^+$

Preparation of *tert*-butyl 4-(4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)-1,2,3,6-tetrahydropyridine-1-carbonyl)-3-methylpiperidine-1-carboxylate

To a stirred solution of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indazole (2.00 g, 3.84 mmol) and 1-(tert-butoxycarbonyl)-3-methylpiperidine-4-carboxylic acid (1.03 g, 4.23 mmol) in DMF (10 mL) was added DIPEA (2.68 mL, 15.37 mmol). The mixture was stirred for 5 minutes followed by the addition of HATU (2.19 g, 5.76 mmol) at 0 °C. The mixture was stirred at room temperature for 18 hours. The reaction mixture was diluted with ethyl acetate (300 mL) and washed with water (100 mL). The organic layer was dried over sodium sulphate and concentrated under reduced pressure to obtain crude product which was triturated with *n*-pentane to afford *tert*-butyl 4-(4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)-1,2,3,6-tetrahydropyridine-1-carbonyl)-3-methylpiperidine-1-carboxylate (2.25 g) as a pale brown semi-solid.

LC-MS (ESI): m/z = 747.93 $[M+H]^+$

Preparation of *tert*-butyl 4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)-3,6-dihydropyridin-1(2*H*)-yl)methyl)-3-methylpiperidine-1-carboxylate

To a stirred solution *tert*-butyl 4-(4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)-1,2,3,6-tetrahydropyridine-1-carbonyl)-3-methylpiperidine-1-carboxylate (2.25 g, 3.01 mmol) in THF (90 mL) was added LAH (2.0 M in THF) (2.25 mL) drop wise over period of 5 minutes by maintaining temperature below 0 °C. The mixture was stirred at room temperature for 0.5 hours. The reaction mixture was cooled to 0 °C, diluted with ethyl acetate (200 mL), and stirred for 5 minutes. The reaction mixture was quenched with saturated ammonium chloride solution (90 mL) and the separated organic layer was washed

with brine solution (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford crude product which was purified by column chromatography (100-200 mesh; 5%-10% Methanol in DCM) to afford *tert*-butyl 4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)-3,6-dihydropyridin-1(2*H*)-yl)methyl)-3-methylpiperidine-1-carboxylate (0.85 g) as pale yellow semi-solid.

LC-MS (ESI): m/z = 732.75 $[M+H]^+$

Preparation of *tert*-butyl (3S,4S)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)-3,6-dihydropyridin-1(2*H*)-yl)methyl)-3-methylpiperidine-1-carboxylate and *tert*-butyl (3*R*,4*R*)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)-3,6-dihydropyridin-1(2*H*)-yl)methyl)-3-methylpiperidine-1-carboxylate

Isomers of *tert*-butyl 4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)-3,6-dihydropyridin-1(2*H*)-yl)methyl)-3-methylpiperidine-1-carboxylate were separated by SFC to afford *tert*-butyl (3S,4S)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)-3,6-dihydropyridin-1(2*H*)-yl)methyl)-3-methylpiperidine-1-carboxylate (peak 1) and *tert*-butyl (3*R*,4*R*)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)-3,6-dihydropyridin-1(2*H*)-yl)methyl)-3-methylpiperidine-1-carboxylate (peak 2) product was purified by chiral prep HPLC.

Preparation of *tert*-butyl (3*R*,4*R*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate

To a stirred solution of *tert*-butyl (3*R*,4*R*)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)-3,6-dihydropyridin-1(2*H*)-yl)methyl)-3-methylpiperidine-1-carboxylate (0.25 g, 0.34 mmol) in THF (25 mL), DMF (1.25 mL), and acetic acid (0.62 mL) was added $Pd(OH)_2$ on carbon (0.75 g, 300 wt%.). The mixture was stirred under hydrogen atmosphere (15 psi) at room temperature for 6 hours. The reaction mixture was diluted with DCM (100 mL) and washed with 30% THF: DCM (100 mL) and filtered through a celite bed. The collected filtrate was concentrated under vacuum to obtain crude product which was triturated with n-pentane to afford *tert*-butyl (3*R*,4*R*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate (0.15 g) as a pale brown semi-solid.

LC-MS (ESI): m/z = 556.38 $[M+H]^+$

Preparation of 3-(5-fluoro-1-methyl-6-(1-(((3*R*,4*R*)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione

To a stirred solution of *tert*-butyl (3*R*,4*R*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate (0.15 g, 0.27 mmol) in DCM (4.5 mL) at 0 °C was added TFA (1.2 mL). The mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure to afford crude product which was triturated with *n*-pentane to afford 3-(5-fluoro-1-methyl-6-(1-(((3*R*,4*R*)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (0.13 g) as a pale brown semi-solid.

LC-MS (ESI): m/z = 456.52 $[M+H]^+$

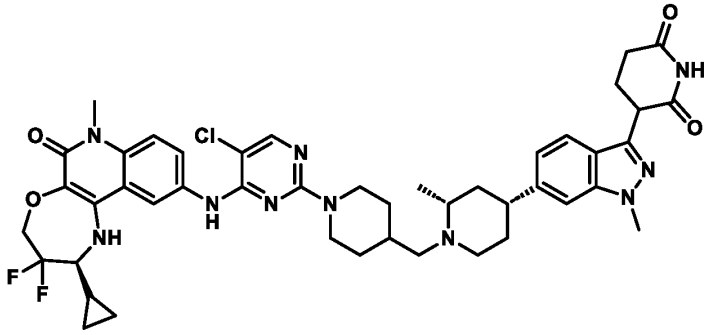
Preparation of 3-(6-(1-(((3*R*,4*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-(1-(((3*R,4*R**)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]**

To a stirred solution of 3-(5-fluoro-1-methyl-6-(1-(((3*R*,4*R*)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (0.13 g, 0.28 mmol, 1 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.03 g, 0.07 mmol, 1 *equiv.*) in DMSO (1.3 mL) was added DIPEA (1.3 mL). The reaction mixture was heated at 100 °C and stirred for 18 hours. The reaction mixture was quenched with ice cold water (100 mL) and the precipitated solid was filtered and dried under vacuum to afford crude product which was purified by prep-HPLC to afford 3-(6-(1-(((3*R*,4*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-(1-(((3*R**,4*R**)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (0.053 g) as an off white solid.

LC-MS (ESI): m/z = 887.50 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.87 (s, 1H), 8.72 (s, 1H), 8.17-8.14 (m, 1H), 8.00 (s, 1H), 7.77 (dd, J = 2.00, 9.20 Hz, 1H),7.56 (d, J = 6.00 Hz, 1H), 7.48-7.45 (m, 2H), 6.17 (brs, 1H), 4.42-4.29 (m, 4H), 3.99 (s, 3H), 3.57 (s, 3H), 3.01 (brs, 1H), 2.92 (d, J = 12.0 Hz, 3H), 2.73 (t, J = 17.6 Hz, 2H), 2.59-2.56 (m, 2H), 2.46-2.1.98 (m, 1H), 2.18-1.90 (m, 8H), 1.79 (brs, 4H), 1.36-1.32 (m, 4H), 1.24 (s, 1H), 0.72 (m, 2H), 0.53 (t, J = 6.00 Hz, 2H), 0.35 (m, 1H).

Example 28. 3-[6-[(2*R*,4*R*)-1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-2-methyl-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (Compound 153a)



To a solution of 3-(1-methyl-6-((2*R*,4*R*)-2-methyl-1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (See Table P6) (70 mg, 159.97 μmol, 1 *equiv.*) in DMSO (1.5 mL) was added TEA (66.80 μL, 479.92 μmol, 3 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (89.89 mg, 191.97 μmol, 1.2 *equiv.*). The mixture was stirred at 100 °C for 1 hour. The reaction mixture was filtered, and the filtrate was concentrated to give a residue. The residue was purified by prep-HPLC to afford 3-[6-[(2*R*,4*R*)-1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-2-methyl-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (36.91 mg) as a yellow solid.

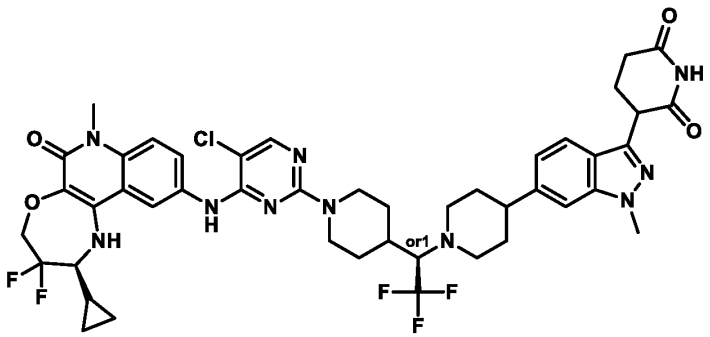
LC-MS (ESI): m/z = 869.6 $[M+H]^+$

Example 29. 3-[6-[1-[(1*R*)-1-[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]-2,2,2-trifluoro-ethyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-

dione

[3-(6-(1-((*R)-1-(1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)-2,2,2-trifluoroethyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]**

(Compound 140b)



To a solution of 3-[1-methyl-6-[1-[(1*R*)-2,2,2-trifluoro-1-(4-piperidyl)ethyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione (See Table P6) (83.0 mg, 169 μmol, 1 *equiv.*) in DMSO (0.5 mL) was added TEA (94.1 μL, 675 μmol, 4 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (79.1 mg, 169 μmol, 1 *equiv.*). The mixture was stirred at 100 °C for 12 hours. The reaction mixture was quenched by addition H_2O (10 mL) and extracted with ethyl acetate (60 mL). The combined organic layers were washed with aqueous sodium chloride (60 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to afford 3-[6-[1-[(1*R*)-1-[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]-2,2,2-trifluoro-ethyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione [3-(6-(1-((*R**)-1-(1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)-2,2,2-trifluoroethyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (57.6 mg) as a white solid.

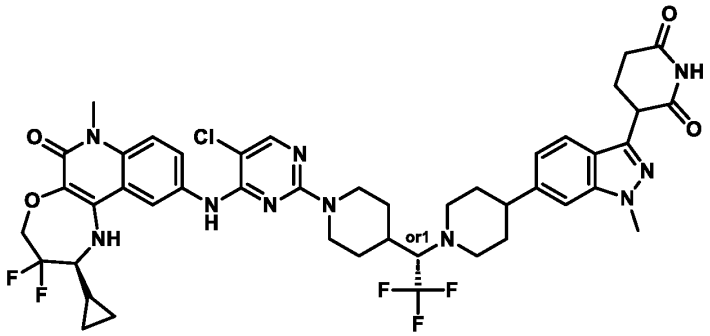
LC-MS (ESI): m/z = 923.3 $[M+H]^+$

Example 30. 3-[6-[1-[(1*S*)-1-[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-

yl]-4-piperidyl]-2,2,2-trifluoro-ethyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione

[3-(6-(1-((*S)-1-(1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)-2,2,2-trifluoroethyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]**

(Compound 140a)

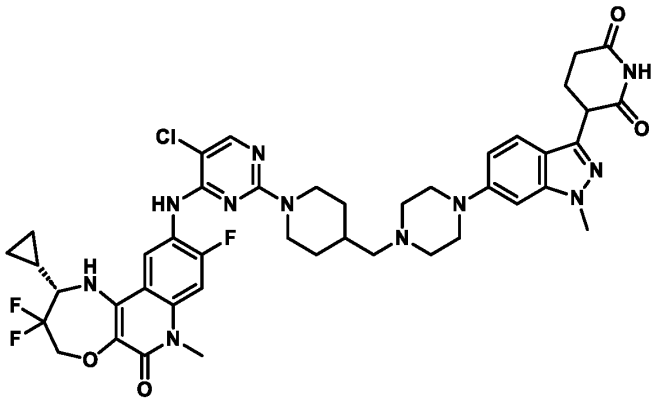


To a solution of 3-[1-methyl-6-[1-[(1*S*)-2,2,2-trifluoro-1-(4-piperidyl)ethyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione (See Table P6) (77 mg, 157 μmol, 1 *equiv.*) in DMSO (0.5 mL) was added TEA (87.20 μL, 627 μmol, 4 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (73.4 mg, 157 μmol, 1 *equiv.*). The mixture was stirred at 100 °C for 12 hours. The reaction mixture was quenched by addition H_2O (5 mL) and extracted with ethyl acetate (60 mL). The combined organic layers were washed with aqueous sodium chloride (60 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to afford 3-[6-[1-[(1*S*)-1-[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]-2,2,2-trifluoro-ethyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione [3-(6-(1-((*S**)-1-(1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)-2,2,2-trifluoroethyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (38.18 mg) as a white solid.

LC-MS (ESI): m/z = 923.3 $[M+H]^+$

Example 31. 3-[6-[4-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-

6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]piperazin-1-yl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (Compound 122a)



Preparation of (2*S*)-2-cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one

To a solution of (2*S*)-10-amino-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (206 mg, 607.11 μmol, 1 *equiv.*) in DMF (3 mL) was added DIPEA (235.39 mg, 1.82 mmol, 317.24 μL, 3 *equiv.*) and 2,4,5-trichloropyrimidine (133.63 mg, 728.53 μmol, 1.2 *equiv.*). The mixture was stirred at 80 °C for 24 hours. The reaction mixture was diluted with H_2O (5 mL) and extracted with ethyl acetate (5 mL × 3). The combined organic layers were washed with brine (10 mL × 3), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (50% ethyl acetate/petroleum ether) to give (2*S*)-2-Cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (315 mg) as a white solid.

LC-MS (ESI): m/z = 486.0 $[M+H]^+$.

Preparation of *tert*-butyl 4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]piperazine-1-carboxylate

A mixture of 6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazole (5.0 g, 9.99 mmol, 1 *equiv.*), *tert*-butyl piperazine-1-carboxylate (1.86 g, 9.99 mmol, 3 *equiv.*), RuPhos (932.55 mg, 2.00 mmol, 0.2 eq), cesium carbonate (9.77 g, 29.98 mmol, 3 *equiv.*) and $Pd(dba)_2$ (574.56 mg, 999.23 μmol, 0.1 *equiv.)* in dioxane (60 mL) was degassed and purged with N_2 three times. The mixture was stirred at 100 °C for 2 hours under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified

by flash silica gel chromatography (0~50% ethyl acetate/petroleum ether) to give *tert*-butyl 4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]piperazine-1-carboxylate (5.0 g) as a yellow solid.

LC-MS (ESI): m/z = 606.5 $[M+H]^+$

Preparation of *tert*-butyl 4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]piperazine-1-carboxylate

To a solution of *tert*-butyl 4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]piperazine-1-carboxylate (9 g, 14.86 mmol, 1 *equiv.*) in THF (10 mL) and EtOH (10 mL) was added Pd on carbon (0.5 g, 1.49 mmol, 10% purity, 0.1 *equiv.*), $Pd(OH)_2$ on carbon (562.50 mg, 4.01 mmol, 0.27 *equiv.*), and AcOH (2.68 g, 44.57 mmol, 2.55 mL, 3 *equiv.*) under N_2 atmosphere. The suspension was degassed and purged with H_2 three times. The mixture was stirred under H_2 (50 Psi) at 50 °C for 12 hours. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (DCM: MeOH =1/0 to 10/1) to afford *tert*-butyl 4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]piperazine-1-carboxylate (4.4 g) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.86 (s, 1H), 7.53 (d, J = 8.8 Hz, 1H), 6.98 - 6.83 (m, 2H), 4.27 (dd, J = 4.8, 9.2 Hz, 1H), 3.90 (s, 3H), 3.50 (s, 4H), 3.19 (s, 4H), 2.65 - 2.59 (m, 2H), 2.33 - 2.13 (m, 2H), 1.44 (s, 9H)

Preparation of 3-(1-methyl-6-(piperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione

A solution of *tert*-butyl 4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]piperazine-1-carboxylate (4.0 g, 9.36 mmol, 1 *equiv.*) in HCl/dioxane (50 mL) was stirred at 25 °C for 2 hours .The reaction mixture was concentrated under reduced pressure to give 3-(1-methyl-6-(piperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (3.0 g) as a white solid.

LC-MS (ESI): m/z = 328.1 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.87 (s, 1H), 9.40 (s, 2H), 7.57 (d, J = 8.8 Hz, 1H), 7.04 - 6.89 (m, 2H), 4.29 (dd, J = 5.2, 9.6 Hz, 1H), 3.92 (s, 3H), 3.54 - 3.41 (m, 4H), 3.25 (s, 4H), 2.72 - 2.58 (m, 2H), 2.40 - 2.24 (m, 1H), 2.23 - 2.09 (m, 1H).

Preparation of *tert*-butyl-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)piperidine-1-carboxylate

To a solution of 3-(1-methyl-6-(piperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione

(0.4 g, 1.23 mmol, 1 *equiv.*) in DCM (7 mL) was added *tert*-butyl-4-formylpiperidine-1-carboxylate (313.64 mg, 1.47 mmol, 1.2 *equiv.*) and acetic acid (7.36 mg, 122.55 μmol, 7.02 μL, 0.1 *equiv.*). The mixture was stirred at 25 °C for 1 hour, then $NaBH(OAc)_3$ (389.61 mg, 1.84 mmol, 1.5 *equiv.*) was added. The reaction mixture was stirred at 25 °C for 1 hour. Afterwards, the reaction mixture was quenched by the addition of aqueous ammonium chloride (5 mL) at 25 °C and then extracted with DCM (7 mL × 3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ ethyl acetate: 5/1 to 3/1) to provide *tert*-butyl-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)piperidine-1-carboxylate (0.3 g) as a white solid.

LC-MS (ESI): m/z = 524.3 $[M+H]^+$.

Preparation of 3-(1-methyl-6-(4-(piperidin-4-ylmethyl)piperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione

To a solution of *tert*-butyl-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)piperidine-1-carboxylate (300 mg, 572.89 μmol, *1 equiv.*) in DCM (2 mL) was added HCl in 1,4-dioxane (4 M, 2.86 mL, 19.96 *equiv.*). The mixture was stirred at 25 °C for 0.5 hours. Afterwards, the reaction mixture was concentrated under reduced pressure to give 3-(1-methyl-6-(4-(piperidin-4-ylmethyl)piperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (250 mg) as a white solid.

LC-MS (ESI): m/z = 424.3 $[M+H]^+$.

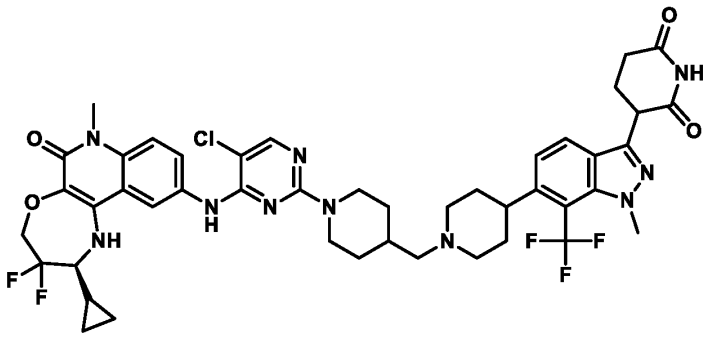
Preparation of 3-[6-[4-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]piperazin-1-yl]-1-methyl-indazol-3-yl]piperidine-2,6-dione

To a solution of 3-(1-methyl-6-(4-(piperidin-4-ylmethyl)piperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (156.78 mg, 370.16 μmol, 1.2 *equiv.*) in DMSO (1.5 mL) was added TEA (128.80 μL, 925.40 μmol, 3 *equiv.*) and (2*S*)-2-cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (150 mg, 308.47 μmol, 1 *equiv.*). The mixture was stirred at 100 °C for 1 hour. The reaction mixture was filtered, and the filtrate was concentrated to give a residue. The residue was purified by prep-HPLC to afford 3-[6-[4-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]piperazin-1-yl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (95.52 mg) as

a white solid.

LC-MS (ESI): m/z = 873.8 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 10.88 (d, J = 2.0 Hz, 1H), 8.84 (s, 1H), 8.20 (d, J = 6.0 Hz, 1H), 8.14 (d, J = 2.8 Hz,1H), 8.02 (d, J = 2.4 Hz, 1H), 7.61 (d, J = 7.4 Hz, 1H), 7.48 - 7.36 (m, 2H), 7.02 (d, J = 8.0 Hz, 1H), 6.45 (s, 1H), 4.50 -4.28 (m, 5H), 3.96 (d, J = 2.4 Hz, 3H), 3.55 (d, J = 2.4 Hz, 3H), 3.10 - 2.97 (m, 3H), 2.71 - 2.61 (m, 6H), 2.37 - 2.31 (m, 2H), 2.19 - 2.13 (m, 2H), 1.82 - 1.64 (m, 6H), 1.34 - 1.27 (m, 1H), 1.02 - 0.91 (m, 2H), 0.71 (d, J = 6.8 Hz, 1H), 0.51 (d, J = 6.4 Hz, 2H), 0.36 - 0.29 (m, 1H).

Example 32. 3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-4-piperidyl]-1-methyl-7-(trifluoromethyl)indazol-3-yl]piperidine-2,6-dione (Compound 158a)



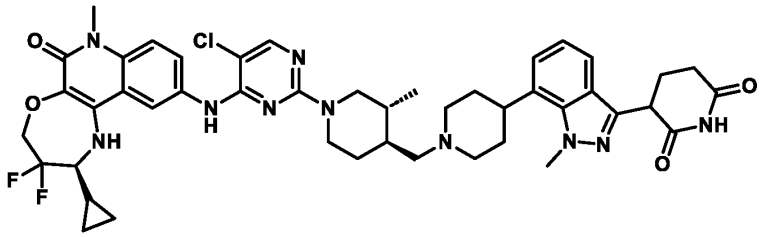
To a solution of 3-[1-methyl-6-[1-(4-piperidylmethyl)-4-piperidyl]-7-(trifluoromethyl)indazol-3-yl]piperidine-2,6-dione (See Table P6) (0.15 g, 305.16 μmol, 1 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (128.61 mg, 274.64 μmol, 0.9 *equiv.*) in DMSO (3 mL) was added TEA (169.90 μL, 1.22 mmol, 4 *equiv.*). The mixture was stirred at 100 °C for 1 hour. The reaction mixture was filtered. The crude product was purified by prep-HPLC to afford 3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-4-piperidyl]-1-methyl-7-(trifluoromethyl)indazol-3-yl]piperidine-2,6-dione (97.69 mg) as a pink solid.

LC-MS (ESI): m/z = 462.5 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ =10.92 (s, 1H), 8.77 (s, 1H), 8.16 (d, J = 1.6Hz, 1H), 8.11 (s, 1H), 8.05 - 7.94 (m, 2H), 7.71 (d, J = 2.0, 9.2Hz, 1H), 7.42 (d, J = 9.2Hz, 1H),

7.36 - 7.25 (m, 1H), 6.22 - 6.07 (m, 1H), 4.50 - 4.26 (m, 5H), 4.05 - 3.95 (m, 3H), 3.55 (s, 3H), 3.22 (d, J = 4.0Hz, 3H), 2.52 (s, 6H), 2.42 - 2.25 (m, 2H), 2.22 - 2.07 (m, 2H), 2.03 - 1.80 (m, 3H), 1.72 (d, J = 11.6Hz, 4H), 1.43 - 1.25 (m, 1H), 1.13 - 0.95 (m, 2H), 0.78 - 0.62 (m, 1H), 0.50 (t, J = 5.6Hz, 2H), 0.33 (d, J = 5.2Hz, 1H).

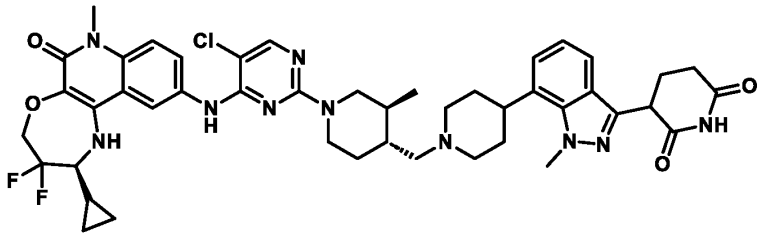
Example 33. 3-(7-(1-(((3*R*,4*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 101b)



A mixture of 3-(1-methyl-7-(1-(((3*R*,4*S*)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (See Table P6) (120 mg, 274.24 μmol, 1.0 *equiv.*), (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (141.26 mg, 301.66 μmol, 1.1 *equiv.*), and TEA (152.68 μL, 1.10 mmol, 4.0 *equiv.*) in DMSO (2 mL) was stirred at 100 °C for 3 hours. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to afford 3-(7-(1-(((3*R*,4*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (51.04 mg) as a yellow solid.

LC-MS (ESI): m/z = 869.3 $[M+H]^+$

Example 34. 3-(7-(1-(((3*S*,4*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methyl-piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 101a)



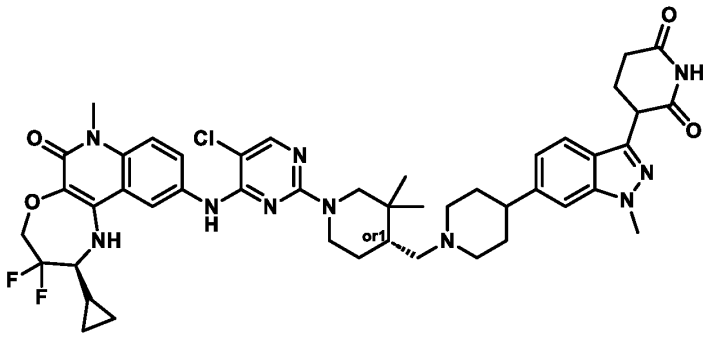
To a solution of 3-(1-methyl-7-(1-(((3*S*,4*R*)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (See Table P6) (150 mg, 316.43 μmol, 1.0 *equiv.*, HCl) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (148.18 mg, 316.43 μmol, 1.0 *equiv.*) in DMSO (4 mL) was added TEA (176.17 μL, 1.27 mmol, 4.0 *equiv.*). The mixture was stirred at 100 °C for 12 hours. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to afford 3-(7-(1-(((3*S*,4*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methyl-piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (86.23 mg) as a pink solid.

LC-MS (ESI): m/z = 869.4 $[M+H]^+$

Example 35. 3-(6-(1-(((*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

[3-(6-(1-(((*R)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]**

(Compound 129b)



To a stirred solution of 3-(6-(1-(((*R*)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (See Table P6) (0.20 g, 0.44 mmol, 2.5 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.082 g, 0.17 mmol, 1.0 *equiv.*) in DMSO (4.0 mL) was added DIPEA (0.7 mL, 4.40 mmol, 10 *equiv.*). The resulting reaction mixture was stirred at 110 °C for 6 hours. The reaction mixture was poured into ice cold water (20 mL) and the precipitated solid was filtered and dried to get crude product which was purified by Prep-HPLC to afford 3-(6-(1-(((*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-(1-(((*R**)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (0.16 g) as an off-white solid.

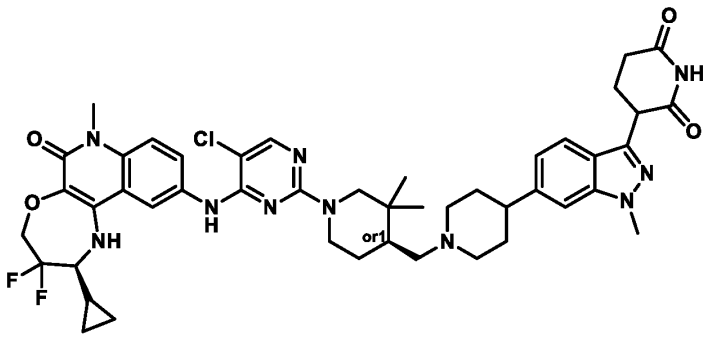
LC-MS (ESI): m/z = 883.76 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.87 (s, 1H), 8.75 (s, 1H), 8.16-8.14 (m, 1H), 8.00 (s, 1H), 7.75 (dd, *J* = 2.00, 9.20 Hz, 1H), 7.60 (d, *J* = 8.40 Hz, 1H), 7.44 (t, *J* = 8.40 Hz, 2H), 7.02 (d, *J* = 8.40 Hz, 1H), 6.15 (s, 1H), 4.46-4.44 (m, 4H), 4.20 (brs, 1H), 3.97 (s, 3H), 3.57 (s, 3H), 3.25 (brs, 1H), 3.07 (d, *J* = 9.20 Hz, 1H), 2.85 (d, *J* = 0.80 Hz, 1H), 2.58-2.56 (m, 4H), 2.37-2.36 (m, 2H), 2.09-2.05 (m, 3H), 1.90-1.70 (m, 4H), 1.51 (brs, 1H), 1.36 (s, 3H), 1.24 (brs, 2H), 0.93 (s, 3H), 0.70 (s, 4H), 0.53 (t, *J* = 5.60 Hz, 2H), 0.36 (d, *J* = 5.20 Hz, 1H).

Example 36. 3-(6-(1-(((*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

[3-(6-(1-(((*S)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]**

(Compound 129a)



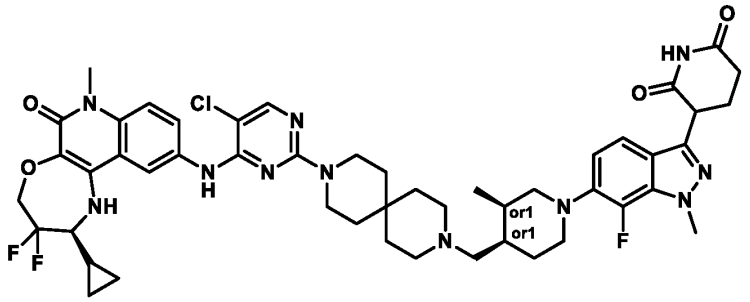
To a stirred solution of 3-(6-(1-(((*S*)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (See Table P6) (0.20 g, 0.50 mmol, 2.5 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.082 g, 0.17 mmol, 1.0 *equiv.*) in DMSO (4 mL) was added DIPEA (0.7 mL, 4.43 mmol, 9.9 *equiv.*). The resulting reaction mixture was stirred at 110 °C for 6 hours. The reaction mixture was poured into ice cold water (20 mL). The solid precipitated was filtered and dried to get crude product which was purified by Prep-HPLC to afford 3-(6-(1-(((*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-(1-(((*S**)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (30.0 mg) as an off-white solid.

LC-MS (ESI): m/z = 883.76 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.87 (s, 1H), 8.73 (s, 1H), 8.16 (s, 1H), 8.00 (s, 1H), 7.76 (d, *J* = 8.80 Hz, 1H), 7.60 (d, *J* = 8.40 Hz, 1H), 7.44-7.42 (m, 2H), 7.02 (d, *J* = 8.40 Hz, 1H), 6.18 (s, 1H), 4.32-4.30 (m, 4H), 4.10 (brs, 1H), 3.97 (s, 3H), 3.58 (s, 3H), 3.20 (brs, 1H), 3.05 (d, *J* = 19.00 Hz, 1H), 2.85 (d, *J* = 19.00 Hz, 1H), 2.60-2.57 (m, 5H), 2.32-2.29 (m, 2H), 2.14-2.05 (m, 3H), 1.77-1.74 (m, 4H), 1.49 (s, 1H), 1.36-1.24 (m, 4H), 0.91 (s, 3H), 0.72-0.69 (m, 4H), 0.52-0.50 (m, 2H), 0.36 (s, 1H).

Example 37. 3-(6-((3*R*,4*R*)-4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-((3*R,4*R**)-4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]**

(Compound 107d)



To a stirred solution of 3-(6-((3*R*,4*R*)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (See Table P6) (0.15 g, 0.28 mmol, 1.0 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.026 g, 0.06 mmol, 0.2 *equiv.*) in DMSO (1.5 mL) was added DIPEA (0.48 mL, 2.80 mmol, 10 *equiv.*). The resulting reaction mixture was stirred at 100 °C for 18 hours. The reaction mixture was poured into ice cold water (20 mL). The solid precipitated was filtered and dried to get crude product which was purified by Prep-HPLC to afford 3-(6-((3*R*,4*R*)-4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-((3*R**,4*R**)-4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (0.03 g) as an off-white solid.

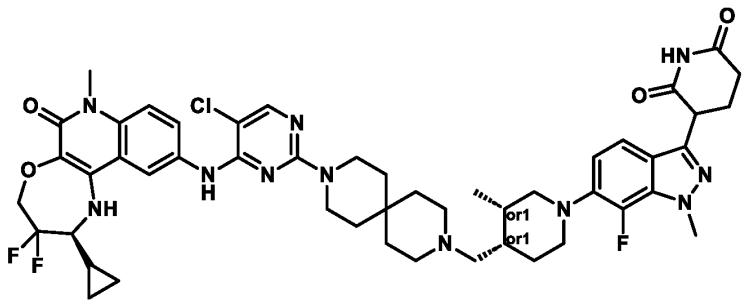
LC-MS (ESI): m/z = 956.58 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.89 (s, 1H), 8.77 (s, 1H), 8.19 (d, J = 2.00 Hz, 1H), 8.02 (s, 1H), 7.73 (dd, J = 1.60, 9.00 Hz, 1H), 7.44 (d, J = 9.20 Hz, 1H), 7.37 (d, J = 8.80 Hz, 1H), 6.89-6.87 (m, 1H), 6.19 (br s, 1H), 4.42-4.41 (m, 3H), 4.06 (s, 3H), 3.57 (s, 7H), 3.21-3.18 (m, 3H), 2.87-2.80 (m, 1H), 2.63-2.61 (m, 1H), 2.60-2.59 (m, 2H), 2.33-2.32 (m, 5H), 2.14-2.13 (m, 3H), 1.93-1.91 (m, 1H), 1.85-1.84 (m, 1H), 1.38-1.36 (m, 11H), 1.00 (d, J = 6.40 Hz, 3H), 0.72-0.70 (m, 1H), 0.53-0.51 (m, 2H), 0.35-0.34 (m, 1H).

Example 38. 3-(6-((3S,4S)-4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

[3-(6-((3S*,4S*)-4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]

(Compound 107b)



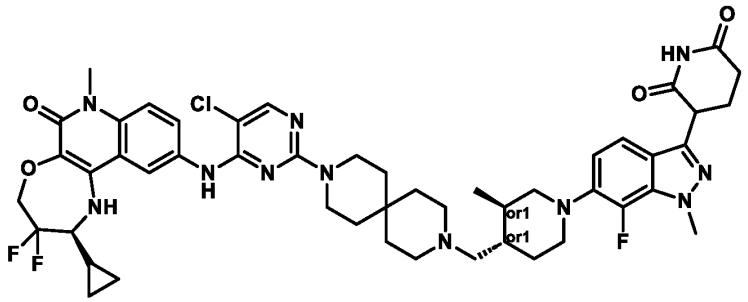
To a stirred solution of 3-(6-((3S,4S)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (See Table P6) (0.10 g, 0.19 mmol, 1.0 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.017 g, 0.04 mmol, 0.2 *equiv.*) in DMSO (1.5 mL) was added DIPEA (0.35 mL, 1.90 mmol, 10 *equiv.*). The resulting reaction mixture was stirred at 100 °C for 18 hours. The reaction mixture was poured into ice cold water (20 mL). The solid precipitated was filtered and dried to obtain crude product which was purified by prep-HPLC to afford 3-(6-((3S,4S)-4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-

[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-((3S*,4S*)-4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (0.03 g) as an off-white solid.

LC-MS (ESI): m/z = 956.58 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.88 (s, 1H), 8.77 (s, 1H), 8.33 (s, 1H), 8.19 (d, *J* = 1.60 Hz, 1H), 7.72 (dd, *J* = 2.00, 9.00 Hz, 1H), 7.44 (d, *J* = 9.20 Hz, 1H), 7.37 (d, *J* = 8.80 Hz, 1H), 6.89-6.87 (m, 1H), 6.18 (br s, 1H), 4.42-4.41 (m, 3H), 4.06 (s, 3H), 3.57 (s, 7H), 3.32-3.18 (m, 3H), 2.87-2.80 (m, 2H), 2.60-2.59 (m, 2H), 2.33-2.31 (m, 5H), 2.14-2.13 (m, 3H), 1.93-1.90 (m, 1H), 1.82-1.81 (m, 1H), 1.38-1.36 (m, 11H), 1.00-0.92 (d, *J* = 6.40 Hz, 3H), 0.72-0.71 (m, 1H), 0.53-0.51 (m, 2H), 0.35-0.34 (m, 1H).

Example 39. 3-(6-((3*R*,4*S*)-4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-((3*R,4*S**)-4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (Compound 107a)**



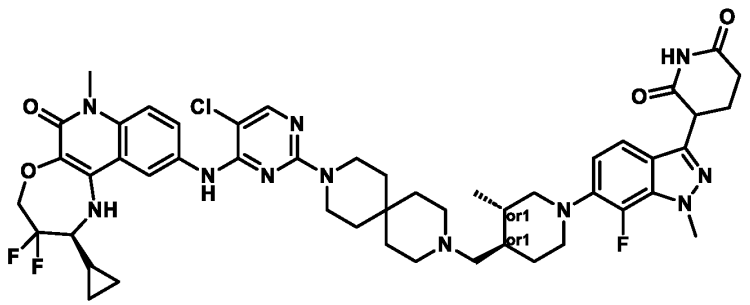
To a stirred solution of 3-(6-((3*R*,4*S*)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (See Table P6)

(0.18 g, 0.343 mmol, 1.0 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.032 g, 0.069 mmol, 0.2 *equiv.*) in DMSO (2.7 mL) was added DIPEA (1.79 mL). The reaction was heated at 100 °C and stirred for 16 hours. The reaction mixture was poured into ice water (10 mL). The solid precipitated was filtered and dried to get crude product which was purified by reverse phase chromatography to afford 3-(6-((3*R*,4*S*)-4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-((3*R**,4*S**)-4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (0.041 g) as off-white solid.

LC-MS (ESI): m/z = 956.79 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.89 (s, 1H), 8.77 (s, 1H), 8.30 (s, 1H), 8.19 (d, *J* = 2.00 Hz, 1H), 8.02 (s, 1H), 7.727 (dd, *J* = 11.2 Hz, 1H), 7.44 (d, *J* = 8.80 Hz, 1H), 7.38 (d, *J* = 8.80 Hz, 1H), 6.91 (t, *J* = 15.60 Hz, 1H), 6.18 (s, 1H), 4.41-4.29 (m, 3H), 4.06 (s, 3H), 3.57 (s, 6H), 3.24-3.17 (brs, 3H), 2.64-2.56 (m, 2H), 2.42 (t, *J* = 11.20 Hz, 5H), 2.22-2.17 (m, 4H), 2.16-2.09 (m, 1H), 1.45-1.23 (m, 13H), 0.94 (d, *J* = 6.40 Hz, 3H), 0.75-0.72 (m, 1H), 0.51 (t, *J* = 10.80 Hz, 2H), 0.36 (m, 1H).

Example 40. 3-(6-((3*S*,4*R*)-4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-((3*S,4*R**)-4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (Compound 107c)**



To a stirred solution of 3-(6-((3*S*,4*R*)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (See Table P6) (0.20 g, 0.38 mmol, 1.0 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.036 g, 0.076 mmol, 0.2 *equiv.*) in DMSO (3.0 mL) was added DIPEA (2.0 mL). The reaction was heated at 100 °C and stirred for 16 hours. The reaction mixture was poured into ice water (20 mL). The solid precipitated was filtered and dried to get crude product which was purified by reverse phase chromatography to afford 3-(6-((3*S*,4*R*)-4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-((3*S**,4*R**)-4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (0.042 g) as a pale brown solid.

LC-MS (ESI): m/z = 956.79 $[M+H]^+$.

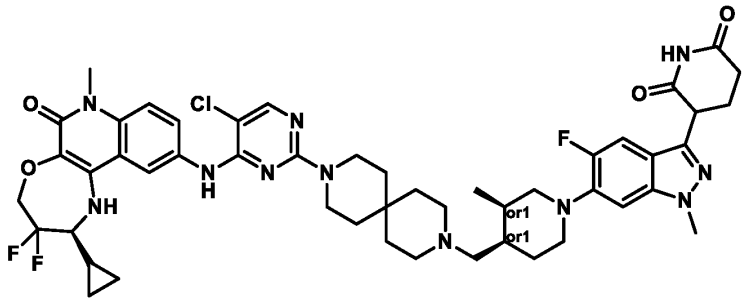
^{1}H NMR (400 MHz, DMSO-d_6): δ 10.89 (s, 1H), 8.77 (s, 1H), 8.22 (s, 1H), 8.19 (d, *J* = 2.00 Hz, 1H), 8.02 (s, 1H), 7.725 (dd, *J* = 11.2 Hz, 1H), 7.44 (d, *J* = 9.20 Hz, 1H), 7.38 (d, *J* = 8.80 Hz, 1H), 6.90 (t, *J* = 22.80 Hz, 1H), 6.18 (s, 1H), 4.41-4.29 (m, 3H), 4.06 (s, 3H), 3.57 (s, 6H), 3.26-3.22 (brs, 3H), 2.64-2.59 (m, 2H), 2.43-2.41 (m, 5H), 2.22-2.09 (m, 4H), 1.93 (m, 1H), 1.45-1.23 (m, 13H), 0.94 (d, *J* = 6.40 Hz, 3H), 0.72 (m, 1H), 0.51 (t, *J* = 11.20 Hz, 2H), 0.35 (m, 1H).

Example 41. 3-(6-((3*R*,4*R*)-4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-

yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

[3-(6-((3*R,4*R**)-4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]**

(Compound 119a)



To a stirred solution of 3-(6-((3*R*,4*R*)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (See Table P6) (0.08 g, 0.15 mmol, 1.0 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.02 g, 0.04 mmol, 0.2 *equiv.*) in DMSO (1.20 mL) was added DIPEA (0.8 mL). The mixture was heated at 100 °C and stirred for 16 hours. The reaction mixture was poured into ice water (10 mL). The solid precipitated was filtered and dried to get crude product which was purified by Prep-HPLC to afford 3-(6-((3*R*,4*R*)-4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-((3*R**,4*R**)-4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (0.026 g) as an off-white solid.

LC-MS (ESI): m/z = 956.52 $[M+H]^+$.

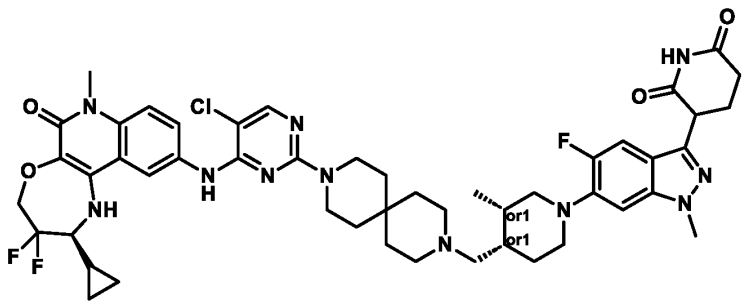
^{1}H NMR (400 MHz, DMSO-d_6): δ 10.85 (s, 1H), 8.92 (s, 1H), 8.72 (brs, 1H), 8.20 (s, 1H), 8.06 (s, 1H), 7.69 (d, *J* = 8.00 Hz, 1H), 7.45 (q, *J* = 19.20 Hz, 2H), 6.24 (s, 1H), 4.28-4.25 (m, 2H), 3.95 (s, 3H), 3.58 (s, 7H), 3.28-3.13 (brs, 8H), 2.97 (m, 2H), 2.65-2.60 (m, 1H), 2.45-

2.42 (m, 1H), 2.34 (s, 1H), 2.15 (m, 1H), 2.09-2.06 (m, 1H), 1.83 (dd, 2H), 1.56 (s, 8H), 1.47 (brs, 3H), 1.24-1.22 (m, 1H), 0.98 (d, J = 5.20 Hz, 3H), 0.73-0.71 (m, 1H), 0.51 (t, J = 5.20 Hz, 2H), 0.35-0.33 (m, 1H).

Example 42. 3-(6-((3S,4S)-4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

[3-(6-((3S*,4S*)-4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]

(Compound 119d)



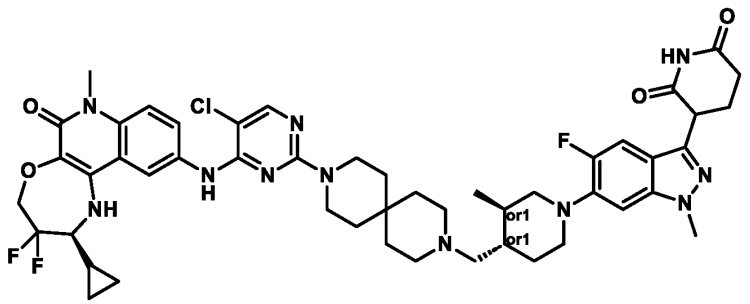
To a stirred solution of 3-(6-((3S,4S)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (See Table P6) (0.30 g, 0.57 mmol, 1.0 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.08 g, 0.17 mmol, 0.3 *equiv.*) in DMSO (4.50 mL) was added DIPEA (3.0 mL). The mixture was heated at 100 °C and stirred for 16 hours. The reaction mixture was poured into ice water (20 mL). The solid precipitated was filtered and dried to get crude product which was purified by Prep-HPLC to afford 3-(6-((3S,4S)-4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-((3S*,4S*)-4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-

yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (0.053 g) as an off-white solid.

LC-MS (ESI): m/z = 956.48 $[M+H]^+$

Example 43. 3-(6-((3*R*,4*S*)-4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-((3*R,4*S**)-4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]**

(Compound 119c)



To a stirred solution of 3-(6-((3*R*,4*S*)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (See Table P6) (0.12 g, 0.22 mmol, 1.0 *equiv.*), (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.03 g, 0.068 mmol, 0.3 *equiv.*) in DMSO (1.8 mL) was added DIPEA (0.8 mL). The mixture was heated at 100 °C and stirred for 16 hours. The reaction mixture was poured into ice water (10 mL). The precipitated solid was filtered and dried under vacuum to obtain crude product which was purified by Prep-HPLC to afford 3-(6-((3*R*,4*S*)-4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-((3*R**,4*S**)-4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-

methylpiperidin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (0.024 g) as off-white solid.

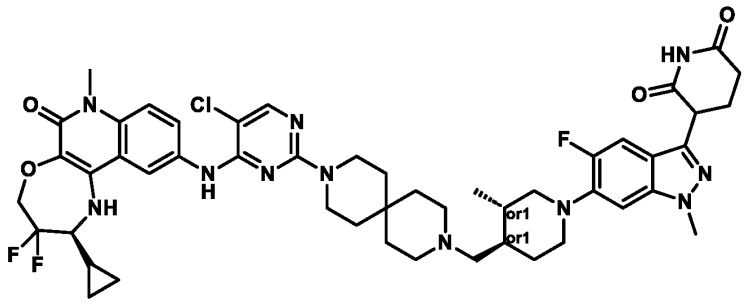
LC-MS (ESI): m/z = 956.62 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.85 (s, 1H), 8.96 (s, 1H), 8.64 (s, 1H), 8.06 (s, 1H), 7.69 (s, 1H),7.44-7.42 (m, 2H),7.21 (s, 1H),6.23 (s, 1H), 4.42 (s, 2H),4.27-4.25 (m, 1H), 3.95 (s, 3H), 3.57-3.46 (m, 7H),2.98 (d, *J* = 11.20 Hz, 2H), 2.61-2.60 (m, 2H), 2.60 (s, 2H), 2.50-2.45 (m, 3H), 2.18 (m, 2H),1.93 (m, 1H), 1.61 (d, *J* = 18.40 Hz, 2H),1.62-1.57 (m, 7H), 1.57-1.62 (m, 7H),0.98 (d, *J* = 5.20 Hz, 3H),0.53 (d, *J* = 5.60 Hz, 1H), 0.51 (t, *J* = 5.20 Hz, 2H), 0.35-0.33 (m, 1H).

Example 44. 3-(6-((3*S*,4*R*)-4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

[3-(6-((3*S,4*R**)-4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]**

(Compound 119b)



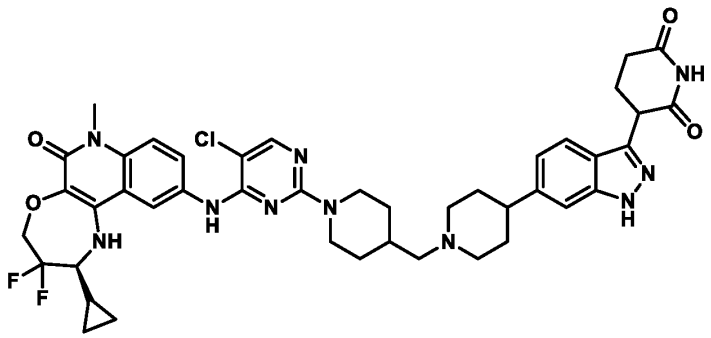
To a stirred solution of 3-(6-((3*S*,4*R*)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (See Table P6) (0.05 g, 0.09 mmol, 1.0 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.02 g, 0.05 mmol, 0.5 *equiv.*) in DMSO (1.0 mL) was added DIPEA (0.13 mL, 0.76 mmol, 8.0 *equiv.*). The mixture was heated to 100 °C and stirred for 3 hours. The reaction mixture was poured into ice water (20 mL). The precipitated solid was filtered and dried under vacuum to obtain crude product which was purified by prep-SFC to afford 3-(6-((3*S*,4*R*)-4-((9-(5-

chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-((3*S**,4*R**)-4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-3-methylpiperidin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (0.0056 g) as off-white solid.

LC-MS (ESI): m/z = 956.58 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.85 (s, 1H), 8.84 (br s, 1H), 8.19 (s, 1H), 8.04 (s, 1H), 7.70 (br s, 1H), 7.46-7.42 (m, 2H), 7.08 (d, J = 6.80 Hz, 1H), 6.22 (br s, 1H), 4.47-4.38 (m, 2H), 4.29-4.25 (m, 1H), 3.95 (s, 3H), 3.61-3.57 (m, 8H), 3.22-3.17 (m, 1H), 2.97 (br s, 1H), 2.62-2.61 (m, 4H), 2.41-2.37 (m, 4H), 2.16-2.05 (m, 4H), 1.85-1.81 (m, 1H), 1.59-1.36 (m, 12H), 0.98-0.96 (d, 3H), 0.72-0.69 (m, 1H), 0.53-0.50 (m, 2H), 0.35-0.33 (m, 1H).

Example 45. 3-(6-(1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 173a)



To a stirred solution of 3-(6-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (See Table P6) (0.3 g, 0.50 mmol, 1.0 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.07 g, 0.15 mmol, 0.3 *equiv.*) in DMSO (3.0 mL) was added DIPEA (0.4 mL, 2.5 mmol, 5.0 *equiv.*). The resulting reaction mixture was stirred at 100 °C for 6 hours. The reaction mixture was cooled to room temperature, quenched with ice-cold water, and the resulting precipitate was filtered and dried to get crude product which was purified by prep-HPLC to afford 3-(6-(1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-

yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (0.057 g) as a pale yellow solid.

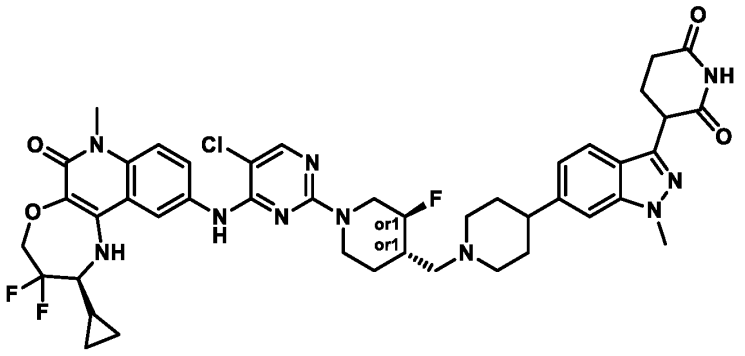
LC-MS (ESI): m/z = 841.64 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.80 (s, 1H), 10.89 (s, 1H), 8.96 (s, 1H), 8.82 (brs, 1H), 8.17 (d, J = 1.60Hz, 1H), 8.08 (s, 1H), 7.74 (dd, J = 2.00, 8.80Hz, 1H), 7.68 (d, J = 8.40Hz, 1H), 7.43 (s, 1H), 6.99-6.96 (m, 2H), 6.25 (s, 1H), 4.34-4.33 (m, 6H), 3.62-3.59 (m, 2H), 3.57 (s, 3H), 3.23-3.13 (m, 2H), 2.99-2.95 (m, 7H), 2.58-2.60 (m, 2H), 2.09-2.02 (m, 6H), 1.75-1.74 (m, 2H), 1.15-1.12 (m, 2H), 0.71-0.70 (m, 1H), 0.51-0.53 (m, 2H), 0.35-0.34 (m, 1H).

Example 46. 3-(6-(1-(((3S,4S)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

[3-(6-(1-(((3S*,4S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]

(Compound 110f)



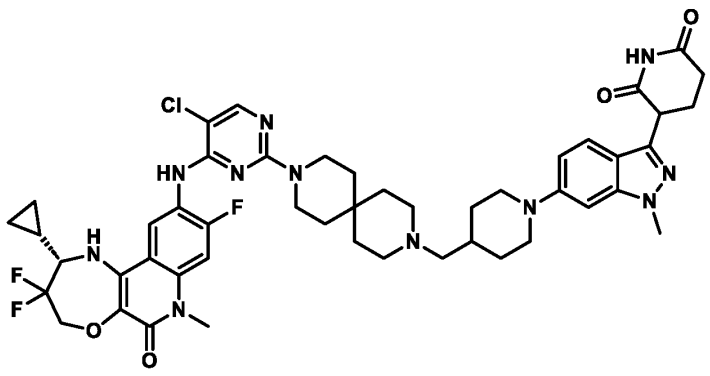
To a stirred solution of 3-(6-(1-(((3S,4S)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (See Table P6) (0.15 g, 0.34 mmol, 1.0 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.04 g, 0.08 mmol, 0.2 *equiv.*) in DMSO (1.5 mL) was added DIPEA (1.5 mL). The reaction mixture was heated at 100 °C for 18 hours. The reaction mixture was quenched with ice cold water (50 mL) and the precipitated solid was filtered and dried under vacuum to afford crude product which was purified by Prep-

HPLC to afford 3-(6-(1-(((3S,4S)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-(1-(((3S*,4S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (0.053 g) as off white solid.

LC-MS (ESI): m/z = 873.50 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.87 (s, 1H), 8.89 (s, 1H), 8.20-8.18 (m, 2H), 7.72 (d, *J* = 1.60 Hz, 1H), 7.70 (d, *J* = 2.00 Hz, 1H), 7.44-7.42 (m, 2H), 7.03 (d, *J* = 8.40 Hz, 1H), 6.22 (brs, 1H), 4.45-4.30 (m, 5H), 4.23 (brs, 1H), 3.96 (s, 3H), 3.57 (s, 3H), 3.25 (s, 2H), 3.21-3.07 (m, 2H), 3.01 (d, *J* = 9.40 Hz, 1H), 2.61-2.60 (brs, 4H), 2.50-2.36 (m, 1H), 2.30-2.28 (m, 1H), 2.18-2.14 (m, 2H), 1.97-1.94 (m, 3H), 1.85-1.77 (m, 4H), 1.38-1.36 (m, 1H), 1.31-1.29 (m, 1H), 0.71-0.68 (m, 1H), 0.52 (t, *J* = 4.80 Hz, 2H), 0.35 (d, *J* = 4.80 Hz, 1H).

Example 47. 3-(6-(4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)piperidin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 165a)

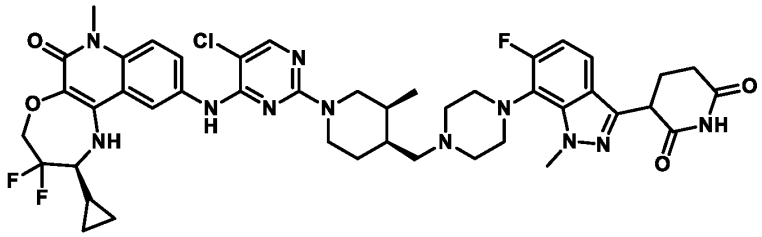


To a solution of 3-[6-[4-(3,9-diazaspiro[5.5]undecan-3-ylmethyl)-1-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (See Table P6) (150 mg, 228.35 μmol, 1 *equiv.*) in DMSO (2 mL) was added TEA (127.14 μL, 913.42 μmol, 4 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3,9-trifluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (88.83 mg, 182.68 μmol, 0.8 *equiv.*). The mixture

was stirred at 100 °C for 2 hours. The reaction mixture was filtered. The residue was purified by prep-HPLC to afford 3-(6-(4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)piperidin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (66.94 mg) as an off-white solid.

LC-MS (ESI): m/z = 942.1 $[M+H]^+$

Example 48. 3-(7-(4-(((3S,4S)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperazin-1-yl)-6-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 148a)



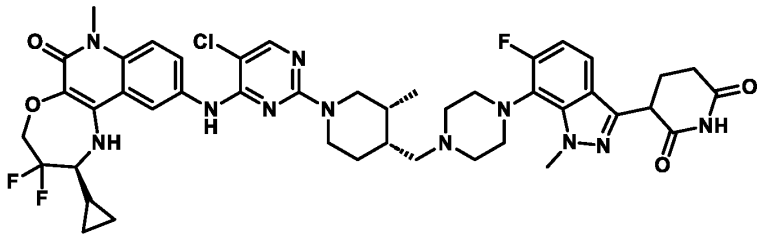
To a solution of 3-[6-fluoro-1-methyl-7-[4-[[(3S,4S)-3-methyl-4-piperidyl]methyl]piperazin-1-yl]indazol-3-yl]piperidine-2,6-dione (See Table P6) (50 mg, 109.52 μmol, 1 *equiv.*) in DMSO (3 mL) was added TEA (60.97 μL, 438.06 μmol, 4 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (51.28 mg, 109.52 μmol, 1 *equiv.*). The mixture was stirred at 100 °C for 2 hours. The reaction mixture was filtered, and the filtrate was concentrated to give a residue. The residue was purified by prep-HPLC to afford 3-(7-(4-(((3S,4S)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperazin-1-yl)-6-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (33.81 mg) as a yellow solid.

LC-MS (ESI): m/z = 888.4 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.88 (s, 1H), 8.71 (s, 1H), 8.24 (s, 1H), 8.01 (s, 1H), 7.78 (dd, J = 2.0, 9.2Hz, 1H), 7.54 (dd, J = 4.4, 8.8Hz, 1H), 7.46 (d, J = 9.2Hz, 1H), 6.97 (dd, J = 8.8, 12.4Hz, 1H), 6.17 (br s, 1H), 4.49 - 4.31 (m, 4H), 4.26 (s, 4H), 3.58 (s, 3H), 3.20-3.30 (m, 2H), 3.00 (br d, J = 3.6Hz, 3H), 2.84 (br d, J = 14.8Hz, 3H), 2.70 - 2.57 (m, 2H), 2.40 - 2.07 (m, 7H), 1.92 (br d, J = 3.2Hz, 2H), 1.49 - 1.28 (m, 3H), 0.76 (br d, J = 6.4Hz, 3H), 0.71

(br d, J = 6.8Hz, 1H), 0.52 (br t, J = 6.0Hz, 2H), 0.35 (br d, J = 5.2Hz, 1H)

Example 49. 3-[7-[4-[[(3*R*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]methyl]piperazin-1-yl]-6-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (Compound 148b)



To a solution of 3-[6-fluoro-1-methyl-7-[4-[[(3*R*,4*R*)-3-methyl-4-piperidyl]methyl]piperazin-1-yl]indazol-3-yl]piperidine-2,6-dione (See Table P6) (100 mg, 219.03 μmol, 1 *equiv.*) in DMSO (4 mL) was added TEA (121.95 μL, 876.13 μmol, 4 *equiv.*) and (2*S*)-2-cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3-difluoro-7-methyl-2,4-dihydro1H-[1,4]oxazepino[2,3-c]quinolin-6-one (102.57 mg, 219.03 μmol, 1 *equiv.*). The mixture was stirred at 100 °C for 2 hours. The reaction mixture was filtered, and the filtrate was concentrated to give a residue. The residue was purified by prep-HPLC to afford 3-[7-[4-[[(3*R*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]methyl]piperazin-1-yl]-6-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (31.56 mg) as a grey solid.

LC-MS (ESI): m/z = 888.4 $[M+H]^+$.

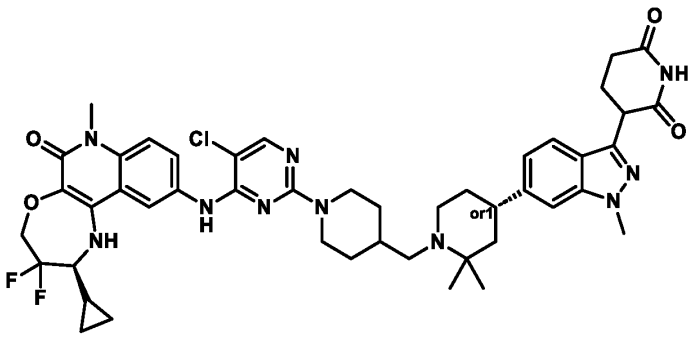
^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.89 (s, 1H), 8.74 (s, 1H), 8.25 (s, 1H), 8.16 (br s, 1H), 8.01 (s, 1H), 7.78 (br d, J = 8.0 Hz, 1H), 7.54 (dd, J = 4.4, 8.8 Hz, 1H), 7.47 (d, J = 9.2 Hz, 1H), 6.98 (dd, J = 8.8, 12.4 Hz, 1H), 6.18 (br s, 1H), 4.52 - 4.31 (m, 4H), 4.27 (s, 4H), 3.58 (s, 3H), 3.11 - 2.74 (m, 7H), 2.72 - 2.59 (m, 2H), 2.42 - 2.04 (m, 7H), 1.94 (br d, J = 4.4 Hz, 2H), 1.50 - 1.23 (m, 3H), 0.78 (br d, J = 6.4 Hz, 3H), 0.71 (br s, 1H), 0.53 (br t, J = 5.6 Hz, 2H), 0.45 - 0.30 (m, 1H)

Example 50. 3-(6-((*S*)-1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-

yl)piperidin-4-yl)methyl)-2,2-dimethylpiperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

[3-(6-((*S)-1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)-2,2-dimethylpiperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]**

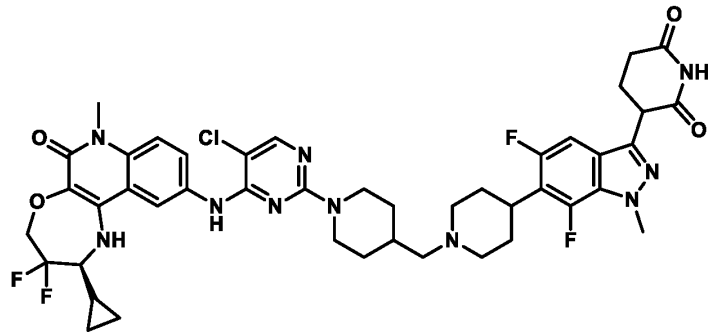
(Compound 112a)



To a solution of 3-[6-[(4S)-2,2-dimethyl-1-(4-piperidylmethyl)-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (See Table P6) (435.00 mg, 963.24 μmol, 1 *equiv.*) in DMSO (1 mL) was added TEA (536.28 μL, 3.85 mmol, 4 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (541.28 mg, 1.16 mmol, 1.2 *equiv.*). The mixture was stirred at 100 °C for 5 hours. The reaction mixture was filtered, and the filtrate was concentrated to give a residue. The residue was purified by prep-HPLC to afford 3-(6-((*S*)-1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)-2,2-dimethylpiperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-((*S**)-1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)-2,2-dimethylpiperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (273 mg) as a yellow solid.

LC-MS (ESI): m/z = 883.9 $[M+H]^+$

Example 51. 3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (Compound 132a)



Preparation of 3-bromo-2,4-difluoro-6-iodo-aniline

To a solution of 3-bromo-2,4-difluoro-aniline (250 g, 1.20 mol, 1 *equiv.*) in EtOH (2500 mL) was added Ag_2SO_4 (374.75 g, 1.20 mol, 203.67 mL, 1 *equiv.*) and I_2 (335.56 g, 1.32 mol, 266.32 mL, 1.1 *equiv.*). The reaction mixture was stirred at 25 °C for 2.5 hours. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 1/0 to 10/1) to afford 3-bromo-2,4-difluoro-6-iodo-aniline (290 g) as a red oil.

LC-MS (ESI): m/z = 333.8 $[M+H]^+$

Preparation of 3-bromo-2,4-difluoro-6-methyl-aniline

A mixture of 3-bromo-2,4-difluoro-6-iodo-aniline (30 g, 89.85 mmol, 1 *equiv.*), 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (33.84 g, 134.77 mmol, 37.68 mL, 1.5 *equiv.*), $PdCl_2$(dtbpf) (4.10 g, 6.29 mmol, 0.07 *equiv.*), and potassium phosphate (1.5 M in water, 179.69 mL, 3 *equiv.*) in dioxane (300 mL) was degassed and purged with N_2 three times. The resulting mixture was stirred at 100 °C for 5 hours under N_2 atmosphere. The reaction mixture was diluted with H_2O (300 mL) and extracted with ethyl acetate (900 mL). The combined organic layers were washed with brine (900 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by reverse-phase HPLC to afford 3-bromo-2,4-difluoro-6-methyl-aniline (5.4 g) as a yellow solid.

LC-MS (ESI): m/z = 221.9 $[M+H]^+$

Preparation of (*E*)-1-(3-bromo-2,4-difluoro-6-methylphenyl)-2-(*tert*-butylthio)diazene

To a solution of 3-bromo-2,4-difluoro-6-methyl-aniline (18 g, 81.07 mmol, 1 *equiv.*) in HCl (8 M, 179.98 mL, 17.76 *equiv.*) was added dropwise sodium nitrite (6.15 g, 89.18 mmol, 1.1 *equiv.*) in H_2O (20 mL) at 0 °C. After addition, the resulting mixture was stirred at 0 °C for

0.5 hours. To this mixture, 2-methylpropane-2-thiol (8.04 g, 89.18 mmol, 10.04 mL, 1.1 *equiv.*) in EtOH (40 mL) was added dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 1 hour. The reaction mixture was diluted with H_2O (200 mL) and extracted with ethyl acetate (600 mL). The combined organic layers were washed with brine (900 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (0% ethyl acetate/petroleum ether) to afford (*E*)-1-(3-bromo-2,4-difluoro-6-methylphenyl)-2-(*tert*-butylthio)diazene (14 g) as a yellow solid.

LC-MS (ESI): m/z = 323.0 $[M+H]^+$

Preparation of 6-bromo-5,7-difluoro-1*H*-indazole

To a solution of (*E*)-1-(3-bromo-2,4-difluoro-6-methylphenyl)-2-(*tert*-butylthio)diazene (42.11 g, 130.29 mmol, 1 *equiv.*) in THF (420 mL) was added *t*-BuOK (1 M, 130.29 mL, 1 *equiv.*). The mixture was stirred at 25 °C for 0.5 hours. The reaction mixture was diluted with H_2O (500 mL), and the mixture was acidified using formic acid to pH = 2~3. The reaction mixture was extracted with ethyl acetate (1500 mL). The combined organic layers were washed with brine (1500 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (5-10% ethyl acetate/petroleum ether) to afford 6-bromo-5,7-difluoro-1*H*-indazole (15.3 g) as a white solid.

LC-MS (ESI): m/z = 232.9 $[M+H]^+$

Preparation of 6-bromo-5,7-difluoro-3-iodo-1*H*-indazole

To a solution of 6-bromo-5,7-difluoro-1*H*-indazole (15.3 g, 65.66 mmol, 1 *equiv.*) in DMF (153 mL) was added KOH (5.53 g, 98.49 mmol, 1.5 *equiv.*) and I_2 (25.00 g, 98.49 mmol, 19.84 mL, 1.5 *equiv.*). The mixture was stirred at 25 °C for 0.5 hours. The mixture was used in the next step without further work up as crude 6-bromo-5,7-difluoro-3-iodo-1*H*-indazole (23.5 g).

Preparation of 6-bromo-5,7-difluoro-3-iodo-1-methyl-indazole

To a stirred solution of 6-bromo-5,7-difluoro-3-iodo-1*H*-indazole (23.5 g, 65.48 mmol, 1 *equiv.*) was added iodomethane (27.88 g, 196.43 mmol, 12.23 mL, 3 *equiv.*). The mixture was stirred at 25 °C for 2 hours. The reaction mixture was diluted with H_2O (200 mL) and extracted with ethyl acetate (600 mL). The combined organic layers were washed with brine (900 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give

a residue. The residue was purified by flash silica gel chromatography (0~5% ethyl acetate/petroleum ether) to afford 6-bromo-5,7-difluoro-3-iodo-1-methyl-indazole (3.8 g) as a black solid.

LC-MS (ESI): m/z = 372.8 $[M+H]^+$

Preparation of 6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazole

A mixture of 6-bromo-5,7-difluoro-3-iodo-1-methyl-indazole (9.5 g, 25.47 mmol, 1 *equiv.*), 2,6-dibenzyloxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (9.57 g, 22.93 mmol, 0.9 *equiv.*), $Pd(dppf)Cl_2$ (1.86 g, 2.55 mmol, 0.1 *equiv.*), and cesium carbonate (20.75 g, 63.68 mmol, 2.5 *equiv.*) in 1,4 dioxane (30 mL) and H_2O (10 mL) was degassed and purged with N_2 three times. The mixture was stirred at 100 °C for 1 hour under N_2 atmosphere. The reaction mixture was diluted with H_2O (20 mL) and extracted with ethyl acetate (90 mL). The combined organic layers were washed with brine (90 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (5% ethyl acetate/petroleum ether) to afford 6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazole (6.3 g) as a white solid.

LC-MS (ESI): m/z = 536.0 $[M+H]^+$

Preparation of 4-bromo-1,2,3,6-tetrahydropyridine

A solution of *tert*-butyl-4-bromo-3,6-dihydro-2*H*-pyridine-1-carboxylate (5 g, 19.07 mmol, 1 *equiv.*) in HCl (4 M, 47.68 mL, 10 *equiv.*) was stirred at 25 °C for 3 hours. The reaction mixture was filtered to afford 4-bromo-1,2,3,6-tetrahydropyridine (3.3 g) as a white solid.

LC-MS (ESI): m/z = 164.2 $[M+H]^+$

Preparation of *tert*-butyl-4-[(4-bromo-3,6-dihydro-2H-pyridin-1-yl)methyl]piperidine-1-carboxylate

A solution of 4-bromo-1,2,3,6-tetrahydropyridine (3 g, 15.11 mmol, 1 *equiv.*) and *tert*-butyl-4-formylpiperidine-1-carboxylate (3.55 g, 16.63 mmol, 1.1 *equiv.*) in DCM (40 mL) was stirred at 25 °C for 2 hours followed by the addition of $NaBH(OAc)_3$ (4.80 g, 22.67 mmol, 1.5 *equiv.*). The reaction mixture was stirred at 25 °C for 1 hour. The reaction mixture was then filtered and concentrated to give a residue. The residue was purified by flash silica gel chromatography (0~5% MeOH/DCM) to give *tert*-butyl-4-[(4-bromo-3,6-dihydro-2H-pyridin-1-yl)methyl]piperidine-1-carboxylate (5 g) as a brown oil.

LC-MS (ESI): m/z = 361.0 $[M+H]^+$

Preparation of *tert*-butyl-4-[[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridin-1-yl]methyl]piperidine-1-carboxylate

To a solution of *tert*-butyl-4-[(4-bromo-3,6-dihydro-2H-pyridin-1-yl)methyl]piperidine-1-carboxylate (2 g, 5.57 mmol, 1 *equiv.*) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1.41 g, 5.57 mmol, 1 *equiv.*) in toluene (30 mL) was added $Pd(dppf)Cl_2$ (407.29 mg, 556.64 μmol, 0.1 *equiv.*) and KOAc (1.64 g, 16.70 mmol, 3 *equiv.*). The reaction was stirred at 70 °C for 2 hours under N_2 atmosphere. The reaction mixture was filtered and concentrated to give *tert*-butyl-4-[[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridin-1-yl]methyl]piperidine-1-carboxylate (4 g, crude) as a black oil.

LC-MS (ESI): m/z = 407.1 $[M+H]^+$

Preparation of *tert*-butyl-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridin-1-yl]methyl]piperidine-1-carboxylate

To a solution of 6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazole (500 mg, 932 μmol, 1 *equiv.*) and *tert*-butyl-4-[[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridin-1-yl]methyl]piperidine-1-carboxylate (3.8 g, 9.33 mmol, 10 *equiv.*) in dioxane (20 mL) and water (5 mL) was added $Pd(dppf)Cl_2$ (20.46 mg, 27.97 μmol, 0.1 *equiv.*) and potassium carbonate (386.53 mg, 2.79 mmol, 3 *equiv.*). The reaction mixture was stirred at 100 °C for 12 hours under N_2 atmosphere. The reaction mixture was filtered and concentrated to give a residue. The residue was purified by flash silica gel chromatography (0~5% MeOH/DCM) to give *tert*-butyl-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridin-1-yl]methyl]piperidine-1-carboxylate (1.1 g) as a black solid.

LC-MS (ESI): m/z = 736.3 $[M+H]^+$

Preparation of *tert*-butyl-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5,7-difluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]piperidine-1-carboxylate

To a solution of *tert*-butyl-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridin-1-yl]methyl]piperidine-1-carboxylate (700 mg, 951.27 μmol, 1 *equiv.*) in CF_3CH_2OH (10 mL) was added $Pd(OH)_2$ on carbon (0.2 g, 142.41

μmol, 10% purity, 0.15 *equiv.*) and Pd on carbon (0.2 g, 187.93 μmol, 10% purity, 0.2 *equiv.*). The reaction mixture was stirred at 25 °C for 12 hours under H_2 (15 psi). The reaction mixture was filtered and concentrated to give a residue. The residue was purified by flash silica gel chromatography (0~10% MeOH/DCM) to give *tert*-butyl-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5,7-difluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]piperidine-1-carboxylate (60 mg) as a brown oil.

LC-MS (ESI): m/z = 560.1 $[M+H]^+$

Preparation of 3-[5,7-difluoro-1-methyl-6-[1-(4-piperidylmethyl)-4-piperidyl]indazol-3-yl]piperidine-2,6-dione

A solution of *tert*-butyl-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5,7-difluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]piperidine-1-carboxylate (0.1 g, 178.68 μmol, 1 *equiv.*) in HCl/dioxane (2 M, 893.42 μL, 10 *equiv.*) was stirred at 25 °C for 1 hour. The reaction mixture was concentrated to give 3-[5,7-difluoro-1-methyl-6-[1-(4-piperidylmethyl)-4-piperidyl]indazol-3-yl]piperidine-2,6-dione (0.1g, crude) as a white solid.

LC-MS (ESI): m/z = 460.0 $[M+H]^+$

Preparation of 3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione

To a solution of 3-[5,7-difluoro-1-methyl-6-[1-(4-piperidylmethyl)-4-piperidyl]indazol-3-yl]piperidine-2,6-dione (see Table P6) (40 mg, 87.05 μmol, 1 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (40.76 mg, 87.05 μmol, 1 *equiv.*) in DMSO (1 mL) was added TEA (48.46 μL, 348.18 μmol, 4 *equiv.*). The reaction mixture was stirred at 100 °C for 2 hours. The reaction mixture was filtered and the collected filtrate was purified by prep-HPLC to afford 3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (25.65 mg) as a yellow solid.

LC-MS (ESI): m/z = 891.0 $[M+H]^+$

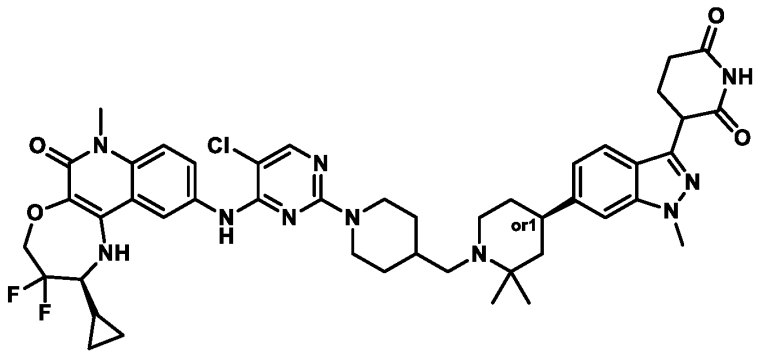
^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.92 (s, 1H), 9.06 - 8.95 (m, 1H), 8.91 (s, 1H), 8.17 (s, 1H), 8.07 (s, 1H), 7.75 (m, 1H), 7.51 - 7.38 (m, 2H), 6.25 (m, 1H), 4.53 - 4.39 (m, 3H), 4.36 (m, 1H), 4.13 (s, 3H), 3.65 - 3.59 (m, 2H), 3.58 (s, 3H), 3.20 - 3.06 (m, 2H), 3.03 - 2.94

(m, 2H), 2.91 - 2.79 (m, 2H), 2.69 - 2.63 (m, 2H), 2.39 - 2.31 (m, 3H), 2.27 - 2.01 (m, 3H), 1.96 (m, 2H), 1.83 - 1.68 (m, 2H), 1.41 - 1.05 (m, 4H), 0.79 - 0.65 (m, 1H), 0.53 (m, 2H), 0.41 - 0.28 (m, 1H)

Example 52. 3-(6-((*R*)-1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)-2,2-dimethylpiperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

[3-(6-((*R)-1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)-2,2-dimethylpiperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]**

(Compound 112b)

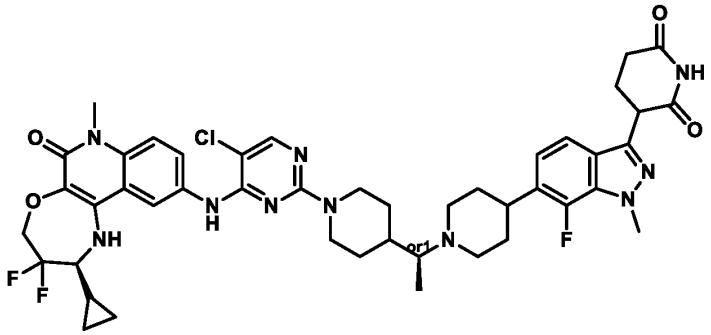


To a solution of 3-[6-[(4R)-2,2-dimethyl-1-(4-piperidylmethyl)-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (See Table P6) (345 mg, 763.95 μmol, 1 *equiv.*) in DMSO (4 mL) was added TEA (425.33 μL, 3.06 mmol, 4 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (429.29 mg, 916.73 μmol, 1.2 *equiv.*). The mixture was stirred at 100 °C for 5 hours. The reaction mixture was filtered, and the filtrate was concentrated to give a residue. The residue was purified by prep-HPLC to afford 3-(6-((*R*)-1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)-2,2-dimethylpiperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-((*R**)-1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)-2,2-dimethylpiperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (255 mg) as a yellow solid.

LC-MS (ESI): m/z = 883.9 $[M+H]^+$

Example 53. 3-[6-[1-[(1S*)-1-[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]ethyl]-4-piperidyl]-7-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione [3-(6-(1-((*S)-1-(1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)ethyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]**

(Compound 124b)



To a solution of 3-[7-fluoro-1-methyl-6-[1-[(1*S*)-1-(4-piperidyl)ethyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione (See Table P6) (100 mg, 219.51 μmol, 1 *equiv.*) in DMSO (2 mL) was added TEA (122.21 μL, 878.03 μmol, 4 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (102.79 mg, 219.51 μmol, 1 *equiv.*). The mixture was stirred at 100 °C for 1 hour. The reaction mixture was filtered and purified by pre-HPLC to afford 3-[6-[1-[(1S*)-1-[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]ethyl]-4-piperidyl]-7-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione [3-(6-(1-((*S**)-1-(1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)ethyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (42.9 mg) as a yellow solid.

LC-MS (ESI): m/z = 444.5 $[M/2+H]^+$.

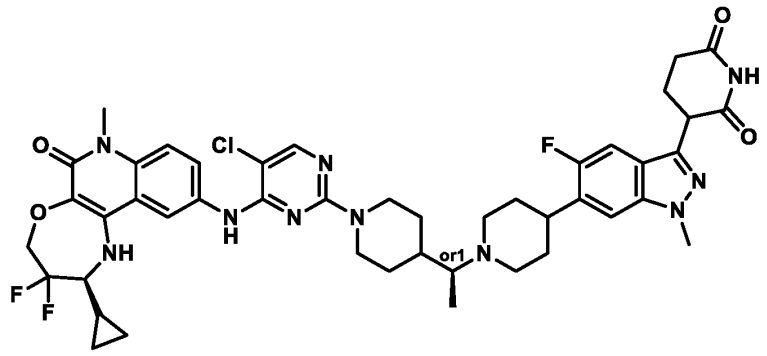
^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.91 (s, 1H), 8.76 (s, 1H), 8.22 (d, J = 1.2 Hz, 1H), 8.03 (s, 1H), 7.73 (d, J = 1.6, 9.2 Hz, 1H), 7.45 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 5.6, 8.4

Hz, 1H), 6.20 (s, 1H), 4.55 - 4.30 (m, 5H), 4.11 (s, 3H), 3.57 (s, 3H), 2.95 - 2.85 (m, 1H), 2.77 - 2.57 (m, 7H), 2.33 (s, 2H), 2.16 (d, J = 5.2, 8.0 Hz, 2H), 2.09 - 2.00 (m, 1H), 1.70 (s, 6H), 1.58 - 1.45 (m, 1H), 1.42 - 1.28 (m, 1H), 1.01 (s, 2H), 0.91 (d, J = 6.4 Hz, 3H), 0.77 - 0.63 (m, 1H), 0.51 (t, J = 5.6 Hz, 2H), 0.36 (d, J = 5.6 Hz, 1H)

Example 54. 3-(6-(1-((*S*)-1-(1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)ethyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

[3-(6-(1-((*S)-1-(1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)ethyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]**

(Compound 113a)



To a solution of 3-[5-fluoro-1-methyl-6-[1-[(1*S*)-1-(4-piperidyl)ethyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione (See Table P6) (58 mg, 127.31 μmol, 1 *equiv.*) in DMSO (2 mL) was added TEA (53.16 μL, 381.94 μmol, 3 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (71.54 mg, 152.78 μmol, 1.2 *equiv.*). The mixture was stirred at 100 °C for 1 hour. The reaction mixture was filtered, and the filtrate was concentrated to give a residue. The residue was purified by prep-HPLC to afford 3-(6-(1-((*S*)-1-(1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)ethyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-(1-((*S**)-1-(1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-

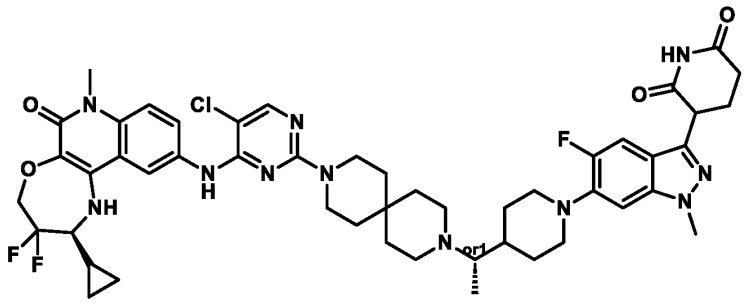
c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)ethyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (32.87 mg) as a yellow solid.

LC-MS (ESI): m/z = 887.7 $[M+H]^+$

Example 55. 3-[6-[4-[(1*S*)-1-[9-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3,9-diazaspiro[5.5]undecan-3-yl]ethyl]-1-piperidyl]-5-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione

[3-(6-(4-((*S)-1-(9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)piperidin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]**

(Compound 146b)

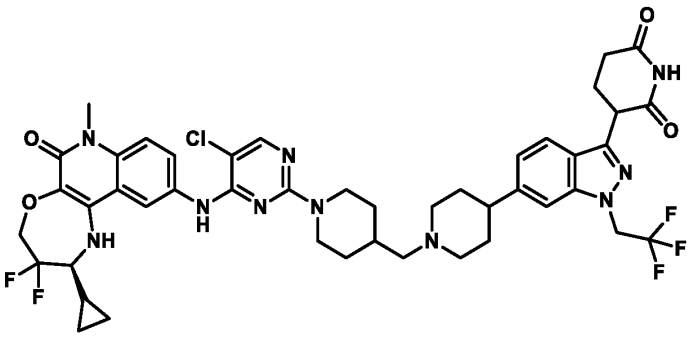


To a solution of 3-[6-[4-[(1*S*)-1-(3,9-diazaspiro[5.5]undecan-3-yl)ethyl]-1-piperidyl]-5-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (See Table P29) (100.00 mg, 190.60 μmol, 1 *equiv.*) in DMSO (3 mL) was added TEA (106.11 μL, 762.38 μmol, 4 *equiv.*) and (2*S*)-2-cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3-difluoro-7-methyl-2,4-dihydro1H-[1,4]oxazepino[2,3-c]quinolin-6-one (80.33 mg, 171.54 μmol, 0.9 *equiv.*). The mixture was stirred at 100 °C for 6 hours. The reaction mixture was filtered, and the filtrate was concentrated to give a residue. The residue was purified by prep-HPLC to afford 3-[6-[4-[(1*S*)-1-[9-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3,9-diazaspiro[5.5]undecan-3-yl]ethyl]-1-piperidyl]-5-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione [3-(6-(4-((*S**)-1-(9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)piperidin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (46.6 mg) as a off-white solid.

LC-MS (ESI): m/z = 956.4 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.85 (s, 1H), 8.77 (s, 1H), 8.24 (s, 1H), 8.21 (d, J = 1.6Hz, 1H), 8.02 (s, 1H), 7.72 (dd, J = 1.6, 9.2Hz, 1H), 7.48 - 7.37 (m, 2H), 7.07 (d, J = 7.2Hz, 1H), 6.18 (br s, 1H), 4.51 - 4.31 (m, 2H), 4.26 (dd, J = 5.2, 9.6Hz, 1H), 3.93 (s, 3H), 3.56 (s, 9H), 2.68 - 2.58 (m, 4H), 2.36 - 2.23 (m, 5H), 2.15 - 2.00 (m, 2H), 1.81 - 1.70 (m, 1H), 1.53 - 1.22 (m, 14H), 0.92 (br d, J = 6.4Hz, 3H), 0.77 - 0.66 (m, 1H), 0.55 - 0.44 (m, 2H), 0.35 (br d, J = 4.0Hz, 1H)

Example 56. 3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-4-piperidyl]-1-(2,2,2-trifluoroethyl)indazol-3-yl]piperidine-2,6-dione (Compound 172a)



To a solution of 3-[6-[1-(4-piperidylmethyl)-4-piperidyl]-1-(2,2,2-trifluoroethyl)indazol-3-yl]piperidine-2,6-dione (See Table P6) (100 mg, 203.44 μmol, 1 *equiv.*) in DMSO (2 mL) was added TEA (113.26 μL, 813.76 μmol, 4 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (85.74 mg, 183.10 μmol, 0.9 *equiv.*). The mixture was stirred at 100 °C for 2 hours. The reaction mixture was filtered, and the filtrate was concentrated to give a residue. The residue was purified by prep-HPLC to afford 3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-4-piperidyl]-1-(2,2,2-trifluoroethyl)indazol-3-yl]piperidine-2,6-dione (94.13 mg) as a yellow solid.

LC-MS (ESI): m/z = 923.3 $[M+H]^+$.

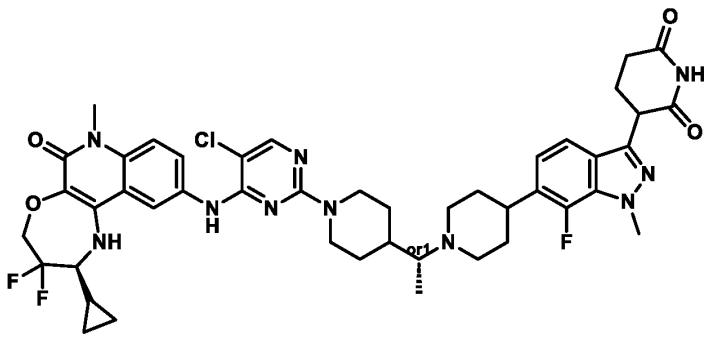
^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.92 (s, 1H), 8.77 (s, 1H), 8.18 (s, 1H), 8.03 (s, 1H), 7.74 (br d, J = 9.6 Hz, 1H), 7.68 - 7.57 (m, 2H), 7.45 (d, J = 9.2 Hz, 1H), 7.17 - 7.04 (m, 1H), 6.16 (br d, J = 0.8 Hz, 1H), 5.45 - 5.24 (m, 2H), 4.56 - 4.23 (m, 5H), 3.57 (s, 3H), 2.95 (br s, 2H), 2.85 - 2.72 (m, 2H), 2.70 - 2.54 (m, 3H), 2.27 - 2.10 (m, 4H), 2.04 - 1.92 (m, 2H), 1.83

- 1.51 (m, 8H), 1.42 - 1.28 (m, 1H), 1.08 - 0.93 (m, 2H), 0.76 - 0.64 (m, 1H), 0.57 - 0.45 (m, 2H), 0.39 - 0.29 (m, 1H)

Example 57. 3-(6-(1-((*R*)-1-(1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)ethyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

[3-(6-(1-((*R)-1-(1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)ethyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]**

(Compound 124a)



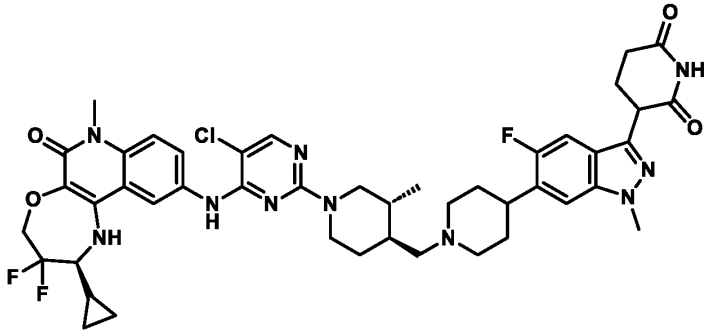
To a solution of 3-[7-fluoro-1-methyl-6-[1-[(1*R*)-1-(4-piperidyl)ethyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione (See Table P6) (90 mg, 197.56 μmol, 1 *equiv.*) in DMSO (2 mL) was added TEA (109.99 μL, 790.22 μmol, 4 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (92.51 mg, 197.56 μmol, 1 *equiv.*). The mixture was stirred at 100 °C for 1 hour. The mixture was filtered purified by prep- HPLC to afford 3-(6-(1-((*R*)-1-(1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)ethyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

[3-(6-(1-((*R**)-1-(1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)ethyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (17.3 mg) as a yellow solid.

LC-MS (ESI): m/z = 444.5 $[M/2+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.91 (s, 1H), 8.75 (s, 1H), 8.22 (s, 1H), 8.03 (s, 1H), 7.73 (d, J = 10.0 Hz, 1H), 7.53 - 7.40 (m, 2H), 7.05 (d, J = 2.8 Hz, 1H), 6.24 - 6.10 (m, 1H), 4.56 - 4.29 (m, 5H), 4.11 (s, 3H), 3.57 (s, 3H), 3.00 - 2.85 (m, 2H), 2.81 - 2.66 (m, 6H), 2.32 (d, J = 2.0 Hz, 2H), 2.22 - 2.14 (m, 2H), 2.08 - 2.00 (m, 1H), 1.82 - 1.60 (m, 6H), 1.56 - 1.47 (m, 1H), 1.39 - 1.29 (m, 1H), 1.08 - 0.95 (m, 2H), 0.91 (d, J = 6.4 Hz, 3H), 0.75 - 0.65 (m, 1H), 0.57 - 0.46 (m, 2H), 0.41 - 0.29 (m, 1H)

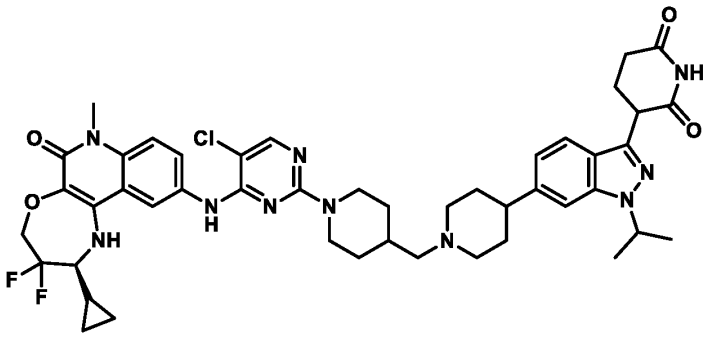
Example 58. 3-[6-[1-[[(3*R*,4*S*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]methyl]-4-piperidyl]-5-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (Compound 121e)



To a solution of 3-[5-fluoro-1-methyl-6-[1-[[(3*R*,4*S*)-3-methyl-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione (See Table P6) (120 mg, 263.41 μmol, 1 *equiv.*) in DMSO (3 mL) was added TEA (146.65 μL, 1.05 mmol, 4 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (123.35 mg, 263.41 μmol, 1 *equiv.*). The reaction mixture was stirred at 100 °C for 1 hour. The reaction mixture was filtered and concentrated under reduced pressure to give a residue which was purified by prep-HPLC to afford 3-[6-[1-[[(3*R*,4*S*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]methyl]-4-piperidyl]-5-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (36.81 mg) as a yellow solid.

LC-MS (ESI): m/z = 887.6 $[M+H]^+$

Example 59. 3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-4-piperidyl]-1-isopropyl-indazol-3-yl]piperidine-2,6-dione (Compound 125a)



Preparation of 3-[6-[1-[[1-[5-chloro-4-[[(2S)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1H-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-4-piperidyl]-1-isopropyl-indazol-3-yl]piperidine-2,6-dione

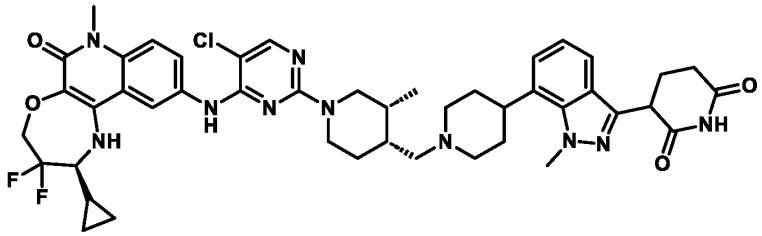
To a solution of (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (195.98 mg, 418.51 μmol, 0.9 *equiv.*) and 3-[1-isopropyl-6-[1-(4-piperidylmethyl)-4-piperidyl]indazol-3-yl]piperidine-2,6-dione (See Table P6) (210.000 mg, 465.01 μmol, 1 *equiv.*) in DMSO (1 mL) was added TEA (258.90 μL, 1.86 mmol, 4 *equiv.*). The mixture was stirred at 100 °C for 6 hours. The reaction mixture was diluted with H_2O (10 mL) and extracted with ethyl acetate (30 mL). The combined organic layers were washed with aqueous sodium chloride (90 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to afford 3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-4-piperidyl]-1-isopropyl-indazol-3-yl]piperidine-2,6-dione (112.67 mg) as a yellow solid.

LC-MS (ESI): m/z = 883.3 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.86 (s, 1H), 8.77 (s, 1H), 8.19 (s, 1H), 8.17 (s, 1H), 8.03 (s, 1H), 7.74 (d, J = 9.2 Hz,1H), 7.57 (d, J = 8.8 Hz, 1H), 7.50 - 7.39 (m, 2H), 7.01 (d, J = 8.8 Hz, 1H), 6.14 (s, 1H), 4.99 - 4.86 (m, 1H), 4.52 - 4.39 (m,3H), 4.39 - 4.29 (m, 1H), 3.57 (s, 3H), 2.95 (d, J = 6.8 Hz, 2H), 2.79 (t, J = 12.8 Hz, 2H), 2.70 - 2.54 (m, 4H), 2.41 - 2.29(m, 2H), 2.20 - 2.09 (m, 3H), 2.05 - 1.92 (m, 2H), 1.81 - 1.69 (m, 6H), 1.44 (d, J = 5.2 Hz, 6H), 1.39 - 1.30 (m, 1H), 1.23 (s,1H), 1.09 - 0.94 (m, 2H), 0.75 - 0.67 (m, 1H), 0.57 - 0.47 (m, 2H), 0.40 - 0.31 (m, 1H)

Example 60. 3-[7-[1-[[(3*R*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-

methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (Compound 101d)



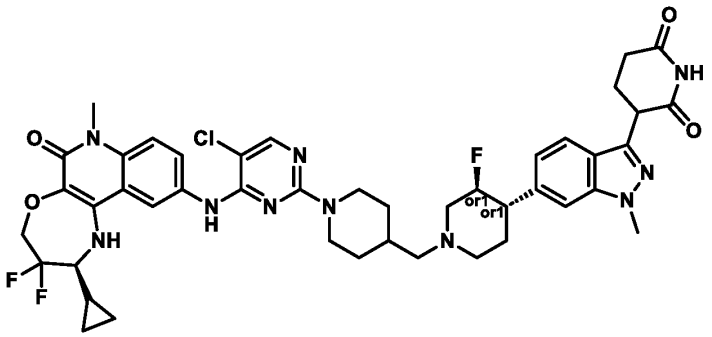
To a solution of 3-[1-methyl-7-[1-[[(3*R*,4*R*)-3-methyl-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione (See Table P6) (0.1 g, 228.53 μmol, 1 *equiv.*) in DMSO (1 mL) was added TEA (127.23 μL, 914.13 μmol, 4 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (107.02 mg, 228.53 μmol, 1 *equiv.*). The mixture was stirred at 100 °C for 6 hours. The reaction mixture was quenched with H_2O (5 mL) and extracted with ethyl acetate (60 mL). The combined organic layers were washed with brine (60 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to afford 3-[7-[1-[[(3*R*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione as a white solid.

LC-MS (ESI): m/z = 869.5 $[M+H]^+$

Example 61. 3-(6-((3S,4S)-1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

[3-(6-((3S*,4S*)-1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]

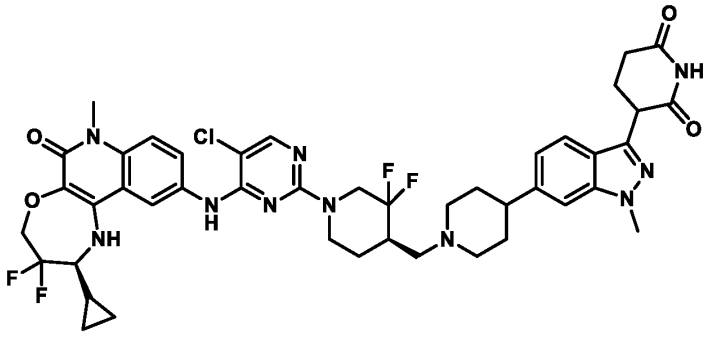
(Compound 127c)



To a solution of 3-[6-[(3S,4S)-3-fluoro-1-(4-piperidylmethyl)-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (See Table P6) (106 mg, 240.07 μmol, 1 *equiv.*) in DMSO (1 mL) was added TEA (100.24 μL, 720.21 μmol, 3 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (134.90 mg, 288.08 μmol, 1.2 *equiv.*). The mixture was stirred at 100 °C for 1 hour. The reaction mixture was filtered, and the filtrate was concentrated to give a residue. The residue was purified by prep-HPLC to afford 3-(6-((3S,4S)-1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-((3S*,4S*)-1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (69.26 mg) as a white solid.

LC-MS (ESI): m/z = 873.3 $[M+H]^+$

Example 62. 3-[6-[1-[[(4R)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3,3-difluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (Compound 120b)



Preparation of *tert*-butyl (4R)-3,3-difluoro-4-(hydroxymethyl)piperidine-1-carboxylate

A solution of (4*R*)-1-tert-butoxycarbonyl-3,3-difluoro-piperidine-4-carboxylic acid (600 mg, 2.26 mmol, 1 *equiv.*) was degassed and purged with N_2 three times. To this mixture was added BH_3.THF (1 M, 9.05 mL, 4 *equiv.*) in THF (8 mL) at 0 °C. The mixture was stirred at 60 °C for 2 hours under N_2 atmosphere. The reaction mixture was quenched by addition of MeOH at 0°C. The mixture was added H_2O (20 mL), extracted with ethyl acetate (20 mL × 3), washed with brine 40 mL (20 mL × 2), dried over sodium sulfate, and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography (0~50% ethyl acetate/petroleum ether) to give *tert*-butyl (4*R*)-3,3-difluoro-4-(hydroxymethyl)piperidine-1-carboxylate (500 mg) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$-d) δ = 4.44 - 4.04 (m, 2H), 4.03 - 3.94 (m, 1H), 3.71 - 3.59 (m, 1H), 3.11 - 2.70 (m, 2H), 2.15 - 1.99 (m, 1H), 1.93 - 1.82 (m, 2H), 1.65 - 1.52 (m, 1H), 1.46 (s, 9H)

Preparation of *tert*-butyl (4R)-3,3-difluoro-4-formyl-piperidine-1-carboxylate

To a solution of *tert*-butyl (4*R*)-3,3-difluoro-4-(hydroxymethyl)piperidine-1-carboxylate (300 mg, 1.19 mmol, 1 *equiv.*) in DCM (5 mL) was added dropwise DMP (1.01 g, 2.39 mmol, 739.80 µL, 2 *equiv.*) at 0 °C. The resulting mixture was stirred at 0 °C for 3 hours. The reaction mixture was concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography (0~20% ethyl acetate/petroleum ether) to give *tert*-butyl (4*R*)-3,3-difluoro-4-formyl-piperidine-1-carboxylate (140 mg) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$-d) δ = 9.85 (s, 1H), 4.27 - 3.83 (m, 2H), 3.28 - 3.09 (m, 1H), 2.91 (br t, J = 10.0 Hz, 1H), 2.82 - 2.67 (m, 1H), 1.93 - 1.80 (m, 2H), 1.40 (s, 9H)

Preparation of *tert*-butyl (4R)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3,3-difluoro-piperidine-1-carboxylate

To a solution of *tert*-butyl (4*R*)-3,3-difluoro-4-formyl-piperidine-1-carboxylate (140.00 mg, 561.68 µmol, 1 *equiv.*) and 3-[1-methyl-6-(4-piperidyl)indazol-3-yl]piperidine-2,6-dione (183.33 mg, 561.68 µmol, 1 *equiv.*) in DMSO (3 mL) was added AcOH (3.37 mg, 56.17 µmol, 3.22 µL, 0.1 *equiv.*) and $NaBH(OAc)_3$ (178.56 mg, 842.52 µmol, 1.5 *equiv.*). The mixture was stirred at 25 °C for 12 hours. The reaction mixture was concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography (0~20% ethyl acetate/petroleum ether) to give *tert*-butyl (4*R*)-4-[[4-[3-(2,6-dioxo-3-

piperidyl)-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3,3-difluoro-piperidine-1-carboxylate (170 mg) as a yellow oil.

LC-MS (ESI): m/z = 560.3 $[M+H]^+$

Preparation of 3-[6-[1-[[(4R)-3,3-difluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione

A solution of *tert*-butyl (4*R*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3,3-difluoro-piperidine-1-carboxylate (120 mg, 130.80 μmol, 1 *equiv.*) in DCM (1 mL) /HCl/dioxane (1 mL) was stirred at 25 °C for 2 hours. The reaction mixture was concentrated under reduced pressure to give 3-[6-[1-[[(4*R*)-3,3-difluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (120 mg) which was used in the next step without further purification.

LC-MS (ESI): m/z = 460.2 $[M+H]^+$

Preparation of 3-[6-[1-[[(4R)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3,3-difluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione

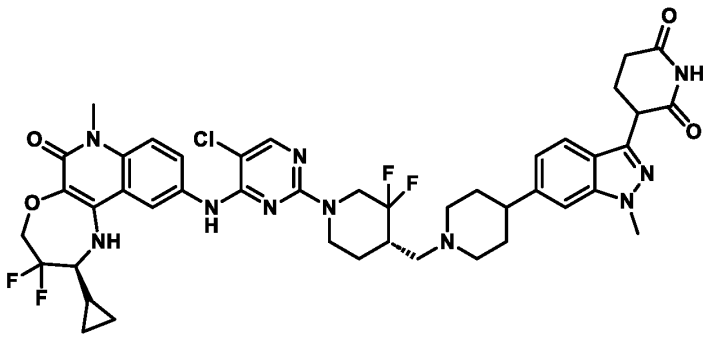
To a solution of 3-[6-[1-[[(4*R*)-3,3-difluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (120 mg, 147.58 μmol, 1 *equiv.*, HCl) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (55.29 mg, 118.07 μmol, 0.8 *equiv.*) in DMSO (2 mL) was added TEA (82.17 μL, 590.33 μmol, 4 *equiv.*). The mixture was stirred at 100 °C for 12 hours. The reaction mixture was filtered to give a residue. The residue was purified by prep-HPLC to afford compound 3-[6-[1-[[(4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-*c*]quinolin-10-yl]amino]pyrimidin-2-yl]-3,3-difluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (29.59 mg) as a white solid.

LC-MS (ESI): m/z = 891.3 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.87 (s, 1H), 8.93 (s, 1H), 8.20 (s, 1H), 8.19 (s, 1H), 8.07 (s, 1H), 7.70 (dd, J = 2.0, 9.0 Hz, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.45 (d, J = 9.1 Hz, 1H), 7.42 (s, 1H), 7.03 (d, J = 8.6 Hz, 1H), 6.17 (s, 1H), 4.72 - 4.57 (m, 1H), 4.51 - 4.35 (m, 3H), 4.32 (dd, J = 5.1, 9.7 Hz, 1H), 3.96 (s, 3H), 3.57 (s, 3H), 3.24 - 3.19 (m, 3H), 3.06 - 2.98 (m, 2H), 2.86 (d, J = 9.8 Hz, 1H), 2.69 - 2.59 (m, 3H), 2.41 - 2.27 (m, 3H), 2.22 - 2.11 (m, 2H),

2.05 - 1.96 (m, 1H), 1.94 - 1.85 (m, 1H), 1.82 - 1.72 (m, 4H), 1.36 (ddd, J = 4.9, 7.7, 9.4 Hz, 2H), 0.75 - 0.65 (m, 1H), 0.60 - 0.47 (m, 2H), 0.41 - 0.29 (m, 1H)

Example 63. 3-[6-[1-[[(4S)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3,3-difluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (Compound 120a)



Preparation of *tert*-butyl (4S)-3,3-difluoro-4-(hydroxymethyl)piperidine-1-carboxylate

A solution of (4*S*)-1-tert-butoxycarbonyl-3,3-difluoro-piperidine-4-carboxylic acid (550.00 mg, 2.07 mmol, 1 *equiv.*) was degassed in THF (8 mL) and purged with N_2 three times. To this solution was added BH_3.THF (1 M, 8.29 mL, 4 *equiv.*) at 0 °C. The mixture was stirred at 60 °C for 2 hours under N_2 atmosphere. The reaction mixture was quenched by addition MeOH at 0°C. To this mixture was added H_2O (20 mL) and extracted with ethyl acetate (20 mL × 3). The mixture was washed with brine (20 mL × 2), dried over sodium sulfate, and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography (0~50% ethyl acetate/petroleum ether) to give *tert*-butyl (4*S*)-3,3-difluoro-4-(hydroxymethyl)piperidine-1-carboxylate (460 mg) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$-d) δ = 4.40 - 4.06 (m, 2H), 4.04 - 3.94 (m, 1H), 3.72 - 3.58 (m, 1H), 3.09 - 2.70 (m, 2H), 2.18 - 1.99 (m, 1H), 1.93 - 1.83 (m, 2H), 1.66 - 1.52 (m, 2H), 1.46 (s, 9H).

Preparation of *tert*-butyl (4S)-3,3-difluoro-4-formyl-piperidine-1-carboxylate

To a solution of *tert*-butyl (4*S*)-3,3-difluoro-4-(hydroxymethyl)piperidine-1-carboxylate (240.00 mg, 955.15 μmol, 1 *equiv.*) in DCM (5 mL) was added DMP (810.23 mg, 1.91 mmol, 591.84 μL, 2 *equiv.*) at 0 °C. The resulting mixture was stirred at 0 °C for 3 hours.

The reaction mixture was concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography (0~20% ethyl acetate/petroleum ether) to give *tert*-butyl (4*S*)-3,3-difluoro-4-formyl-piperidine-1-carboxylate (100 mg) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$-d) δ = 4.40 - 4.06 (m, 2H), 4.04 - 3.94 (m, 1H), 3.72 - 3.58 (m, 1H), 3.09 - 2.70 (m, 2H), 2.18 - 1.99 (m, 1H), 1.93 - 1.83 (m, 2H), 1.66 - 1.52 (m, 2H), 1.46 (s, 9H)

Preparation of *tert*-butyl (4S)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3,3-difluoro-piperidine-1-carboxylate

To a solution of *tert*-butyl (4*S*)-3,3-difluoro-4-formyl-piperidine-1-carboxylate (70 mg, 280.84 μmol, 1 *equiv.*) and 3-[1-methyl-6-(4-piperidyl)indazol-3-yl]piperidine-2,6-dione (91.66 mg, 280.84 μmol, 1 *equiv.*) in DMSO (3 mL) was added AcOH (1.69 mg, 28.08 μmol, 1.61 μL, 0.1 *equiv.*) and $NaBH(OAc)_3$ (89.28 mg, 421.26 μmol, 1.5 *equiv.*). The mixture was stirred at 25 °C for 12 hours. The reaction mixture was concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography (0~20% ethyl acetate/petroleum ether) to give *tert*-butyl (4*S*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3,3-difluoro-piperidine-1-carboxylate (150 mg) as a yellow oil.

LC-MS (ESI): m/z = 560.3 $[M+H]^+$

Preparation of 3-[6-[1-[[(4S)-3,3-difluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione

A solution of *tert*-butyl (4*S*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3,3-difluoro-piperidine-1-carboxylate (150.00 mg, 163.50 μmol, 1 *equiv.*) in DCM (1 mL)/HCl/dioxane (1 mL) was stirred at 25 °C for 2 hours. The reaction mixture was concentrated under reduced pressure to give 3-[6-[1-[[(4*S*)-3,3-difluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (150 mg) which was used into the next step without further purification.

LC-MS (ESI): m/z = 460.0 $[M+H]^+$

Preparation of 3-[6-[1-[[(4S)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3,3-difluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-

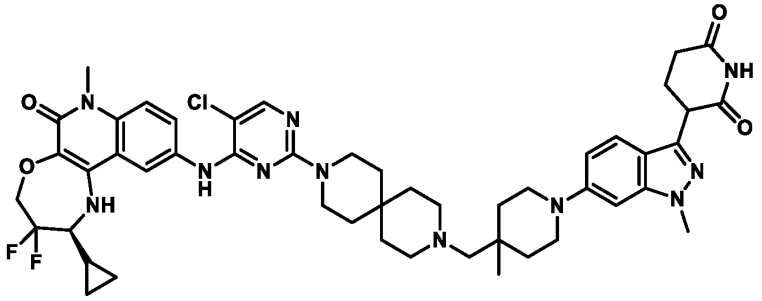
dione

To a solution of 3-[6-[1-[[(4*S*)-3,3-difluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (150.00 mg, 184.48 μmol, 1 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (69.11 mg, 147.58 μmol, 0.8 *equiv.*) in DMSO (2 mL) was added TEA (102.71 μL, 737.92 μmol, 4 *equiv.*). The mixture was stirred at 100 °C for 12 hours. The reaction mixture was filtered to give a residue. The residue was purified by prep-HPLC to afford 3-[6-[1-[[(4*S*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-*c*]quinolin-10-yl]amino]pyrimidin-2-yl]-3,3-difluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (13.07 mg) as a white solid.

LC-MS (ESI): m/z = 891.3 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6) δ =10.87 (s, 1H), 8.93 (s, 1H), 8.18 (s, 1H), 8.16 (d, J = 1.8 Hz, 1H), 8.07 (s, 1H), 7.72 (dd, J = 1.8, 8.9 Hz, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.46 (d, J = 9.1 Hz, 1H), 7.42 (s, 1H), 7.03 (d, J = 8.6 Hz, 1H), 6.23 (d, J = 1.0 Hz, 1H), 4.69 - 4.55 (m, 1H), 4.49 - 4.26 (m, 4H), 3.96 (s, 3H), 3.57 (s, 3H), 3.23 (s, 3H), 3.06 - 2.97 (m, 2H), 2.89 (d, J = 10.5 Hz, 1H), 2.69 - 2.59 (m, 3H), 2.40 - 2.26 (m, 3H), 2.23 - 2.10 (m, 2H), 1.99 (d, J = 13.1 Hz, 1H), 1.94 - 1.86 (m, 1H), 1.83 - 1.67 (m, 4H), 1.44 - 1.28 (m, 2H), 0.76 - 0.65 (m, 1H), 0.51 (t, J = 5.8 Hz, 2H), 0.38 - 0.29 (m, 1H)

Example 64. 3-[6-[4-[[3-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3,9-diazaspiro[5.5]undecan-9-yl]methyl]-4-methyl-1-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (Compound 108a)



To a solution of 3-[6-[4-(3,9-diazaspiro[5.5]undecan-3-ylmethyl)-4-methyl-1-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (See Table P29) (100 mg, 197.36 μmol, 1 *equiv.*) in DMSO (2 mL) was added TEA (109.88 μL, 789.45 μmol, 4 *equiv.*) and (*S*)-2-

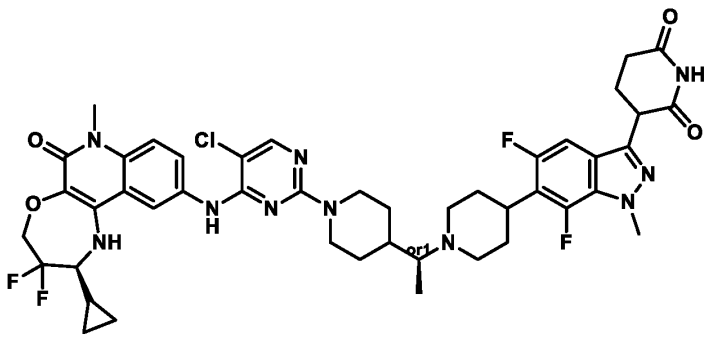
cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (101.66 mg, 217.10 μmol, 1.1 *equiv.*). The mixture was stirred at 100 °C for 1 hour. The reaction mixture was filtered and purified by reverse-phase HPLC to afford 3-[6-[4-[[3-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3,9-diazaspiro[5.5]undecan-9-yl]methyl]-4-methyl-1-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (48.51 mg) as a yellow solid.

LC-MS (ESI): m/z = 938.3 $[M+H]^+$

Example 65. 3-[6-[1-[(1*S*)-1-[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]ethyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione

[3-(6-(1-((*S)-1-(1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)ethyl)piperidin-4-yl)-5,7-difluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]**

(Compound 135a)

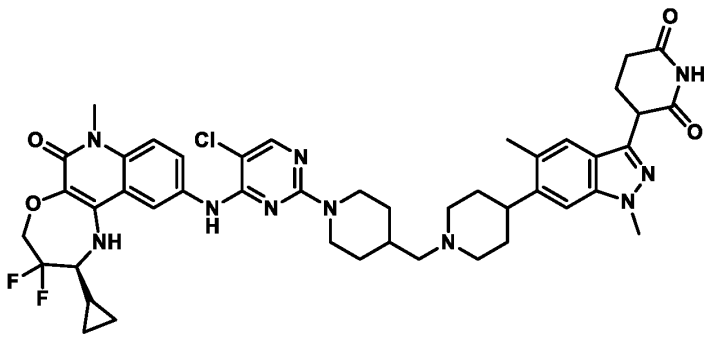


To a solution of 3-[5,7-difluoro-1-methyl-6-[1-[(1*S*)-1-(4-piperidyl)ethyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione (See Table P6) (0.2 g, 422.34 μmol, 1 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (158.22 mg, 337.87 μmol, 0.8 *equiv.*) in DMSO (2 mL) was added TEA (235.14 μL, 1.69 mmol, 4 *equiv.*). The reaction mixture was stirred at 100 °C for 2 hours. The reaction mixture was filtered and purified by prep-HPLC to afford 3-[6-[1-[(1*S*)-1-[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-

dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]ethyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione [3-(6-(1-((*S**)-1-(1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)ethyl)piperidin-4-yl)-5,7-difluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (77.46 mg) as a yellow solid.

LC-MS (ESI): m/z = 905.1 $[M+H]^+$

Example 66. 3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-4-piperidyl]-1,5-dimethyl-indazol-3-yl]piperidine-2,6-dione (Compound 128a)



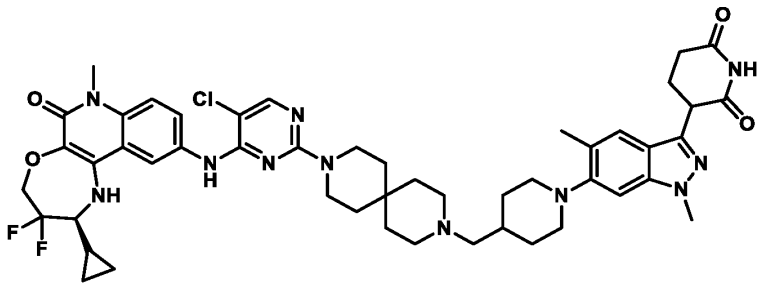
To a solution of 3-[1,5-dimethyl-6-[1-(4-piperidylmethyl)-4-piperidyl]indazol-3-yl]piperidine-2,6-dione (See Table P6) (120 mg, 253.14 μmol, 1 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (83 mg, 177.20 μmol, 0.7 *equiv.*) in DMSO (2 mL) was added TEA (140.94 μL, 1.01 mmol, 4 *equiv.*). The mixture was stirred at 100 °C for 5 hours. The reaction mixture was filtered and purified by prep-HPLC to afford 3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-4-piperidyl]-1,5-dimethyl-indazol-3-yl]piperidine-2,6-dione (39.1 mg) as yellow solid.

LC-MS (ESI): m/z: 435.5 $[M+H]^+$.

^{1}H NMR (400 MHz, MeOD-d4) δ = 8.56 - 8.45 (m, 1H), 8.09 (s, 1H), 7.96 (s, 1H), 7.93 (br d, *J* = 9.2 Hz, 1H), 7.55 (br d, *J* = 9.2 Hz, 1H), 7.51 (s, 1H), 7.34 (s, 1H), 4.60 (br d, *J* = 13.2 Hz, 2H), 4.52 - 4.40 (m, 2H), 4.33 (br dd, *J* = 4.8, 9.2 Hz, 1H), 4.00 (s, 3H), 3.72 (s, 3H), 3.51 - 3.37 (m, 2H), 3.10 - 3.02 (m, 1H), 2.90 (br t, *J* = 12.8 Hz, 2H), 2.82 - 2.68 (m, 5H),

2.66 (s, 1H), 2.55 - 2.47 (m, 1H), 2.45 (s, 3H), 2.30 (br dd, *J* = 6.4, 13.2 Hz, 1H), 2.09 - 1.91 (m, 5H), 1.88 - 1.80 (m, 2H), 1.51 - 1.37 (m, 2H), 1.29 - 1.18 (m, 2H), 0.86 - 0.74 (m, 1H), 0.71 - 0.56 (m, 2H), 0.40 - 0.27 (m, 1H).

Example 67. 3-[6-[4-[[3-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3,9-diazaspiro[5.5]undecan-9-yl]methyl]-1-piperidyl]-1,5-dimethyl-indazol-3-yl]piperidine-2,6-dione (Compound 176a)



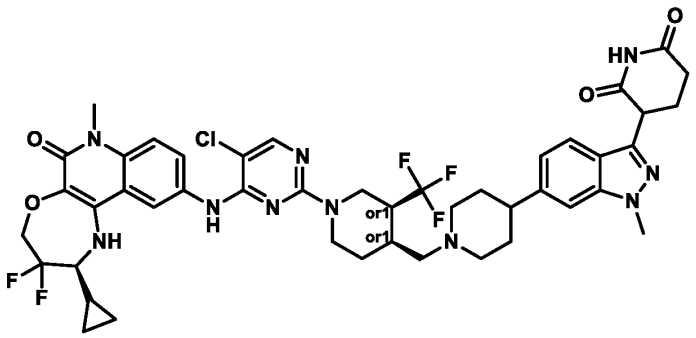
To a solution of 3-[6-[4-(3,9-diazaspiro[5.5]undecan-3-ylmethyl)-1-piperidyl]-1,5-dimethyl-indazol-3-yl]piperidine-2,6-dione (See Table P29) (220 mg, 434.20 μmol, 1 *equiv.*) in DMSO (3 mL) was added TEA (181.30 μL, 1.30 mmol, 3 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (162.66 mg, 347.36 μmol, 0.8 *equiv.*). The mixture was stirred at 100 °C for 2 hours. The residue was diluted with water (50 mL) and extracted with ethyl-acetate (100 mL). The combined organic layers were washed with brine (80 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to afford 3-[6-[4-[[3-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3,9-diazaspiro[5.5]undecan-9-yl]methyl]-1-piperidyl]-1,5-dimethyl-indazol-3-yl]piperidine-2,6-dione (113.9 mg) as a purple solid.

LC-MS (ESI): m/z = 938.4 $[M+H]^+$

Example 68. 3-[6-[1-[[(3S,4S)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-(trifluoromethyl)-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione

[3-(6-(1-(((3S*,4S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-(trifluoromethyl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]

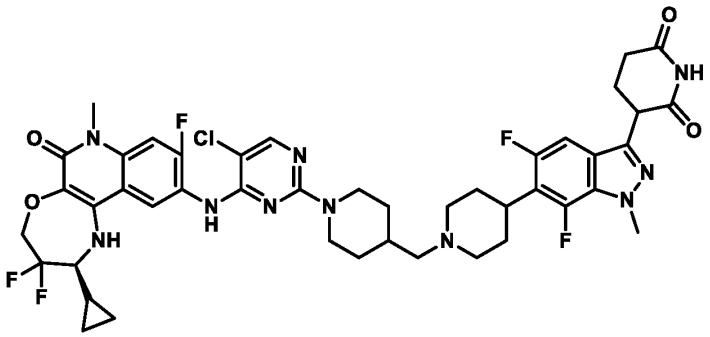
(Compound 139b)



To a solution of 3-[1-methyl-6-[1-[[(3*S*,4*S*)-3-(trifluoromethyl)-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione (See Table P6) (0.15 g, 305.16 μmol, 1 *equiv.*) in DMSO (1.5 mL) was added TEA (127.42 μL, 915.48 μmol, 3 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (142.90 mg, 305.16 μmol, 1 *equiv.*). The mixture was stirred at 100 °C for 16 hours. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to afford 3-[6-[1-[[(3*S*,4*S*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-(trifluoromethyl)-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione [3-(6-(1-(((3S*,4S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-(trifluoromethyl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (60.55 mg) as a yellow solid.

LC-MS (ESI): m/z = 923.4 $[M+H]^+$

Example 69. 3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (Compound 171a)



Preparation of 6-bromo-7-fluoro-1*H*-3,1-benzoxazine-2,4-dione

To a solution of 2-amino-5-bromo-4-fluoro-benzoic acid (90 g, 384.58 mmol, 1 *equiv.*) in THF (900 mL) was added bis (trichloromethyl) carbonate (39.94 g, 134.60 mmol, 0.35 *equiv.*) at 0 °C under N_2. The mixture was stirred at 70 °C for 2 hours. The reaction mixture was filtered and washed with THF. The filtrate solid was concentrated under reduced pressure to give 6-bromo-7-fluoro-1*H*-3,1-benzoxazine-2,4-dione (81.2 g, crude) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.98 (s, 1H), 8.19 (d, J = 7.6 Hz, 1H), 7.03 (d, J = 9.2 Hz, 1H).

Preparation of 6-bromo-7-fluoro-1-methyl-3,1-benzoxazine-2,4-dione

To a solution of 6-bromo-7-fluoro-1*H*-3,1-benzoxazine-2,4-dione (81.2 g, 312.29 mmol, 1 *equiv.*) in dimethylacetamide (90 mL) was added iodomethane (132.98 g, 936.86 mmol, 58.32 mL, 3 *equiv.*) and DIPEA (80.72 g, 624.58 mmol, 108.79 mL, 2 *equiv.*). The mixture was stirred at 25 °C for 2 hours. The reaction mixture was diluted with H_2O (100 mL) and filtered to obtain 6-bromo-7-fluoro-1-methyl-3,1-benzoxazine-2,4-dione (80 g, crude) as a white solid.

LC-MS (ESI): m/z = 273.9 $[M+H]^+$

Preparation of ethyl 6-bromo-7-fluoro-4-hydroxy-1-methyl-2-oxo-quinoline-3-carboxylate

A mixture of 6-bromo-7-fluoro-1-methyl-3,1-benzoxazine-2,4-dione (80 g, 291.92 mmol, 1 *equiv.*), diethyl propanedioate (140.27 g, 875.77 mmol, 132.96 mL, 3 *equiv.*) and NaH (23.35 g, 583.85 mmol, 60% purity, 2 *equiv.*) in DMF (1000 mL) was degassed and purged with N_2 three times. The mixture was stirred at 25 °C for 2 hours under N_2 atmosphere. The reaction mixture was diluted with saturated ammonium chloride (1500 mL), filtered, and

concentrated under reduced pressure to give a residue which was triturated with ethyl acetate at 25 °C for 30 minutes to obtain ethyl 6-bromo-7-fluoro-4-hydroxy-1-methyl-2-oxo-quinoline-3-carboxylate (37 g) as a white solid.

LC-MS (ESI): m/z = 343.9 $[M+H]^+$

Preparation of ethyl 6-bromo-4-chloro-7-fluoro-1-methyl-2-oxo-quinoline-3-carboxylate

To a solution of ethyl 6-bromo-7-fluoro-4-hydroxy-1-methyl-2-oxo-quinoline-3-carboxylate (15 g, 43.59 mmol, 1 *equiv.*) in DMF (150 mL) was added dropwise $(COCl)_2$ (16.60 g, 130.76 mmol, 11.45 mL, 3 *equiv.*). The mixture was stirred at 70 °C for 0.5 hours. The reaction mixture was quenched by H_2O (500 mL) and then filtered and concentrated under reduced pressure to give a residue which was triturated with petroleum ether at 25 °C for 10 minutes to obtain ethyl 6-bromo-4-chloro-7-fluoro-1-methyl-2-oxo-quinoline-3-carboxylate (11.2 g) as a white solid.

LC-MS (ESI): m/z = 362.0 $[M+H]^+$

Preparation of 6-bromo-4-[[(1*S*)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-7-fluoro-1-methyl-quinolin-2-one

Ethyl 6-bromo-4-chloro-7-fluoro-1-methyl-2-oxo-quinoline-3-carboxylate (700 mg, 1.93 mmol, 1 *equiv.*), (3*S*)-3-amino-3-cyclopropyl-2,2-difluoro-propan-1-ol (398.43 mg, 2.12 mmol, 1.1 *equiv.*, HCl) and DIPEA (748.56 mg, 5.79 mmol, 1.01 mL, 3 *equiv.*) were taken up into a microwave tube with NMP (15 mL). The sealed tube was heated at 200 °C for 2 hours in a microwave reactor. The reaction mixture was diluted with H_2O (120 mL) and extracted with ethyl acetate (360 mL). The combined organic layers were washed with brine (2400 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography (60% ethyl acetate/petroleum ether) to afford 6-bromo-4-[[(1*S*)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-7-fluoro-1-methyl-quinolin-2-one as a yellow solid.

LC-MS (ESI): m/z = 404.9 $[M+H]^+$

Preparation of 3,6-dibromo-4-[[(1*S*)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-7-fluoro-1-methyl-quinolin-2-one

To a solution of 6-bromo-4-[[(1*S*)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-7-fluoro-1-methyl-quinolin-2-one (3.6 g, 8.47 mmol, 1 *equiv.*) in DMF (36 mL)

was added NBS (1.36 g, 7.62 mmol, 0.9 *equiv.*) at 0 °C. The mixture was stirred at 0 °C for 20 minutes. The reaction mixture was diluted with H_2O (40 mL) and extracted with ethyl acetate (150 mL). The combined organic layers were washed with brine 150 mL (50 mL × 3), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography (25% ethyl acetate/petroleum ether) to afford 3,6-dibromo-4-[[(1*S*)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-7-fluoro-1-methyl-quinolin-2-one (2.7 g) as a yellow solid.

LC-MS (ESI): m/z = 484.9 $[M+H]^+$

Preparation of (2*S*)-10-bromo-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one

To a solution of 3,6-dibromo-4-[[(1*S*)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-7-fluoro-1-methyl-quinolin-2-one (2.7 g, 5.58 mmol, 1 *equiv.*) in THF (10 mL) was added t-BuOK (1 M, 2.79 mL, 0.5 *equiv.*). The mixture was stirred at 60 °C for 1 hour, then t-BuOK (1 M, 2.79 mL, 0.5 *equiv.*) was added. The resulting mixture was stirred at 60 °C for 0.1 hours. The reaction mixture was concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography (40% ethyl acetate/petroleum ether) to afford (2*S*)-10-bromo-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (2.2 g) as a white solid.

LC-MS (ESI): m/z = 402.9 $[M+H]^+$

Preparation of (2*S*)-10-(benzhydrylideneamino)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one

A mixture of (2*S*)-10-bromo-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (2.2 g, 5.46 mmol, 1 *equiv.*), diphenylmethanimine (1.19 g, 6.55 mmol, 1.10 mL, 1.2 *equiv.*), $Pd_2(dba)_3$ (499.66 mg, 545.64 μmol, 0.1 *equiv.*), XantPhos (631.44 mg, 1.09 mmol, 0.2 *equiv.*) and cesium carbonate (4.44 g, 13.64 mmol, 2.5 *equiv.*) in toluene (25 mL) was degassed and purged with N_2 three times. The mixture was stirred at 100 °C for 12 hours under N_2 atmosphere. The reaction mixture was diluted with H_2O (30 mL) and extracted with ethyl acetate (90 mL). The combined organic layers were washed with brine (90 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography (50% ethyl acetate/petroleum ether) to afford (2*S*)-10-(benzhydrylideneamino)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (2.07 g) as a yellow solid.

LC-MS (ESI): m/z = 504.1 $[M+H]^+$

Preparation of (2*S*)-10-amino-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one

To a solution of (2*S*)-10-(benzhydrylideneamino)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (2.07 g, 4.12 mmol, 1 *equiv.*) in dioxane (7 mL) was added HCl/dioxane (14 mL). The mixture was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give a residue which was purified by prep-HPLC to afford (2*S*)-10-amino-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (931 mg) as a pink solid.

LC-MS (ESI): m/z = 340.1 $[M+H]^+$

Preparation of (2*S*)-2-cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one

To a solution of (2*S*)-10-amino-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (206 mg, 607.11 μmol, 1 *equiv.*) in DMF (3 mL) was added DIPEA (235.39 mg, 1.82 mmol, 317.24 μL, 3 *equiv.*) and 2,4,5-trichloropyrimidine (133.63 mg, 728.53 μmol, 1.2 *equiv.*). The mixture was stirred at 80 °C for 24 hours. The reaction mixture was diluted with H_2O (5 mL) and extracted with ethyl acetate (15 mL). The combined organic layers were washed with brine (30 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to afford (2*S*)-2-cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (315 mg) as a white solid.

LC-MS (ESI): m/z = 486.0 $[M+H]^+$

Preparation of 4-bromo-1,2,3,6-tetrahydropyridine

A solution of *tert*-butyl-4-bromo-3,6-dihydro-2*H*-pyridine-1-carboxylate (5 g, 19.07 mmol, 1 *equiv.*) in HCl (4 M, 47.68 mL, 10 *equiv.*) was stirred at 25 °C for 3 hours. The reaction mixture was filtered to afford 4-bromo-1,2,3,6-tetrahydropyridine (3.3 g) as a white solid.

LC-MS (ESI): m/z = 164.2 $[M+H]^+$

Preparation of *tert*-butyl-4-[(4-bromo-3,6-dihydro-2H-pyridin-1-yl)methyl]piperidine-1-carboxylate

A solution of 4-bromo-1,2,3,6-tetrahydropyridine (3 g, 15.11 mmol, 1 *equiv.*) and *tert*-butyl-4-formylpiperidine-1-carboxylate (3.55 g, 16.63 mmol, 1.1 *equiv.*) in DCM (40 mL) was stirred at 25 °C for 2 hours followed by the addition of $NaBH(OAc)_3$ (4.80 g, 22.67 mmol, 1.5 *equiv.*). The reaction mixture was stirred at 25 °C for 1 hour. The reaction mixture was then filtered and concentrated to give a residue. The residue was purified by flash silica gel chromatography (0~5% MeOH/DCM) to give *tert*-butyl-4-[(4-bromo-3,6-dihydro-2H-pyridin-1-yl)methyl]piperidine-1-carboxylate (5 g) as a brown oil.

LC-MS (ESI): m/z = 361.0 $[M+H]^+$

Preparation of *tert*-butyl-4-[[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridin-1-yl]methyl]piperidine-1-carboxylate

To a solution of *tert*-butyl-4-[(4-bromo-3,6-dihydro-2H-pyridin-1-yl)methyl]piperidine-1-carboxylate (2 g, 5.57 mmol, 1 *equiv.*) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1.41 g, 5.57 mmol, 1 *equiv.*) in toluene (30 mL) was added $Pd(dppf)Cl_2$ (407.29 mg, 556.64 μmol, 0.1 *equiv.*) and KOAc (1.64 g, 16.70 mmol, 3 *equiv.*). The reaction was stirred at 70 °C for 2 hours under N_2 atmosphere. The reaction mixture was filtered and concentrated to give *tert*-butyl-4-[[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridin-1-yl]methyl]piperidine-1-carboxylate (4 g, crude) as a black oil.

LC-MS (ESI): m/z = 407.1 $[M+H]^+$

Preparation of *tert*-butyl-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridin-1-yl]methyl]piperidine-1-carboxylate

To a solution of 6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazole (500 mg, 932 μmol, 1 *equiv.*) and *tert*-butyl-4-[[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridin-1-yl]methyl]piperidine-1-carboxylate (3.8 g, 9.33 mmol, 10 *equiv.*) in dioxane (20 mL) and water (5 mL) was added $Pd(dppf)Cl_2$ (20.46 mg, 27.97 μmol, 0.1 *equiv.*) and potassium carbonate (386.53 mg, 2.79 mmol, 3 *equiv.*). The reaction mixture was stirred at 100 °C for 12 hours under N_2 atmosphere. The reaction mixture was filtered and concentrated to give a residue. The residue was purified by flash silica gel chromatography (0~5% MeOH/DCM) to give *tert*-butyl-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridin-1-yl]methyl]piperidine-1-carboxylate (1.1 g) as a black solid.

LC-MS (ESI): m/z = 736.3 $[M+H]^+$

Preparation of *tert*-butyl-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5,7-difluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]piperidine-1-carboxylate

To a solution of *tert*-butyl-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridin-1-yl]methyl]piperidine-1-carboxylate (700 mg, 951.27 μmol, 1 *equiv.*) in CF_3CH_2OH (10 mL) was added $Pd(OH)_2$ on carbon (0.2 g, 142.41 μmol, 10% purity, 0.15 *equiv.*) and Pd on carbon (0.2 g, 187.93 μmol, 10% purity, 0.2 *equiv.*). The reaction mixture was stirred at 25 °C for 12 hours under H_2 (15 psi). The reaction mixture was filtered and concentrated to give a residue. The residue was purified by flash silica gel chromatography (0~10% MeOH/DCM) to give *tert*-butyl-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5,7-difluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]piperidine-1-carboxylate (60 mg) as a brown oil.

LC-MS (ESI): m/z = 560.1 $[M+H]^+$

Preparation of 3-[5,7-difluoro-1-methyl-6-[1-(4-piperidylmethyl)-4-piperidyl]indazol-3-yl]piperidine-2,6-dione

A solution of *tert*-butyl-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5,7-difluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]piperidine-1-carboxylate (0.1 g, 178.68 μmol, 1 *equiv.*) in HCl/dioxane (2 M, 893.42 μL, 10 *equiv.*) was stirred at 25 °C for 1 hour. The reaction mixture was concentrated to give 3-[5,7-difluoro-1-methyl-6-[1-(4-piperidylmethyl)-4-piperidyl]indazol-3-yl]piperidine-2,6-dione (0.1g, crude) as a white solid.

LC-MS (ESI): m/z = 460.0 $[M+H]^+$

Preparation of 3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione

To a solution of 3-[5,7-difluoro-1-methyl-6-[1-(4-piperidylmethyl)-4-piperidyl]indazol-3-yl]piperidine-2,6-dione (0.1 g, 217.61 μmol, 1 *equiv.*) and (2*S*)-2-cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (74.07 mg, 152.33 μmol, 0.7 *equiv.*) in DMSO (3 mL) was added TEA (120.1 μL, 870.4 μmol, 4 *equiv.*). The reaction mixture was stirred at 100 °C

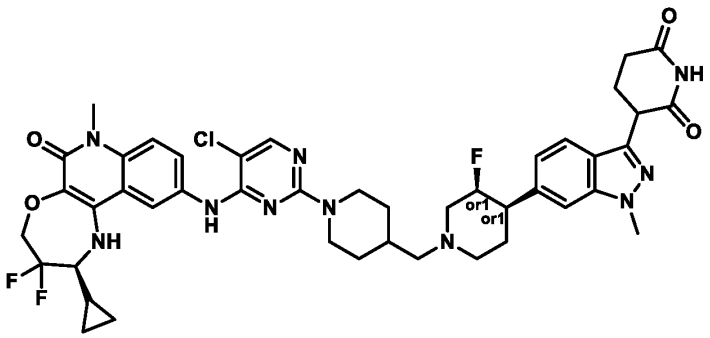
for 2 hours. The reaction mixture was filtered and the collected filtrate was purified by prep-HPLC to afford 3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (39.76 mg) as a yellow solid.

LC-MS (ESI): m/z = 909.0 $[M+H]^+$;

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.91 (s, 1H), 8.82 (s, 1H), 8.20 (d, J = 7.6 Hz, 1H), 8.02 (s, 1H), 7.49 - 7.35 (m, 2H), 6.46 (d, J = 4.8 Hz, 1H), 4.45 - 4.25 (m, 4H), 4.11 (s, 3H), 3.56 (s, 3H), 3.05 - 2.87 (m, 4H), 2.60 (d, J = 4.0 Hz, 2H), 2.18 - 1.91 (m, 8H), 1.74 - 1.60 (m, 5H), 1.39 - 1.21 (m, 3H), 1.15 (s, 1H), 1.04 - 0.86 (m, 2H), 0.78 - 0.62 (m, 1H), 0.57 - 0.44 (m, 2H), 0.31 (d, J = 6.4 Hz, 1H).

Example 70. 3-[6-[(3*S*,4*R*)-1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-3-fluoro-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione [3-(6-((3*S,4*R**)-1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]**

(Compound 127a)



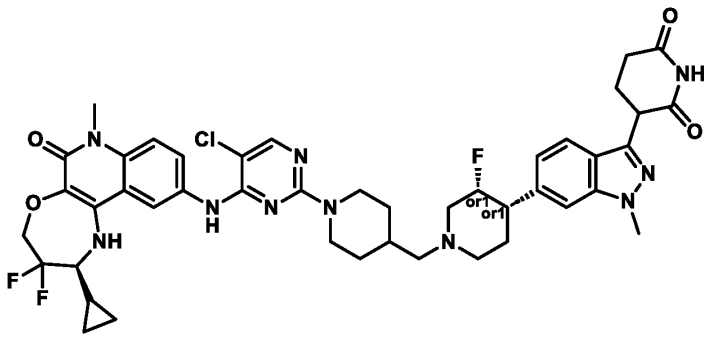
To a solution of 3-[6-[(3*S*,4*R*)-3-fluoro-1-(4-piperidylmethyl)-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (See Table P6) (200 mg, 418.41 μmol, 1 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (176.34 mg, 376.57 μmol, 0.9 *equiv.*) in DMSO (3 mL) was added TEA (232.95 μL, 1.67 mmol, 4 *equiv.*). The mixture was stirred at

100 °C for 12 hours. The reaction mixture was filtered to give a residue. The residue was purified by prep-HPLC to afford compound 3-[6-[(3*S*,4*R*)-1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-3-fluoro-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione [3-(6-((3*S**,4*R**)-1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (50 mg) as a pink solid.

LC-MS (ESI): m/z = 873.3 $[M+H]^+$

Example 71. 3-[6-[(3*R*,4*S*)-1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-3-fluoro-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione [3-(6-((3*R,4*S**)-1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]**

(Compound 127b)

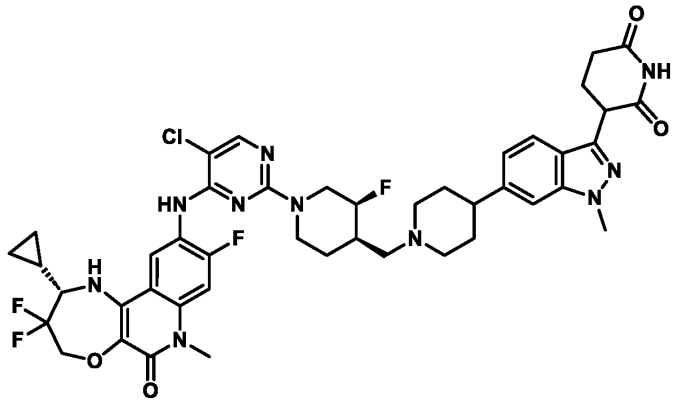


To a solution of 3-[6-[(3*R*,4*S*)-3-fluoro-1-(4-piperidylmethyl)-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (See Table P6) (245 mg, 554.88 μmol, 1 *equiv.*) in DMSO (3 mL) was added TEA (231.69 μL, 1.66 mmol, 3 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (259.84 mg, 554.88 μmol, 1 *equiv.*). The mixture was stirred at 100 °C for 1 hour. The reaction mixture was filtered, and the filtrate was concentrated to give a residue. The residue was purified by prep-HPLC to afford 3-[6-[(3*R*,4*S*)-1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-

yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-3-fluoro-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione [3-(6-((3*R**,4*S**)-1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (151.59 mg) as a yellow solid.

LC-MS (ESI): m/z = 873.8 $[M+H]^+$

Example 72. 3-[6-[1-[[(3*S*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (Compound 118b)



Preparation of 6-bromo-7-fluoro-1*H*-3,1-benzoxazine-2,4-dione

To a solution of 2-amino-5-bromo-4-fluoro-benzoic acid (90 g, 384.58 mmol, 1 *equiv.*) in THF (900 mL) was added bis (trichloromethyl) carbonate (39.94 g, 134.60 mmol, 0.35 *equiv.*) at 0 °C under N_2. The mixture was stirred at 70 °C for 2 hours. The reaction mixture was filtered and washed with THF. The filtrate solid was concentrated under reduced pressure to give 6-bromo-7-fluoro-1*H*-3,1-benzoxazine-2,4-dione (81.2 g, crude) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.98 (s, 1H), 8.19 (d, J = 7.6 Hz, 1H), 7.03 (d, J = 9.2 Hz, 1H).

Preparation of 6-bromo-7-fluoro-1-methyl-3,1-benzoxazine-2,4-dione

To a solution of 6-bromo-7-fluoro-1*H*-3,1-benzoxazine-2,4-dione (81.2 g, 312.29 mmol, 1 *equiv.*) in dimethylacetamide (90 mL) was added iodomethane (132.98 g, 936.86 mmol, 58.32 mL, 3 *equiv.*) and DIPEA (80.72 g, 624.58 mmol, 108.79 mL, 2 *equiv.*). The mixture was stirred at 25 °C for 2 hours. The reaction mixture was diluted with H_2O (100 mL)

and filtered to obtain 6-bromo-7-fluoro-1-methyl-3,1-benzoxazine-2,4-dione (80 g, crude) as a white solid.

LC-MS (ESI): m/z = 273.9 $[M+H]^+$

Preparation of ethyl 6-bromo-7-fluoro-4-hydroxy-1-methyl-2-oxo-quinoline-3-carboxylate

A mixture of 6-bromo-7-fluoro-1-methyl-3,1-benzoxazine-2,4-dione (80 g, 291.92 mmol, 1 *equiv.*), diethyl propanedioate (140.27 g, 875.77 mmol, 132.96 mL, 3 *equiv.*) and NaH (23.35 g, 583.85 mmol, 60% purity, 2 *equiv.*) in DMF (1000 mL) was degassed and purged with N_2 three times. The mixture was stirred at 25 °C for 2 hours under N_2 atmosphere. The reaction mixture was diluted with saturated ammonium chloride (1500 mL), filtered, and concentrated under reduced pressure to give a residue which was triturated with ethyl acetate at 25 °C for 30 minutes to obtain ethyl 6-bromo-7-fluoro-4-hydroxy-1-methyl-2-oxo-quinoline-3-carboxylate (37 g) as a white solid.

LC-MS (ESI): m/z = 343.9 $[M+H]^+$

Preparation of ethyl 6-bromo-4-chloro-7-fluoro-1-methyl-2-oxo-quinoline-3-carboxylate

To a solution of ethyl 6-bromo-7-fluoro-4-hydroxy-1-methyl-2-oxo-quinoline-3-carboxylate (15 g, 43.59 mmol, 1 *equiv.*) in DMF (150 mL) was added dropwise $(COCl)_2$ (16.60 g, 130.76 mmol, 11.45 mL, 3 *equiv.*). The mixture was stirred at 70 °C for 0.5 hours. The reaction mixture was quenched by H_2O (500 mL) and then filtered and concentrated under reduced pressure to give a residue which was triturated with petroleum ether at 25 °C for 10 minutes to obtain ethyl 6-bromo-4-chloro-7-fluoro-1-methyl-2-oxo-quinoline-3-carboxylate (11.2 g) as a white solid.

LC-MS (ESI): m/z = 362.0 $[M+H]^+$

Preparation of 6-bromo-4-[[(1*S*)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-7-fluoro-1-methyl-quinolin-2-one

Ethyl 6-bromo-4-chloro-7-fluoro-1-methyl-2-oxo-quinoline-3-carboxylate (700 mg, 1.93 mmol, 1 *equiv.*), (3*S*)-3-amino-3-cyclopropyl-2,2-difluoro-propan-1-ol (398.43 mg, 2.12 mmol, 1.1 *equiv.*, HCl) and DIPEA (748.56 mg, 5.79 mmol, 1.01 mL, 3 *equiv.*) were taken up into a microwave tube with NMP (15 mL). The sealed tube was heated at 200 °C for 2 hours

in a microwave reactor. The reaction mixture was diluted with H_2O (120 mL) and extracted with ethyl acetate (360 mL). The combined organic layers were washed with brine (2400 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography (60% ethyl acetate/petroleum ether) to afford 6-bromo-4-[[(1*S*)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-7-fluoro-1-methyl-quinolin-2-one as a yellow solid.

LC-MS (ESI): m/z = 404.9 $[M+H]^+$

Preparation of 3,6-dibromo-4-[[(1*S*)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-7-fluoro-1-methyl-quinolin-2-one

To a solution of 6-bromo-4-[[(1*S*)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-7-fluoro-1-methyl-quinolin-2-one (3.6 g, 8.47 mmol, 1 *equiv.*) in DMF (36 mL) was added NBS (1.36 g, 7.62 mmol, 0.9 *equiv.*) at 0 °C. The mixture was stirred at 0 °C for 20 minutes. The reaction mixture was diluted with H_2O (40 mL) and extracted with ethyl acetate (150 mL). The combined organic layers were washed with brine 150 mL (50 mL × 3), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography (25% ethyl acetate/petroleum ether) to afford 3,6-dibromo-4-[[(1*S*)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-7-fluoro-1-methyl-quinolin-2-one (2.7 g) as a yellow solid.

LC-MS (ESI): m/z = 484.9 $[M+H]^+$

Preparation of (2*S*)-10-bromo-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one

To a solution of 3,6-dibromo-4-[[(1*S*)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-7-fluoro-1-methyl-quinolin-2-one (2.7 g, 5.58 mmol, 1 *equiv.*) in THF (10 mL) was added t-BuOK (1 M, 2.79 mL, 0.5 *equiv.*). The mixture was stirred at 60 °C for 1 hour, then t-BuOK (1 M, 2.79 mL, 0.5 *equiv.*) was added. The resulting mixture was stirred at 60 °C for 0.1 hours. The reaction mixture was concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography (40% ethyl acetate/petroleum ether) to afford (2*S*)-10-bromo-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (2.2 g) as a white solid.

LC-MS (ESI): m/z = 402.9 $[M+H]^+$

Preparation of (2*S*)-10-(benzhydrylideneamino)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one

A mixture of (2*S*)-10-bromo-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (2.2 g, 5.46 mmol, 1 *equiv.*), diphenylmethanimine (1.19 g, 6.55 mmol, 1.10 mL, 1.2 *equiv.*), $Pd_2(dba)_3$ (499.66 mg, 545.64 μmol, 0.1 *equiv.*), XantPhos (631.44 mg, 1.09 mmol, 0.2 *equiv.*) and cesium carbonate (4.44 g, 13.64 mmol, 2.5 *equiv.*) in toluene (25 mL) was degassed and purged with N_2 three times. The mixture was stirred at 100 °C for 12 hours under N_2 atmosphere. The reaction mixture was diluted with H_2O (30 mL) and extracted with ethyl acetate (90 mL). The combined organic layers were washed with brine (90 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography (50% ethyl acetate/petroleum ether) to afford (2*S*)-10-(benzhydrylideneamino)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (2.07 g) as a yellow solid.

LC-MS (ESI): m/z = 504.1 $[M+H]^+$

Preparation of (2*S*)-10-amino-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one

To a solution of (2*S*)-10-(benzhydrylideneamino)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (2.07 g, 4.12 mmol, 1 *equiv.*) in dioxane (7 mL) was added HCl/dioxane (14 mL). The mixture was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give a residue which was purified by prep-HPLC to afford (2*S*)-10-amino-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (931 mg) as a pink solid.

LC-MS (ESI): m/z = 8340.1 $[M+H]^+$

Preparation of (2*S*)-2-cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one

To a solution of (2*S*)-10-amino-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (206 mg, 607.11 μmol, 1 *equiv.*) in DMF (3 mL) was added DIPEA (235.39 mg, 1.82 mmol, 317.24 μL, 3 *equiv.*) and 2,4,5-trichloropyrimidine (133.63 mg, 728.53 μmol, 1.2 *equiv.*). The mixture was stirred at 80 °C for 24 hours. The reaction mixture was diluted with H_2O (5 mL) and extracted with ethyl acetate (15 mL). The combined organic layers were washed with brine (30 mL), dried over sodium sulfate, filtered,

and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to afford (2*S*)-2-cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (315 mg) as a white solid.

LC-MS (ESI): m/z = 486.0 $[M+H]^+$

Preparation of *tert*-butyl (3*S*,4*R*)-3-fluoro-4-formyl-piperidine-1-carboxylate

To a solution of *tert*-butyl (3*S*,4*R*)-3-fluoro-4-(hydroxymethyl)piperidine-1-carboxylate (550 mg, 2.36 mmol, 1 *equiv.*) in DCM (6 mL) was added DMP (2.00 g, 4.72 mmol, 1.46 mL, 2 *equiv.*) at 0 °C. The mixture was stirred at 0 °C for 2 hours. The reaction mixture was filtered and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography (20% ethyl acetate/petroleum ether) to afford *tert*-butyl (3*S*,4*R*)-3-fluoro-4-formyl-piperidine-1-carboxylate (150 mg) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.66 (s, 1H), 5.49 - 5.18 (m, 1H), 4.35 - 3.93 (m, 2H), 2.91 - 2.69 (m, 2H), 1.76 - 1.67 (m, 1H), 1.64 - 1.51 (m, 1H), 1.42 - 1.36 (m, 10H).

Preparation of *tert*-butyl (3*S*,4*R*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridin-1-yl]methyl]-3-fluoro-piperidine-1-carboxylate

To a solution of *tert*-butyl (3*S*,4*R*)-3-fluoro-4-formyl-piperidine-1-carboxylate (290 mg, 1.25 mmol, 1 *equiv.*) and 3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)indazole (675.98 mg, 1.25 mmol, 1 *equiv.*, HCl) in DMSO (4 mL) was added dropwise AcOH (7.53 mg, 125.40 μmol, 7.18 μL, 0.1 *equiv.*) and $NaBH(OAc)_3$ (398.65 mg, 1.88 mmol, 1.5 *equiv.*). The resulting mixture was stirred at 25 °C for 1 hour. The reaction mixture was diluted with H_2O (10 mL) and extracted with ethyl acetate (60 mL). The combined organic layers were washed with brine (90 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography (60-100% ethyl acetate/petroleum ether) to afford *tert*-butyl (3*S*,4*R*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridin-1-yl]methyl]-3-fluoro-piperidine-1-carboxylate (310 mg) as a yellow solid.

LC-MS (ESI): m/z = 718.3 $[M+H]^+$

Preparation of *tert*-butyl (3*S*,4*R*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-fluoro-piperidine-1-carboxylate

To a solution of *tert*-butyl (3*S*,4*R*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-

indazol-6-yl]-3,6-dihydro-2H-pyridin-1-yl]methyl]-3-fluoro-piperidine-1-carboxylate (300 mg, 417.90 μmol, 1 *equiv.*) in CF_3CH_2OH (3 mL) was added Pd on carbon (151.21 mg, 142.09 μmol, 10% purity, 0.34 *equiv.*) and $Pd(OH)_2$ on carbon (149.66 mg, 213.13 μmol, 20% purity, 0.51 *equiv.*) under N_2 atmosphere. The suspension was degassed and purged with H_2 three times. The mixture was stirred under H_2 (15 psi) at 25 °C for 36 hours. The reaction mixture was filtered and concentrated under reduced pressure to give *tert*-butyl (3*S*,4*R*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-fluoro-piperidine-1-carboxylate (174 mg, crude) as a black solid.

LC-MS (ESI): m/z = 542.3 $[M+H]^+$

Preparation of 3-[6-[1-[[(3*S*,4*R*)-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione

To a solution of *tert*-butyl (3*S*,4*R*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-fluoro-piperidine-1-carboxylate (174 mg, 321.24 μmol, 1 *equiv.*) in DCM (1.5 mL) was added HCl/dioxane (1.5 mL). The mixture was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give 3-[6-[1-[[(3*S*,4*R*)-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (160 mg, crude, HCl) as a black solid.

LC-MS (ESI): m/z = 442.2 $[M+H]^+$

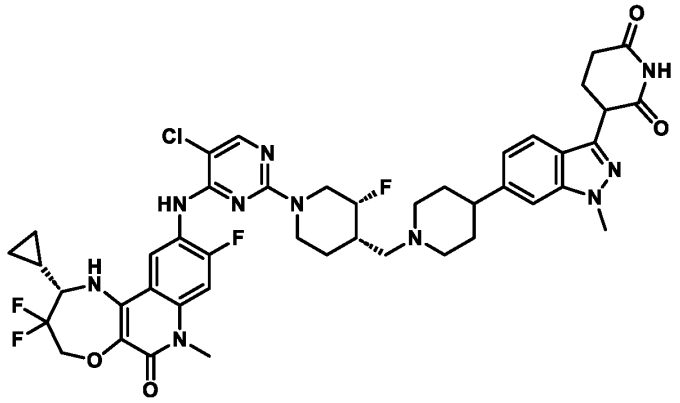
Preparation of 3-[6-[1-[[(3*S*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione

To a solution of 3-[6-[1-[[(3*S*,4*R*)-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (117.96 mg, 246.77 μmol, 1.2 *equiv.*) and (2*S*)-2-cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (100 mg, 205.65 μmol, 1 *equiv.*) in DMSO (1 mL) was added TEA (114.49 μL, 822.58 μmol, 4 *equiv.*). The mixture was stirred at 100 °C for 1 hour. The reaction mixture was filtered to give a residue. The residue was purified by prep-HPLC to afford 3-[6-[1-[[(3*S*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (19.1 mg) as a purple solid.

LC-MS (ESI): m/z = 891.4 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.87 (s, 1H), 8.85 (s, 1H), 8.24 - 8.19 (m, 1H), 8.18 (s, 1H), 8.02 (s, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.48 - 7.31 (m, 2H), 7.02 (d, J = 8.4 Hz, 1H), 6.41 (s, 1H), 4.88 - 4.60 (m, 2H), 4.53 - 4.28 (m, 4H), 3.96 (s, 3H), 3.56 (s, 3H), 3.05 - 2.79 (m, 4H), 2.76 - 2.58 (m, 4H), 2.41 - 2.28 (m, 2H), 2.22 - 2.10 (m, 2H), 2.09 - 1.86 (m, 3H), 1.77 - 1.76 (m, 4H), 1.54 - 1.42 (m, 1H), 1.38 - 1.19 (m, 2H), 0.77 - 0.63 (m, 1H), 0.51 (t, J = 6.0 Hz, 2H), 0.38 - 0.25 (m, 1H).

Example 73. 3-(6-(1-(((3*R*,4*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 118a)



Preparation of 6-bromo-7-fluoro-1*H*-3,1-benzoxazine-2,4-dione

To a solution of 2-amino-5-bromo-4-fluoro-benzoic acid (90 g, 384.58 mmol, 1 *equiv.*) in THF (900 mL) was added bis (trichloromethyl) carbonate (39.94 g, 134.60 mmol, 0.35 *equiv.*) at 0 °C under N_2. The mixture was stirred at 70 °C for 2 hours. The reaction mixture was filtered and washed with THF. The filtrate solid was concentrated under reduced pressure to give 6-bromo-7-fluoro-1*H*-3,1-benzoxazine-2,4-dione (81.2 g, crude) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.98 (s, 1H), 8.19 (d, J = 7.6 Hz, 1H), 7.03 (d, J = 9.2 Hz, 1H).

Preparation of 6-bromo-7-fluoro-1-methyl-3,1-benzoxazine-2,4-dione

To a solution of 6-bromo-7-fluoro-1*H*-3,1-benzoxazine-2,4-dione (81.2 g, 312.29

mmol, 1 *equiv.*) in dimethylacetamide (90 mL) was added iodomethane (132.98 g, 936.86 mmol, 58.32 mL, 3 *equiv.*) and DIPEA (80.72 g, 624.58 mmol, 108.79 mL, 2 *equiv.*). The mixture was stirred at 25 °C for 2 hours. The reaction mixture was diluted with H_2O (100 mL) and filtered to obtain 6-bromo-7-fluoro-1-methyl-3,1-benzoxazine-2,4-dione (80 g, crude) as a white solid.

LC-MS (ESI): m/z = 273.9 $[M+H]^+$

Preparation of ethyl 6-bromo-7-fluoro-4-hydroxy-1-methyl-2-oxo-quinoline-3-carboxylate

A mixture of 6-bromo-7-fluoro-1-methyl-3,1-benzoxazine-2,4-dione (80 g, 291.92 mmol, 1 *equiv.*), diethyl propanedioate (140.27 g, 875.77 mmol, 132.96 mL, 3 *equiv.*) and NaH (23.35 g, 583.85 mmol, 60% purity, 2 *equiv.*) in DMF (1000 mL) was degassed and purged with N_2 three times. The mixture was stirred at 25 °C for 2 hours under N_2 atmosphere. The reaction mixture was diluted with saturated ammonium chloride (1500 mL), filtered, and concentrated under reduced pressure to give a residue which was triturated with ethyl acetate at 25 °C for 30 minutes to obtain ethyl 6-bromo-7-fluoro-4-hydroxy-1-methyl-2-oxo-quinoline-3-carboxylate (37 g) as a white solid.

LC-MS (ESI): m/z = 343.9 $[M+H]^+$

Preparation of ethyl 6-bromo-4-chloro-7-fluoro-1-methyl-2-oxo-quinoline-3-carboxylate

To a solution of ethyl 6-bromo-7-fluoro-4-hydroxy-1-methyl-2-oxo-quinoline-3-carboxylate (15 g, 43.59 mmol, 1 *equiv.*) in DMF (150 mL) was added dropwise $(COCl)_2$ (16.60 g, 130.76 mmol, 11.45 mL, 3 *equiv.*). The mixture was stirred at 70 °C for 0.5 hours. The reaction mixture was quenched by H_2O (500 mL) and then filtered and concentrated under reduced pressure to give a residue which was triturated with petroleum ether at 25 °C for 10 minutes to obtain ethyl 6-bromo-4-chloro-7-fluoro-1-methyl-2-oxo-quinoline-3-carboxylate (11.2 g) as a white solid.

LC-MS (ESI): m/z = 362.0 $[M+H]^+$

Preparation of 6-bromo-4-[[(1*S*)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-7-fluoro-1-methyl-quinolin-2-one

Ethyl 6-bromo-4-chloro-7-fluoro-1-methyl-2-oxo-quinoline-3-carboxylate (700 mg,

1.93 mmol, 1 *equiv.*), (3*S*)-3-amino-3-cyclopropyl-2,2-difluoro-propan-1-ol (398.43 mg, 2.12 mmol, 1.1 *equiv.*, HCl) and DIPEA (748.56 mg, 5.79 mmol, 1.01 mL, 3 *equiv.*) were taken up into a microwave tube with NMP (15 mL). The sealed tube was heated at 200 °C for 2 hours in a microwave reactor. The reaction mixture was diluted with H_2O (120 mL) and extracted with ethyl acetate (360 mL). The combined organic layers were washed with brine (2400 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography (60% ethyl acetate/petroleum ether) to afford 6-bromo-4-[[(1*S*)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-7-fluoro-1-methyl-quinolin-2-one as a yellow solid.

LC-MS (ESI): m/z = 404.9 $[M+H]^+$

Preparation of 3,6-dibromo-4-[[(1*S*)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-7-fluoro-1-methyl-quinolin-2-one

To a solution of 6-bromo-4-[[(1*S*)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-7-fluoro-1-methyl-quinolin-2-one (3.6 g, 8.47 mmol, 1 *equiv.*) in DMF (36 mL) was added NBS (1.36 g, 7.62 mmol, 0.9 *equiv.*) at 0 °C. The mixture was stirred at 0 °C for 20 minutes. The reaction mixture was diluted with H_2O (40 mL) and extracted with ethyl acetate (150 mL). The combined organic layers were washed with brine 150 mL (50 mL × 3), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography (25% ethyl acetate/petroleum ether) to afford 3,6-dibromo-4-[[(1*S*)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-7-fluoro-1-methyl-quinolin-2-one (2.7 g) as a yellow solid.

LC-MS (ESI): m/z = 484.9 $[M+H]^+$

Preparation of (2*S*)-10-bromo-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one

To a solution of 3,6-dibromo-4-[[(1*S*)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-7-fluoro-1-methyl-quinolin-2-one (2.7 g, 5.58 mmol, 1 *equiv.*) in THF (10 mL) was added t-BuOK (1 M, 2.79 mL, 0.5 *equiv.*). The mixture was stirred at 60 °C for 1 hour, then t-BuOK (1 M, 2.79 mL, 0.5 *equiv.*) was added. The resulting mixture was stirred at 60 °C for 0.1 hours. The reaction mixture was concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography (40% ethyl acetate/petroleum ether) to afford (2*S*)-10-bromo-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (2.2 g) as a white solid.

LC-MS (ESI): m/z = 402.9 $[M+H]^+$

Preparation of (2*S*)-10-(benzhydrylideneamino)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one

A mixture of (2*S*)-10-bromo-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (2.2 g, 5.46 mmol, 1 *equiv.*), diphenylmethanimine (1.19 g, 6.55 mmol, 1.10 mL, 1.2 *equiv.*), $Pd_2(dba)_3$ (499.66 mg, 545.64 μmol, 0.1 *equiv.*), XantPhos (631.44 mg, 1.09 mmol, 0.2 *equiv.*) and cesium carbonate (4.44 g, 13.64 mmol, 2.5 *equiv.*) in toluene (25 mL) was degassed and purged with N_2 three times. The mixture was stirred at 100 °C for 12 hours under N_2 atmosphere. The reaction mixture was diluted with H_2O (30 mL) and extracted with ethyl acetate (90 mL). The combined organic layers were washed with brine (90 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography (50% ethyl acetate/petroleum ether) to afford (2*S*)-10-(benzhydrylideneamino)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (2.07 g) as a yellow solid.

LC-MS (ESI): m/z = 504.1 $[M+H]^+$

Preparation of (2*S*)-10-amino-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one

To a solution of (2*S*)-10-(benzhydrylideneamino)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (2.07 g, 4.12 mmol, 1 *equiv.*) in dioxane (7 mL) was added HCl/dioxane (14 mL). The mixture was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give a residue which was purified by prep-HPLC to afford (2*S*)-10-amino-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (931 mg) as a pink solid.

LC-MS (ESI): m/z = 8340.1 $[M+H]^+$

Preparation of (2*S*)-2-cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one

To a solution of (2*S*)-10-amino-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (206 mg, 607.11 μmol, 1 *equiv.*) in DMF (3 mL) was added DIPEA (235.39 mg, 1.82 mmol, 317.24 μL, 3 *equiv.*) and 2,4,5-trichloropyrimidine (133.63 mg, 728.53 μmol, 1.2 *equiv.*). The mixture was stirred at 80 °C for 24 hours. The reaction mixture was diluted with H_2O (5 mL) and extracted with ethyl acetate (15 mL). The

combined organic layers were washed with brine (30 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to afford (2*S*)-2-cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (315 mg) as a white solid.

LC-MS (ESI): m/z = 486.0 $[M+H]^+$

Preparation of *tert*-butyl (3*R*,4*S*)-3-fluoro-4-formylpiperidine-1-carboxylate

To a mixture of *tert*-butyl (3*R*,4*S*)-3-fluoro-4-(hydroxymethyl)piperidine-1-carboxylate (0.3 g, 1.29 mmol, 1 *equiv.*) in DCM (6 mL) was added DMP (1.09 g, 2.57 mmol, 2 *equiv.*) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to give a residue which was purified by column chromatography (petroleum ether/ethyl acetate=10/1 to 5/1) to afford *tert*-butyl (3*R*,4*S*)-3-fluoro-4-formylpiperidine-1-carboxylate (0.12 g) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$-d) δ = 9.76 (s, 1H), 5.31 - 5.01 (m, 1H), 4.60 - 4.10 (m, 2H), 3.18 - 2.64 (m, 2H), 2.59 - 2.31 (m, 1H), 2.00 (dq, *J* = 4.4, 12.8 Hz, 1H), 1.84 (br d, *J* = 12.0 Hz, 1H), 1.47 (s, 9H).

Preparation of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate

To a mixture of *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylate (2.01 g, 6.49 mmol, 1.3 *equiv.*), 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-1-methyl-1*H*-indazole (2.5 g, 5.00 mmol, 1 *equiv.*), and cesium carbonate (4.88 g, 14.99 mmol, 3 *equiv.*) in dioxane (200 mL) and H_2O (10 mL) was added $Pd(dppf)Cl_2$ (365.57 mg, 499.61 μmol, 0.1 *equiv.*) under N_2. The reaction mixture was degassed and purged with N_2 three times. The mixture was stirred at 100 °C for 1 hour under N_2 atmosphere. The reaction mixture was poured into H_2O (100 mL) and extracted with ethyl acetate (300 mL). The combined organic layers were washed with aqueous sodium chloride (100 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue which was purified by column chromatography (petroleum ether/ethyl acetate=20/1 to 8/1) to afford *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (11.2 g) as a yellow solid.

LC-MS (ESI): m/z = 603.3 $[M+H]^+$

Preparation of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indazole

A mixture of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (5 g, 8.30 mmol, 1 *equiv.*) in DCM (50 mL) and HCl/dioxane (2M, 50 mL) was stirred at 25 °C for 4 hours. The reaction mixture was concentrated under reduced pressure to give 3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indazole (4.5 g, crude, HCl) as a yellow solid, which was used in the next step without further purification.

LC-MS (ESI): m/z = 503.2 $[M+H]^+$

Preparation of *tert*-butyl (3*R*,4*S*)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)-3,6-dihydropyridin-1(2*H*)-yl)methyl)-3-fluoropiperidine-1-carboxylate

A mixture of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indazole (240 mg, 445.21 μmol, 1 *equiv.*, HCl), *tert*-butyl (3*R*,4*S*)-3-fluoro-4-formyl-piperidine-1-carboxylate (102.96 mg, 445.21 μmol, 1 *equiv.*), AcOH (2.67 mg, 44.52 μmol, 0.1 *equiv.*), and $NaBH(OAc)_3$ (141.54 mg, 667.82 μmol, 1.5 *equiv.*) in DMSO (5 mL) was stirred at 25 °C for 1 hour. The reaction mixture was diluted with H_2O (20 mL) and extracted with ethyl acetate (30 mL). The combined organic layers were washed with aqueous sodium chloride (10 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue which was purified by column chromatography (petroleum ether/ethyl acetate=3/1 to 1/1) to afford *tert*-butyl (3*R*,4*S*)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)-3,6-dihydropyridin-1(2*H*)-yl)methyl)-3-fluoropiperidine-1-carboxylate (202 mg) as a yellow solid.

LC-MS (ESI): m/z = 718.3 $[M+H]^+$

Preparation of *tert*-butyl (3*R*,4*S*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate

To a solution of Pd on carbon (200.00 mg, 187.93 μmol, 10 wt%, 0.67 *equiv.*) and $Pd(OH)_2$ on carbon (200.00 mg, 284.83 μmol, 20 wt%, 1.02 *equiv.*) in CF_3CH_2OH (10 mL) was added *tert*-butyl (3*R*,4*S*)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)-3,6-dihydropyridin-1(2*H*)-yl)methyl)-3-fluoropiperidine-1-carboxylate (200 mg, 278.60 μmol, 1 *equiv.*) under N_2. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 psi) at 25 °C for 12 hours. The reaction

mixture was filtered and concentrated under reduced pressure to give a residue which was purified by prep-TLC (DCM : methanol=10:1) to afford *tert*-butyl (3*R*,4*S*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (137 mg) as a yellow solid.

LC-MS (ESI): m/z = 542.3 $[M+H]^+$

Preparation of 3-(6-(1-(((3*R*,4*S*)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

To a mixture of *tert*-butyl (3*R*,4*S*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (127 mg, 234.47 μmol, 1 *equiv.*) in DCM (2 mL) was added HCl/dioxane (2M, 2 mL). The mixture was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give 3-(6-(1-(((3*R*,4*S*)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (120 mg, crude, HCl) as a yellow solid, which was used in the next step without further purification.

LC-MS (ESI): m/z = 442.2 $[M+H]^+$

Preparation of 3-(6-(1-(((3*R*,4*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

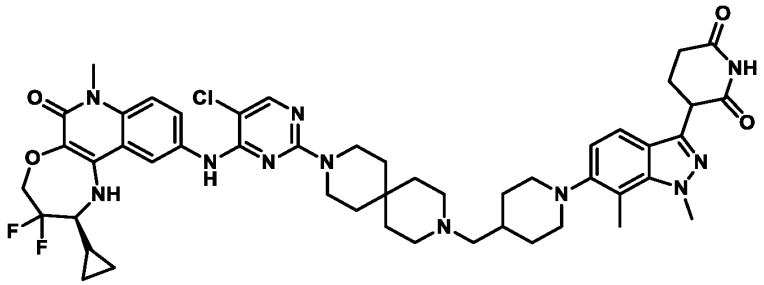
A solution of (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3,9-trifluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (109.87 mg, 225.94 μmol, 0.9 *equiv.*), 3-(6-(1-(((3*R*,4*S*)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (120 mg, 251.05 μmol, 1 *equiv.*), TEA (140 μL, 1.00 mmol, 4 *equiv.*) in DMSO (2 mL) was stirred at 100 °C for 6 hours. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to afford 3-(6-(1-(((3*R*,4*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-*c*]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (45.81 mg) as a pink solid.

LC-MS (ESI): m/z = 891.4 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.87 (s, 1H), 8.84 (s, 1H), 8.20 (s, 1H), 8.02 (s, 1H), 7.60 (m, 1H), 7.48 - 7.37 (m, 2H), 7.02 (m, 1H), 6.45 (m, 1H), 4.89 - 4.62 (m, 2H), 4.56

- 4.22 (m, 4H), 3.96 (s, 3H), 3.55 (s, 3H), 3.04 - 2.79 (m, 4H), 2.77 - 2.56 (m, 4H), 2.40 - 2.27 (m, 2H), 2.24 - 2.09 (m, 2H), 2.08 - 1.84 (m, 3H), 1.82 - 1.67 (m, 4H), 1.55 - 1.40 (m, 1H), 1.36 - 1.21 (m, 2H), 0.70 (m, 1H), 0.51 (m, 2H), 0.39 - 0.24 (m, 1H).

Example 74. 3-[6-[4-[[3-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3,9-diazaspiro[5.5]undecan-9-yl]methyl]-1-piperidyl]-1,7-dimethyl-indazol-3-yl]piperidine-2,6-dione (Compound 177a)



To a solution of 3-[6-[4-(3,9-diazaspiro[5.5]undecan-3-ylmethyl)-1-piperidyl]-1,7-dimethyl-indazol-3-yl]piperidine-2,6-dione (See Table 29) (0.1 g, 197.36 μmol, 1 *equiv.*) in DMSO (2 mL) was added TEA (82.41 μL, 592.09 μmol, 3 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (92.42 mg, 197.36 μmol, 1 *equiv.*). The mixture was stirred at 100 °C for 6 hours. The reaction mixture was quenched with H_2O (5 mL) and extracted with ethyl acetate (60 mL). The combined organic layers were washed with brine (60 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to afford 3-[6-[4-[[3-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3,9-diazaspiro[5.5]undecan-9-yl]methyl]-1-piperidyl]-1,7-dimethyl-indazol-3-yl]piperidine-2,6-dione (57.62 mg) as a gray solid.

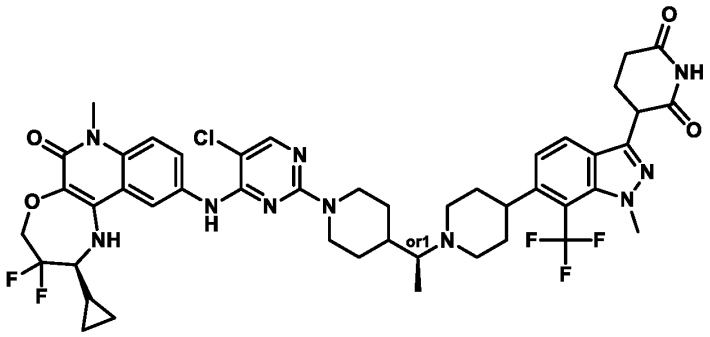
LC-MS (ESI): m/z = 938.5 $[M+H]^+$

Example 75. 3-[6-[1-[(1*S*)-1-[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]ethyl]-4-piperidyl]-1-methyl-7-(trifluoromethyl)indazol-3-yl]piperidine-2,6-dione

[3-(6-(1-((*S)-1-(1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-**

yl)piperidin-4-yl)ethyl)piperidin-4-yl)-1-methyl-7-(trifluoromethyl)-1*H*-indazol-3-yl)piperidine-2,6-dione]

(Compound 109b)



To a solution of 3-[1-methyl-6-[1-[(1*S*)-1-(4-piperidyl)ethyl]-4-piperidyl]-7-(trifluoromethyl)indazol-3-yl]piperidine-2,6-dione (See Table P6) (50 mg, 98.90 μmol, 1 *equiv.*) in DMSO (2 mL) was added TEA (55.06 μL, 395.59 μmol, 4 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (32.42 mg, 69.23 μmol, 0.7 *equiv.*). The mixture was stirred at 95 °C for 1 hour. The reaction mixture was filtered, and the filtrate was concentrated to give a residue. The residue was purified by prep-HPLC to afford 3-[6-[1-[(1*S*)-1-[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]ethyl]-4-piperidyl]-1-methyl-7-(trifluoromethyl)indazol-3-yl]piperidine-2,6-dione [3-(6-(1-((*S**)-1-(1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)ethyl)piperidin-4-yl)-1-methyl-7-(trifluoromethyl)-1*H*-indazol-3-yl)piperidine-2,6-dione] (15.84 mg) as a yellow solid.

LC-MS (ESI): m/z = 937.3 $[M+H]^+$.

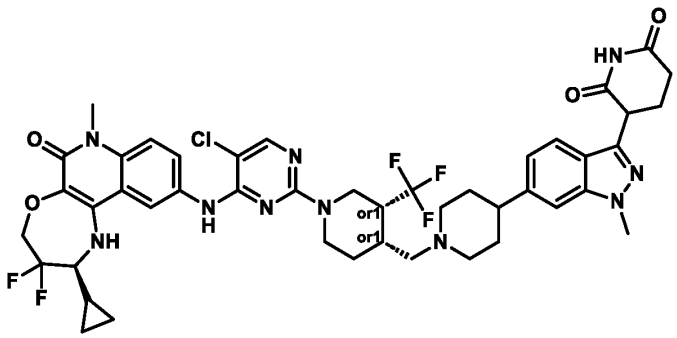
^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.95 (s, 1H), 8.77 (s, 1H), 8.30 (s, 1H), 8.24 (s, 1H), 8.03 (s, 1H), 7.97 (br d, J = 8.4 Hz, 1H), 7.72 (br d, J = 8.8 Hz, 1H), 7.46 (d, J = 9.2 Hz, 1H), 7.37 (br d, J = 8.8 Hz, 1H), 6.20 (br s, 1H), 4.61 - 4.30 (m, 5H), 4.01 (br d, J = 3.2 Hz, 3H), 3.58 (s, 3H), 3.08 - 2.94 (m, 1H), 2.84 - 2.63 (m, 6H), 2.55 (br d, J = 5.2 Hz, 1H), 2.42 (br s, 1H), 2.29 - 2.03 (m, 5H), 1.92 - 1.74 (m, 2H), 1.68 (br d, J = 7.2 Hz, 3H), 1.58 - 1.46 (m, 1H), 1.35 (dt, J = 0.8, 2.8 Hz, 1H), 1.07 - 0.97 (m, 2H), 0.91 (br d, J = 6.0 Hz, 3H), 0.75 - 0.64 (m, 1H), 0.52 (br t, J = 6.0 Hz, 2H), 0.43 - 0.31 (m, 1H)

Example 76. 3-[6-[1-[[(3*R*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-

yl]-3-(trifluoromethyl)-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione

[3-(6-(1-(((3*R,4*R**)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-(trifluoromethyl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]**

(Compound 139a)



To a solution of 3-[1-methyl-6-[1-[[(3*R*,4*R*)-3-(trifluoromethyl)-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione (See Table P6) (80.00 mg, 97.65 μmol, 1 *equiv.*) in DMSO (1 mL) was added TEA (40.78 μL, 292.95 μmol, 3 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (45.73 mg, 97.65 μmol, 1 *equiv.*). The mixture was stirred at 100 °C for 16 hours. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to afford 3-[6-[1-[[(3*R*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-(trifluoromethyl)-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione [3-(6-(1-(((3*R**,4*R**)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-(trifluoromethyl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (9.65 mg) as a yellow solid.

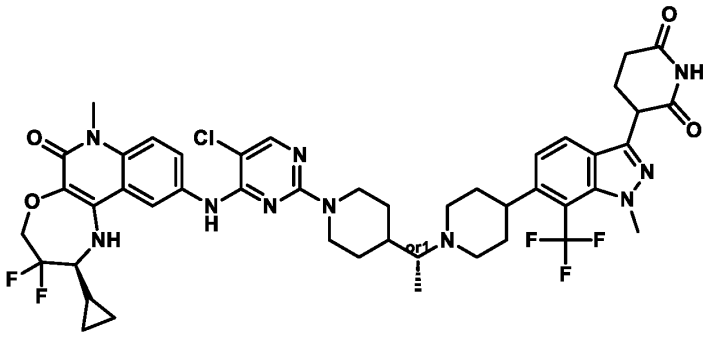
LC-MS (ESI): m/z = 923.3 $[M+H]^+$

Example 77. 3-[6-[1-[(1*R*)-1-[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]ethyl]-4-piperidyl]-1-methyl-7-(trifluoromethyl)indazol-3-yl]piperidine-

2,6-dione

[3-(6-(1-((*R)-1-(1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)ethyl)piperidin-4-yl)-1-methyl-7-(trifluoromethyl)-1*H*-indazol-3-yl)piperidine-2,6-dione]**

(Compound 109a)



To a solution of 3-[1-methyl-6-[1-[(1*R*)-1-(4-piperidyl)ethyl]-4-piperidyl]-7-(trifluoromethyl)indazol-3-yl]piperidine-2,6-dione (See Table P6) (50.00 mg, 98.90 μmol, 1 *equiv.*) in DMSO (2 mL) was added TEA (55.06 μL, 395.59 μmol, 4 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (32.42 mg, 69.23 μmol, 0.7 *equiv.*). The mixture was stirred at 95 °C for 1 hour. The reaction mixture was filtered, and the filtrate was concentrated to give a residue. The residue was purified by prep-HPLC to afford 3-[6-[1-[(1*R*)-1-[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]ethyl]-4-piperidyl]-1-methyl-7-(trifluoromethyl)indazol-3-yl]piperidine-2,6-dione [3-(6-(1-((*R**)-1-(1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)ethyl)piperidin-4-yl)-1-methyl-7-(trifluoromethyl)-1*H*-indazol-3-yl)piperidine-2,6-dione] (16.3 mg) as a yellow solid.

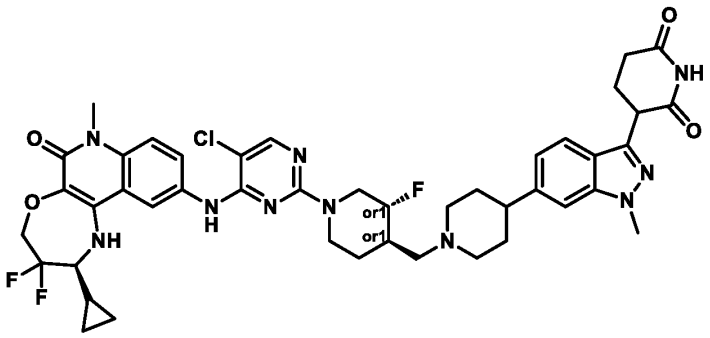
LC-MS (ESI): m/z = 937.3 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.95 (s, 1H), 8.76 (s, 1H), 8.31 (s, 1H), 8.24 (s, 1H), 8.03 (s, 1H), 7.97 (br d, J = 8.4 Hz, 1H), 7.73 (br d, J = 9.2 Hz, 1H), 7.46 (d, J = 9.2 Hz, 1H), 7.37 (br d, J = 8.4 Hz, 1H), 6.19 (br s, 1H), 4.58 - 4.32 (m, 5H), 4.01 (br d, J = 2.8 Hz, 3H), 3.58 (s, 3H), 3.07 - 2.96 (m, 1H), 2.87 - 2.62 (m, 6H), 2.55 (br s, 1H), 2.42 (br s, 1H), 2.28 - 2.01 (m, 5H), 1.90 - 1.62 (m, 5H), 1.58 - 1.47 (m, 1H), 1.38 - 1.27 (m, 1H), 1.10 - 0.96 (m, 2H), 0.91 (br d, J = 6.4 Hz, 3H), 0.76 - 0.65 (m, 1H), 0.51 (br d, J = 6.4 Hz, 2H), 0.41 -

0.29 (m, 1H)

Example 78. 3-(6-(1-(((3*R*,4*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-(1-(((3*R,4*R**)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]**

(Compound 110a)

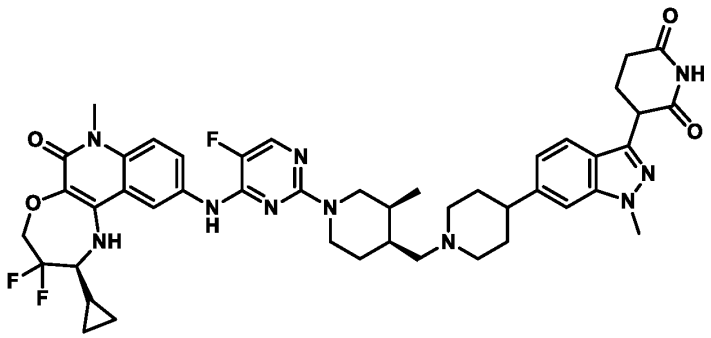


To a stirred solution of 3-(6-(1-(((3*R*,4*R*)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (See Table P6) (0.15 g, 0.34 mmol, 1.0 *equiv.*) in DMSO (1.50 mL) and DIPEA (1.50 mL) was added (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.064 g, 0.14 mmol, 0.4 *equiv.*). The mixture was stirred at 100 °C for 16 hours. The reaction mixture was cooled to room temperature and was added to ice water. The precipitated solid was filtered and dried to obtain crude product which was purified by prep-HPLC to afford 3-(6-(1-(((3*R*,4*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-(1-(((3*R**,4*R**)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (0.066 g) as an off white solid.

LC-MS (ESI): m/z = 873.84 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.89 (s, 1H), 8.98 (s, 1H), 8.16 (d, J = 2.00 Hz, 1H), 8.10 (s, 1H), 7.72 (dd, J = 1.60, 9.00 Hz, 1H), 7.68 (d, J = 8.40 Hz, 1H), 7.42 (t, J = 7.60 Hz, 2H), 7.03 (d, J = 8.00 Hz, 1H), 6.27 (br s, 1H), 4.45-4.32 (m, 3H), 3.98 (s, 3H), 3.68-3.57 (m, 5H), 3.31-2.94 (m, 9H), 2.62-2.61 (m, 2H), 2.50-2.35 (m, 2H), 2.29-1.91 (m, 6H), 1.31-1.36 (m, 4H), 0.76-0.68 (m, 1H), 0.52 (t, J = 5.60 Hz, 2H), 0.37-0.28 (m, 1H).

Example 79. 3-(6-(1-(((3S,4S)-1-(4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)-5-fluoropyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 117a)



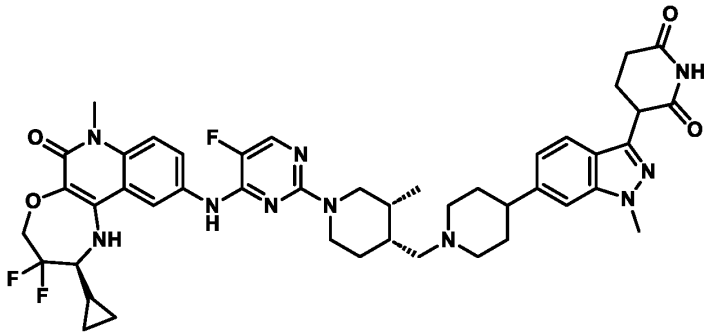
To a stirred solution of 3-(1-methyl-6-(1-(((3S,4S)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (See Table P6) (0.20 g, 0.46 mmol, 1.0 *equiv.*) in DMSO (2.0 mL) and DIPEA (2.0 mL) was added (*S*)-10-((2-chloro-5-fluoropyrimidin-4-yl)amino)-2-cyclopropyl-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.04 g, 0.09 mmol, 0.2 *equiv.*). The mixture was stirred at 100 °C for 16 hours. The mixture was cooled to room temperature and was added ice water. The precipitated solid was filtered and dried to obtain crude product which was purified by reverse phase purification to afford 3-(6-(1-(((3S,4S)-1-(4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)-5-fluoropyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.032 g).

LC-MS (ESI): m/z = 853.72 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.87 (s, 1H), 9.23 (s, 1H), 8.19 (d, J = 1.60 Hz, 1H), 7.98 (d, J = 3.60 Hz, 1H), 7.81 (dd, J = 2.00, 9.20 Hz, 1H), 7.60 (d, J = 8.40 Hz, 1H), 7.46 (d, J = 9.20 Hz, 1H), 7.43 (s, 1H), 7.03 (d, J = 8.00 Hz, 1H), 5.98 (s, 1H), 4.43-4.31 (m, 5H),

3.97 (s, 3H), 3.57 (s, 3H), 3.25-3.19 (m, 1H), 3.03-2.81 (m, 4H), 2.65-2.51 (m, 5H), 2.39-2.31 (m, 1H), 2.20-2.14 (m, 3H), 2.02-1.91 (m, 4H), 1.80-1.71 (m, 4H), 1.43-1.32 (m, 4H), 0.78-0.72 (m, 1H), 0.53 (t, *J* = 5.20 Hz, 2H), 0.41-0.38 (m, 1H).

Example 80. 3-(6-(1-(((3*R*,4*R*)-1-(4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)-5-fluoropyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 117b)



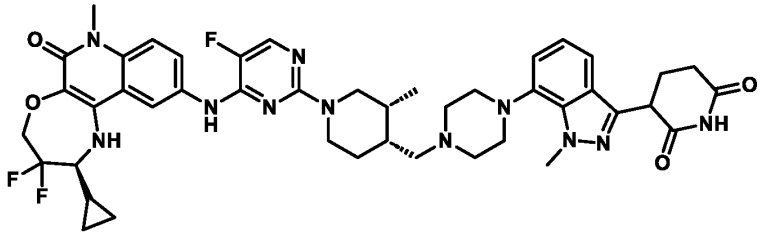
To a stirred solution of 3-(1-methyl-6-(1-(((3*R*,4*R*)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (See Table P6) (0.20 g, 0.45 mmol, 1.0 *equiv.*) in DMSO (2.0 mL) was added DIPEA (2.0 mL), and (*S*)-10-((2-chloro-5-fluoropyrimidin-4-yl)amino)-2-cyclopropyl-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.04 g, 0.09 mmol, 0.2 *equiv.*). The mixture was stirred at 110 °C for 16 hours. The reaction mixture was then cooled to room temperature and was added ice water. The precipitated solid was filtered and dried to obtain crude product which was purified by reverse phase purification to afford 3-(6-(1-(((3*R*,4*R*)-1-(4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)-5-fluoropyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.045 g) as an off white solid.

LC-MS (ESI): m/z = 853.72 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.98 (s, 1H), 9.24 (s, 1H), 8.21 (d, *J* = 1.60 Hz, 1H), 7.98 (d, *J* = 3.60 Hz, 1H), 7.82-7.79 (m, 1H), 7.61 (d, *J* = 7.60 Hz, 1H), 7.47-7.43 (m, 2H), 7.03 (d, *J* = 8.40 Hz, 1H), 5.97 (s, 1H), 4.34-4.31 (m, 2H), 3.97 (s, 3H), 3.57 (s, 3H), 3.26-3.24 (m, 1H), 3.01-2.97 (m, 4H), 2.67-2.65 (m, 2H), 2.63-2.57 (m, 2H), 2.33-2.32 (m, 1H),

2.18-2.14 (m, 3H), 2.01-1.87 (m, 5H), 1.77-1.75 (m, 4H), 1.36-1.32 (m, 4H), 0.80-0.70 (m, 4H), 0.54-0.52 (m, 2H), 0.36-0.34 (m, 1H).

Example 81. 3-(7-(4-(((3*R*,4*R*)-1-(4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)-5-fluoropyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 143a)

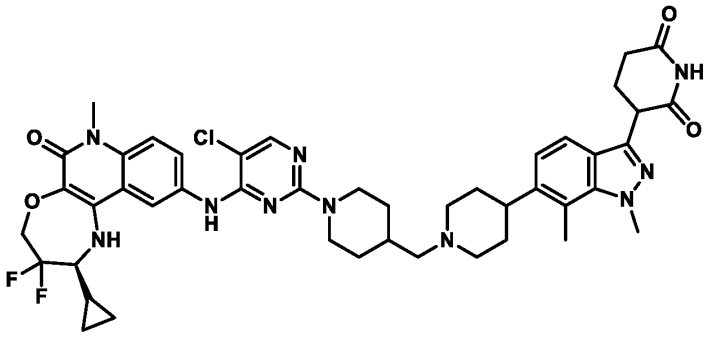


To a stirred solution of 3-(1-methyl-7-(4-(((3*R*,4*R*)-3-methylpiperidin-4-yl)methyl)piperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (See Table P6) (0.20 g, 0.45 mmol, 1.0 *equiv.*) in DMSO (2.0 mL) and DIPEA (2.0 mL) was added (*S*)-10-((2-chloro-5-fluoropyrimidin-4-yl)amino)-2-cyclopropyl-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.041 g, 0.09 mmol, 0.2 *equiv.*) and stirred at 100 °C for 16 hours. The reaction mixture was cooled to room temperature and was added ice water. The precipitated solid was filtered and dried to obtain crude product which was purified by reverse phase chromatography to afford 3-(7-(4-(((3*R*,4*R*)-1-(4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)-5-fluoropyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.049 g). as an off white solid.

LC-MS (ESI): m/z = 854.71 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.98 (s, 1H), 9.24 (s, 1H), 8.19 (d, *J* = 2.00 Hz, 1H), 7.98 (d, *J* = 3.60 Hz, 1H), 7.82 (dd, *J* = 10.80, Hz, 1H), 7.46 (d, *J* = 9.20 Hz, 1H), 7.40-7.38 (m, 1H), 7.05-7.00 (m, 2H), 5.99 (s, 1H), 4.43-4.32 (m, 2H), 4.24 (s, 3H), 3.57 (s, 3H), 3.04-2.87 (m, 8H), 2.64-2.54 (m, 2H), 2.52-2.51 (m, 1H), 2.30-2.24 (m, 5H), 2.20-2.15 (m, 2H), 1.95-1.94 (m, 1H), 1.43-1.36 (m, 4H), 1.23 (s, 2H), 0.80-0.73 (m, 4H), 0.55-0.52 (m, 2H), 0.36-0.34 (m, 1H)

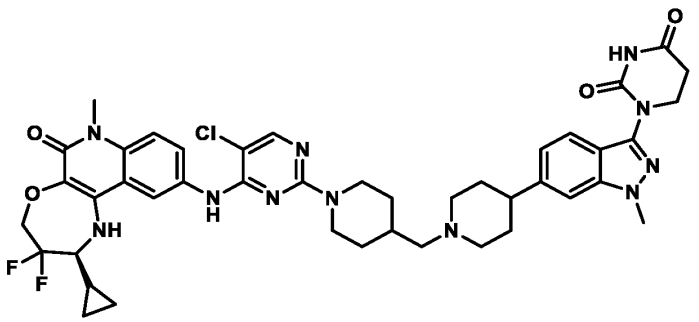
Example 82. 3-(6-(1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-1,7-dimethyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 154a)



To a solution of 3-(1,7-dimethyl-6-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (140 mg, 319.94 μmol, 1 *equiv.*) in DMSO (2 mL) was added TEA (178.13 μL, 1.28 mmol, 4 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-*c*]quinolin-6(7*H*)-one (134.84 mg, 287.95 μmol, 0.9 *equiv.*). The mixture was stirred at 100 °C for 2 hours. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to afford 3-(6-(1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-*c*]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-1,7-dimethyl-1*H*-indazol-3-yl)piperidine-2,6-dione (73.15 mg) as a yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.86 (s, 1H), 8.77 (s, 1H), 8.19 (s, 1H), 8.03 (s, 1H), 7.74 (d, J = 9.6 Hz, 1H), 7.45 (d, J = 9.6 Hz, 2H), 7.02 (d, J = 8.0 Hz, 1H), 6.15 (s, 1H), 4.48 - 4.39 (m, 3H), 4.31 - 4.26 (m, 1H), 4.23 (s, 3H), 3.57 (s, 3H), 2.97 - 2.89 (m, 4H), 2.82 - 2.74 (m, 4H), 2.67 (s, 3H), 2.35 - 2.30 (m, 2H), 2.16 (d, J = 5.2 Hz, 3H), 2.09 - 2.00 (m, 3H), 1.77 - 1.70 (m, 4H), 1.64 (s, 2H), 1.38 - 1.31 (m, 1H), 1.07 - 0.99 (m, 2H), 0.73 - 0.68 (m, 1H), 0.52 (d, J = 5.6 Hz, 2H), 0.39 - 0.33 (m, 1H)

Example 83: (*S*)-1-(6-(1-((1-(5-chloro-4-((2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Compound 167a)



Preparation of *tert*-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1-methyl-1*H*-indazol-6-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate

A mixture of 1-(6-bromo-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (595.0 mg, 1 *equiv.*, 1.841 mmol), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (740.1 mg, 1.3 *equiv.*, 2.394 mmol), XantPhos-Pd-G2 (49.09 mg, 0.03 *equiv.*, 55.24 μmol), and cesium carbonate (1.620 g, 2.7 *equiv.*, 4.971 mmol) were suspended in 1,4-dioxane (10.0 mL) and water (1.50 mL). The reaction mixture was heated to 85°C and stirred for 1.5 hours. The reaction mixture was cooled to room temperature, filtered through celite, and concentrated. The resulting residue was purified via C18 flash column using a gradient 10-100% (A: water + 0.1% formic acid; B: MeCN + 0.1% formic acid) to afford *tert*-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1-methyl-1*H*-indazol-6-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (262.1 mg).

LC-MS (ESI): m/z = 426.2 $[M+H]^+$.

Preparation of *tert*-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1-methyl-1*H*-indazol-6-yl)piperidine-1-carboxylate

tert-Butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1-methyl-1*H*-indazol-6-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (262.1 mg, 1 *equiv.*, 616.0 μmol) was dissolved in iPrOH (10.0 mL) and DMF (2.0 mL). The mixture was degassed with nitrogen for 2 minutes. $Pd(OH)_2$ on carbon (86.50 mg, 25.1 μL, 20 wt%, 0.2 *equiv.*, 123.2 μmol) was then added. The resulting mixture was degassed and then charged with a hydrogen balloon. The reaction mixture was stirred for 2 hours. The reaction mixture was filtered through celite and then concentrated to afford *tert*-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1-methyl-1*H*-indazol-6-yl)piperidine-1-carboxylate (397 mg).

LC-MS (ESI): m/z = 372.2 $[M+H]^+$.

Preparation of 1-(1-methyl-6-(piperidin-4-yl)-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione, 3HCl

tert-Butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1-methyl-1*H*-indazol-6-yl)piperidine-1-carboxylate (250 mg, 1 *equiv.*, 585 μmol) was dissolved in DCM (5.0 mL). HCl in 1,4-dioxane (1.17 mL, 4.0 M, 8 *equiv.*, 4.68 mmol) was added. The resulting reaction mixture was stirred at room temperature. After 16 hours, the reaction mixture was concentrated to afford 1-(1-methyl-6-(piperidin-4-yl)-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione, 3HCl (282.3 mg).

LC-MS (ESI): m/z = 328.2 $[M+H]^+$.

Preparation of *tert*-butyl 4-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate, formic Acid

A mixture of *tert*-butyl 4-formylpiperidine-1-carboxylate (300.8 mg, 2.0 *equiv.*, 1.410 mmol), 1-(1-methyl-6-(piperidin-4-yl)-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione, 2HCl (282.3 mg, 1.0 *equiv.*, 705.2 μmol) and potassium acetate (692.1 mg, 10 *equiv.*, 7.052 mmol) was suspended in THF (6 mL) and DMF (0.9 mL). The mixture was stirred at room temperature for 40 minutes. The mixture was then treated with sodium triacetoxyborohydride (224.2 mg, 1.50 *equiv.*, 1.058 mmol). After 16 hours, the reaction mixture was diluted into EtOAc, washed with saturated aqueous ammonium chloride, back-extracted once with EtOAc, and concentrated. The residue was purified via C18 flash column using a gradient 10-100% (A: water + 0.1% formic acid; B: MeCN + 0.1% formic acid) to afford *tert*-butyl 4-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate, formic Acid (358 mg).

LC-MS (ESI): m/z = 525.3 $[M+H]^+$.

Preparation of 1-(1-methyl-6-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione, 2HCl

tert-Butyl 4-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate (358 mg, 1 *equiv.*, 682 μmol) was dissolved in DCM (3.58 mL). The mixture was treated with HCl in 1,4-dioxane (199 mg, 1.36 mL, 4.0 M, 8 *equiv.*, 5.46 mmol) and stirred at room temperature. After 16 hours, the reaction mixture was evaporated to dryness. The resulting residue was redissolved in methanol and concentrated again to afford 1-(1-methyl-6-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione, 2HCl (320.5 mg).

LC-MS (ESI): m/z = 425.3 $[M+H]^+$.

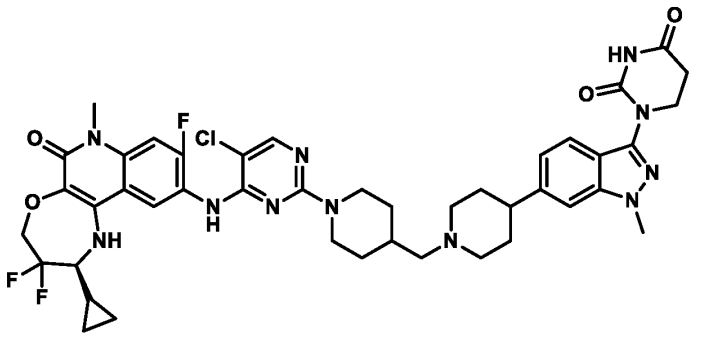
Preparation of (*S*)-1-(6-(1-((1-(5-chloro-4-((2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

A mixture of (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (69.5 mg, 1.5 *equiv.*, 148 μmol), 1-(1-methyl-6-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione, 2.5HCl (51.0 mg, 1.00 *equiv.*, 98.9 μmol), and CsF (45.1 mg, 3.00 *equiv.*, 297 μmol) in DMSO (2.00 mL) was treated with DIPEA (63.9 mg, 86.1 μL, 5.00 *equiv.*, 494 μmol) and warmed to 80 °C. After 1.5 hours, the reaction mixture was filtered and purified directly via preparative HPLC using a gradient 10-100% (A: water + 0.1% formic acid; B: MeCN + 0.1% formic acid) to afford (*S*)-1-(6-(1-((1-(5-chloro-4-((2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione, formic acid (53.8 mg).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.54 (s, 1H), 8.77 (s, 1H), 8.21 – 8.12 (m, 2H), 8.03 (s, 1H), 7.77 – 7.70 (m, 1H), 7.58 – 7.51 (m, 1H), 7.48 – 7.40 (m, 2H), 7.06 – 6.99 (m, 1H), 6.15 (s, 1H), 4.45 (s, 3H), 4.44 – 4.30 (m, 1H), 3.96 (s, 3H), 3.94 – 3.86 (m, 2H), 3.57 (s, 3H), 2.96 (s, 2H), 2.84 – 2.71 (m, 4H), 2.63 (s, 1H), 2.21 – 2.14 (m, 2H), 2.02 (s, 2H), 1.85 – 1.64 (m, 7H), 1.41 – 1.32 (m, 1H), 1.23 (s, 1H), 1.06 – 0.98 (m, 2H), 0.74 – 0.66 (m, 1H), 0.56 – 0.48 (m, 2H), 0.40 – 0.32 (m, 1H).

LC-MS (ESI): m/z = 856.5 $[M+H]^+$.

Example 84: (*S*)-1-(6-(1-((1-(5-chloro-4-((2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (Compound 159a)



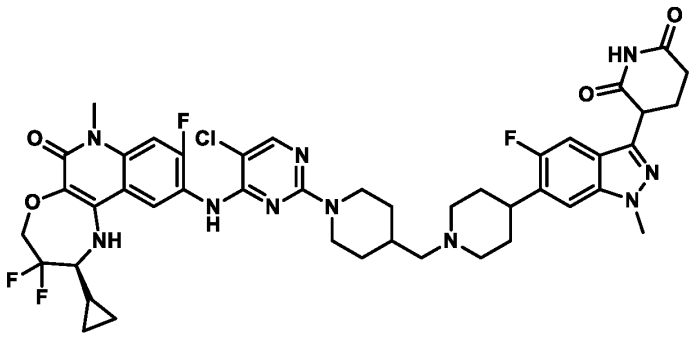
Preparation of (*S*)-1-(6-(1-((1-(5-chloro-4-((2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

A mixture of (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3,9-trifluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (98.1 mg, 1.0 *equiv.*, 202 μmol), 1-(1-methyl-6-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione, 2.5HCl (104 mg, 1.00 *equiv.*, 202 μmol), and CsF (91.9 mg, 3.00 *equiv.*, 605 μmol) in DMSO (2.00 mL) was treated with DIPEA (130 mg, 176 μL, 5.00 *equiv.*, 1.01 mmol) and warmed to 80 °C. After 24 hours, the reaction mixture was filtered and purified directly via preparative HPLC using a gradient 10-100% (A: water + 0.1% formic acid; B: MeCN + 0.1% formic acid) to afford (*S*)-1-(6-(1-((1-(5-chloro-4-((2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione, formic acid (64.4 mg).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.53 (s, 1H), 8.81 (s, 1H), 8.23 – 8.15 (m, 1H), 8.01 (s, 1H), 7.57 – 7.51 (m, 1H), 7.46 – 7.38 (m, 2H), 7.05 – 6.98 (m, 1H), 6.47 – 6.41 (m, 1H), 4.53 – 4.20 (m, 4H), 3.96 (s, 3H), 3.94 – 3.86 (m, 2H), 3.55 (s, 3H), 2.97 – 2.90 (m, 2H), 2.81 – 2.55 (m, 6H), 2.16 – 2.10 (m, 2H), 2.03 – 1.93 (m, 2H), 1.80 – 1.58 (m, 7H), 1.34 – 1.28 (m, 1H), 1.01 – 0.85 (m, 2H), 0.75 – 0.66 (m, 1H), 0.55 – 0.48 (m, 2H), 0.33 (s, 1H).

LC-MS (ESI): m/z = 874.5 $[M+H]^+$.

Example 85: 3-(6-(1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 136a)



Preparation of *tert*-butyl 4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate

A mixture of *tert*-butyl 4-formylpiperidine-1-carboxylate (310 mg, 1 *equiv.*, 1.45 mmol), 3-[5-fluoro-1-methyl-6-(4-piperidyl)indazol-3-yl]piperidine-2,6-dione (500 mg, 1 *equiv.*, 1.45 mmol), and potassium acetate (1.42 g, 10 *equiv.*, 14.5 mmol) was suspended in THF (6 mL) and DMF (0.9 mL). The reaction mixture was stirred at room temperature for 40 minutes. The mixture was then treated with sodium triacetoxyborohydride (462 mg, 1.50 *equiv.*, 2.18 mmol). After 16 hours, the reaction mixture was diluted into EtOAc and washed with saturated aqueous ammonium chloride. The organics were concentrated. The resulting residue was purified via C18 flash column using a gradient 10-100% (A: water + 0.1% formic acid; B: MeCN + 0.1% formic acid) to afford *tert*-butyl 4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate (786.7 mg).

LC-MS (ESI): m/z = 542.4 $[M+H]^+$.

Preparation of 3-(5-fluoro-1-methyl-6-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione

tert-Butyl 4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate (786.7 mg, 1 *equiv.*, 1.452 mmol) was dissolved in DCM (7.262 mL), and then HCl in 1,4-dioxane (423.6 mg, 2.905 mL, 4.0 M, 8 *equiv.*, 11.62 mmol) was added. The reaction mixture was stirred at room temperature. After 4 hours, the reaction mixture was concentrated. The resulting residue was then redissolved in methanol and concentrated again to give 3-(5-fluoro-1-methyl-6-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (633.9 mg).

LC-MS (ESI): m/z = 442.3 $[M+H]^+$.

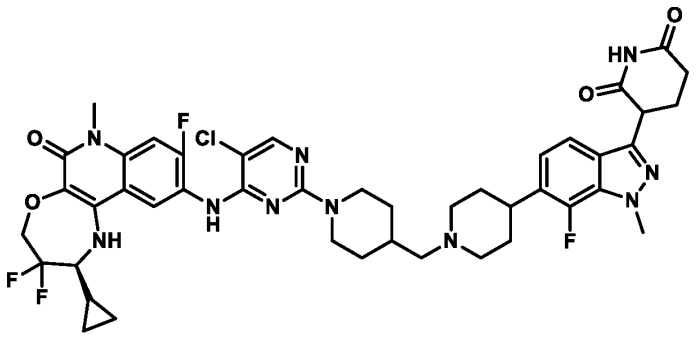
Preparation of 3-(6-(1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

A mixture of (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3,9-trifluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (138 mg, 1 *equiv.*, 283 μmol), 3-(5-fluoro-1-methyl-6-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (150 mg, 1.2 *equiv.*, 340 μmol), and CsF (129 mg, 3.00 *equiv.*, 849 μmol) in DMSO (10.00 mL) was treated with DIPEA (183 mg, 247 μL, 5.00 *equiv.*, 1.42 mmol) and warmed to 70 °C. After 24 hours, the reaction mixture was filtered and purified directly via preparative HPLC using a gradient 10-100% (A: water + 0.1% formic acid; B: MeCN + 0.1% formic acid) to afford 3-(6-(1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (130.4 mg).

LC-MS (ESI): m/z = 891.4 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.86 (s, 1H), 8.81 (s, 1H), 8.23 – 8.16 (m, 1H), 8.01 (s, 1H), 7.57 – 7.51 (m, 1H), 7.50 – 7.38 (m, 2H), 6.47 – 6.40 (m, 1H), 4.51 – 4.21 (m, 3H), 3.99 (s, 3H), 3.55 (s, 3H), 3.39 – 3.16 (m, 3H), 3.02 – 2.90 (m, 2H), 2.90 – 2.76 (m, 1H), 2.76 – 2.57 (m, 3H), 2.43 – 2.28 (m, 1H), 2.23 – 2.08 (m, 3H), 2.08 – 1.92 (m, 2H), 1.88 – 1.54 (m, 8H), 1.40 – 1.20 (m, 1H), 1.03 – 0.84 (m, 2H), 0.77 – 0.63 (m, 1H), 0.58 – 0.42 (m, 2H), 0.39 – 0.25 (m, 1H).

Example 86: 3-(6-(1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 175a)



Preparation of *tert*-butyl 4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate

A mixture of *tert*-butyl 4-formylpiperidine-1-carboxylate (310 mg, 1 *equiv.*, 1.45 mmol), 3-(7-fluoro-1-methyl-6-(piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (500 mg, 1 *equiv.*, 1.45 mmol), and potassium acetate (1.42 g, 10 *equiv.*, 14.5 mmol) was suspended in THF (6 mL) and DMF (0.9 mL). The reaction mixture was stirred for 40 minutes. The mixture was then treated with sodium triacetoxyborohydride (462 mg, 1.50 *equiv.*, 2.18 mmol). After 16 hours, the reaction mixture was diluted into EtOAc and washed with saturated aqueous ammonium chloride. The organics were concentrated. The resulting residue was purified via C18 flash column using a gradient 10-100% (A: water + 0.1% formic acid; B: MeCN + 0.1% formic acid) to afford *tert*-butyl 4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate (748.3 mg).

LC-MS (ESI): m/z = 542.4 $[M+H]^+$.

Preparation of 3-(7-fluoro-1-methyl-6-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione, 2HCl

tert-butyl 4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate (748.3 mg, 1 *equiv.*, 1.381 mmol) was dissolved in DCM (6.907 mL). The mixture was then treated with HCl in 1,4-dioxane (402.9 mg, 2.763 mL, 4.0 M, 8 *equiv.*, 11.05 mmol) and stirred at room temperature. After 4 hours, the reaction mixture was concentrated. The resulting residue was redissolved in methanol and concentrated again to give 3-(7-fluoro-1-methyl-6-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione, 2HCl (697.2 mg).

LC-MS (ESI): m/z = 442.3 $[M+H]^+$.

Preparation of (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3,9-trifluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one

2,4,5-trichloropyrimidine (398.2 mg, 0.25 mL, 1.015 *equiv.*, 2.171 mmol) was dissolved in DCM (1.00 mL) and then added through a 0.45µm filter into a stirring solution of (2*S*)-10-amino-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (725.8 mg, 1.000 *equiv.*, 2.139 mmol) and DIPEA (1.659 g, 2.24 mL, 6.00 *equiv.*, 12.83 mmol) in DMSO (5.00 mL). The reaction mixture was stirred to 70°C for 16 hours. The resulting mixture was filtered and purified via C18 flash column using a gradient 10-100% (A: water + 0.1% formic acid; B: MeCN + 0.1% formic acid) to afford (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3,9-trifluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (888.3 mg).

LC-MS (ESI): m/z = 486.4 $[M+H]^+$.

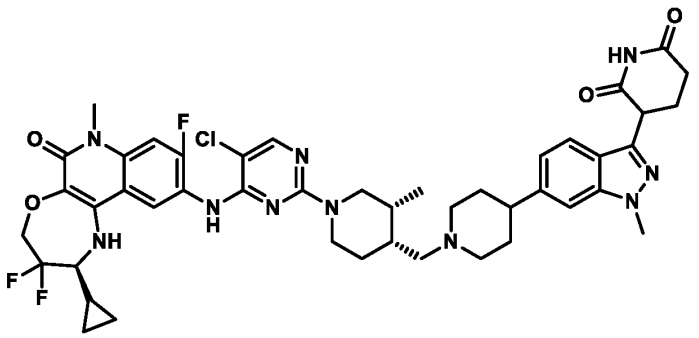
Preparation of 3-(6-(1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

A mixture of (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3,9-trifluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (138 mg, 1 *equiv.*, 283 µmol), 3-(7-fluoro-1-methyl-6-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (150 mg, 1.2 *equiv.*, 340 µmol), and CsF (129 mg, 3.00 *equiv.*, 849 µmol) in DMSO (10.00 mL) was treated with DIPEA (183 mg, 247 µL, 5.00 *equiv.*, 1.42 mmol) and warmed to 70 °C. After 24 hours, the reaction mixture was filtered and purified directly via preparative HPLC using a gradient 10-100% (A: water + 0.1% formic acid; B: MeCN + 0.1% formic acid) to afford 3-(6-(1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (125.5 mg, 0.13 mmol).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.90 (s, 1H), 8.80 (s, 1H), 8.25 – 8.16 (m, 1H), 8.01 (s, 1H), 7.49 – 7.38 (m, 2H), 7.11 – 6.97 (m, 1H), 6.44 (s, 1H), 4.52 – 4.22 (m, 3H), 4.10 (s, 3H), 3.55 (s, 3H), 3.44 – 3.10 (m, 1H), 3.05 – 2.80 (m, 3H), 2.77 – 2.59 (m, 3H), 2.38 – 2.23 (m, 2H), 2.20 – 2.09 (m, 3H), 2.04 – 1.91 (m, 2H), 1.84 – 1.56 (m, 7H), 1.38 – 1.17 (m, 2H), 1.04 – 0.82 (m, 3H), 0.77 – 0.65 (m, 1H), 0.60 – 0.43 (m, 2H), 0.40 – 0.21 (m, 1H).

LC-MS (ESI): m/z = 891.5 $[M+H]^+$.

Example 87: 3-(6-(1-(((3*R*,4*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 105a)



Preparation of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate

3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-1-methyl-1*H*-indazole (9.00 g, 1 *equiv.*, 18.0 mmol), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (8.34 g, 1.5 *equiv.*, 27.0 mmol), XantPhos-Pd-G2 (320 mg, 0.02 *equiv.*, 360 μmol), and cesium carbonate (17.6 g, 3 *equiv.*, 54.0 mmol) were suspended in 1,4-dioxane (156 mL) and water (23.5 mL). The reaction was heated to 85°C. After 18 hours, the reaction mixture was filtered and purified via flash column chromatography 0-100% (A: heptanes; B: ethyl acetate) to afford *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (9.7763 g).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (d, J = 8.1 Hz, 1H), 7.66 – 7.57 (m, 2H), 7.47 (d, J = 7.4 Hz, 2H), 7.44 – 7.23 (m, 8H), 7.17 (d, J = 8.6 Hz, 1H), 6.59 (d, J = 8.1 Hz, 1H), 6.26 (s, 1H), 5.44 (d, J = 13.1 Hz, 4H), 4.06 (m, 5H), 3.58 (t, J = 5.8 Hz, 2H), 2.57 (m, 2H), 1.44 (s, 9H).

Preparation of *tert*-butyl (3*R*,4*R*)-4-(4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)-1,2,3,6-tetrahydropyridine-1-carbonyl)-3-methylpiperidine-1-carboxylate

(3*R*,4*R*)-1-(tert-butoxycarbonyl)-3-methylpiperidine-4-carboxylic acid (123.9 mg, 1.026 *equiv.*, 509.2 μmol), 3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indazole, 2.5HCl (294.6 mg, 1.0 *equiv.*, 496.2 μmol), and HATU

(226.4 mg, 1.2 *equiv.*, 595.4 μmol) were dissolved in DMF (5.0 mL). DIPEA (384.8 mg, 519 μL, 6.0 *equiv.*, 2.977 mmol) was then added. The resulting reaction mixture was stirred at room temperature. After 1 hour, the mixture was filtered and purified via C18 flash column using a gradient 10-100% (A: water + 0.1% formic acid; B: MeCN + 0.1% formic acid) to afford *tert*-butyl (3*R*,4*R*)-4-(4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)-1,2,3,6-tetrahydropyridine-1-carbonyl)-3-methylpiperidine-1-carboxylate (213.1 mg).

LC-MS (ESI): m/z=628.4 $[M\text{-}Boc]^-$.

Preparation of (4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)-3,6-dihydropyridin-1(2*H*)-yl)((3*R*,4*R*)-3-methylpiperidin-4-yl)methanone

tert-Butyl (3*R*,4*R*)-4-(4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)-1,2,3,6-tetrahydropyridine-1-carbonyl)-3-methylpiperidine-1-carboxylate (213.1 mg, 1 *equiv.*, 292.8 μmol) was dissolved in DCM (7.0 mL). HCl in 1,4-dioxane (85.39 mg, 585.5 μL, 4 M, 8 *equiv.*, 2.342 mmol) was added. The resulting reaction mixture was stirred at room temperature. After 2 hours, the reaction mixture was concentrated and then passed through a carbonate plug using methanol. The resulting mixture was evaporated to dryness to give (4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)-3,6-dihydropyridin-1(2*H*)-yl)((3*R*,4*R*)-3-methylpiperidin-4-yl)methanone (189.4 mg).

LC-MS (ESI): m/z = 628.5 $[M+H]^+$.

Preparation of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-6-(1-(((3*R*,4*R*)-3-methylpiperidin-4-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indazole

(4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)-3,6-dihydropyridin-1(2*H*)-yl)((3*R*,4*R*)-3-methylpiperidin-4-yl)methanone (2.1887 g, 1.0 *equiv.*, 3.4864 mmol) was dissolved in THF (110.000 mL). Molecular sieves were added followed by the addition of $LiAlH_4$ in THF (264.6 mg, 3.4864 mL, 2.0 M, 2.0 *equiv.*, 6.9727 mmol) dropwise. The reaction mixture was stirred at room temperature for 1 hour. The reaction was quenched by the addition of sodium sulfate decahydrate (4.4931 g, 3.075 mL, 4 *equiv.*, 13.945 mmol), stirred for 2 hours at room temperature, filtered, and concentrated to afford 3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-6-(1-(((3*R*,4*R*)-3-methylpiperidin-4-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indazole.

LC-MS (ESI): m/z = 307.7 $[M+H]^+$.

Preparation of *tert*-butyl (3*R*,4*R*)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)-3,6-dihydropyridin-1(2*H*)-yl)methyl)-3-methylpiperidine-1-carboxylate

3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-6-(1-(((3*R*,4*R*)-3-methylpiperidin-4-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indazole (2.14 g, 1.0 *equiv.*, 3.49 mmol) was dissolved in DCM (17.4 mL). The mixture was then degassed with nitrogen for 10 minutes. The reaction mixture was charged with di-*tert*-butyl dicarbonate (1.52 g, 1.55 mL, 2.0 *equiv.*, 6.97 mmol) under the flow of nitrogen. DIPEA (2.70 g, 3.64 mL, 6.0 *equiv.*, 20.9 mmol) was then added to the reaction mixture. After 16 hours, the reaction mixture was diluted into DCM, washed with HCl (0.25 M), and then back-extracted once with DCM. Organic layers were combined and evaporated to dryness to give *tert*-butyl (3*R*,4*R*)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)-3,6-dihydropyridin-1(2*H*)-yl)methyl)-3-methylpiperidine-1-carboxylate (3.45 g).

LC-MS (ESI): m/z = 714.5 $[M+H]^+$.

Preparation of *tert*-butyl (3*R*,4*R*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate

tert-Butyl (3*R*,4*R*)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)-3,6-dihydropyridin-1(2*H*)-yl)methyl)-3-methylpiperidine-1-carboxylate (3.45 g, 75 wt%, 1 *equiv.*, 3.62 mmol) was dissolved in a mixture of iPrOH (15.1 mL) and DMF (3.02 mL). Degassed with nitrogen, and $Pd(OH)_2$ on carbon (509 mg, 20 wt%, 0.2 *equiv.*, 725 μmol) was added. After further degassing, charged with hydrogen (732 mg, 100 *equiv.*, 362 mmol) and warmed the reaction mixture to 50°C. After 24 hours, filtered through celite and concentrated the filtrate. The residue was directly purified via C18 flash column using a gradient 10-100% (A: water +0.1% formic acid; B: MeCN +0.1% formic acid) to afford *tert*-butyl (3*R*,4*R*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate (442 mg).

LC-MS (ESI): m/z = 538.5 $[M+H]^+$.

Preparation of 3-(1-methyl-6-(1-(((3*R*,4*R*)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione, HCl

tert-Butyl (3*R*,4*R*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate (442 mg, 1 *equiv.*, 822 μmol) was dissolved in DCM (4.11 mL). HCl in 1,4-dioxane (240 mg, 1.64 mL, 4.0 M, 8 *equiv.*, 6.58

mmol) was then added. The resulting reaction mixture was stirred at room temperature. After 2 hours, the reaction mixture was concentrated to afford 3-(1-methyl-6-(1-(((3*R*,4*R*)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione, HCl (363.8 mg).

LC-MS (ESI): m/z = 438.4 $[M+H]^+$.

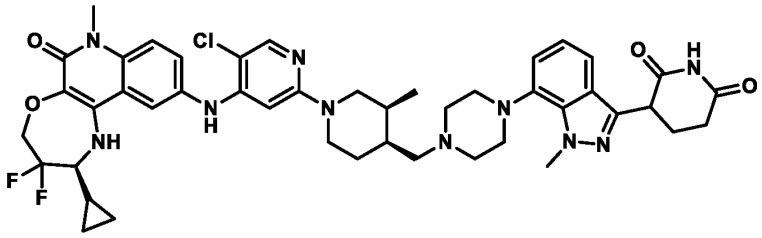
Preparation of 3-(6-(1-(((3*R*,4*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

A mixture of (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3,9-trifluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (25 mg, 1 *equiv.*, 51 μmol), 3-(1-methyl-6-(1-(((3*R*,4*R*)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (22 mg, 1 *equiv.*, 51 μmol), and CsF (23 mg, 3.00 *equiv.*, 0.15 mmol) in DMSO (10.00 mL) was treated with DIPEA (33 mg, 45 μL, 5.00 *equiv.*, 0.26 mmol) and heated to 70 °C. After 24 hours, the reaction mixture was filtered and purified directly via preparative HPLC using a gradient 10-100% (A: water + 0.1% formic acid; B: MeCN + 0.1% formic acid) to afford 3-(6-(1-(((3*R*,4*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (3.6 mg).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.80 (s, 1H), 8.72 (s, 1H), 8.24 (s, 1H), 8.14 – 8.08 (m, 1H), 7.91 (s, 1H), 7.55 – 7.49 (m, 1H), 7.39 – 7.31 (m, 2H), 6.98 – 6.92 (m, 1H), 6.38 (s, 1H), 4.44 – 4.14 (m, 2H), 3.89 (s, 3H), 3.48 (s, 3H), 2.90 – 2.86 (m, 2H), 2.57 – 2.52 (m, 1H), 2.18 – 1.57 (m, 15H), 1.33 – 1.03 (m, 7H), 0.65 – 0.59 (m, 4H), 0.47 – 0.43 (m, 2H), 0.27 – 0.22 (m, 1H).

LC-MS (ESI): m/z = 887.6 $[M+H]^+$.

Example 88: 3-(7-(4-(((3S,4S)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyridin-2-yl)-3-methylpiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 147a)



Preparation of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-7-(piperazin-1-yl)-1*H*-indazole, 2HCl

tert-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-7-yl)piperazine-1-carboxylate (1.00 g, 1.0 *equiv.*, 1.65 mmol) was dissolved in DCM (1.0 mL). HCl in 1,4-dioxane (482 mg, 3.30 mL, 4.0 M, 8.0 *equiv.*, 13.2 mmol) was added. The resulting reaction mixture was stirred at room temperature. After 24 hours, the reaction mixture was concentrated to afford 3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-7-(piperazin-1-yl)-1*H*-indazole, 2HCl (1069.8 mg).

LC-MS (ESI): m/z = 506.3 $[M+H]^+$.

Preparation of *tert*-butyl (3S,4S)-4-(4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-7-yl)piperazine-1-carbonyl)-3-methylpiperidine-1-carboxylate

(3S,4S)-1-(tert-butoxycarbonyl)-3-methylpiperidine-4-carboxylic acid (455.3 mg, 1.0 *equiv.*, 1.871 mmol), 3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-7-(piperazin-1-yl)-1*H*-indazole (951.4 mg, 1.006 *equiv.*, 1.882 mmol), and HATU (868.8 mg, 1.221 *equiv.*, 2.285 mmol) were dissolved in DMF (10.0 mL). DIPEA (1.451 g, 1.96 mL, 6.0 *equiv.*, 11.23 mmol) was then added. The resulting reaction mixture was stirred at room temperature. After 24 hours, the reaction mixture was diluted into ethyl acetate, washed once with HCl (0.5 M), then with water, and then with brine. The organic phase was concentrated, and the resulting residue was purified via flash column chromatography 0-100% (A: heptanes; B: ethyl acetate) to afford *tert*-butyl (3S,4S)-4-(4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-7-yl)piperazine-1-carbonyl)-3-methylpiperidine-1-carboxylate (902 mg).

LC-MS (ESI): m/z = 338.1 $[M+H]^+$.

Preparation of *tert*-butyl (3S,4S)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-7-yl)piperazin-1-yl)methyl)-3-methylpiperidine-1-carboxylate

tert-Butyl (3S,4S)-4-(4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-7-yl)piperazine-1-carbonyl)-3-methylpiperidine-1-carboxylate (897 mg, 1 *equiv.*, 1.23

mmol) was dissolved in THF (5.000 mL). The mixture was warmed to 50°C. Borane dimethyl sulfide complex (1.12 g, 1.40 mL, 12 *equiv.*, 14.7 mmol) was added dropwise. The mixture was stirred for 1.5 hours. The reaction was quenched by dropwise addition into stirring methanol (5 mL). The resulting mixture was warmed to 50°C for 30 minutes and then concentrated. The resulting residue was purified via C18 flash column using a gradient 10-100% (A: water + 0.1% formic acid; B: MeCN + 0.1% formic acid) to afford *tert*-butyl (3S,4S)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-7-yl)piperazin-1-yl)methyl)-3-methylpiperidine-1-carboxylate (586.6 mg).

LC-MS (ESI): m/z = 717.5 $[M+H]^+$.

Preparation of *tert*-butyl (3S,4S)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-7-yl)piperazin-1-yl)methyl)-3-methylpiperidine-1-carboxylate

tert-Butyl (3S,4S)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-7-yl)piperazin-1-yl)methyl)-3-methylpiperidine-1-carboxylate (688.1 mg, 1 *equiv.*, 959.8 µmol) was dissolved in a mixture of iPrOH (150 mL) and DMF (15.0 mL). The mixture was then purged with N_2 and treated with $Pd(OH)_2$ on carbon (134.8 mg, 20 wt%, 0.2 *equiv.*, 192.0 µmol). Hydrogen (194 mg, 100 *equiv.*, 95.98 mmol) was bubbled through the reaction mixture at 50°C. The reaction was monitored for conversion throughout the day and recharged with H_2 as needed. After 24 hours, the mixture was filtered through a pad of celite and then evaporated to dryness to afford *tert*-butyl (3S,4S)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-7-yl)piperazin-1-yl)methyl)-3-methylpiperidine-1-carboxylate (532.9 mg).

LC-MS (ESI): m/z = 539.5 $[M+H]^+$.

Preparation of 3-(1-methyl-7-(4-(((3S,4S)-3-methylpiperidin-4-yl)methyl)piperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione, 1.5HCl

tert-Butyl (3S,4S)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-7-yl)piperazin-1-yl)methyl)-3-methylpiperidine-1-carboxylate (532.9 mg, 1 *equiv.*, 989.3 µmol) was dissolved in DCM (15 mL). The mixture was treated with HCl (288.5 mg, 1.979 mL, 4.0 M, 8 *equiv.*, 7.914 mmol) and then stirred at room temperature. After 16 hours, the reaction mixture was concentrated. The resulting residue was redissolved in methanol and then evaporated again to afford 3-(1-methyl-7-(4-(((3S,4S)-3-methylpiperidin-4-yl)methyl)piperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione, 1.5HCl (464.8 mg).

LC-MS (ESI): m/z = 439.3 $[M+H]^+$.

Preparation of 3-(7-(4-(((3S,4S)-1-(5-chloro-4-iodopyridin-2-yl)-3-methylpiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

A mixture of 5-chloro-2-fluoro-4-iodopyridine (269.7 mg, 1.194 *equiv.*, 1.048 mmol) and 3-(1-methyl-7-(4-(((3S,4S)-3-methylpiperidin-4-yl)methyl)piperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (384.8 mg, 1.00 *equiv.*, 877.4 μmol) in DMSO (10.00 mL) was treated with DIPEA (453.6 mg, 611 μL, 4.00 *equiv.*, 3.510 mmol) and warmed to 80 °C. After 16 hours, the reaction mixture was filtered and purified directly via C18 flash column using a gradient 10-100% (A: water +0.1% formic acid; B: MeCN +0.1% formic acid) to afford 3-(7-(4-(((3S,4S)-1-(5-chloro-4-iodopyridin-2-yl)-3-methylpiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (268.7 mg).

LC-MS (ESI): m/z = 676.3 $[M+H]^+$.

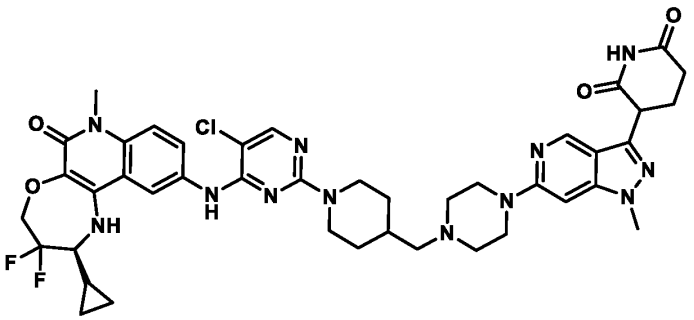
Preparation of 3-(7-(4-(((3S,4S)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyridin-2-yl)-3-methylpiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

A mixture of (*S*)-10-amino-2-cyclopropyl-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (28.0 mg, 1.2 *equiv.*, 87.0 μmol), 3-(7-(4-(((3S,4S)-1-(5-chloro-4-iodopyridin-2-yl)-3-methylpiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (49.0 mg, 1 *equiv.*, 72.5 μmol), cesium carbonate (70.9 mg, 3 *equiv.*, 217 μmol), and RuPhos-Pd-G3 (12.1 mg, 0.2 *equiv.*, 14.5 μmol) in 1,4-dioxane (2.00 mL) was degassed with nitrogen gas. The reaction mixture was then warmed to 100 °C. After 1.5 hours, the reaction mixture was filtered and purified directly via preparative HPLC using a gradient 10-100% (A: water + 0.1% formic acid; B: MeCN + 0.1% formic acid) to afford 3-(7-(4-(((3S,4S)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyridin-2-yl)-3-methylpiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (41.2 mg).

^{1}H NMR (400 MHz, DMSO) δ 10.87 (s, 1H), 8.10 – 7.85 (m, 3H), 7.53 – 7.42 (m, 2H), 7.41 – 7.35 (m, 1H), 7.05 – 6.97 (m, 2H), 6.42 – 6.37 (m, 1H), 6.07 (s, 1H), 4.51 – 4.27 (m, 3H), 4.23 (s, 3H), 3.90 – 3.69 (m, 2H), 3.57 (s, 3H), 3.25 – 2.53 (m, 11H), 2.37 – 2.10 (m, 4H), 1.98 – 1.80 (m, 3H), 1.52 – 1.21 (m, 4H), 0.84 – 0.76 (m, 3H), 0.76 – 0.63 (m, 1H), 0.55 – 0.43 (m, 2H), 0.38 – 0.25 (m, 1H).

LC-MS (ESI): m/z = 869.5 $[M+H]^+$.

Example 89. 3-(6-(4-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-pyrazolo[4,3-c]pyridin-3-yl)piperidine-2,6-dione (Compound 170a)



Preparation of (*S*)-1-(5-chloro-4-((2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidine-4-carbaldehyde

To a vial containing (*S*)-10-((2-(4-(1,3-dioxolan-2-yl)piperidin-1-yl)-5-chloropyrimidin-4-yl)amino)-2-cyclopropyl-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (272 mg, 1 *equiv.*, 462 μmol) was added formic acid (3.7 g, 3.0 mL, 170 *equiv.*, 80 mmol). The reaction mixture was stirred at 80 °C for 1 hour. Volatile organics were removed under reduced pressure to give (*S*)-1-(5-chloro-4-((2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidine-4-carbaldehyde (282 mg) as a dark yellow solid, which was carried forward without further purification.

LC-MS (ESI): m/z = 545.2 $[M+H]^+$.

Preparation of 6-chloro-3-iodo-1*H*-pyrazolo[4,3-c]pyridine

A mixture of 6-chloro-1*H*-pyrazolo[4,3-c]pyridine (17 g, 110.70 mmol, 1 *equiv.*), I_2 (42.14 g, 166.05 mmol, 33.45 mL, 1.5 *equiv.*), and KOH (15.53 g, 276.75 mmol, 2.5 *equiv.*) in DMF (1000 mL) was degassed and purged with N_2 three times. The mixture was stirred at 25 °C for 16 hours under N_2 atmosphere. The reaction mixture was partitioned between H_2O and ethyl acetate. The organic phase was separated, washed with ethyl acetate, dried over sodium sulfate, filtered and concentrated under reduced pressure to give 6-chloro-3-iodo-1*H*-pyrazolo[4,3-c]pyridine (60 g) as a brown oil.

LC-MS (ESI): m/z = 280.0 $[M+H]^+$

Preparation of 6-chloro-3-iodo-1-methyl-pyrazolo[4,3-c]pyridine

To a solution of 6-chloro-3-iodo-1*H*-pyrazolo[4,3-c]pyridine (30 g, 107.35 mmol, 1 *equiv.*) and potassium carbonate (44.51 g, 322.04 mmol, 3 *equiv.*) in DMF (2000 mL) was added iodomethane (30.47 g, 214.70 mmol, 13.37 mL, 2 *equiv.*) dropwise under 0 °C. The resulting mixture was purged with N_2 three times. Then the mixture was stirred at 20 °C for 16 hours. The mixture was filtered, and the filter cake was washed by ethyl acetate (200 mL). The filtrate was concentrated under reduced pressure to give a residue which was purified by reverse-phase HPLC to afford 6-chloro-3-iodo-1-methyl-pyrazolo[4,3-c]pyridine (26 g) as a yellow solid

LC-MS (ESI): m/z = 293.9 $[M+H]^+$

Preparation of 6-chloro-3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-pyrazolo[4,3-c]pyridine

A mixture of 6-chloro-3-iodo-1-methyl-pyrazolo[4,3-c]pyridine (13.5 g, 46.00 mmol, 1 *equiv.*), 2,6-dibenzyloxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (21.11 g, 50.60 mmol, 1.1 *equiv.*), cesium carbonate (44.96 g, 137.99 mmol, 3 *equiv.*), and $Pd(dppf)Cl_2$ (2.69 g, 3.68 mmol, 0.08 *equiv.*) in THF (300 mL) and H_2O (30 mL) was degassed and purged with N_2 three times. The mixture was stirred at 60 °C for 2 hours under N_2 atmosphere. The reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layers were washed with ethyl acetate, dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (0~13% ethyl acetate/petroleum ether) to give 6-chloro-3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-pyrazolo[4,3-c]pyridine (10.8 g) as a white solid.

LC-MS (ESI): m/z = 457.1 $[M+H]^+$

Preparation of *tert*-butyl 4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-pyrazolo[4,3-c]pyridin-6-yl]piperazine-1-carboxylate

A mixture of 6-chloro-3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-pyrazolo[4,3-c]pyridine (5 g, 10.94 mmol, 1 *equiv.*), *tert*-butyl piperazine-1-carboxylate (6.11 g, 32.83 mmol, 3 *equiv.*), cesium carbonate (10.70 g, 32.83 mmol, 3 *equiv.*), RuPhos (1.02 g, 2.19 mmol, 0.2 *equiv.*) and $Pd_2(dba)_3$ (1.00 g, 1.09 mmol, 0.1 *equiv.*) in dioxane (100 mL) was degassed and purged with N_2 three times. The mixture was stirred at 100 °C for 3 hours under N_2 atmosphere. The reaction mixture was diluted with H_2O and extracted with ethyl acetate.

The combined organic layers were washed with ethyl acetate, dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (0~25% ethyl acetate/petroleum ether) to afford *tert*-butyl 4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-pyrazolo[4,3-c]pyridin-6-yl]piperazine-1-carboxylate (6 g) as a yellow solid.

LC-MS (ESI): m/z = 607.4 $[M+H]^+$

Preparation of *tert*-butyl 4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-pyrazolo[4,3-c]pyridin-6-yl]piperazine-1-carboxylate

A mixture of *tert*-butyl 4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-pyrazolo[4,3-c]pyridin-6-yl]piperazine-1-carboxylate (6 g, 9.89 mmol, 1 *equiv.*), Pd on carbon (28.42 g, 26.70 mmol, 10% purity, 2.7 *equiv.*), $Pd(OH)_2$ on carbon (27.78 g, 19.78 mmol, 10% purity, 2 *equiv.*) in THF (30 mL) and EtOH (30 mL) was degassed and purged with H_2 three times. The mixture was stirred at 40 °C for 16 hours under H_2 (15Psi) atmosphere. The reaction was filtered through the diatom soil layer in a moderate N_2 atmosphere to afford *tert*-butyl 4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-pyrazolo[4,3-c]pyridin-6-yl]piperazine-1-carboxylate (4.5 g, crude) as a brown solid.

LC-MS (ESI): m/z = 429.3 $[M+H]^+$

Preparation of 3-(1-methyl-6-(piperazin-1-yl)-1*H*-pyrazolo[4,3-c]pyridin-3-yl)piperidine-2,6-dione

A solution of *tert*-butyl 4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-pyrazolo[4,3-c]pyridin-6-yl]piperazine-1-carboxylate (4.5 g, 10.50 mmol, 1 *equiv.*) in HCl/dioxane (40 mL) was stirred at 20 °C for 16 hours. The reaction mixture was filtered and concentrated under reduced pressure to give 3-(1-methyl-6-(piperazin-1-yl)-1*H*-pyrazolo[4,3-c]pyridin-3-yl)piperidine-2,6-dione (2.17 g) as a green solid.

LC-MS (ESI): m/z = 329.3 $[M+H]^+$

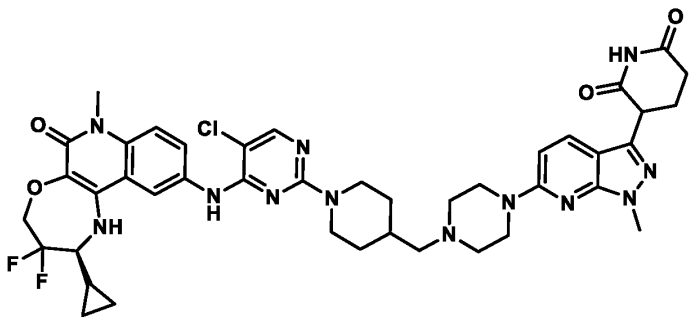
Preparation of 3-(6-(4-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-pyrazolo[4,3-c]pyridin-3-yl)piperidine-2,6-dione

To a solution of (*S*)-1-(5-chloro-4-((2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidine-4-carbaldehyde (140 mg, 1 *equiv.*, 257 μmol) in THF (3.0 mL) and DMF (0.5 mL) was added 3-(1-methyl-6-(piperazin-1-yl)-1*H*-pyrazolo[4,3-c]pyridin-3-yl)piperidine-2,6-dione (101 mg, 1.2 *equiv.*, 308 μmol) and potassium acetate (126 mg, 5.0 *equiv.*, 1.28 mmol). The reaction mixture was stirred at ambient temperature for 30 minutes followed by addition of sodium triacetoxyborohydride (109 mg, 2.0 *equiv.*, 514 μmol). The resulting mixture was stirred for an additional 18 hours. The reaction mixture was partitioned between DCM and saturated ammonium chloride (*aq.*). The organic layer was removed, and the aqueous layer was extracted with DCM twice more. The combined organic layer was washed with brine, dried over sodium sulfate, and filtered. The filtrate was taken, and volatile organics were removed under reduced pressure to give a yellow solid. The solid was taken up in DMSO and purified by reverse phase HPLC to give 3-(6-(4-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-pyrazolo[4,3-c]pyridin-3-yl)piperidine-2,6-dione (79 mg) as an off white solid.

^{1}H NMR (400 MHz, DMSO-d_6, 300 K) δ (ppm) = 10.90 (s, 1H), 8.76 (s, 1H), 8.63 (s, 1H), 8.18 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H), 7.74 (dd, J = 2.0, 9.0 Hz, 1H), 7.44 (d, J = 9.3 Hz, 1H), 6.66 (s, 1H), 6.15 (br s, 1H), 4.51 - 4.29 (m, 5H), 3.85 (s, 3H), 3.60 - 3.44 (m, 7H), 3.28 - 3.17 (m, 1H), 2.79 (br t, J = 12.6 Hz, 2H), 2.72 - 2.53 (m, 2H), 2.48 - 2.31 (m, 5H), 2.24 - 2.10 (m, 3H), 1.86 - 1.66 (m, 3H), 1.41 - 1.27 (m, 1H), 1.11 - 0.95 (m, 2H), 0.77 - 0.64 (m, 1H), 0.58 - 0.46 (m, 2H), 0.35 (q, J = 5.5 Hz, 1H).

LC-MS (ESI): m/z = = 857.5 $[M+H]^+$.

Example 90. 3-(6-(4-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-pyrazolo[3,4-b]pyridin-3-yl)piperidine-2,6-dione (Compound 155a)



Preparation of 6-chloro-3-iodo-1*H*-pyrazolo[4,3-c]pyridine

A mixture of 6-chloro-1*H*-pyrazolo[4,3-c]pyridine (17 g, 110.70 mmol, 1 *equiv.*), I_2 (42.14 g, 166.05 mmol, 33.45 mL, 1.5 *equiv.*), and KOH (15.53 g, 276.75 mmol, 2.5 *equiv.*) in DMF (1000 mL) was degassed and purged with N_2 three times. The mixture was stirred at 25 °C for 16 hours under N_2 atmosphere. The reaction mixture was partitioned between H_2O and ethyl acetate. The organic phase was separated, washed with ethyl acetate, dried over sodium sulfate, filtered and concentrated under reduced pressure to give 6-chloro-3-iodo-1*H*-pyrazolo[4,3-c]pyridine (60 g) as a brown oil.

LC-MS (ESI): m/z = 280.0 $[M+H]^+$

Preparation of 6-chloro-3-iodo-1-methyl-pyrazolo[4,3-c]pyridine

To a solution of 6-chloro-3-iodo-1*H*-pyrazolo[4,3-c]pyridine (30 g, 107.35 mmol, 1 *equiv.*) and potassium carbonate (44.51 g, 322.04 mmol, 3 *equiv.*) in DMF (2000 mL) was added iodomethane (30.47 g, 214.70 mmol, 13.37 mL, 2 *equiv.*) dropwise under 0 °C. The resulting mixture was purged with N_2 three times. Then the mixture was stirred at 20 °C for 16 hours. The mixture was filtered, and the filter cake was washed by ethyl acetate (200 mL). The filtrate was concentrated under reduced pressure to give a residue which was purified by reverse-phase HPLC to afford 6-chloro-3-iodo-1-methyl-pyrazolo[4,3-c]pyridine (26 g) as a yellow solid

LC-MS (ESI): m/z = 293.9 $[M+H]^+$

Preparation of 6-chloro-3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-pyrazolo[4,3-c]pyridine

A mixture of 6-chloro-3-iodo-1-methyl-pyrazolo[4,3-c]pyridine (13.5 g, 46.00 mmol, 1 *equiv.*), 2,6-dibenzyloxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (21.11 g, 50.60 mmol, 1.1 *equiv.*), cesium carbonate (44.96 g, 137.99 mmol, 3 *equiv.*), and $Pd(dppf)Cl_2$ (2.69 g, 3.68 mmol, 0.08 *equiv.*) in THF (300 mL) and H_2O (30 mL) was degassed and purged with N_2 three times. The mixture was stirred at 60 °C for 2 hours under N_2 atmosphere. The reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layers were washed with ethyl acetate, dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (0~13% ethyl acetate/petroleum ether) to give 6-chloro-3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-pyrazolo[4,3-c]pyridine (10.8 g) as a white solid.

LC-MS (ESI): m/z = 457.1 $[M+H]^+$

Preparation of *tert*-butyl 4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-pyrazolo[4,3-c]pyridin-6-yl]piperazine-1-carboxylate

A mixture of 6-chloro-3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-pyrazolo[4,3-c]pyridine (5 g, 10.94 mmol, 1 *equiv.*), *tert*-butyl piperazine-1-carboxylate (6.11 g, 32.83 mmol, 3 *equiv.*), cesium carbonate (10.70 g, 32.83 mmol, 3 *equiv.*), RuPhos (1.02 g, 2.19 mmol, 0.2 *equiv.*) and $Pd_2(dba)_3$ (1.00 g, 1.09 mmol, 0.1 *equiv.*) in dioxane (100 mL) was degassed and purged with N_2 three times. The mixture was stirred at 100 °C for 3 hours under N_2 atmosphere. The reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layers were washed with ethyl acetate, dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (0~25% ethyl acetate/petroleum ether) to afford *tert*-butyl 4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-pyrazolo[4,3-c]pyridin-6-yl]piperazine-1-carboxylate (6 g) as a yellow solid.

LC-MS (ESI): m/z = 607.4 $[M+H]^+$

Preparation of *tert*-butyl 4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-pyrazolo[4,3-c]pyridin-6-yl]piperazine-1-carboxylate

A mixture of *tert*-butyl 4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-pyrazolo[4,3-c]pyridin-6-yl]piperazine-1-carboxylate (6 g, 9.89 mmol, 1 *equiv.*), Pd on carbon (28.42 g, 26.70 mmol, 10% purity, 2.7 *equiv.*), $Pd(OH)_2$ on carbon (27.78 g, 19.78 mmol, 10% purity, 2 *equiv.*) in THF (30 mL) and EtOH (30 mL) was degassed and purged with H_2 three times. The mixture was stirred at 40 °C for 16 hours under H_2 (15Psi) atmosphere. The reaction was

filtered through the diatom soil layer in a moderate N_2 atmosphere to afford *tert*-butyl 4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-pyrazolo[4,3-c]pyridin-6-yl]piperazine-1-carboxylate (4.5 g, crude) as a brown solid.

LC-MS (ESI): m/z = 429.3 $[M+H]^+$

Preparation of 3-(1-methyl-6-(piperazin-1-yl)-1*H*-pyrazolo[4,3-c]pyridin-3-yl)piperidine-2,6-dione

A solution of *tert*-butyl 4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-pyrazolo[4,3-c]pyridin-6-yl]piperazine-1-carboxylate (4.5 g, 10.50 mmol, 1 *equiv.*) in HCl/dioxane (40 mL) was stirred at 20 °C for 16 hours. The reaction mixture was filtered and concentrated under reduced pressure to give 3-(1-methyl-6-(piperazin-1-yl)-1*H*-pyrazolo[4,3-c]pyridin-3-yl)piperidine-2,6-dione (2.17 g) as a green solid.

LC-MS (ESI): m/z = 329.3 $[M+H]^+$

Preparation of 3-(6-(4-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-pyrazolo[3,4-b]pyridin-3-yl)piperidine-2,6-dione

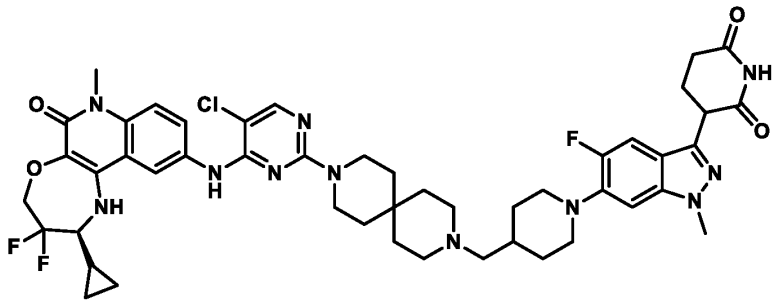
To a solution of (*S*)-1-(5-chloro-4-((2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidine-4-carbaldehyde (140 mg, 1 *equiv.*, 257 μmol) in THF (3.0 mL) and DMF (0.5 mL) was added 3-(1-methyl-6-(piperazin-1-yl)-1*H*-pyrazolo[4,3-c]pyridin-3-yl)piperidine-2,6-dione (115 mg, 1.2 *equiv.*, 308 μmol) and potassium acetate (126 mg, 5.0 *equiv.*, 1.28 mmol). The reaction mixture was stirred at ambient temperature for 30 minutes, followed by the addition of sodium triacetoxyborohydride (109 mg, 2.0 *equiv.*, 514 μmol). The resulting mixture was stirred for an additional 18 hours. The reaction was quenched by the addition of ammonium chloride (*aq.* saturated) and diluted with DMSO (4 mL). Volatile organics were removed under reduced pressure until mostly DMSO remained. The DMSO mixture was filtered and purified by reverse phase HPLC to give 3-(6-(4-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-pyrazolo[3,4-b]pyridin-3-yl)piperidine-2,6-dione (35 mg) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6, 300 K) δ (ppm) = 10.85 (s, 1H), 8.76 (s, 1H), 8.17 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H), 7.84 (d, J = 9.0 Hz, 1H), 7.74 (dd, J = 2.1, 9.1 Hz, 1H), 7.44 (d,

J = 9.1 Hz, 1H), 6.76 (d, J = 9.1 Hz, 1H), 6.15 (br s, 1H), 4.53 - 4.29 (m, 4H), 4.20 (dd, J = 5.0, 9.5 Hz, 1H), 3.81 (s, 3H), 3.62 (br s, 4H), 3.56 (s, 3H), 3.28 - 3.16 (m, 1H), 2.79 (br t, J = 12.9 Hz, 2H), 2.69 - 2.55 (m, 2H), 2.43 (br s, 4H), 2.37 - 2.25 (m, 1H), 2.21 - 2.10 (m, 3H), 1.86 - 1.66 (m, 3H), 1.40 - 1.26 (m, 1H), 1.11 - 0.93 (m, 2H), 0.77 - 0.65 (m, 1H), 0.58 - 0.47 (m, 2H), 0.35 (q, J = 5.6 Hz, 1H).

LC-MS (ESI): m/z 857.4 $[M+1]^+$

Example 91. 3-(6-(4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)piperidin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 149a)



Preparation of *tert*-butyl 9-((1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate

To a solution of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-5-fluoro-1-methyl-1*H*-indazole (1.00 g, 1 *equiv.*, 1.93 mmol) in 1,4-dioxane (8 mL) was added *tert*-butyl 9-(piperidin-4-ylmethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (746 mg, 1.1 *equiv.*, 2.12 mmol), t-BuONa (556 mg, 2.89 mL, 2.0 M, 3.0 *equiv.*, 5.79 mmol), and RuPhos-Pd-G3 (121 mg, 0.075 *equiv.*, 145 μmol). The reaction vial was sealed and heated to 100 °C for 1 hours. The reaction mixture was partitioned between ethyl acetate and saturated ammonium chloride (*aq.*). The organic layer was removed and the aqueous layer was extracted with ethyl acetate twice more. The combined organic layer was washed with brine, dried over sodium sulfate, and filtered. The filtrate was taken, and volatile organics were removed under reduced pressure to give a foamy brown solid. The solid was taken up in DCM and purified on a silica gel column (0-20% methanol in DCM) to give *tert*-butyl 9-((1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (1.088 g) as an orange solid.

LC-MS (ESI): m/z = 789.5 $[M+H]^+$.

Preparation of *tert*-butyl 9-((1-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate

A solution of *tert*-butyl 9-((1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (1.088 g, 1 *equiv.*, 1.379 mmol) in THF (30.0 mL) and DMF (6.00 mL) was treated with $Pd(OH)_2$ on carbon (193.6 mg, 20 wt%, 0.20 *equiv.*, 275.8 μmol). The flask was evacuated and backfilled with hydrogen (3x). The resulting mixture was stirred under hydrogen (balloon) for 21 hours at 40 °C. The reaction mixture was filtered through celite. The filter cake was washed with DCM. The filtrate was taken, and volatile organics were removed under reduced pressure to give *tert*-butyl 9-((1-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (930 mg) as a dark brown solid, which was carried forward without further purification.

LC-MS (ESI): m/z = 611.4 $[M+H]^+$

Preparation of 3-(6-(4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)piperidin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione, 3HCl

To a solution of *tert*-butyl 9-((1-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (930 mg, 1 *equiv.*, 1.52 mmol) in 1,4-dioxane (5.0 mL) was added HCl (7.00 mL, 13.1 *equiv.*, 20.0 mmol) (4.0 M in 1,4-dioxane). The reaction mixture was stirred at ambient temperature for 1 hour. Volatile organics were removed under reduced pressure to give 3-(6-(4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)piperidin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione, 3HCl (785 mg) as a dark brown solid. Carried forward without further purification.

LC-MS (ESI): m/z = 511.4 $[M+H]^+$.

Preparation of (*S*)-10-((5-chloro-2-fluoropyrimidin-4-yl)amino)-2-cyclopropyl-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one

To a solution of (*S*)-10-amino-2-cyclopropyl-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (1.36 g, 1 *equiv.*, 4.23 mmol) and 5-chloro-2,4-difluoropyrimidine (764 mg, 1.2 *equiv.*, 5.08 mmol) in N-methyl-2-pyrrolidinone (14.0 mL) was added DIPEA (1.64 g, 2.21 mL, 3.0 *equiv.*, 12.7 mmol). The reaction mixture was stirred

at 80 °C for 16 hours. The reaction mixture was quenched with water (150 mL). The resulting mixture was stirred for 5 minutes, and the resulting light yellow precipitate was collected by vacuum filtration. The precipitate was taken up in DCM/methanol and purified on a silica gel column (0-20% methanol in DCM) to give (*S*)-10-((5-chloro-2-fluoropyrimidin-4-yl)amino)-2-cyclopropyl-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (1.21 g) as a light yellow solid.

LC-MS (ESI): m/z = 452.2 $[M+1]^+$

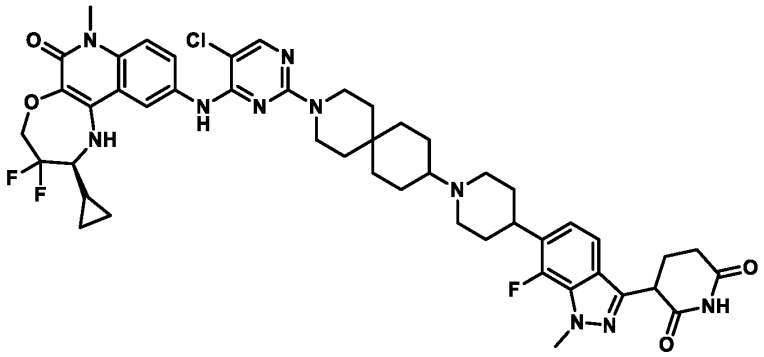
Preparation of 3-(6-(4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)piperidin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

To a solution of (*S*)-10-((5-chloro-2-fluoropyrimidin-4-yl)amino)-2-cyclopropyl-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (180 mg, 1 *equiv.*, 398 μmol) in DMSO (2.0 mL) was added 3-(6-(4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)piperidin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione, 3HCl (371 mg, 1.5 *equiv.*, 598 μmol) and DIPEA (257 mg, 347 μL, 5.0 *equiv.*, 1.99 mmol). The reaction mixture was stirred at 80 °C for 20 hours. The reaction mixture was filtered and purified by reverse phase HPLC to give 3-(6-(4-((9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)piperidin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (208 mg) as a light blue solid.

^{1}H NMR (400 MHz, DMSO-d_6, 300 K) δ (ppm) = 10.84 (s, 1H), 8.76 (s, 1H), 8.19 (d, J = 1.8 Hz, 1H), 8.02 (s, 1H), 7.72 (dd, J = 1.9, 9.1 Hz, 1H), 7.49 - 7.38 (m, 2H), 7.07 (d, J = 7.0 Hz, 1H), 6.17 (br s, 1H), 4.51 - 4.31 (m, 2H), 4.26 (dd, J = 5.1, 9.6 Hz, 1H), 3.93 (s, 3H), 3.57 (s, 7H), 3.41 (br d, J = 11.6 Hz, 2H), 3.26 - 3.16 (m, 1H), 2.75 - 2.57 (m, 4H), 2.43 - 2.19 (m, 7H), 2.18 - 2.07 (m, 1H), 1.87 - 1.75 (m, 2H), 1.73 - 1.62 (m, 1H), 1.56 - 1.43 (m, 4H), 1.43 - 1.22 (m, 7H), 0.76 - 0.66 (m, 1H), 0.58 - 0.45 (m, 2H), 0.41 - 0.28 (m, 1H).

LC-MS (ESI): m/z = 471.9 $[M+2H]^{2+}$.

Example 92. 3-(6-(1-(3-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-azaspiro[5.5]undecan-9-yl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 115a)



Preparation of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidine-1-carboxylate

To a solution of *tert*-butyl-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (See Table P34) (200 mg, 1 *equiv.*, 322 μmol) in isopropanol (5.0 mL) and DMF (1.0 mL) was added $Pd(OH)_2$ on carbon (45.2 mg, 20 wt%, 0.2 *equiv.*, 64.4 μmol). Air in the reaction flask was evacuated and replaced with hydrogen (3x). The reaction mixture was stirred at 40 °C under hydrogen balloon for 18 hours. The reaction mixture was filtered through celite. The filter cake was washed with DCM. The filtrate was taken and volatile organics were removed under reduced pressure to give *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidine-1-carboxylate (170 mg) as a light yellow solid, which was carried forward without further purification.

LC-MS (ESI): m/z = 445.4 $[M+H]^+$

Preparation of 3-(7-fluoro-1-methyl-6-(piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione, HCl

To a solution of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidine-1-carboxylate (143 mg, 1 *equiv.*, 322 μmol) in 1,4-dioxane (2.0 mL) was added HCl (2.00 mL, 24.9 *equiv.*, 8.00 mmol) (4.0 M in dioxane). The reaction mixture was stirred at ambient temperature for 1 hour. Volatile organics were removed under reduced pressure to give 3-(7-fluoro-1-methyl-6-(piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione, HCl (140 mg) as an off white solid, which was carried forward without further purification.

LC-MS (ESI): m/z = 345.1 $[M+H]^+$

Preparation of *tert*-butyl 9-(4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)-3-azaspiro[5.5]undecane-3-carboxylate

To a solution of 3-(7-fluoro-1-methyl-6-(piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione, HCl (110 mg, 1.1 *equiv.*, 288 μmol) in THF (4.0 mL) and DMF (1.0 mL) was added *tert*-butyl 9-oxo-3-azaspiro[5.5]undecane-3-carboxylate (70.0 mg, 1 *equiv.*, 262 μmol) and potassium acetate (128 mg, 5.0 *equiv.*, 1.31 mmol). The reaction mixture was stirred for 30 minutes, followed by addition of sodium triacetoxyborohydride (111 mg, 2.0 *equiv.*, 524 μmol). Additional *tert*-butyl 9-oxo-3-azaspiro[5.5]undecane-3-carboxylate (70.0 mg, 1 *equiv.*, 262 μmol) and sodium triacetoxyborohydride (111 mg, 2.0 *equiv.*, 524 μmol) were added, and The resulting mixture was stirred for an additional 4 hours. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was removed, and the aqueous layer was extracted with ethyl acetate once more. The combined organic layer was washed with brine, dried over sodium sulfate and filtered. The filtrate was taken, and volatile organics were removed under reduced pressure to give a white solid. The solid was taken up in DMSO and purified by reverse phase HPLC to give *tert*-butyl 9-(4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)-3-azaspiro[5.5]undecane-3-carboxylate (63 mg) as a white solid.

LC-MS (ESI): m/z = 596.4 $[M+H]^+$

Preparation of 3-(6-(1-(3-azaspiro[5.5]undecan-9-yl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione, 2HCl

To a solution of *tert*-butyl 9-(4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)-3-azaspiro[5.5]undecane-3-carboxylate (63 mg, 1 *equiv.*, 0.11 mmol) in 1,4-dioxane (1.0 mL) was added HCl (0.15 g, 1.0 mL, 38 *equiv.*, 4.0 mmol) (4.0 M in 1,4-dioxane). The reaction mixture was stirred at ambient temperature for 1 hour. Volatile organics were removed under reduced pressure to give 3-(6-(1-(3-azaspiro[5.5]undecan-9-yl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione, 2HCl (62 mg) as a white solid.

LC-MS (ESI): m/z = 496.4 $[M+H]^+$

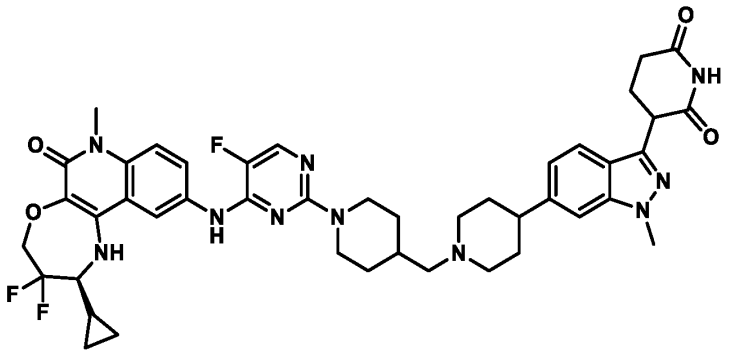
Preparation of 3-(6-(1-(3-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-azaspiro[5.5]undecan-9-yl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

To a solution of (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (42.0 mg, 1 *equiv.*, 89.7 μmol) in DMSO (0.50 mL) was added 3-(6-(1-(3-azaspiro[5.5]undecan-9-yl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione, 2HCl (61.2 mg, 1.2 *equiv.*, 108 μmol) and DIPEA (58.0 mg, 78.1 μL, 5.0 *equiv.*, 448 μmol). The reaction mixture was stirred at 80 °C for 20 hours. The reaction mixture was filtered and purified by reverse phase HPLC to give 3-(6-(1-(3-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-azaspiro[5.5]undecan-9-yl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (23 mg) as an off-white solid.

^{1}H NMR (400 MHz, DMSO-d_6, 299 K) δ (ppm) = 10.90 (s, 1H), 8.76 (s, 1H), 8.18 (d, J = 1.6 Hz, 1H), 8.01 (s, 1H), 7.72 (dd, J = 1.6, 9.1 Hz, 1H), 7.44 (d, J = 8.1 Hz, 2H), 7.05 (dd, J = 5.8, 8.3 Hz, 1H), 6.18 (br s, 1H), 4.50 - 4.29 (m, 3H), 4.10 (s, 3H), 3.25 - 3.16 (m, 4H), 3.02 - 2.85 (m, 4H), 2.75 - 2.54 (m, 3H), 2.42 - 2.22 (m, 4H), 2.21 - 2.11 (m, 1H), 2.07 (s, 3H), 1.81 - 1.65 (m, 5H), 1.64 - 1.51 (m, 2H), 1.50 - 1.20 (m, 7H), 1.16 - 1.00 (m, 2H), 0.77 - 0.64 (m, 1H), 0.51 (br t, J = 5.7 Hz, 2H), 0.40 - 0.28 (m, 1H).

LC-MS (ESI): m/z = 464.4 $[M+2H]^{2+}$

Example 93. 3-(6-(1-((1-(4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)-5-fluoropyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 157a)



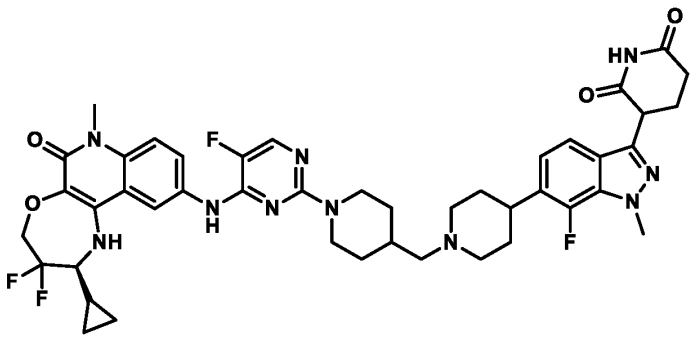
Preparation of 3-(6-(1-((1-(4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)-5-fluoropyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

To a solution of (*S*)-10-((2-chloro-5-fluoropyrimidin-4-yl)amino)-2-cyclopropyl-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (275 mg, 1 *equiv.*, 609 μmol) in DMSO (2.0 mL) was added 3-(1-methyl-6-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione, 2HCl (453 mg, 1.50 *equiv.*, 913 μmol) and DIPEA (393 mg, 530 μL, 5.0 *equiv.*, 3.04 mmol). The reaction mixture was stirred at 100 °C for 20 hours. An additional 250 mg of 3-(1-methyl-6-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione, 2HCl was added, and heating was continued for an additional 12 hours. The reaction mixture was diluted with DMSO to a total volume of 6 mL, filtered, and purified by reverse phase HPLC to give 3-(6-(1-((1-(4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)-5-fluoropyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (210 mg) as an off-white solid.

^{1}H NMR (400 MHz, DMSO-d_6, 300 K) δ (ppm) = 10.87 (s, 1H), 9.27 (s, 1H), 8.23 (d, J = 1.6 Hz, 1H), 8.00 (d, J = 3.6 Hz, 1H), 7.78 (dd, J = 1.6, 9.0 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.49 - 7.38 (m, 2H), 7.03 (d, J = 8.5 Hz, 1H), 5.96 (br s, 1H), 4.55 - 4.27 (m, 5H), 3.97 (s, 3H), 3.57 (s, 3H), 3.28 - 3.20 (m, 1H), 2.98 (br s, 2H), 2.80 (br t, J = 12.5 Hz, 2H), 2.73 - 2.56 (m, 3H), 2.34 (ddt, J = 4.6, 9.5, 13.8 Hz, 1H), 2.27 - 2.12 (m, 3H), 2.11 - 1.98 (m, 2H), 1.88 - 1.65 (m, 7H), 1.42 - 1.29 (m, 1H), 1.05 (br d, J = 11.4 Hz, 2H), 0.78 - 0.65 (m, 1H), 0.53 (br t, J = 5.8 Hz, 2H), 0.43 - 0.31 (m, 1H).

LC-MS (ESI): m/z = 420.4 $[M+2H]^{2+}$

Example 94. 3-(6-(1-((1-(4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)-5-fluoropyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 152a)



Preparation of (*S*)-10-((2-(4-(1,3-dioxolan-2-yl)piperidin-1-yl)-5-fluoropyrimidin-4-yl)amino)-2-cyclopropyl-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one

To a solution of (*S*)-10-((2-chloro-5-fluoropyrimidin-4-yl)amino)-2-cyclopropyl-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (300 mg, 1 *equiv.*, 664 μmol) in DMSO (3.00 mL) was added 4-(1,3-dioxolan-2-yl)piperidine (157 mg, 1.5 *equiv.*, 996 μmol) and DIPEA (257 mg, 347 μL, 3.0 *equiv.*, 1.99 mmol). The reaction mixture was heated to 100 °C for 6 hours, followed by 18 hours at 80 °C. The reaction mixture was partitioned between DCM and water. The organic layer was removed, and the aqueous layer was extracted with DCM once more. The combined organic layer was washed with brine, dried over sodium sulfate, and filtered. The filtrate was taken, and the volatile organics were removed under reduced pressure to give an orange solid. The solid was taken up in DCM and purified on a silica gel column (0-20% methanol in DCM) to give (*S*)-10-((2-(4-(1,3-dioxolan-2-yl)piperidin-1-yl)-5-fluoropyrimidin-4-yl)amino)-2-cyclopropyl-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (302 mg) as a light yellow solid.

LC-MS (ESI): m/z = 537.3 $[M+H]^+$

Preparation of (*S*)-1-(4-((2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)-5-fluoropyrimidin-2-yl)piperidine-4-carbaldehyde, formic Acid

To a vial containing (*S*)-10-((2-(4-(1,3-dioxolan-2-yl)piperidin-1-yl)-5-fluoropyrimidin-4-yl)amino)-2-cyclopropyl-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (300 mg, 1 *equiv.*, 524 μmol) was added formic acid (4.88 g, 4.00 mL, 202 *equiv.*, 106 mmol). The reaction mixture was stirred at 80 °C for 90 minutes. Volatile organics were removed under reduced pressure to give (*S*)-1-(4-((2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)-5-fluoropyrimidin-2-yl)piperidine-4-carbaldehyde, formic Acid (330 mg) as a light brown solid, which was carried forward without further purification.

LC-MS (ESI): m/z = 529.3 $[M+H]^+$

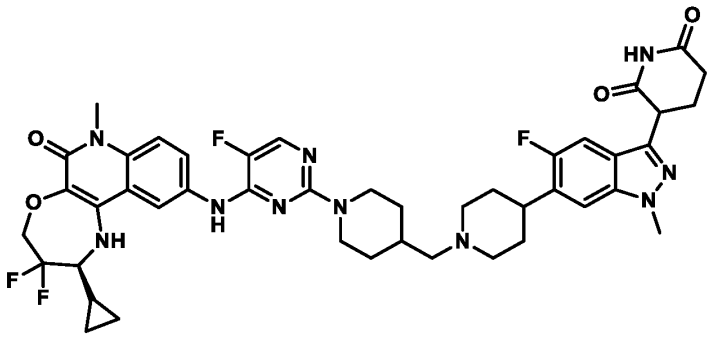
Preparation of 3-(6-(1-((1-(4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)-5-fluoropyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

To a solution of (*S*)-1-(4-((2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)-5-fluoropyrimidin-2-yl)piperidine-4-carbaldehyde, formic acid (150 mg, 1 *equiv.*, 261 μmol) in THF (4.00 mL) and DMF (1.00 mL) was added 3-(7-fluoro-1-methyl-6-(piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione, HCl (149 mg, 1.5 *equiv.*, 392 μmol) and potassium acetate (128 mg, 5.0 *equiv.*, 1.31 mmol). The reaction mixture was stirred at ambient temperature for 30 minutes followed by the addition of sodium triacetoxyborohydride (111 mg, 2.0 *equiv.*, 522 μmol). The resulting mixture was stirred for an additional 18 hours. The reaction mixture was partitioned between ethyl acetate and saturated ammonium chloride (*aq.*). The organic layer was removed, and the aqueous layer was extracted with ethyl acetate twice more and DCM twice more. The combined organic layer was washed with brine, dried over sodium sulfate, and filtered. The filtrate was taken, and volatile organics were removed to give an off-white solid. Solids were taken up in DMSO and purified by reverse phase HPLC to give 3-(6-(1-((1-(4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)-5-fluoropyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (73 mg) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6, 300 K) δ (ppm) = 10.90 (s, 1H), 9.27 (s, 1H), 8.24 (d, J = 1.9 Hz, 1H), 8.00 (d, J = 3.6 Hz, 1H), 7.78 (dd, J = 1.8, 9.1 Hz, 1H), 7.46 (dd, J = 2.6, 8.8 Hz, 2H), 7.05 (dd, J = 5.8, 8.3 Hz, 1H), 5.96 (br s, 1H), 4.53 - 4.30 (m, 5H), 4.11 (s, 3H), 3.57 (s, 3H), 3.29 - 3.24 (m, 1H), 3.02 - 2.88 (m, 3H), 2.80 (br t, J = 12.4 Hz, 2H), 2.74 - 2.56 (m, 2H), 2.43 - 2.28 (m, 1H), 2.24 - 2.10 (m, 3H), 2.08 - 1.95 (m, 2H), 1.89 - 1.61 (m, 7H), 1.42 - 1.28 (m, 1H), 1.14 - 0.94 (m, 2H), 0.77 - 0.65 (m, 1H), 0.53 (br t, J = 5.8 Hz, 2H), 0.43 - 0.32 (m, 1H).

LC-MS (ESI): m/z = 429.4 $[(M/2)+H]^+$

Example 95. 3-(6-(1-((1-(4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)-5-fluoropyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 162a)



Preparation of 3-(6-(1-((1-(4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)-5-fluoropyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

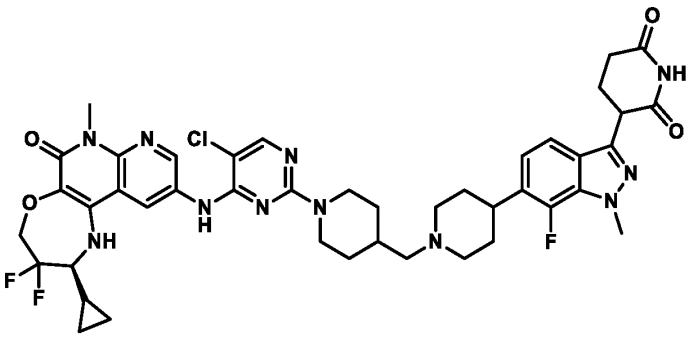
To a solution of (*S*)-1-(4-((2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)-5-fluoropyrimidin-2-yl)piperidine-4-carbaldehyde, formic acid (150 mg, 1 *equiv.*, 261 μmol) in THF (4.00 mL) and DMF (1.00 mL) was added 3-[5-fluoro-1-methyl-6-(4-piperidyl)indazol-3-yl]piperidine-2,6-dione, HCl (See Table P6) (149 mg, 1.5 *equiv.*, 392 μmol) and potassium acetate (128 mg, 5.0 *equiv.*, 1.31 mmol). The reaction mixture was stirred at ambient temperature for 30 minutes followed by the addition of sodium triacetoxyborohydride (111 mg, 2.0 *equiv.*, 522 μmol). The resulting mixture was stirred for an additional 18 hours. The reaction mixture was partitioned between DCM and saturated ammonium chloride (*aq.*). The organic layer was removed, and the aqueous layer was extracted with DCM twice more. The combined organic layer was washed with brine, dried over sodium sulfate, and filtered. The filtrate was taken, and volatile organics were removed to give a brown solid. Solids were taken up in DMSO and purified by reverse phase HPLC to give 3-(6-(1-((1-(4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)-5-fluoropyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (107 mg) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6, 300 K) δ (ppm) = 10.87 (s, 1H), 9.27 (s, 1H), 8.23 (d, J = 1.6 Hz, 1H), 8.00 (d, J = 3.6 Hz, 1H), 7.78 (dd, J = 1.7, 9.1 Hz, 1H), 7.54 (d, J = 5.9 Hz, 1H), 7.46 (dd, J = 7.4, 9.9 Hz, 2H), 5.97 (br s, 1H), 4.58 - 4.24 (m, 5H), 3.99 (s, 3H), 3.56 (s, 3H), 3.31 - 3.19 (m, 2H), 3.04 - 2.91 (m, 2H), 2.90 - 2.73 (m, 3H), 2.72 - 2.55 (m, 2H), 2.44 - 2.30 (m, 1H), 2.23 - 2.09 (m, 3H), 2.08 - 1.97 (m, 2H), 1.89 - 1.68 (m, 6H), 1.43 - 1.27 (m,

1H), 1.04 (br d, J = 11.4 Hz, 2H), 0.78 - 0.63 (m, 1H), 0.53 (br t, J = 5.8 Hz, 2H), 0.43 - 0.31 (m, 1H).

LC-MS (ESI): m/z = 429.4 $[M+2H]^{2+}$

Example 96. 3-(6-(1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 174a)



Preparation of methyl 2-(methylamino) nicotinate

A mixture of methyl 2-chloronicotinate (50 g, 292.80 mmol) and Methylamine (2M in THF) (500 mL) was heated at 70 °C for 16 hours. The reaction mixture was concentrated and dried under vacuum to afford methyl 2-(methylamino) nicotinate (40.0 g) as a brown solid.

Crude product was used as such for next step.

LC-MS (ESI): m/z = 167.00 $[M+H]^{+}$

Preparation of methyl 2-(methylamino)-5-nitronicotinate

To a stirred solution of methyl 2-(methylamino) nicotinate (40.0 g, 264.65 mmol) in sulphuric acid (100 mL) was drop wise added nitric acid (40 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was poured in crushed ice (2000 mL) and the solid was filtered and dried under vacuum to afford the methyl 2-(methylamino)-5-nitronicotinate (30 g) as a yellow solid.

LC-MS (ESI): m/z = 212.21 $[M+H]^{+}$

Preparation of 2-(methylamino)-5-nitronicotinic acid

To a stirred solution of methyl 2-(methylamino)-5-nitronicotinate (30.0 g, 142.13 mmol) in THF (300 mL), methanol (300 mL) and water (60 mL) was added lithium hydroxide

monohydrate (17.89 g, 426.41 mmol) at 0 °C. The resulting reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was concentrated under vacuum and the crude product was acidified to pH ~ 2 with 1N HCl solution. The resulting solid was filtered and dried under reduced pressure to afford 2-(methylamino)-5-nitronicotinic acid (20.0 g) as an off-white solid.

LC-MS (ESI): m/z = 198.10 $[M+H]^+$

Preparation of 3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl 2-(methylamino)-5-nitronicotinate

To a stirred solution of 2-(methylamino)-5-nitronicotinic acid (20.0 g, 101.50 mmol) in DMF (200 mL) was added HATU (57.89 g, 152.25 mmol), and DIPEA (53 mL, 304.50 mmol) at 0 °C. The mixture was stirred at room temperature for 3 hours. The reaction mixture was quenched with ice cold water (1000 mL) and the precipitated solid was filtered, washed with n-pentane and dried under vacuum to afford 3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl 2-(methylamino)-5-nitronicotinate (15 g) as a brown solid.

LC-MS (ESI): m/z = 316.09 $[M+H]^+$

Preparation of ethyl 4-hydroxy-1-methyl-6-nitro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate

To a suspension of NaH (11.43 g, 476.08 mmol) in DMF (150 mL) was added diethyl malonate (76.25 g, 476.08 mmol) at 0 °C and stirred reaction mixture at room temperature for 2 hours. The reaction mixture was cooled to 0 °C and 3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl 2-(methylamino)-5-nitronicotinate (15.0 g, 47.60 mmol) was added portion wise at 0 °C. The mixture was stirred at room temperature for 2 hours followed by the addition of potassium carbonate (2.84 g, 20.61 mmol). The resulting reaction mixture was stirred at 100 °C for 16 hours. The reaction mixture was quenched with ice cold water (500 mL) and the precipitated solid was filtered, washed with n-pentane and dried under vacuum to afford ethyl 4-hydroxy-1-methyl-6-nitro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate (10 g) as a brown solid.

LC-MS (ESI): m/z = 294.04 $[M+H]^+$

Preparation of ethyl 4-chloro-1-methyl-6-nitro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate

A stirred suspension of ethyl 4-hydroxy-1-methyl-6-nitro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate (15.0 g, 61.04 mmol) in $POCl_3$ (50 mL) was stirred at 80 °C for 3 hours. The reaction mixture was quenched with sodium bicarbonate solution (150 mL) and

extracted with ethyl acetate (3 x100 mL). The organic layer was separated, dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was washed with n-pentane and dried under reduced pressure to afford ethyl 4-chloro-1-methyl-6-nitro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate (8 g) as a brown solid.

LC-MS (ESI): m/z = 312.00 $[M+H]^+$

Preparation of ethyl (*S*)-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl) amino)-1-methyl-6-nitro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate

To a stirred solution of ethyl 4-chloro-1-methyl-6-nitro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate (8.0 g, 25.72 mmol) and (*S*)-3-amino-3-cyclopropyl-2,2-difluoropropan-1-ol (7.77 g, 51.44 mmol) in MeCN (80 mL) was added DIPEA (13.30 mL, 70.78 mmol). The mixture was stirred at 130 °C in an autoclave for 48 hours. The reaction mixture was quenched with ice cold water (150 mL) and the precipitated solid was filtered, washed with n-pentane (100 mL) and dried under vacuum to afford ethyl (*S*)-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl) amino)-1-methyl-6-nitro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate (8 g) as a yellow solid.

LC-MS (ESI): m/z = 427.33 $[M+H]^+$

Preparation of (*S*)-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl) amino)-1-methyl-6-nitro-1,8-naphthyridin-2(1H)-one

To a stirred solution of ethyl (*S*)-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl) amino)-1-methyl-6-nitro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate (8.0 g, 18.81 mmol) in MeCN (40 mL) was added 2M NaOH solution (40 mL). The resulting mixture was stirred at 85 °C for 3 hours. The reaction mixture was diluted with ice-water (200 mL) and acidified with 1N HCl to pH~6. The resulting solid was filtered off, washed with water (100 mL), n-pentane (100 mL) and dried under vacuum to afford (*S*)-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl) amino)-1-methyl-6-nitro-1,8-naphthyridin-2(1H)-one (4.0 g) as a yellow solid.

LC-MS (ESI): m/z = 355.36 $[M+H]^+$

Preparation of (*S*)-3-bromo-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl) amino)-1-methyl-6-nitro-1,8-naphthyridin-2(1H)-one

To a stirred solution of (*S*)-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl) amino)-1-methyl-6-nitro-1,8-naphthyridin-2(1H)-one (4.0 g, 11.29 mmol) in DCM (40 mL) was added NBS (2.0 g, 11.29 mmol) at 0 °C. The mixture was stirred for 5 minutes, followed by the addition of trifluoroacetic acid (4.0 mL). The resulting reaction mixture was stirred at 0 °C for 10 minutes. The reaction mixture was diluted with water (100 mL) and extracted with DCM (2 x 200 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (100 mL), brine (100 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure to obtain crude. The crude product was triturated with petroleum ether (100 mL) and dried under vacuum to afford (*S*)-3-bromo-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl) amino)-1-methyl-6-nitro-1,8-naphthyridin-2(1H)-one (4.0 g) as a yellow solid.

LC-MS (ESI): m/z = 433.27 $[M+H]^+$

Preparation of (*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-10-nitro-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-6(7*H*)-one

To a stirred solution (*S*)-3-bromo-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl) amino)-1-methyl-6-nitro-1,8-naphthyridin-2(1H)-one (4.0 g, 9.25 mmol) in THF (40 mL) was added LiOtBu (1M in THF) (13.8 mL). The reaction was stirred at 60 °C for 4 hours. The reaction mixture was diluted with water (100 mL) and extracted with DCM (2 x 200 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure to obtain crude product which was triturated with petroleum ether (100 mL) and dried under vacuum to afford (*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-10-nitro-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-6(7*H*)-one (2.0 g) as a yellow solid.

LC-MS (ESI): m/z = 353.31 $[M+H]^+$

Preparation of (*S*)-10-amino-2-cyclopropyl-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-6(7*H*)-one

To a stirred solution of (S)-2-cyclopropyl-3,3-difluoro-7-methyl-10-nitro-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-6(7H)-one (2.0 g, 5.68 mmol) in DMF (20 mL) were added 4,4'-dipyridyl (0.044 g, 0.28 mmol) and hypodiboric acid (1.52 g, 17.01 mmol) portion wise at 0 °C. The mixture was stirred at 0 °C for 10 minutes. The crude was diluted with water (50 mL) and the resulting solid was filtered off, washed with water (100 mL), n-pentane (100 mL) and dried under vacuum to afford to get (*S*)-10-amino-2-

cyclopropyl-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-6(7*H*)-one (1.5 g) as a yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.02 (d, J = 2.00 Hz, 1H), 7.59 (d, J = 2.40 Hz, 1H), 6.21 (d, J = 2.40 Hz, 1H), 5.19 (s, 2H), 4.49-4.30 (m, 2H), 3.53 (s, 3H), 3.26-3.18 (m, 1H), 1.30 (t, J = 4.40 Hz, 1H), 0.71-0.68 (m, 1H), 0.52-0.49 (m, 2H), 0.34-0.32 (m, 1H).

LC-MS (ESI): m/z = 323.36 $[M+H]^+$

Preparation of (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-6(7*H*)-one

To a stirred solution of (*S*)-10-amino-2-cyclopropyl-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-6(7*H*)-one (0.5 g, 1.55 mmol) in DMSO (5.0 mL) was added DIPEA (1.35 mL, 7.75 mmol) and 2,4,5-trichloropyrimidine (0.42 g, 2.32 mmol) at 0 °C. The mixture was stirred at room temperature for 4 hours. The reaction mixture was quenched with ice-cold water, and the solid was filtered to get crude product which was triturated with diethyl ether (20 mL) and dried under vacuum to afford (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-6(7*H*)-one (0.35 g) as a yellow solid.

LC-MS (ESI): m/z = 469.32 $[M+H]^+$

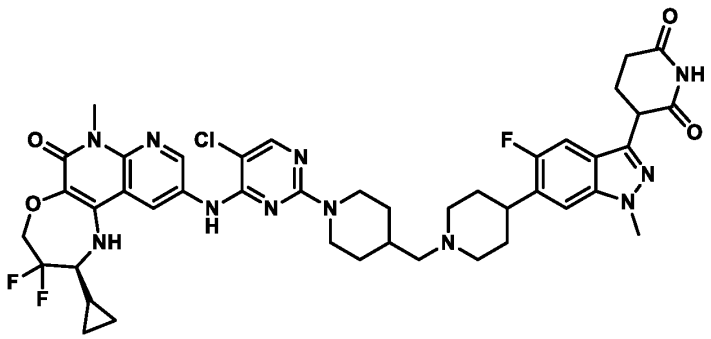
Preparation of 3-(6-(1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

To a solution of (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-6(7*H*)-one (140 mg, 1 *equiv.*, 298 μmol) in DMSO (2.0 mL) was added 3-(7-fluoro-1-methyl-6-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione, 2HCl (230 mg, 1.50 *equiv.*, 448 μmol) and DIPEA (193 mg, 260 μL, 5.0 *equiv.*, 1.49 mmol). The reaction mixture was stirred at 80 °C for 20 hours. The reaction mixture was diluted with DMSO to a total volume of 3 mL, filtered, and purified by reverse phase HPLC to give 3-(6-(1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (201 mg) as a tan solid.

^{1}H NMR (400 MHz, DMSO-d_6, 300 K) δ (ppm) = 10.90 (s, 1H), 9.04 (s, 1H), 8.70 (s, 1H), 8.64 (d, J = 1.9 Hz, 1H), 8.06 (s, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.05 (dd, J = 5.8, 8.3 Hz, 1H), 6.40 (br s, 1H), 4.56 - 4.30 (m, 5H), 4.15 - 4.06 (m, 3H), 3.62 (s, 3H), 2.96 (br s, 3H), 2.85 - 2.74 (m, 2H), 2.73 - 2.55 (m, 2H), 2.43 - 2.24 (m, 2H), 2.22 - 2.10 (m, 3H), 2.10 - 1.97 (m, 2H), 1.89 - 1.63 (m, 7H), 1.38 - 1.25 (m, 1H), 1.10 - 0.94 (m, 2H), 0.77 - 0.65 (m, 1H), 0.53 (br t, J = 5.7 Hz, 2H), 0.42 - 0.30 (m, 1H).

LC-MS (ESI): m/z = 874.6 $[M+H]^+$

Example 97. 3-(6-(1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 138a)



Preparation of methyl 2-(methylamino) nicotinate

A mixture of methyl 2-chloronicotinate (50 g, 292.80 mmol) and Methylamine (2M in THF) (500 mL) was heated at 70 °C for 16 hours. The reaction mixture was concentrated and dried under vacuum to afford methyl 2-(methylamino) nicotinate (40.0 g) as a brown solid.

LC-MS (ESI): m/z = 167.00 $[M+H]^+$

Preparation of methyl 2-(methylamino)-5-nitronicotinate

To a stirred solution of methyl 2-(methylamino) nicotinate (40.0 g, 264.65 mmol) in sulphuric acid (100 mL) was drop wise added nitric acid (40 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was poured in crushed ice (2000 mL) and the solid was filtered and dried under vacuum to afford the methyl 2-(methylamino)-5-nitronicotinate (30 g) as a yellow solid.

LC-MS (ESI): m/z = 212.21 $[M+H]^+$

Preparation of 2-(methylamino)-5-nitronicotinic acid

To a stirred solution of methyl 2-(methylamino)-5-nitronicotinate (30.0 g, 142.13 mmol) in THF (300 mL), methanol (300 mL) and water (60 mL) was added lithium hydroxide monohydrate (17.89 g, 426.41 mmol) at 0 °C. The resulting reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was concentrated under vacuum and the crude product was acidified to pH ~ 2 with 1N HCl solution. The resulting solid was filtered and dried under reduced pressure to afford 2-(methylamino)-5-nitronicotinic acid (20.0 g) as an off-white solid.

LC-MS (ESI): m/z = 198.10 $[M+H]^+$

Preparation of 3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl 2-(methylamino)-5-nitronicotinate

To a stirred solution of 2-(methylamino)-5-nitronicotinic acid (20.0 g, 101.50 mmol) in DMF (200 mL) was added HATU (57.89 g, 152.25 mmol), and DIPEA (53 mL, 304.50 mmol) at 0 °C. The mixture was stirred at room temperature for 3 hours. The reaction mixture was quenched with ice cold water (1000 mL) and the precipitated solid was filtered, washed with n-pentane and dried under vacuum to afford 3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl 2-(methylamino)-5-nitronicotinate (15 g) as a brown solid.

LC-MS (ESI): m/z = 316.09 $[M+H]^+$

Preparation of ethyl 4-hydroxy-1-methyl-6-nitro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate

To a suspension of NaH (11.43 g, 476.08 mmol) in DMF (150 mL) was added diethyl malonate (76.25 g, 476.08 mmol) at 0 °C and stirred reaction mixture at room temperature for 2 hours. The reaction mixture was cooled to 0 °C and 3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl 2-(methylamino)-5-nitronicotinate (15.0 g, 47.60 mmol) was added portion wise at 0 °C. The mixture was stirred at room temperature for 2 hours followed by the addition of potassium carbonate (2.84 g, 20.61 mmol). The resulting reaction mixture was stirred at 100 °C for 16 hours. The reaction mixture was quenched with ice cold water (500 mL) and the precipitated solid was filtered, washed with n-pentane and dried under vacuum to afford ethyl 4-hydroxy-1-methyl-6-nitro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate (10 g) as a brown solid.

LC-MS (ESI): m/z = 294.04 $[M+H]^+$

Preparation of ethyl 4-chloro-1-methyl-6-nitro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate

A stirred suspension of ethyl 4-hydroxy-1-methyl-6-nitro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate (15.0 g, 61.04 mmol) in $POCl_3$ (50 mL) was stirred at 80 °C for 3 hours. The reaction mixture was quenched with sodium bicarbonate solution (150 mL) and extracted with ethyl acetate (3 x100 mL). The organic layer was separated, dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was washed with n-pentane and dried under reduced pressure to afford ethyl 4-chloro-1-methyl-6-nitro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate (8 g) as a brown solid.

LC-MS (ESI): m/z = 312.00 $[M+H]^+$

Preparation of ethyl (*S*)-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl) amino)-1-methyl-6-nitro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate

To a stirred solution of ethyl 4-chloro-1-methyl-6-nitro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate (8.0 g, 25.72 mmol) and (*S*)-3-amino-3-cyclopropyl-2,2-difluoropropan-1-ol (7.77 g, 51.44 mmol) in MeCN (80 mL) was added DIPEA (13.30 mL, 70.78 mmol). The mixture was stirred at 130 °C in an autoclave for 48 hours. The reaction mixture was quenched with ice cold water (150 mL) and the precipitated solid was filtered, washed with n-pentane (100 mL) and dried under vacuum to afford ethyl (*S*)-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl) amino)-1-methyl-6-nitro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate (8 g) as a yellow solid.

LC-MS (ESI): m/z = 427.33 $[M+H]^+$

Preparation of (*S*)-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl) amino)-1-methyl-6-nitro-1,8-naphthyridin-2(1H)-one

To a stirred solution of ethyl (*S*)-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl) amino)-1-methyl-6-nitro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate (8.0 g, 18.81 mmol) in MeCN (40 mL) was added 2M NaOH solution (40 mL). The resulting mixture was stirred at 85 °C for 3 hours. The reaction mixture was diluted with ice-water (200 mL) and acidified with 1N HCl to pH~6. The resulting solid was filtered off, washed with water (100 mL), n-pentane (100 mL) and dried under vacuum to afford (*S*)-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl) amino)-1-methyl-6-nitro-1,8-naphthyridin-2(1H)-one (4.0 g) as a yellow solid.

LC-MS (ESI): m/z = 355.36 $[M+H]^+$

Preparation of (*S*)-3-bromo-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl) amino)-1-methyl-6-nitro-1,8-naphthyridin-2(1H)-one

To a stirred solution of (*S*)-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl) amino)-1-methyl-6-nitro-1,8-naphthyridin-2(1H)-one (4.0 g, 11.29 mmol) in DCM (40 mL) was added NBS (2.0 g, 11.29 mmol) at 0 °C. The mixture was stirred for 5 minutes, followed by the addition of trifluoracetic acid (4.0 mL). The resulting reaction mixture was stirred at 0 °C for 10 minutes. The reaction mixture was diluted with water (100 mL) and extracted with DCM (2 x 200 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (100 mL), brine (100 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure to obtain crude. The crude product was triturated with petroleum ether (100 mL) and dried under vacuum to afford (*S*)-3-bromo-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl) amino)-1-methyl-6-nitro-1,8-naphthyridin-2(1H)-one (4.0 g) as a yellow solid.

LC-MS (ESI): m/z = 433.27 $[M+H]^+$

Preparation of (*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-10-nitro-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-6(7*H*)-one

To a stirred solution (*S*)-3-bromo-4-((1-cyclopropyl-2,2-difluoro-3-hydroxypropyl) amino)-1-methyl-6-nitro-1,8-naphthyridin-2(1H)-one (4.0 g, 9.25 mmol) in THF (40 mL) was added LiOtBu (1M in THF) (13.8 mL). The reaction was stirred at 60 °C for 4 hours. The reaction mixture was diluted with water (100 mL) and extracted with DCM (2 x 200 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure to obtain crude product which was triturated with petroleum ether (100 mL) and dried under vacuum to afford (*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-10-nitro-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-6(7*H*)-one (2.0 g) as a yellow solid.

LC-MS (ESI): m/z = 353.31 $[M+H]^+$

Preparation of (*S*)-10-amino-2-cyclopropyl-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-6(7*H*)-one

To a stirred solution of 3(*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-10-nitro-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-6(7*H*)-one (2.0 g, 5.68 mmol) in DMF (20 mL) were added 4,4'-dipyridyl (0.044 g, 0.28 mmol) and hypodiboric acid (1.52 g, 17.01 mmol) portion wise at 0 °C. The mixture was stirred at 0 °C for 10 minutes. The crude

was diluted with water (50 mL) and the resulting solid was filtered off, washed with water (100 mL), n-pentane (100 mL) and dried under vacuum to afford to get (*S*)-10-amino-2-cyclopropyl-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-6(7*H*)-one (1.5 g) as a yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.02 (d, J = 2.00 Hz, 1H), 7.59 (d, J = 2.40 Hz, 1H), 6.21 (d, J = 2.40 Hz, 1H), 5.19 (s, 2H), 4.49-4.30 (m, 2H), 3.53 (s, 3H), 3.26-3.18 (m, 1H), 1.30 (t, J = 4.40 Hz, 1H), 0.71-0.68 (m, 1H), 0.52-0.49 (m, 2H), 0.34-0.32 (m, 1H).

LC-MS (ESI): m/z = 323.36 $[M+H]^+$

Preparation of (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-6(7*H*)-one

To a stirred solution of (*S*)-10-amino-2-cyclopropyl-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-6(7*H*)-one (0.5 g, 1.55 mmol) in DMSO (5.0 mL) was added DIPEA (1.35 mL, 7.75 mmol) and 2,4,5-trichloropyrimidine (0.42 g, 2.32 mmol) at 0 °C. The mixture was stirred at room temperature for 4 hours. The reaction mixture was quenched with ice-cold water, and the solid was filtered to get crude product which was triturated with diethyl ether (20 mL) and dried under vacuum to afford (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-6(7*H*)-one (0.35 g) as a yellow solid.

LC-MS (ESI): m/z = 469.32 $[M+H]^+$

Preparation of 3-(6-(1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

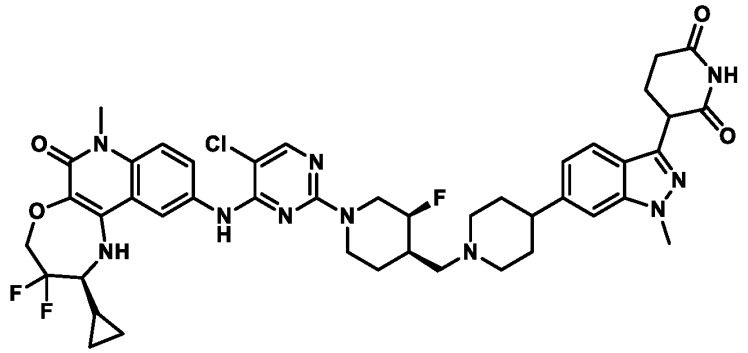
To a solution of (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-6(7*H*)-one (140 mg, 1 *equiv.*, 298 μmol) in DMSO (1.0 mL) was added 3-(5-fluoro-1-methyl-6-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione, 2HCl (230 mg, 1.50 *equiv.*, 448 μmol) and DIPEA (193 mg, 260 μL, 5.0 *equiv.*, 1.49 mmol). The reaction mixture was stirred at 80 °C for 20 hours. The reaction mixture was diluted with DMSO to a total volume of 3 mL, filtered, and purified by reverse phase HPLC to give a light pink solid. The solid was taken up in acetonitrile:water, frozen, and lyophilized to give 3-(6-(1-((1-(5-chloro-4-(((*S*)-2-

cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c][1,8]naphthyridin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (199 mg) as a light pink solid.

^{1}H NMR (400 MHz, DMSO-d_6, 300 K) δ (ppm) = 10.87 (s, 1H), 9.04 (s, 1H), 8.69 (s, 1H), 8.65 (d, J = 1.9 Hz, 1H), 8.06 (s, 1H), 7.54 (d, J = 5.9 Hz, 1H), 7.47 (d, J = 10.8 Hz, 1H), 6.40 (br s, 1H), 4.55 - 4.27 (m, 5H), 3.99 (s, 3H), 3.62 (s, 3H), 3.27 - 3.22 (m, 1H), 2.97 (br s, 2H), 2.90 - 2.73 (m, 3H), 2.72 - 2.56 (m, 2H), 2.44 - 2.31 (m, 1H), 2.23 - 2.10 (m, 3H), 2.05 (br s, 2H), 1.88 - 1.65 (m, 7H), 1.38 - 1.26 (m, 1H), 1.10 - 0.94 (m, 2H), 0.78 - 0.65 (m, 1H), 0.59 - 0.47 (m, 2H), 0.41 - 0.31 (m, 1H).

LC-MS (ESI): m/z = 437.9 $[M+2H]^{2+}$

Example 98. 3-(6-(1-(((3*S*,4*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 110b)



Preparation of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-6-(piperidin-4-yl)-1*H*-indazole, HCl

To a solution of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperidine-1-carboxylate (2.50 g, 1 *equiv.*, 4.13 mmol) in 1,4-dioxane (10.0 mL) was added HCl (10.0 mL, 9.68 *equiv.*, 40.0 mmol) (4.0 M in 1,4-dioxane). The reaction mixture was stirred at ambient temperature for 30 minutes. Volatile organics were removed under reduced pressure to give 3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-6-(piperidin-4-yl)-1*H*-indazole, HCl (2.53 g) as an orange solid. Carried forward without further purification.

LC-MS (ESI): m/z = 505.3 $[M+H]^+$

Preparation of *tert*-butyl (3*S*,4*R*)-4-(4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperidine-1-carbonyl)-3-fluoropiperidine-1-carboxylate

To a solution of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-6-(piperidin-4-yl)-1*H*-indazole, HCl (1.26 g, 1.15 *equiv.*, 2.33 mmol) in DMF (10.0 mL) was added (3*S*,4*R*)-1-(tert-butoxycarbonyl)-3-fluoropiperidine-4-carboxylic acid (500 mg, 1 *equiv.*, 2.02 mmol), DIPEA (784 mg, 1.06 mL, 3.0 *equiv.*, 6.07 mmol), and HATU (846 mg, 1.1 *equiv.*, 2.22 mmol). The reaction mixture was stirred at ambient temperature for 18 hours. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was removed, and the aqueous layer was extracted with ethyl acetate twice more. The combined organic layer was washed with brine, dried over sodium sulfate, and filtered. The filtrate was taken, and volatile organics were removed under reduced pressure to give a green oil. The oil was taken up in ethyl acetate and purified on a silica gel column (30-100% ethyl acetate in heptanes) to give *tert*-butyl (3*S*,4*R*)-4-(4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperidine-1-carbonyl)-3-fluoropiperidine-1-carboxylate (666 mg) as a white solid.

LC-MS (ESI): m/z = 644.5 $[M\text{-benzyl}]^+$

Preparation of *tert*-butyl (3*S*,4*R*)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate

A solution of *tert*-butyl (3*S*,4*R*)-4-(4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperidine-1-carbonyl)-3-fluoropiperidine-1-carboxylate (1.82 g, 1 *equiv.*, 2.48 mmol) in THF (40 mL) was cooled to 0 °C. To this mixture, borane dimethyl sulfide complex (3.20 g, 4.00 mL, 17.0 *equiv.*, 42.2 mmol) was slowly added dropwise. The reaction mixture was stirred for 18 hours at ambient temperature. The reaction was quenched by the slow addition of the reaction mixture to stirring methanol (100 mL) at 65 °C. The resulting mixture was stirred for 20 minutes. Volatile organics were removed under reduced pressure to give a white solid. The solid was taken up in DMSO and purified by reverse phase flash chromatography using 10-100% acetonitrile (+0.1% formic acid) in water (+0.1% formic acid) to give *tert*-butyl (3*S*,4*R*)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (730 mg) as a light yellow solid.

LC-MS (ESI): m/z = 720.4 $[M+H]^+$

Preparation of *tert*-butyl (3*S*,4*R*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate

A solution of *tert*-butyl (3*S*,4*R*)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (712 mg, 1 *equiv.*, 989 μmol) in THF (25.0 mL) and DMF (5.00 mL) was treated with $Pd(OH)_2$ on carbon (174 mg, 20 wt%, 0.25 *equiv.*, 247 μmol). The flask was evacuated and backfilled with hydrogen (3x). The resulting mixture was stirred under hydrogen (balloon) for 18 hours at 50 °C. LCMS shows reaction is incomplete. Balloon was refreshed with more hydrogen and more $Pd(OH)_2$ on carbon (174 mg, 20 wt%, 0.25 *equiv.*, 247 μmol) was added. The resulting mixture was stirred for an additional 8 hours. The reaction mixture was filtered through celite. The filter cake was washed with DCM. The filtrate was taken, and volatile organics were removed under reduced pressure to give *tert*-butyl (3*S*,4*R*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (600 mg) as a brown solid, which was carried forward without further purification.

LC-MS (ESI): m/z = 542.4 $[M+H]^+$

Preparation of 3-(6-(1-(((3*S*,4*R*)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione, 2HCl

To a solution of *tert*-butyl (3*S*,4*R*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (600 mg, 1 *equiv.*, 1.11 mmol) in 1,4-dioxane (4.0 mL) was added HCl (4.0 mL, 14 *equiv.*, 16 mmol) (4.0 M in 1,4-dioxane). The reaction mixture was stirred at ambient temperature for 1 hour. Volatile organics were removed under reduced pressure to give 3-(6-(1-(((3*S*,4*R*)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione, 2HCl (676 mg) as a light gray solid, which was carried forward without further purification.

LC-MS (ESI): m/z = 442.2 $[M+H]^+$

Preparation of 3-(6-(1-(((3*S*,4*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

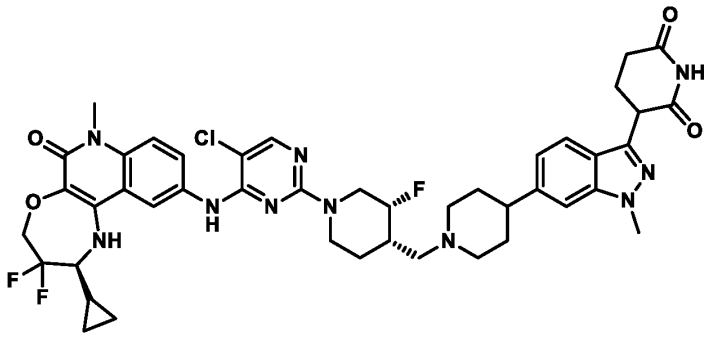
To a solution of (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (493 mg, 1 *equiv.*, 1.05 mmol) in DMSO (3.50 mL) was added 3-(6-(1-(((3*S*,4*R*)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione, 2HCl (677 mg, 1.25 *equiv.*, 1.32 mmol) and DIPEA (680 mg, 917 μL, 5.0 *equiv.*, 5.26 mmol). The reaction

mixture was stirred at 90 °C for 20 hours. The reaction mixture was diluted with DMSO to a total volume of 7.0 mL, filtered, and purified by reverse phase HPLC to give 3-(6-(1-(((3*S*,4*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (489 mg) as an off-white solid.

^{1}H NMR (400 MHz, DMSO-d_6, 300 K) δ (ppm) = 10.87 (s, 1H), 8.82 (s, 1H), 8.16 (d, J = 1.4 Hz, 1H), 8.04 (s, 1H), 7.73 (dd, J = 1.8, 9.0 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.46 (d, J = 9.1 Hz, 1H), 7.42 (s, 1H), 7.03 (d, J = 8.5 Hz, 1H), 6.13 - 5.83 (m, 1H), 4.99 - 4.75 (m, 2H), 4.66 - 4.53 (m, 1H), 4.53 - 4.37 (m, 2H), 4.33 (dd, J = 5.1, 9.7 Hz, 1H), 3.97 (s, 3H), 3.58 (s, 3H), 3.27 - 3.18 (m, 1H), 3.12 - 2.76 (m, 4H), 2.74 - 2.55 (m, 3H), 2.45 - 2.28 (m, 2H), 2.25 - 1.91 (m, 5H), 1.79 (br s, 4H), 1.53 (br d, J = 10.5 Hz, 1H), 1.46 - 1.30 (m, 2H), 0.75 - 0.64 (m, 1H), 0.52 (br d, J = 4.9 Hz, 2H), 0.41 - 0.29 (m, 1H).

LC-MS (ESI): m/z = 873.7 $[M+H]^+$

Example 99. 3-(6-(1-(((3*R*,4*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 110d)



Preparation of *tert*-butyl (3*R*,4*S*)-4-(4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperidine-1-carbonyl)-3-fluoropiperidine-1-carboxylate

To a solution of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-6-(piperidin-4-yl)-1*H*-indazole, HCl (1.26 g, 1.15 *equiv.*, 2.33 mmol) in DMF (10.0 mL) was added (3*R*,4*S*)-1-(tert-butoxycarbonyl)-3-fluoropiperidine-4-carboxylic acid (500 mg, 1 *equiv.*, 2.02 mmol), DIPEA (784 mg, 1.06 mL, 3.0 *equiv.*, 6.07 mmol), and HATU (846 mg, 1.1 *equiv.*, 2.22 mmol). The reaction mixture was stirred at ambient temperature for 18 hours. The reaction mixture was

partitioned between ethyl acetate and water. The organic layer was removed, and the aqueous layer was extracted with ethyl acetate twice more. The combined organic layer was washed with brine, dried over sodium sulfate, and filtered. The filtrate was taken, and volatile organics were removed under reduced pressure to give a light green oil. The oil was taken up in ethyl acetate and purified on a silica gel column (0-100% ethyl acetate in heptanes) to give *tert*-butyl (3*R*,4*S*)-4-(4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperidine-1-carbonyl)-3-fluoropiperidine-1-carboxylate (953 mg) as a white solid.

LC-MS (ESI): m/z = 644.3 $[M\text{-benzyl}]^+$

Preparation of *tert*-butyl (3*R*,4*S*)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate

A solution of *tert*-butyl (3*R*,4*S*)-4-(4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperidine-1-carbonyl)-3-fluoropiperidine-1-carboxylate (950 mg, 1 *equiv.*, 1.29 mmol) in THF (20 mL) was cooled to 0 °C. To this mixture, borane dimethyl sulfide complex (1.60 g, 2.00 mL, 16.3 *equiv.*, 21.1 mmol) was slowly added dropwise. The reaction mixture was stirred for 18 hours at ambient temperature. The reaction was quenched by the slow addition to stirring methanol (100 mL) at 65 °C. The resulting mixture was stirred for 20 minutes. Volatile organics were removed under reduced pressure to give a white solid. The solid was taken up in DMSO and purified by reverse phase flash chromatography using 10-100% acetonitrile (+0.1% formic acid) in water (+0.1% formic acid) to give *tert*-butyl (3*R*,4*S*)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (307 mg) as a light yellow solid.

LC-MS (ESI): m/z = 720.4 $[M+H]^+$

Preparation of *tert*-butyl (3*R*,4*S*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate

A solution of *tert*-butyl (3*R*,4*S*)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (597 mg, 1 *equiv.*, 829 μmol) in THF (20.0 mL) and DMF (4.00 mL) was treated with $Pd(OH)_2$ on carbon (146 mg, 20 wt%, 0.25 *equiv.*, 207 μmol). The flask was evacuated and backfilled with hydrogen (3x). The resulting mixture was stirred under hydrogen (balloon) for 18 hours at 50 °C. Balloon was refreshed with more hydrogen, and more $Pd(OH)_2$ on carbon (146 mg, 20 wt%, 0.25 *equiv.*, 207 μmol) was added. The resulting mixture was stirred for an additional 8 hours. The reaction mixture was filtered through celite. The filter cake was washed with DCM. The filtrate was

taken, and volatile organics were removed under reduced pressure to give *tert*-butyl (3*R*,4*S*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (495 mg) as a brown solid, which was carried forward without further purification.

LC-MS (ESI): m/z = 542.4 $[M+H]^+$

Preparation of 3-(6-(1-(((3*R*,4*S*)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione, 2HCl

To a solution of *tert*-butyl (3*R*,4*S*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (495 mg, 1 *equiv.*, 914 μmol) in 1,4-dioxane (4.0 mL) was added HCl (4.0 mL, 18 *equiv.*, 16 mmol) (4.0 M in 1,4-dioxane). The reaction mixture was stirred at ambient temperature for 1 hour. Volatile organics were removed under reduced pressure to give 3-(6-(1-(((3*R*,4*S*)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione, 2HCl (635 mg) as a light gray solid, which was carried forward without further purification.

LC-MS (ESI): m/z = 442.3 $[M+H]^+$.

Preparation of 3-(6-(1-(((3*R*,4*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

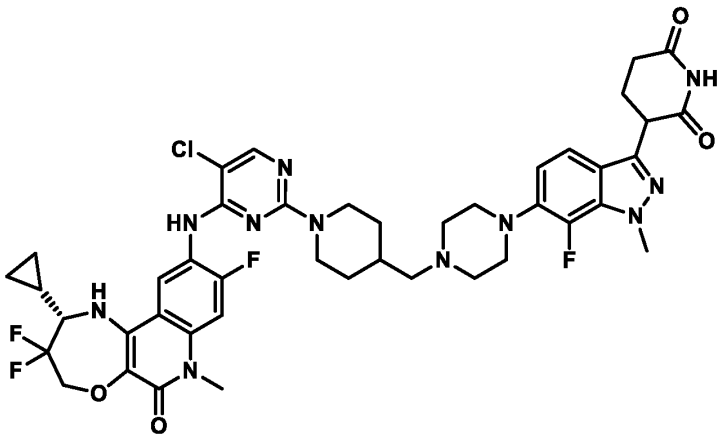
To a solution of (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (465 mg, 1 *equiv.*, 993 μmol) in DMSO (3.25 mL) was added 3-(6-(1-(((3*R*,4*S*)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione, 2HCl (636 mg, 1.245 *equiv.*, 1.24 mmol) and DIPEA (642 mg, 865 μL, 5.0 *equiv.*, 4.96 mmol). The reaction mixture was stirred at 90 °C for 20 hours. The reaction mixture was diluted with DMSO to a total volume of 7.0 mL, filtered, and purified by reverse phase HPLC to give 3-(6-(1-(((3*R*,4*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (405 mg) as an off-white solid.

^{1}H NMR (400 MHz, DMSO-d_6, 300 K) δ (ppm) = 10.87 (s, 1H), 8.80 (s, 1H), 8.18 (s, 1H), 8.03 (s, 1H), 7.75 (br d, J = 9.3 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.46 (d, J = 9.1 Hz, 1H),

7.43 (s, 1H), 7.03 (d, J = 8.5 Hz, 1H), 6.16 (br s, 1H), 4.95 - 4.74 (m, 2H), 4.64 - 4.52 (m, 1H), 4.51 - 4.34 (m, 2H), 4.36 - 4.29 (m, 1H), 3.97 (s, 3H), 3.57 (s, 3H), 3.29 - 3.18 (m, 1H), 3.09 - 2.88 (m, 3H), 2.81 (br t, J = 12.0 Hz, 1H), 2.72 - 2.55 (m, 3H), 2.45 - 2.28 (m, 2H), 2.25 - 1.89 (m, 5H), 1.78 (br s, 4H), 1.54 (br d, J = 10.9 Hz, 1H), 1.45 - 1.27 (m, 2H), 0.78 - 0.65 (m, 1H), 0.60 - 0.46 (m, 2H), 0.42 - 0.30 (m, 1H).

LC-MS (ESI): m/z = 873.5 $[M+H]^+$

Example 100. 3-(6-(4-(((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperazin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 126a)



Preparation of benzyl 4-((1-(*tert*- butoxycarbonyl)piperidin-4-yl)methyl)piperazine-1-carboxylate

To a stirred solution of *tert*- butyl 4-formylpiperidine-1-carboxylate (5.0 g, 23.45 mmol) and benzyl piperazine-1-carboxylate (5.16 g, 23.45 mmol) in THF (100 ml) was added acetic acid (0.5 mL) at 0 °C. The mixture was stirred for 2 h followed by the addition of $NaBH(OAc)_3$ (9.93 g, 46.90 mmol) at 0 °C. The mixture was stirred at room temperature for 16 hours. The reaction mixture was quenched with water (20 mL) and extracted with DCM (30 mL). The organic layer was separated and washed with $NaHCO_3$ solution (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to get a crude product, which was purified by flash column chromatography (100% ethyl acetate) to afford benzyl 4-((1-(*tert*-butoxycarbonyl)piperidin-4-yl)methyl)piperazine-1-carboxylate (6.0 g) as a brown gum

LC-MS (ESI): m/z = 418.43 $[M+H]^+$

Preparation of *tert*-butyl 4-(piperazin-1-ylmethyl)piperidine-1-carboxylate

To a stirred solution of benzyl 4-((1-(*tert*- butoxycarbonyl)piperidin-4-yl)methyl)piperazine-1-carboxylate (4.5 g, 10.79 mmol) in THF (50 mL) at room temperature was added Pd on carbon (10 wt%) (4.5g) under inert atmosphere. The reaction mixture was kept under hydrogen pressure (90 psi) at room temperate and stirred for 16 hours. The reaction mixture was filtered through celite and the filtrate was concentrated under reduced pressure to get *tert*- butyl 4-(piperazin-1-ylmethyl)piperidine-1-carboxylate (1.9 g) as a brown gum

LC-MS (ESI): m/z = 284.30 $[M+H]^+$

Preparation of *tert*-butyl 4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)piperidine-1-carboxylate

A stirred solution of *tert*-butyl 4-(piperazin-1-ylmethyl)piperidine-1-carboxylate (1.9 g, 6.70 mmol) and 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-7-fluoro-1-methyl-1*H*-indazole (3.68 g, 7.37 mmol) in 1,4-dioxane (6.0 mL) was degassed using nitrogen for 15 minutes. To this mixture was added BrettPhos Pd G3 (0.60 g, 0.67 mmol) and NaOtBu (1.93 g, 20.1 mmol). The mixture was stirred at 100 °C for 10 hours. The reaction mixture was filtered through celite, and the filtrate was concentrated under reduced pressure to get a crude product which was purified by flash column chromatography (20-30% ethyl acetate in petroleum ether) to afford *tert*-butyl 4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)piperidine-1-carboxylate (0.65 g) as a brown gum

LC-MS (ESI): m/z = 721.68 $[M+H]^+$

Preparation of *tert*-butyl 4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)piperidine-1-carboxylate

To a stirred solution of *tert*-butyl 4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)piperidine-1-carboxylate (0.65 g, 0.90 mmol) in THF (6.5 mL) was added $Pd(OH)_2$ on carbon (20 wt%) (0.65 g). The mixture was kept under hydrogen pressure (90 psi) at room temperature and stirred for 16 hours. The reaction mixture was filtered through celite, and the filtrate was concentrated under reduced pressure to get *tert*-butyl 4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)piperidine-1-carboxylate (0.3 g) as an off white solid

LC-MS (ESI): m/z = 543.46 $[M+H]^+$

Preparation of 3-(7-fluoro-1-methyl-6-(4-(piperidin-4-ylmethyl)piperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione

To a stirred solution of *tert*-butyl 4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)piperidine-1-carboxylate (0.3 g, 0.55 mmol) in DCM (3.0 ml) was added TFA (3.0 ml) at 0 °C. The reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure to afford 3-(7-fluoro-1-methyl-6-(4-(piperidin-4-ylmethyl)piperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (0.3 g) as a brown solid.

LC-MS (ESI): m/z = 443.40 $[M+H]^+$

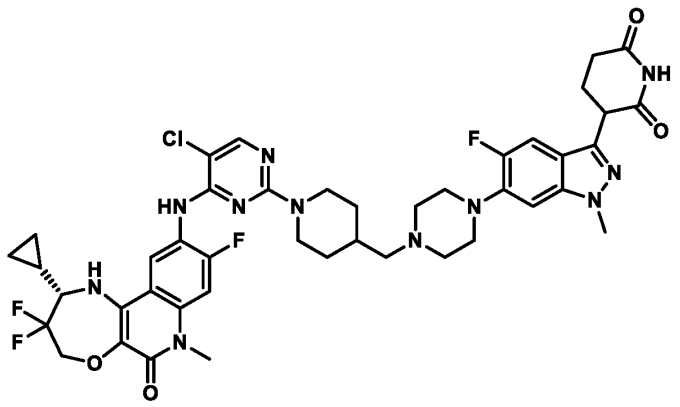
Preparation of 3-(6-(4-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperazin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

To a solution of (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3,9-trifluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (200 mg, 1 *equiv.*, 411 μmol) in DMSO (1.50 mL) was added 3-(7-fluoro-1-methyl-6-(4-(piperidin-4-ylmethyl)piperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione, 3HCl (306 mg, 1.35 *equiv.*, 555 μmol) and DIPEA (266 mg, 358 μL, 5.0 *equiv.*, 2.06 mmol). The reaction mixture was stirred at 90 °C for 20 hours. The reaction mixture was diluted with DMSO to a total volume of 3.5 mL, filtered, and purified by reverse phase HPLC to give 3-(6-(4-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperazin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (163 mg) as a light blue solid.

^{1}H NMR (400 MHz, DMSO-d_6, 300 K) δ = 10.88 (s, 1H), 8.81 (s, 1H), 8.19 (d, J = 8.0Hz, 1H), 8.01 (s, 1H), 7.42 (br d, J = 7.8Hz, 1H), 7.39 (br d, J = 3.9Hz, 1H), 6.96 - 6.84 (m, 1H), 6.44 (br d, J = 2.5Hz, 1H), 4.54 - 4.21 (m, 5H), 4.06 (s, 3H), 3.54 (s, 3H), 3.29 - 3.18 (m, 2H), 3.08 (br s, 4H), 2.76 - 2.54 (m, 7H), 2.39 - 2.27 (m, 1H), 2.23 - 2.09 (m, 3H), 1.82 - 1.57 (m, 3H), 1.38 - 1.25 (m, 1H), 1.05 - 0.85 (m, 2H), 0.77 - 0.65 (m, 1H), 0.51 (br t, J = 5.8Hz, 2H), 0.37 - 0.26 (m, 1H).

LC-MS (ESI): m/z = 892.5 $[M+H]^+$

Example 101. 3-(6-(4-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperazin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 161a)



Preparation of *tert*-butyl 4-((1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-4-yl)methyl)piperazine-1-carboxylate

To a stirred solution of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-5-fluoro-1-methyl-1*H*-indazole (1.50 g, 2.89 mmol) and *tert*-butyl 4-(piperazin-1-ylmethyl)piperidine-1-carboxylate (2.46 g, 8.68 mmol) in dioxane (30 mL) was added t-BuONa (0.83 g, 8.68 mmol). The reaction mixture was purged with N_2 for 15 minutes. To this mixture was added RuPhos-Pd-G3 (0.24 g, 0.29 mmol). The mixture was heated at 100 °C and stirred for 6 hours. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (300 mL), filtered through a celite bed, and washed with DCM (200 mL). The filtrate was concentrated to get a crude product which was purified by flash chromatography (5-10% of ethyl acetate in petroleum ether) to obtain *tert*-butyl 4-((1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-4-yl)methyl)piperazine-1-carboxylate as a pale-yellow semi-solid (0.65 g).

LC-MS (ESI): m/z = 721.66 $[M+H]^+$

Preparation of *tert*-butyl 4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)piperidine-1-carboxylate

To a stirred solution of *tert*-butyl 4-((1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-4-yl)methyl)piperazine-1-carboxylate (0.65 g, 0.90 mmol) in THF (80 mL) was added $Pd(OH)_2$ on carbon (20 wt%) (0.65 g). The mixture was stirred under hydrogen atmosphere (60 psi) at room temperature for 3 hours. The reaction mixture was

diluted with DCM (200 mL), washed with 30% THF:DCM (300 mL), and filtered through a celite bed. The collected filtrate was concentrated under vacuum to obtain a crude product which was triturated with n-pentane to afford *tert*-butyl 4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)piperidine-1-carboxylate (0.46 g) as a pale-brown semi-solid.

LC-MS (ESI): m/z = 543.56 $[M+H]^+$

Preparation of 3-(5-fluoro-1-methyl-6-(4-(piperidin-4-ylmethyl)piperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione

To a stirred solution of *tert*-butyl 4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)piperidine-1-carboxylate (0.46 g, 0.85 mmol) in DCM (5 mL) at 0 °C, was added TFA (3.68 mL). The mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure to afford crude product which was triturated with n-pentane to afford 3-(5-fluoro-1-methyl-6-(4-(piperidin-4-ylmethyl)piperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (0.45 g) as a pale brown semi-solid.

LC-MS (ESI): m/z = 443.40 $[M+H]^+$

Preparation of 3-(6-(4-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperazin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

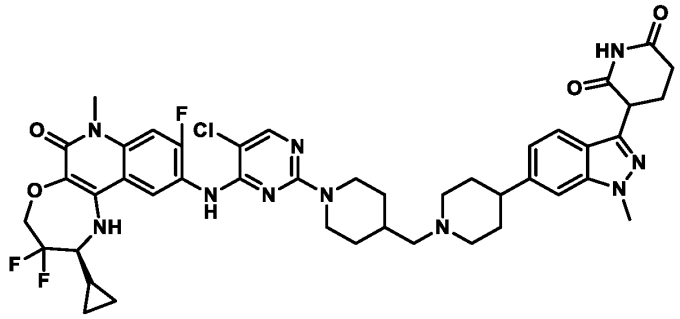
To a solution of (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3,9-trifluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (135 mg, 1 *equiv.*, 278 μmol) in DMSO (0.75 mL) was added 3-(5-fluoro-1-methyl-6-(4-(piperidin-4-ylmethyl)piperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione, 3HCl (230 mg, 1.5 *equiv.*, 416 μmol) and DIPEA (179 mg, 242 μL, 5.0 *equiv.*, 1.39 mmol). The reaction mixture was stirred at 90 °C for 20 hours. The reaction mixture was diluted with DMSO to a total volume of 3.0 mL, filtered, and purified by reverse phase HPLC to give 3-(6-(4-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperazin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (120 mg) as a tan solid.

^{1}H NMR (400 MHz, DMSO-d_6, 300 K) δ (ppm) = 10.84 (s, 1H), 8.81 (s, 1H), 8.19 (d, J = 8.0Hz, 1H), 8.01 (s, 1H), 7.48 - 7.38 (m, 2H), 7.08 (d, J = 7.0Hz, 1H), 6.44 (br d, J = 2.8Hz,

1H), 4.51 - 4.21 (m, 5H), 3.94 (s, 3H), 3.54 (s, 3H), 3.29 - 3.18 (m, 2H), 3.05 (br s, 4H), 2.75 - 2.55 (m, 7H), 2.40 - 2.28 (m, 1H), 2.24 - 2.06 (m, 3H), 1.82 - 1.58 (m, 3H), 1.37 - 1.25 (m, 1H), 1.04 - 0.86 (m, 2H), 0.77 - 0.64 (m, 1H), 0.58 - 0.45 (m, 2H), 0.38 - 0.27 (m, 1H).

LC-MS (ESI): m/z = 892.5 $[M+H]^+$.

Example 102. 3-(6-(1-((1-(5-Chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 163a)



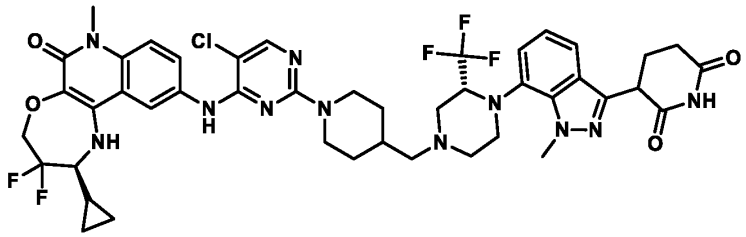
Preparation of 3-(6-(1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

(*S*)-2-Cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3,9-trifluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (synthesis described herein, 29 mg, 1 *equiv.*, 59 μmol) and 3-(1-methyl-6-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (See Table P6) (synthesis described herein, 30 mg, 1.2 *equiv.*, 71 μmol) were combined in DMSO (1.0 mL). To this mixture was added DIPEA (38 mg, 51 μL, 5.00 *equiv.*, 0.30 mmol) and CsF (27 mg, 3.00 *equiv.*, 0.18 mmol). The reaction was stirred at 80 °C for 16 hours. The reaction was then diluted with an additional 1 mL of DMSO, filtered, and directly purified by preparative reverse phase HPLC (MeCN/water, each with 0.1% formic acid) to afford 3-(6-(1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (27.1 mg).

LC-MS (ESI): m/z = 437.4 $[M+2H]^{2+}$.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.25 - 0.38 (m, 1 H) 0.45 - 0.59 (m, 2 H) 0.66 - 0.76 (m, 1 H) 0.89 - 1.04 (m, 2 H) 1.28 - 1.37 (m, 1 H) 1.59 - 1.88 (m, 8 H) 1.93 - 2.08 (m, 2 H) 2.09 - 2.23 (m, 3 H) 2.59 - 2.75 (m, 5 H) 2.88 - 3.05 (m, 2 H) 3.17 - 3.24 (m, 1 H) 3.55 (s, 3 H) 3.96 (s, 3 H) 4.24 - 4.52 (m, 5 H) 6.36 - 6.49 (m, 1 H) 7.02 (d, *J*=8.25 Hz, 1 H) 7.35 - 7.49 (m, 2 H) 7.60 (d, *J*=8.13 Hz, 1 H) 8.01 (s, 1 H) 8.20 (d, *J*=8.26 Hz, 1 H) 8.81 (s, 1 H) 10.82 - 10.93 (m, 1 H).

Example 103. 3-(7-((*R*)-4-((1-(5-Chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)-2-(trifluoromethyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 103b)



Preparation of *tert*-butyl (*R*)-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-7-yl)-3-(trifluoromethyl)piperazine-1-carboxylate

3-(2,6-Bis(benzyloxy)pyridin-3-yl)-7-bromo-1-methyl-1*H*-indazole (see, e.g. WO 2021/262812) (500 mg, 1 *equiv.*, 999 μmol), *tert*-butyl (*R*)-3-(trifluoromethyl)piperazine-1-carboxylate (305 mg, 1.2 *equiv.*, 1.20 mmol), and RuPhos-Pd-G3 (83.6 mg, 0.1 *equiv.*, 99.9 μmol) were dissolved in 1,4-dioxane (9.0 mL). t-BuONa was added (288 mg, 1.50 mL, 2.0 M, 3 *equiv.*, 3.00 mmol) as a solution in THF. The reaction was stirred at 80 °C for 45 minutes using microwave heating. Afterwards, the reaction mixture was diluted with ethyl acetate (150 mL), water (25 mL), and brine (25 mL). They layers were separated. The organics were dried over anhydrous magnesium sulfate, filtered, and concentrated to an oil that was purified by silica gel chromatography (heptane/ethyl acetate) to afford *tert*-butyl (*R*)-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-7-yl)-3-(trifluoromethyl)piperazine-1-carboxylate (438 mg).

LC-MS (ESI): m/z = 674.2 $[M+H]^+$.

Preparation of *tert*-butyl (3*R*)-4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-7-yl)-3-(trifluoromethyl)piperazine-1-carboxylate

To a solution containing *tert*-butyl (*R*)-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-7-yl)-3-(trifluoromethyl)piperazine-1-carboxylate (438 mg, 1 *equiv.*, 650 μmol) and ethyl acetate (30.0 mL) was added Pd on carbon (346 mg, 10 wt%, 0.5 *equiv.*, 325 μmol) then evacuated and backfilled reaction with hydrogen (3x). The reaction mixture was stirred under a hydrogen atmosphere for 120 hours. Filtered reaction through a pad of Celite and concentrated filtrate to afford *tert*-butyl (3*R*)-4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-7-yl)-3-(trifluoromethyl)piperazine-1-carboxylate assuming theoretical yield (322 mg, 650 μmol).

LC-MS (ESI): m/z = 496.3 $[M+H]^+$.

Preparation of 3-(1-methyl-7-((*R*)-2-(trifluoromethyl)piperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione hydrochloride

To a solution containing *tert*-butyl (3*R*)-4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-7-yl)-3-(trifluoromethyl)piperazine-1-carboxylate (322 mg, 1 *equiv.*, 650 μmol) in DCM (10 mL) was added 4N HCl in 1,4-dioxane (711 mg, 4.87 mL, 30 *equiv.*, 19.5 mmol). The mixture was stirred at ambient temperature for 48 hours. The mixture was concentrated to dryness under reduced pressure and triturated with diethyl ether to afford 3-(1-methyl-7-((*R*)-2-(trifluoromethyl)piperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione hydrochloride (260 mg).

LC-MS (ESI): m/z = 396.2 $[M+H]^+$.

Preparation of 3-(7-((*R*)-4-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)-2-(trifluoromethyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

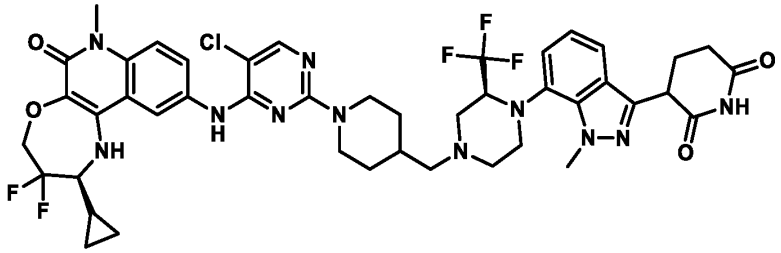
(*S*)-1-(5-chloro-4-((2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidine-4-carbaldehyde (64 mg, 1 *equiv.*, 0.12 mmol) and 3-(1-methyl-7-((*R*)-2-(trifluoromethyl)piperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione hydrochloride (61 mg, 1.2 *equiv.*, 0.14 mmol) were dissolved in a mixture of THF (3.0 mL) and DMF (0.5 mL). To this mixture was added potassium acetate (58 mg, 5.0 *equiv.*, 0.59 mmol), and the resulting mixture was stirred for a few minutes at ambient temperature. Sodium triacetoxyborohydride (50 mg, 2.0 *equiv.*, 0.23 mmol) was then added, and the mixture was stirred at ambient temperature for 16 hours. The THF was removed under reduced pressure, and the resulting

residue purified by preparative reverse phase HPLC (MeCN/water, both with 0.1% formic acid) to afford 3-(7-((*R*)-4-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)-2-(trifluoromethyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (35 mg).

LC-MS (ESI): m/z = 462.8 $[M+2H]^{2+}$.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.29 - 0.41 (m, 1 H) 0.47 - 0.57 (m, 2 H) 0.66 - 0.78 (m, 1 H) 0.97 - 1.11 (m, 2 H) 1.28 - 1.41 (m, 1 H) 1.67 - 1.85 (m, 3 H) 2.33 (br s, 5 H) 2.61 - 2.70 (m, 3 H) 2.76 - 2.85 (m, 2 H) 2.89 - 3.10 (m, 3 H) 3.10 - 3.22 (m, 2 H) 3.57 (s, 3 H) 4.23 (br s, 3 H) 4.31 - 4.38 (m, 2 H) 4.39 - 4.52 (m, 4 H) 6.13 - 6.24 (m, 1 H) 6.99 - 7.09 (m, 1 H) 7.35 - 7.55 (m, 3 H) 7.73 (dd, *J*=8.94, 1.69 Hz, 1 H) 8.03 (s, 1 H) 8.15 - 8.25 (m, 2 H) 8.78 (s, 1 H) 10.69 - 11.09 (m, 1 H).

Example 104. 3-(7-((*S*)-4-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)-2-(trifluoromethyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 103a)



Preparation of *tert*-butyl (*S*)-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-7-yl)-3-(trifluoromethyl)piperazine-1-carboxylate

To a solution containing 3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-bromo-1-methyl-1*H*-indazole (see, e.g. WO 2021/262812) (500 mg, 1 *equiv.*, 999 μmol), *tert*-butyl (*S*)-3-(trifluoromethyl)piperazine-1-carboxylate (305 mg, 1.2 *equiv.*, 1.20 mmol), and RuPhos-Pd-G3 (83.6 mg, 0.1 *equiv.*, 99.9 μmol) in 1,4-dioxane (9.0 mL) was added t-BuONa (288 mg, 1.50 mL, 2.0 M, 3 *equiv.*, 3.00 mmol) as a solution in THF. The reaction was heated at 80 °C and stirred for 1 hour using microwave heating. The reaction was then diluted with ethyl acetate (100 mL), water (15 mL), and brine (10 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated to an oil that was purified by silica gel chromatography (heptane/ethyl acetate) to afford *tert*-butyl (*S*)-4-(3-(2,6-

bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-7-yl)-3-(trifluoromethyl)piperazine-1-carboxylate (262 mg).

LC-MS (ESI): m/z = 674.2 $[M+H]^+$.

Preparation of *tert*-butyl (3*S*)-4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-7-yl)-3-(trifluoromethyl)piperazine-1-carboxylate

To a solution containing *tert*-butyl (*S*)-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-7-yl)-3-(trifluoromethyl)piperazine-1-carboxylate (438 mg, 1 *equiv.*, 650 μmol) in ethyl acetate (30.0 mL) was added Pd on carbon (346 mg, 10 wt%, 0.5 *equiv.*, 325 μmol) then evacuated and backfilled reaction with hydrogen (3x). The reaction mixture was stirred under a hydrogen atmosphere for 48 hours. The mixture was filtered through a pad of Celite and the filtrate was concentrated to afford *tert*-butyl (3*S*)-4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-7-yl)-3-(trifluoromethyl)piperazine-1-carboxylate assuming theoretical yield (322 mg, 650 μmol).

LC-MS (ESI): m/z = 496.3 $[M+H]^+$.

Preparation of 3-(1-methyl-7-((*S*)-2-(trifluoromethyl)piperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione dihydrochloride

To a solution containing *tert*-butyl (3*S*)-4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-7-yl)-3-(trifluoromethyl)piperazine-1-carboxylate (332 mg, 1 *equiv*, 670 μmol) in DCM (10.0 mL) was added HCl in 1,4-dioxane (1.22 g, 8.38 mL, 4.0 M, 50 *equiv.*, 33.5 mmol). The mixture was stirred at ambient temperature for 16 hours. The mixture was concentrated to dryness, triturated with diethyl ether/hexanes, and re-evaporated to afford 3-(1-methyl-7-((*S*)-2-(trifluoromethyl)piperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione dihydrochloride (318 mg).

LC-MS (ESI): m/z = 396.2 $[M+H]^+$.

Preparation of (*S*)-10-((2-(4-(1,3-dioxolan-2-yl)piperidin-1-yl)-5-chloropyrimidin-4-yl)amino)-2-cyclopropyl-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinoline-6(7*H*)-one

To a stirred solution of (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (211.0 mg, 450.6 μmol, 1 *equiv.*) and 4-(1,3-dioxolan-2-yl)piperidine, HCl (174.5 mg, 901.2 μmol, 2.0 *equiv.*) in DMSO was added DIPEA (232.9 mg, 314 μL, 1.802 mmol, 4.00 *equiv.*). The mixture

was stirred at 60 °C for 2 hours. The mixture was then diluted with ethyl acetate and, washed with H_2O, and extracted again with ethyl acetate. The organic layer was concentrated under reduced pressure to afford (*S*)-10-((2-(4-(1,3-dioxolan-2-yl)piperidin-1-yl)-5-chloropyrimidin-4-yl)amino)-2-cyclopropyl-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinoline-6(7*H*)-one (206.1 mg).

LC-MS (ESI): m/z = 589 $[M+H]^+$

Preparation of (*S*)-1-(5-chloro-4-((2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidine-4-carbaldehyde

A solution of (*S*)-10-((2-(4-(1,3-dioxolan-2-yl)piperidin-1-yl)-5-chloropyrimidin-4-yl)amino)-2-cyclopropyl-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinoline-6(7*H*)-one (206.1 mg, 349.9 µmol, 1 *equiv.*) in formic acid (2 mL) was stirred at heated at 80 °C for 2 hours. The mixture was concentrated under reduced pressure to afford (*S*)-1-(5-chloro-4-((2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidine-4-carbaldehyde (205.3 mg).

LC-MS (ESI): m/z = 545.1 $[M+H]^+$

Preparation of 3-(7-((*S*)-4-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)-2-(trifluoromethyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

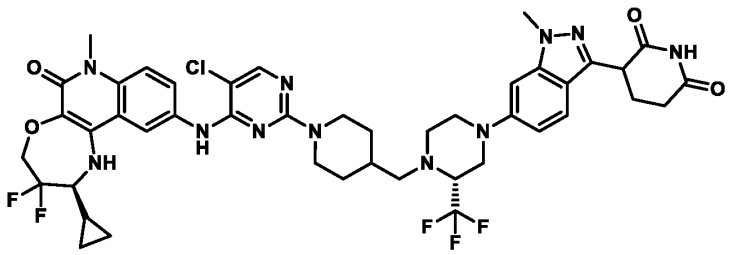
Combined (*S*)-1-(5-chloro-4-((2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidine-4-carbaldehyde (64 mg, 1 *equiv.*, 0.12 mmol) and 3-(1-methyl-7-((*S*)-2-(trifluoromethyl)piperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione dihydrochloride (56 mg, 1.2 *equiv.*, 0.14 mmol) in a mixture of THF (3.0 mL) and DMF (0.5 mL). To this mixture was added potassium acetate (58 mg, 5.0 *equiv.*, 0.59 mmol). The mixture was stirred for ~10 minutes at ambient temperature. To this mixture was added sodium triacetoxyborohydride (50 mg, 2.0 *equiv.*, 0.23 mmol) and the resulting mixture was stirred at ambient temperature for 16 hours. The THF was removed under reduced pressure and the resulting residue purified by preparative reverse phase HPLC (MeCN/water, both with 0.1% formic acid) to afford 3-(7-((*S*)-4-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-

hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)-2-(trifluoromethyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (4.7 mg).

LC-MS (ESI): m/z = 462.8 $[M+2H]^{2+}$.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.29 - 0.41 (m, 1 H) 0.47 - 0.57 (m, 2 H) 0.66 - 0.78 (m, 1 H) 0.97 - 1.11 (m, 2 H) 1.28 - 1.41 (m, 1 H) 1.67 - 1.85 (m, 3 H) 2.33 (br s, 5 H) 2.61 - 2.70 (m, 3 H) 2.76 - 2.85 (m, 2 H) 2.89 - 3.10 (m, 3 H) 3.10 - 3.22 (m, 2 H) 3.57 (s, 3 H) 4.23 (br s, 3 H) 4.31 - 4.38 (m, 2 H) 4.39 - 4.52 (m, 4 H) 6.13 - 6.24 (m, 1 H) 6.99 - 7.09 (m, 1 H) 7.35 - 7.55 (m, 3 H) 7.73 (dd, *J*=8.94, 1.69 Hz, 1 H) 8.03 (s, 1 H) 8.15 - 8.25 (m, 2 H) 8.78 (s, 1 H) 10.69 - 11.09 (m, 1 H).

Example 105. 3-(6-((*R*)-4-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)-3-(trifluoromethyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 166b)



Preparation of *tert*-butyl (*R*)-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)-2-(trifluoromethyl)piperazine-1-carboxylate

A mixture of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-1-methyl-1*H*-indazole (prepared using published methods, e.g., in International Application Publication No. WO 2021/127586) (650 mg, 1.30 mmol, 1.0 *equiv.*), *tert*-butyl (*R*)-2-(trifluoromethyl)piperazine-1-carboxylate (495.40 mg, 1.95 mmol, 1.5 *equiv.*), $Pd_2(dba)_3$ (118.95 mg, 129.90 µmol, 0.1 *equiv.*), RuPhos (121.23 mg, 259.80 µmol, 0.2 *equiv.*), and cesium carbonate (1.27 g, 3.90 mmol, 3.0 *equiv.*) in toluene (10 mL) was purged with N_2. The resulting mixture was stirred at 100 °C for 16 hours under N_2 atmosphere and then cooled, filtered, and concentrated under pressure to give a residue that was purified by silica gel chromatography (ethyl acetate/hexanes) to afford *tert*-butyl (*R*)-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)-2-(trifluoromethyl)piperazine-1-carboxylate (700 mg).

LC-MS (ESI): m/z = 674.3 $[M+H]^+$.

Preparation of *tert*-butyl (2R)-4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)-2-(trifluoromethyl)piperazine-1-carboxylate

To a solution of *tert*-butyl (*R*)-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)-2-(trifluoromethyl)piperazine-1-carboxylate (700 mg, 1.04 mmol, 1.0 *equiv.*) in THF (10 mL) and EtOH (10 mL) was added Pd on carbon (10 wt%, 350 mg, 328.89 μmol, 0.3 *equiv.*) and $Pd(OH)_2$ on carbon (20 wt%, 350 mg, 0.50 mmol, 0.5 *equiv.*). The suspension was evacuated and purged with H_2 three times. The mixture was stirred under H_2 at 40 °C for 16 hours. The reaction mixture was filtered, and the filter cake was washed with THF (100 mL). The filtrate was concentrated under reduced pressure to afford *tert*-butyl (2R)-4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)-2-(trifluoromethyl)piperazine-1-carboxylate (600 mg, crude).

LC-MS (ESI): m/z = 496.4 $[M+H]^+$.

Preparation of 3-(1-methyl-6-((*R*)-3-(trifluoromethyl)piperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione hydrochloride

A mixture of *tert*-butyl (2R)-4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)-2-(trifluoromethyl)piperazine-1-carboxylate (600 mg, 1.21 mmol, 1.0 *equiv.*) in a solution of 4 N HCl in 1,4-dioxane (10 mL, 40 mmol, 33.3 *equiv.*) was stirred at 25 °C for 16 hours. The reaction mixture was filtered to afford 3-(1-methyl-6-((*R*)-3-(trifluoromethyl)piperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione hydrochloride (400 mg, crude).

LC-MS (ESI): m/z = 396.1 $[M+H]^+$.

Preparation of 3-(6-((*R*)-4-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)-3-(trifluoromethyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

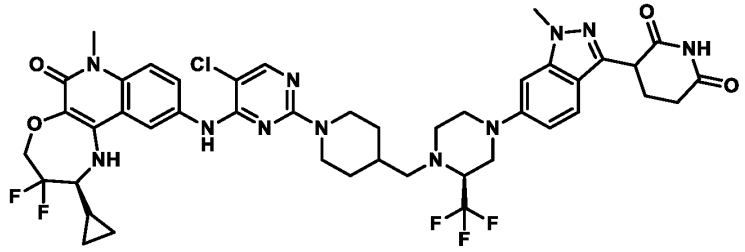
Combined (*S*)-1-(5-chloro-4-((2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidine-4-carbaldehyde (64 mg, 1 *equiv*, 0.12 mmol) and 3-(1-methyl-6-((*R*)-3-(trifluoromethyl)piperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione hydrochloride (61 mg, 1.2 *equiv.*, 0.14 mmol) in a mixture of THF (3.0 mL) and DMF (0.5 mL). To this mixture was added potassium acetate (58 mg, 5.0 *equiv.*, 0.59 mmol) and sodium triacetoxyborohydride (50 mg, 2.0 *equiv.*, 0.23 mmol). The resulting reaction mixture was stirred for 16 hours at ambient

temperature. To this mixture was added an additional portion of sodium triacetoxyborohydride (50 mg, 2.0 *equiv.*, 0.23 mmol) and the resulting mixture was stirred for 16 hours at ambient temperature. THF was removed under a stream of nitrogen and the resulting residue was purified by preparative reverse phase HPLC (MeCN/water, both with 0.1% formic acid) to afford 3-(6-((*R*)-4-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)-3-(trifluoromethyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (30 mg).

LC-MS (ESI): m/z = 462.9 $[M+2H]^{2+}$.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.87 - 10.81 (m, 1H), 8.76 (s, 1H), 8.18 (d, J = 1.9 Hz, 1H), 8.03 (s, 1H), 7.74 (dd, J = 1.9, 9.1 Hz, 1H), 7.52 (d, J = 8.8 Hz, 1H), 7.44 (d, J = 9.3 Hz, 1H), 6.89 - 6.79 (m, 2H), 6.21 - 6.14 (m, 1H), 4.54 - 4.23 (m, 5H), 3.89 (s, 3H), 3.72 - 3.64 (m, 1H), 3.56 (s, 4H), 3.48 - 3.41 (m, 1H), 3.25 - 3.16 (m, 2H), 3.06 (br t, J = 8.9 Hz, 2H), 2.85 - 2.73 (m, 3H), 2.65 - 2.55 (m, 3H), 2.30 - 2.23 (m, 1H), 2.20 - 2.13 (m, 1H), 1.84 - 1.66 (m, 4H), 1.37 - 1.30 (m, 1H), 1.08 - 0.95 (m, 2H), 0.75 - 0.66 (m, 1H), 0.56 - 0.48 (m, 2H), 0.40 - 0.31 (m, 1H).

Example 106. 3-(6-((*S*)-4-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)-3-(trifluoromethyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 166a)



Preparation of *tert*-butyl (*S*)-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)-2-(trifluoromethyl)piperazine-1-carboxylate

A mixture of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-1-methyl-1*H*-indazole (prepared using published methods, e.g., in International Application Publication No. WO 2021/127586) (1.3 g, 2.60 mmol, 1.0 *equiv.*), *tert*-butyl (*S*)-2-(trifluoromethyl)piperazine-1-carboxylate (990.81 mg, 3.90 mmol, 1.5 *equiv.*), $Pd_2(dba)_3$ (237.90 mg, 259.80 μmol, 0.1 *equiv.*), RuPhos (242.47 mg, 519.60 μmol, 0.2 *equiv.*), and cesium carbonate (2.54 g, 7.79

mmol, 3.0 *equiv.*) in toluene (20 mL) was purged with N_2. The resulting mixture was stirred at 100 °C for 16 hours under N_2 atmosphere and then cooled, filtered, and concentrated under pressure to give a residue that was silica gel chromatography (ethyl acetate/hexanes) to afford *tert*-butyl (*S*)-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)-2-(trifluoromethyl)piperazine-1-carboxylate (1.1 g).

LC-MS (ESI): m/z = 674.3 $[M+H]^+$.

Preparation of *tert*-butyl (2*S*)-4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)-2-(trifluoromethyl)piperazine-1-carboxylate

To a solution of *tert*-butyl (*S*)-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)-2-(trifluoromethyl)piperazine-1-carboxylate (290 mg, 430.44 μmol 1.0 *equiv.*) in THF (5 mL) and EtOH (5 mL) was added Pd on carbon (10 wt%, 150 mg, 140.95 μmol, 0.3 *equiv.*) and $Pd(OH)_2$ on carbon (20 wt%, 150 mg, 0.215 mmol, 0.5 *equiv.*). The suspension was evacuated and purged with H_2 three times. The mixture was stirred under H_2 at 40 °C for 16 hours. The reaction mixture was filtered, and the filter cake was washed with THF (50 mL). The filtrate was concentrated under reduced pressure to afford *tert*-butyl (2*S*)-4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)-2-(trifluoromethyl)piperazine-1-carboxylate (600 mg, crude).

LC-MS (ESI): m/z = 496.3 $[M+H]^+$.

Preparation of 3-(1-methyl-6-((*S*)-3-(trifluoromethyl)piperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione hydrochloride

A mixture of *tert*-butyl (2*S*)-4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)-2-(trifluoromethyl)piperazine-1-carboxylate (260.00 mg, 524.73 μmol, 1.0 *equiv.*) in a solution of 4 N HCl in dioxane (10 mL, 40 mmol, 80 *equiv.*) was stirred at 25 °C for 16 hours. The reaction mixture was filtered to afford 3-(1-methyl-6-((*S*)-3-(trifluoromethyl)piperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione hydrochloride (170 mg, crude).

LC-MS (ESI): m/z = 396.2 $[M+H]^+$.

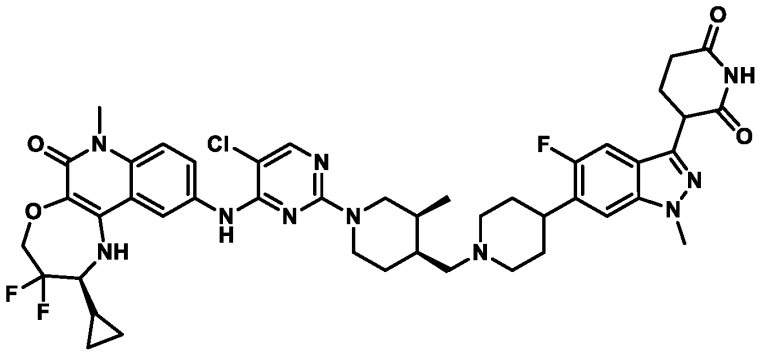
Preparation of 3-(6-((*S*)-4-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)-3-(trifluoromethyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

Combined (*S*)-1-(5-chloro-4-((2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidine-4-carbaldehyde (64 mg, 1 *equiv*, 0.12 mmol) and 3-(1-methyl-6-((*S*)-3-(trifluoromethyl)piperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione hydrochloride (61 mg, 1.2 *equiv.*, 0.14 mmol) in a mixture of THF (3.0 mL) and DMF (0.5 mL). To this mixture was added potassium acetate (58 mg, 5.0 *equiv.*, 0.59 mmol) and sodium triacetoxyborohydride (50 mg, 2.0 *equiv.*, 0.23 mmol). The resulting mixture was stirred for 40 hours at ambient temperature. THF was removed under a stream of nitrogen and the resulting residue was purified by preparative reverse phase HPLC (MeCN/water, both with 0.1% formic acid) to afford 3-(6-((*S*)-4-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)-3-(trifluoromethyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (21.2 mg).

LC-MS (ESI): m/z = 462.8 $[M+2H]^{2+}$.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.31 - 0.40 (m, 1 H) 0.47 - 0.57 (m, 2 H) 0.67 - 0.76 (m, 1 H) 0.95 - 1.09 (m, 2 H) 1.29 - 1.37 (m, 1 H) 1.67 - 1.83 (m, 3 H) 2.11 - 2.20 (m, 1 H) 2.25 - 2.31 (m, 1 H) 2.55 - 2.64 (m, 4 H) 2.74 - 2.85 (m, 3 H) 3.00 - 3.11 (m, 2 H) 3.15 - 3.26 (m, 2 H) 3.46 (br d, *J*=1.38 Hz, 1 H) 3.56 (s, 4 H) 3.64 - 3.72 (m, 1 H) 3.89 (s, 3 H) 4.23 - 4.51 (m, 5 H) 6.16 - 6.21 (m, 1 H) 6.80 - 6.89 (m, 2 H) 7.40 - 7.46 (m, 1 H) 7.50 - 7.55 (m, 1 H) 7.71 - 7.76 (m, 1 H) 8.03 (s, 1 H) 8.18 (d, *J*=2.00 Hz, 1 H) 8.76 (s, 1 H) 10.84 (s, 1 H).

Example 107. 3-(6-(1-(((3*S*,4*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-*c*]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 121c)



Preparation of *tert*-butyl (3*S*,4*S*)-4-(hydroxymethyl)-3-methylpiperidine-1-carboxylate

A room-temperature solution of (3*S*,4*S*)-1-(*tert*-butoxycarbonyl)-3-methylpiperidine-4-carboxylic acid (1.290 g, 5.302 mmol) in THF (10.0 mL) was treated with borane-methyl sulfide complex (4.833 g, 6.03 mL, 63.63 mmol) dropwise over 1 minute under a stream of $N_{2(g)}$. The reaction mixture was stirred at room temperature for 1 hour and then slowly treated with MeOH (10.0 mL) over 20 minutes. The reaction mixture was warmed to 50 °C for 2 hours. The reaction mixture was diluted with DMSO (1.50 mL), concentrated under reduced pressure to a colorless DMSO solution, then purified by reverse phase ISCO (30-60% MeCN-H_2O [+0.1% formic acid]) to afford *tert*-butyl (3*S*,4*S*)-4-(hydroxymethyl)-3-methylpiperidine-1-carboxylate (1.039 g).

LC-MS (ESI): m/z = 174.1 $[M+H]^+$.

Preparation of *tert*-butyl (3*S*,4*S*)-4-formyl-3-methylpiperidine-1-carboxylate

A solution of oxalyl chloride (789 µL, 9.02 mmol) in DCM (20.0 mL) was cooled to -78 °C and then treated dropwise with DMSO (1.28 mL, 18.0 mmol). The reaction mixture was stirred at -78 °C for 45 minutes and then treated with a solution of *tert*-butyl (3*S*,4*S*)-4-(hydroxymethyl)-3-methylpiperidine-1-carboxylate (1.03 g, 4.51 mmol) in DCM (18.0 mL) dropwise over 4 minutes. The reaction mixture was stirred at -78 °C for 1 hour, treated with TEA (3.77 mL, 27.05 mmol), and warmed to room temperature for 30 minutes. The volatiles were removed under reduced pressure, and then the residue was partitioned between water and DCM. The aqueous layer was extracted twice more with DCM. The pooled organics were dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford a beige residue, which was dissolved in DCM, added to a RediSep dryloader, and purified by ISCO: 0-30% ethyl acetate/heptane to afford *tert*-butyl (3*S*,4*S*)-4-formyl-3-methylpiperidine-1-carboxylate (282 mg) as a white foam.

LC-MS (ESI): m/z = 172.1 $[M+H]^+$.

Preparation of *tert*-butyl (3*S*,4*S*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate

A mixture of *tert*-butyl (3*S*,4*S*)-4-formyl-3-methylpiperidine-1-carboxylate (281 mg, 1.24 mmol) and 3-[5-fluoro-1-methyl-6-(4-piperidyl)indazol-3-yl]piperidine-2,6-dione (see Table P6) (565 mg, 1.48 mmol) in THF (6.00 mL) and DMF (1.00 mL) was stirred at room temperature for 25 minutes. The mixture was treated with $NaBH(OAc)_3$ (407 mg, 1.92 mmol),

and the resulting reaction mixture was stirred at room temperature for 2.5 hours. The volatiles were removed under reduced pressure, and the residue was partitioned between DCM and saturated aqueous ammonium chloride. The aqueous layer was extracted twice more with DCM, and the pooled organics were dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford a crude residue, which was purified by column chromatography (0-50-100% (3:1 EtOAc/EtOH)/heptane) to afford *tert*-butyl (3*S*,4*S*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate (375 mg).

LC-MS (ESI): m/z = 556.4 $[M+H]^+$.

Preparation of 3-(5-fluoro-1-methyl-6-(1-(((3*S*,4*S*)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione dihydrochloride

A solution of *tert*-butyl (3*S*,4*S*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate (350 mg, 630 μmol) in 1,4-dioxane (3.00 mL) was treated with HCl (4.0 M in 1,4-dioxane) (3.00 mL, 12.0 mmol). The resulting mixture was stirred under a blanket of $N_{2(g)}$ at room temperature for 5 hours. The volatiles were removed under reduced pressure, and the resulting white solid was suspended in DCM and again concentrated under reduced pressure to afford 3-(5-fluoro-1-methyl-6-(1-(((3*S*,4*S*)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione dihydrochloride (333 mg) as a white solid.

LC-MS (ESI): m/z = 456.3 $[M+H]^+$.

Preparation of 3-(6-(1-(((3*S*,4*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-*c*]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

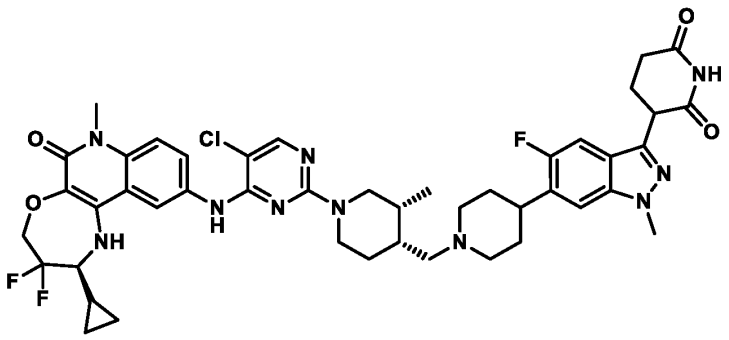
A mixture of (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (415 mg, 1.41 *equiv.*, 886 μmol), 3-(5-fluoro-1-methyl-6-(1-(((3*S*,4*S*)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione dihydrochloride (333 mg, 630 μmol), and CsF (316 mg, 2.08 mmol) in DMSO (4.00 mL) was treated with DIPEA (439 μL, 2.52 mmol). The resulting mixture was warmed to 80 °C for 15 hours. The reaction mixture was then cooled to room temperature, filtered, and purified by prep-HPLC to afford 3-(6-(1-(((3*S*,4*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-

[1,4]oxazepino[2,3-*c*]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (429 mg) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.86 (s, 1H), 8.72 (s, 1H), 8.14 (s, 1H), 8.00 (s, 1H), 7.77 (d, J = 9.1 Hz, 1H), 7.55 (d, J = 5.9 Hz, 1H), 7.47 (d, J = 5.4 Hz, 1H), 7.45 (d, J = 3.8 Hz, 1H), 6.17 (s, 1H), 4.52 – 4.19 (m, 4H), 3.99 (s, 3H), 3.57 (s, 3H), 3.29 – 3.16 (m, 2H), 3.07 – 2.92 (m, 3H), 2.91 – 2.79 (m, 2H), 2.74 – 2.55 (m, 2H), 2.43 – 2.29 (m, 2H), 2.26 – 2.10 (m, 3H), 2.08 – 1.99 (m, 2H), 1.96 – 1.87 (m, 2H), 1.86 – 1.74 (m, 4H), 1.45 – 1.28 (m, 2H), 0.74 (d, J = 6.5 Hz, 3H), 0.72 – 0.68 (m, 1H), 0.57 – 0.46 (m, 2H), 0.40 – 0.30 (m, 1H).

LC-MS (ESI): m/z = 887.6 $[M+H]^+$.

Example 108. 3-(6-(1-(((3*R*,4*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-*c*]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 121b)



Preparation of *tert*-butyl (3*R*,4*R*)-4-(hydroxymethyl)-3-methylpiperidine-1-carboxylate

A room temperature solution of (3*R*,4*R*)-1-(*tert*-butoxycarbonyl)-3-methylpiperidine-4-carboxylic acid (2.542 g, 10.45 mmol) in THF (18.0 mL) was treated with borane-methyl sulfide complex (11.9 mL, 125 mmol) dropwise over 1 minute under a stream of $N_{2(g)}$. The reaction mixture was stirred at room temperature for 80 minutes, and then treated with MeOH (20.0 mL, 494 mmol) slowly over 4 minutes. The resulting reaction mixture was warmed to 50 °C for 2 hours. The mixture was then cooled to room temperature and diluted with DMSO (1.50 mL). The resulting solution was concentrated under reduced pressure to a colorless DMSO solution and purified by reverse phase ISCO (25-60% MeCN-H_2O [+0.1% formic

acid]) to afford *tert*-butyl (3*R*,4*R*)-4-(hydroxymethyl)-3-methylpiperidine-1-carboxylate (2.215 g) as a white solid.

LC-MS (ESI): m/z = 174.1 $[M+H]^+$.

Preparation of *tert*-butyl (3*R*,4*R*)-4-formyl-3-methylpiperidine-1-carboxylate

A solution of oxalyl chloride (950 μL, 10.9 mmol) in DCM (29.0 mL) was cooled to -78 °C and then treated dropwise with DMSO (1.54 mL, 21.7 mmol). The reaction mixture was stirred at -78 °C for 30 minutes, and then treated with a solution of *tert*-butyl (3*R*,4*R*)-4-(hydroxymethyl)-3-methylpiperidine-1-carboxylate (1.24 g, 5.425 mmol) in DCM (25.0 mL) dropwise over 10 minutes. The reaction mixture was stirred at -78 °C for 1 hour, then treated with TEA (4.54 mL, 32.6 mmol) dropwise over 7 minutes. Afterwards, the mixture was warmed to room temperature for 45 minutes. Water (40 mL) was added, and the layers separated. The organic layer was extracted with DCM (40 mL each). The pooled organics were washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was dissolved in DCM and purified by ISCO (0-30% EtOAc/heptane) to afford *tert*-butyl (3*R*,4*R*)-4-formyl-3-methylpiperidine-1-carboxylate (989 mg) as a white solid.

LC-MS (ESI): m/z = 172.1 $[M+H]^+$.

Preparation of *tert*-butyl (3*R*,4*R*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate

A mixture of *tert*-butyl (3*R*,4*R*)-4-formyl-3-methylpiperidine-1-carboxylate (311 mg, 1.37 mmol) and 3-[5-fluoro-1-methyl-6-(4-piperidyl)indazol-3-yl]piperidine-2,6-dione (585 mg, 1.54 mmol) in THF (10.0 mL) and DMF (2.00 mL) was stirred at room temperature for 30 minutes followed by the addition of $NaBH(OAc)_3$ (438 mg, 2.07 mmol). The reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was diluted with water and then extracted with DCM. The pooled organics were dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford a viscous yellow oil that was purified by ISCO (0-20% MeOH/DCM) to afford *tert*-butyl (3*R*,4*R*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate (610 mg) as an off-white solid.

LC-MS (ESI): m/z = 556.4 $[M+H]^+$.

Preparation of 3-(5-fluoro-1-methyl-6-(1-(((3*R*,4*R*)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione dihydrochloride

A solution of *tert*-butyl (3*R*,4*R*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate (613 mg, 1.10 mmol) in 1,4-dioxane (5.00 mL) was treated with HCl (4.0 M in dioxane) (7.00 mL, 28.0 mmol). The reaction mixture was stirred for 2 hours and then concentrated under reduced pressure. The white solid was suspended in DCM and concentrated again under reduced pressure to afford 3-(5-fluoro-1-methyl-6-(1-(((3*R*,4*R*)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione dihydrochloride (583 mg).

LC-MS (ESI): m/z = 456.4 $[M+H]^+$.

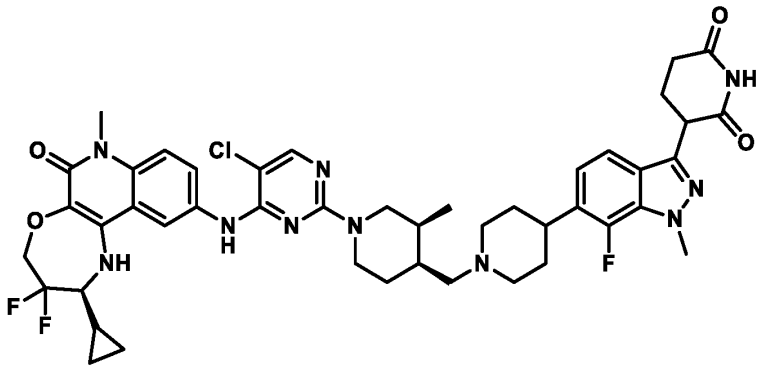
Preparation of 3-(6-(1-(((3*R*,4*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-*c*]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

A mixture of (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-*c*]quinolin-6(7*H*)-one (639 mg, 1.36 mmol), 3-(5-fluoro-1-methyl-6-(1-(((3*R*,4*R*)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione dihydrochloride (583 mg, 1.10 mmol), and CsF (524 mg, 3.45 mmol) in DMSO (6.00 mL) was treated with DIPEA (769 µL, 4.41 mmol). The mixture was stirred at 80 °C for 18 hours. The reaction mixture was then cooled to room temperature, filtered, and purified by prep-HPLC to afford 3-(6-(1-(((3*R*,4*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-*c*]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (627 mg) as an off-white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.87 (s, 1H), 8.73 (s, 1H), 8.15 (s, 1H), 8.00 (s, 1H), 7.76 (d, *J* = 9.1 Hz, 1H), 7.60 – 7.51 (m, 1H), 7.50 – 7.40 (m, 2H), 6.16 (s, 1H), 4.52 – 4.21 (m, 4H), 4.00 (s, 3H), 3.57 (s, 3H), 3.29 – 3.19 (m, 2H), 3.08 – 2.92 (m, 3H), 2.91 – 2.79 (m, 2H), 2.70 – 2.58 (m, 2H), 2.44 – 2.35 (m, 2H), 2.25 – 2.10 (m, 3H), 2.09 – 1.97 (m, 2H), 1.97 – 1.87 (m, 2H), 1.86 – 1.70 (m, 4H), 1.46 – 1.26 (m, 2H), 0.76 (d, *J* = 6.2 Hz, 3H), 0.75 – 0.68 (m, 1H), 0.58 – 0.47 (m, 2H), 0.43 – 0.31 (m, 1H).

LC-MS (ESI): m/z = 887.5 $[M+H]^+$.

Example 109. 3-(6-(1-(((3S,4S)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 130c)



Preparation of *tert*-butyl (3*S*,4*S*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate

A mixture of *tert*-butyl (3*S*,4*S*)-4-formyl-3-methylpiperidine-1-carboxylate (56.9 mg, 250 μmol) and 3-(7-fluoro-1-methyl-6-(piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione dihydrochloride (99.0 mg, 260 μmol) in a 1 dram vial was suspended in DCM (0.750 mL). The mixture was immediately treated with sodium triacetoxyborohydride (212 mg, 1.00 mmol). The reaction mixture was stirred for 45 minutes and then partitioned between DCM and water. The layers were separated, and the aqueous phase was extracted with DCM (3x). The pooled organics were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was dissolved in minimal DCM and purified by ISCO: 0-100% (3:1 ethyl acetate/EtOH)/heptane to afford *tert*-butyl (3*S*,4*S*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate (49 mg).

LC-MS (ESI): m/z = 556.3 $[M+H]^+$.

Preparation of 3-(7-fluoro-1-methyl-6-(1-(((3*S*,4*S*)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione dihydrochloride

A solution of *tert*-butyl (3*S*,4*S*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate (49.0 mg, 88.2 μmol) in 1,4-dioxane was treated with HCl (4.0 M in 1,4-dioxane) (1.00 mL, 4.00 mmol). The resulting reaction mixture was stirred at room temperature for 2 hours, and then the volatiles were removed under reduced pressure. The resulting white solid was suspended in DCM, and

then concentrated once more under reduced pressure to afford 3-(7-fluoro-1-methyl-6-(1-(((3*S*,4*S*)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione dihydrochloride (46 mg).

LC-MS (ESI): m/z = 456.4 $[M+H]^+$.

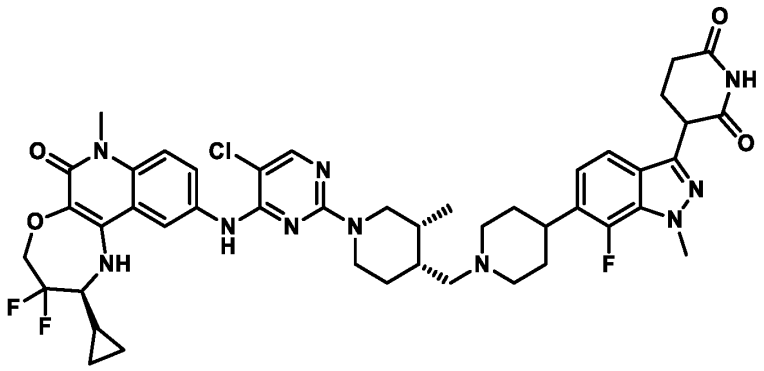
Preparation of 3-(6-(1-(((3*S*,4*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-*c*]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

A mixture of (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-*c*]quinolin-6(7*H*)-one (53.0 mg, 113 μmol), 3-(7-fluoro-1-methyl-6-(1-(((3*S*,4*S*)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione dihydrochloride (46.0 mg, 87.0 μmol), and CsF (38.6 mg, 254 μmol) in DMSO (1.00 mL) was treated with DIPEA (60.6 μL, 348 μmol) and warmed to 80 °C for 17 hours. The reaction mixture was cooled to room temperature, filtered, and purified by prep-HPLC to afford 3-(6-(1-(((3*S*,4*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-*c*]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (39.5 mg).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.90 (s, 1H), 8.73 (s, 1H), 8.15 (s, 1H), 8.13 (s, 1H), 8.01 (s, 1H), 7.80 – 7.73 (m, 1H), 7.52 – 7.41 (m, 1H), 7.04 (s, 1H), 6.18 (s, 1H), 4.59 – 4.18 (m, 4H), 4.11 (s, 3H), 3.57 (s, 3H), 3.29 – 3.18 (m, 2H), 3.08 – 2.77 (m, 4H), 2.74 – 2.61 (m, 2H), 2.42 – 2.27 (m, 2H), 2.19 – 2.09 (m, 3H), 2.06 – 1.97 (m, 2H), 1.96 – 1.87 (m, 2H), 1.86 – 1.64 (m, 4H), 1.48 – 1.19 (m, 3H), 0.76 (d, J = 6.5 Hz, 3H), 0.74 – 0.70 (m, 1H), 0.58 – 0.41 (m, 2H), 0.38 – 0.26 (m, 1H).

LC-MS (ESI): m/z = 887.5 $[M+H]^+$.

Example 110. 3-(6-(1-(((3*R*,4*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-*c*]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 130b)



Preparation of *tert*-butyl (3*R*,4*R*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate

A mixture of *tert*-butyl (3*R*,4*R*)-4-formyl-3-methylpiperidine-1-carboxylate (568 mg, 2.50 mmol) and 3-(7-fluoro-1-methyl-6-(piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione hydrochloride (1098 mg, 2.883 mmol) in THF (18.0 mL) and DMF (3.50 mL) was stirred at room temperature for 20 minutes, treated with sodium triacetoxyborohydride (803 mg, 3.79 mmol), and then stirred at room temperature for 3 hours. Additional DCM (6.00 mL) and additional sodium triacetoxyborohydride (603 mg, 2.85 mmol) were added. The reaction mixture was stirred for 30 minutes, diluted with water (30 mL), and then extracted four times with (DCM, 40 mL each). The pooled organics were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified by ISCO: 0-100% (3:1 EtOAc/EtOH)/heptane to afford *tert*-butyl (3*R*,4*R*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate (855 mg).

LC-MS (ESI): m/z = 556.4 $[M+H]^+$.

Preparation of 3-(7-fluoro-1-methyl-6-(1-(((3*R*,4*R*)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione dihydrochloride

A solution of *tert*-butyl (3*R*,4*R*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-methylpiperidine-1-carboxylate (395 mg, 711 μmol) in 1,4-dioxane (2.50 mL) was treated with HCl (4.0 M in dioxane) (4.00 mL, 16.0 mmol) and stirred for 2 hours, then concentrated under reduced pressure. The solid was suspended and stirred in DCM for 15 minutes, then again concentrated under reduced pressure to afford 3-(7-fluoro-1-methyl-6-(1-(((3*R*,4*R*)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione dihydrochloride (376 mg).

LC-MS (ESI): m/z = 456.4 $[M+H]^+$.

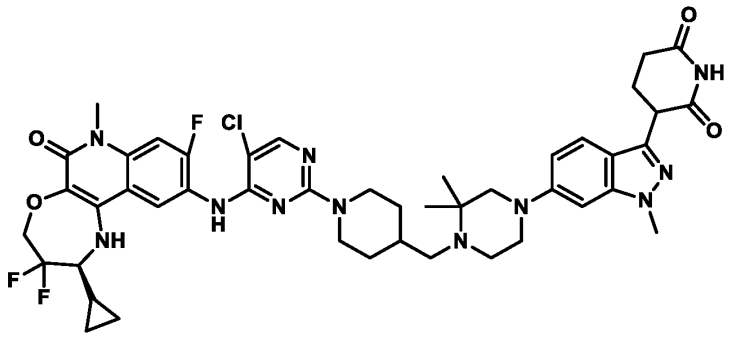
Preparation of 3-(6-(1-(((3*R*,4*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-*c*]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

A mixture of (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (402 mg, 858 μmol), 3-(7-fluoro-1-methyl-6-(1-(((3*R*,4*R*)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione dihydrochloride (376 mg, 711 μmol), and CsF (338 mg, 2.23 mmol) in DMSO (4.00 mL) was treated with DIPEA (496 μL, 2.85 mmol). The reaction mixture was warmed to 80 °C for 18 hours. The reaction mixture was cooled to room temperature, filtered, and purified by prep-HPLC to afford 3-(6-(1-(((3*R*,4*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-*c*]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (450 mg) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.90 (s, 1H), 8.73 (s, 1H), 8.16 (s, 1H), 8.00 (s, 1H), 7.76 (d, J = 9.0 Hz, 1H), 7.47 (s, 1H), 7.45 (s, 1H), 7.05 (t, J = 7.2 Hz, 1H), 6.17 (s, 1H), 4.53 – 4.19 (m, 4H), 4.11 (s, 3H), 3.57 (s, 3H), 3.28 – 3.18 (m, 2H), 3.08 – 2.79 (m, 4H), 2.78 – 2.56 (m, 2H), 2.45 – 2.29 (m, 2H), 2.23 – 2.09 (m, 3H), 2.08 – 1.97 (m, 2H), 1.97 – 1.87 (m, 2H), 1.85 – 1.61 (m, 4H), 1.49 – 1.26 (m, 3H), 0.76 (d, J = 6.5 Hz, 3H), 0.73 – 0.67 (m, 1H), 0.58 – 0.47 (m, 2H), 0.41 – 0.31 (m, 1H).

LC-MS (ESI): m/z = 887.6 $[M+H]^+$.

Example 111. 3-(6-(4-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-*c*]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)-3,3-dimethylpiperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 137a)



Preparation of *tert*-butyl 4-((1-((benzyloxy)carbonyl)piperidin-4-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate

To a stirred solution of *tert*-butyl 3,3-dimethylpiperazine-1-carboxylate (1.0 g, 4.66 mmol) and benzyl 4-formylpiperidine-1-carboxylate (1.38 g, 5.60 mmol) in THF (10.0 ml) was added acetic acid (0.20 ml, 4.66 mmol) and anhydrous sodium acetate (1.14 g, 13.99 mmol). The reaction was stirred at room temperature for 1 hour followed by the addition of sodium triacetoxyborohydride (2.96 g, 13.99 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. The reaction mixture was quenched with water (50 mL) and extracted with ethyl acetate (100 mL). The organic layer was separated and concentrated under reduced pressure to get a crude product which was purified by flash column chromatography (25% ethyl acetate in petroleum ether) to afford *tert*-butyl 4-((1-((benzyloxy)carbonyl)piperidin-4-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate as a pure product (1.0 g).

LC-MS (ESI): m/z = 446.57 $[M+H]^+$

Preparation of benzyl 4-((2,2-dimethylpiperazin-1-yl)methyl)piperidine-1-carboxylate

To a stirred solution of *tert*-butyl 4-((1-((benzyloxy)carbonyl)piperidin-4-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate (2 g, 4.48 mmol) in DCM (20 mL) was added TFA (2 mL) at 0 °C. The reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure to get a crude product which was purified by trituration with diethyl ether (20 mL) to afford benzyl 4-((2,2-dimethylpiperazin-1-yl)methyl)piperidine-1-carboxylate (1.5 g) as a solid.

LC-MS (ESI): m/z = 346.47 $[M+H]^+$

Preparation of benzyl 4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)-2,2-dimethylpiperazin-1-yl)methyl)piperidine-1-carboxylate

To a stirred solution of benzyl 4-((2,2-dimethylpiperazin-1-yl)methyl)piperidine-1-carboxylate (1.0 g, 2.89 mmol), 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-1-methyl-1*H*-indazole (0.72 g, 1.44 mmol), and ^{t}BuONa (2 M in THF) (4.33 mL, 8.67 mmol) in 1-4 dioxane (10 mL) was added Ruphos-Pd-G3 (0.24 g, 0.28 mmol) under N_2. The reaction mixture was heated at 100 °C and stirred for 16 hours. The reaction mixture was quenched with ice cold water (20 mL) and extracted with ethyl acetate (100 mL). The organic layer was separated and concentrated under reduced pressure to get crude product which was purified by flash column chromatography (50-60 % ethyl acetate in petroleum ether) to afford benzyl 4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)-2,2-dimethylpiperazin-1-yl)methyl)piperidine-1-carboxylate (0.53 g).

LC-MS (ESI): m/z = 765.80 $[M+H]^+$

Preparation of 3-(6-(3,3-dimethyl-4-(piperidin-4-ylmethyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

A stirred solution of benzyl 4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)-2,2-dimethylpiperazin-1-yl)methyl)piperidine-1-carboxylate (0.80 g, 1.04 mmol) in THF (24 mL) was degassed with nitrogen for 5 minutes followed by the addition of $Pd(OH)_2$ on carbon (0.80 g, 20 wt%). The mixture was stirred under hydrogen pressure (80 Psi) at room temperature for 16 hours. The reaction mixture was diluted with ethyl acetate (50 mL), filtered through a celite bed, and concentrated to get a crude product which was purified by trituration with diethyl ether to afford 3-(6-(3,3-dimethyl-4-(piperidin-4-ylmethyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.20 g) as a solid.

LC-MS (ESI): m/z = 553.51 $[M+H]^+$

Preparation of 3-(6-(4-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-*c*]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)-3,3-dimethylpiperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

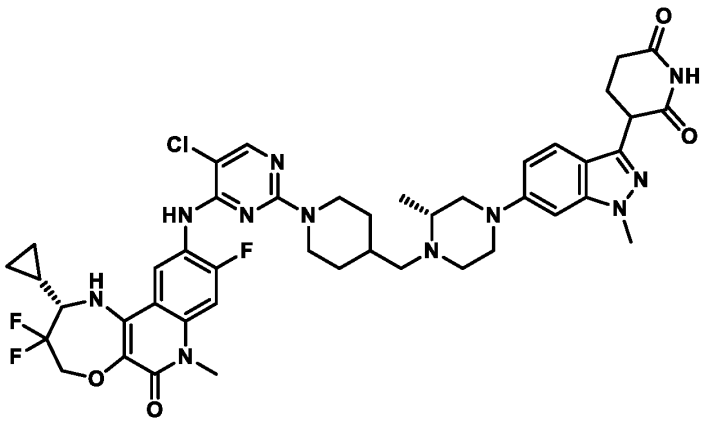
A mixture of (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3,9-trifluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (93.0 mg, 191 µmol), 3-(6-(3,3-dimethyl-4-(piperidin-4-ylmethyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione trihydrochloride (126 mg, 224 µmol), CsF (87.2 mg, 574 µmol),

and DIPEA (167 µL, 956 µmol) in DMSO (1.50 mL) was warmed to 80 °C under a blanket of $N_{2(g)}$ for 19 hours. The reaction mixture was cooled to room temperature, filtered, and purified by prep-HPLC to afford 3-(6-(4-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-*c*]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)-3,3-dimethylpiperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (89.0 mg).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.83 (s, 1H), 8.80 (s, 1H), 8.20 (d, *J* = 7.9 Hz, 1H), 8.01 (s, 1H), 7.47 (d, *J* = 8.9 Hz, 1H), 7.40 (d, *J* = 12.4 Hz, 1H), 6.87 (d, *J* = 9.0 Hz, 1H), 6.79 (s, 1H), 6.44 (s, 1H), 4.50 – 4.37 (m, 1H), 4.37 – 4.27 (m, 1H), 4.25 (dd, *J* = 9.1, 5.2 Hz, 1H), 3.88 (s, 3H), 3.54 (s, 3H), 3.27 – 3.21 (m, 2H), 3.19 – 3.10 (m, 2H), 2.93 (s, 2H), 2.71-2.56 (m, 5H), 2.56 – 2.52 (m, 1H), 2.34 – 2.24 (m, 1H), 2.22 – 2.07 (m, 4H), 1.67 (d, *J* = 12.8 Hz, 2H), 1.59 (s, 1H), 1.31 (s, 1H), 1.01 (s, 6H), 0.91 (d, *J* = 12.5 Hz, 2H), 0.75 – 0.65 (m, 1H), 0.51 (t, *J* = 6.1 Hz, 2H), 0.32 (d, *J* = 5.6 Hz, 1H).

LC-MS (ESI): m/z = 902.7 $[M+H]^+$.

Example 112. 3-[6-[(3*R*)-4-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-3-methyl-piperazin-1-yl]-1-methylindazol-3-yl]piperidine-2,6-dione (Compound 102b)



To a solution of 3-[1-methyl-6-[(3*R*)-3-methyl-4-(4-piperidylmethyl)piperazin-1-yl]indazol-3-yl]piperidine-2,6-dione (97.40 mg, 222.10 µmol, *1.2 equiv.*) and (2*S*)-2-cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (90 mg, 185.08 µmol, 1 *equiv.*) in DMSO (2 mL) was added TEA (74.91 mg, 740.32 µmol, 103.04 µL, 4 *equiv.*). The mixture was stirred at 100 °C

for 1 hour. The reaction mixture was filtered and the filtrate was concentrated to give a residue which was purified by prep-HPLC to afford 3-[6-[(3*R*)-4-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-3-methyl-piperazin-1-yl]-1-methylindazol-3-yl]piperidine-2,6-dione (49.73 mg) as an off-white solid.

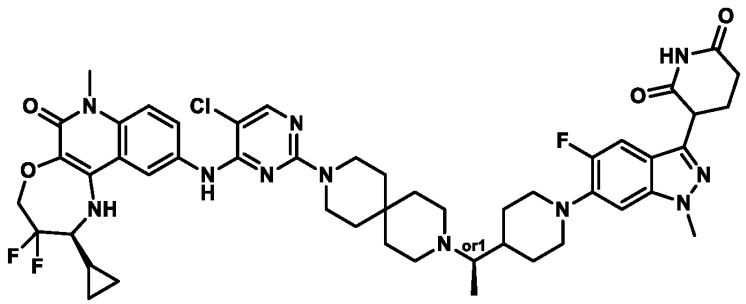
LC-MS (ESI): m/z = 888.3 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.83 (s, 1H), 8.80 (s, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 8.01 (s, 1H), 7.48 (d, *J* = 8.8 Hz, 1H), 7.41 (d, *J* = 12.4 Hz, 1H), 6.89 (d, *J* = 9.2 Hz, 1H), 6.80 (s, 1H), 6.44 (s, 1H), 4.49 -4.22 (m, 5H), 3.88 (s, 3H), 3.54 (s, 3H), 3.48 (d, *J* = 10.4 Hz, 2H), 2.96 -2.82 (m, 2H), 2.76 -2.52 (m, 6H), 2.35 -2.22 (m, 3H), 2.17 (d, *J* = 5.6 Hz, 1H), 1.94 (dd, *J* = 4.0, 12.0 Hz, 1H), 1.79 -1.63 (m, 2H), 1.58 (d, *J* = 12.4 Hz, 1H), 1.30 (dt, *J* = 3.2, 6.0 Hz, 1H), 1.03 (d, *J* = 6.0 Hz, 3H), 0.98 (dd, *J* = 2.8, 11.2 Hz, 3H), 0.70 (q, *J* = 6.4 Hz, 1H), 0.53 (t, J = 5.6 Hz, 2H), 0.36 -0.25 (m, 1H)

Example 113. 3-[6-[4-[(1*R*)-1-[9-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3,9-diazaspiro[5.5]undecan-3-yl]ethyl]-1-piperidyl]-5-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione

[3-(6-(4-((*R)-1-(9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)piperidin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]**

(Compound 146a)



To a solution of 3-[6-[4-[(1*R*)-1-(3,9-diazaspiro[5.5]undecan-3-yl)ethyl]-1-piperidyl]-5-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (100.00 mg, 190.60 μmol, 1 *equiv.*) in DMSO (3 mL) was added TEA (77.14 mg, 762.38 μmol, 106.11 μL, 4 *equiv.*) and (2*S*)-2-

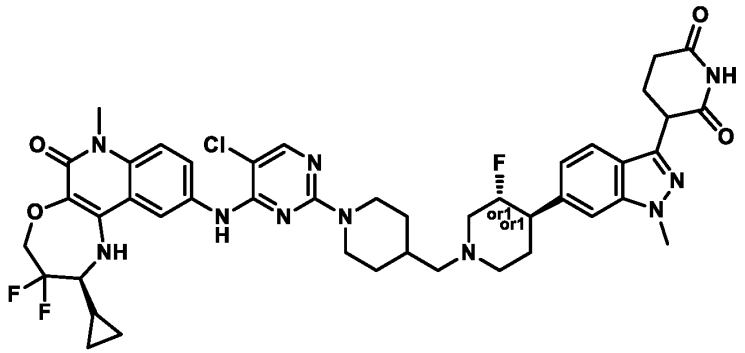
cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3-difluoro-7-methyl-2,4-dihydro1H-[1,4]oxazepino[2,3-c]quinolin-6-one (80.33 mg, 171.54 μmol, 0.9 *equiv.*). The mixture was stirred at 100 °C for 6 hours. The reaction mixture was filtered and the filtrate was concentrated to give a residue which was purified by prep-HPLC to afford 3-[6-[4-[(1*R*)-1-[9-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3,9-diazaspiro[5.5]undecan-3-yl]ethyl]-1-piperidyl]-5-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione [3-(6-(4-((*R**)-1-(9-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)piperidin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (35.31 mg) as a blue solid.

LC-MS (ESI): m/z = 956.5 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.91 -10.75 (m, 1H), 8.77 (s, 1H), 8.21 (d, *J* = 2.8 Hz, 2H), 8.02 (s, 1H), 7.72 (dd, *J* = 1.6, 9.2 Hz, 1H), 7.49 -7.31 (m, 2H), 7.11 -6.93 (m, 1H), 6.18 (s, 1H), 4.53 -4.32 (m, 2H), 4.26 (dd, *J* = 5.2, 9.6 Hz, 1H), 3.93 (s, 3H), 3.56 (s, 8H), 2.70 -2.56 (m, 4H), 2.40 -2.23 (m, 5H), 2.18 -2.03 (m, 2H), 1.87 -1.70 (m, 1H), 1.55 -1.19 (m, 14H), 0.92 (d, *J* = 6.4 Hz, 3H), 0.77 -0.64 (m, 1H), 0.57 -0.45 (m, 2H), 0.40 -0.31 (m, 1H)

Example 114. 3-[6-[(3*R*,4*R*)-1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-3-fluoro-4-piperidyl]-1-methylindazol-3-yl]piperidine-2,6-dione [3-(6-((3*R,4*R**)-1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]**

(Compound 127d)



To a solution of 3-[6-[(3*R*,4*R*)-3-fluoro-1-(4-piperidylmethyl)-4-piperidyl]-1-methyl-

indazol-3-yl]piperidine-2,6-dione (100 mg, 226.48 μmol, 1 *equiv.*) in DMSO (2 mL) was added TEA (91.67 mg, 905.92 μmol, 126.09 μL, 4 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (106.06 mg, 226.48 μmol, 1 *equiv.*). The mixture was stirred at 100 °C for 6 hours. The reaction mixture was filtered and the filtrate was concentrated to give a residue. The residue was purified by prep-HPLC to afford 3-[6-[(3*R*,4*R*)-1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-3-fluoro-4-piperidyl]-1-methylindazol-3-yl]piperidine-2,6-dione [3-(6-((3*R**,4*R**)-1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)-3-fluoropiperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (18.01 mg) as a yellow solid.

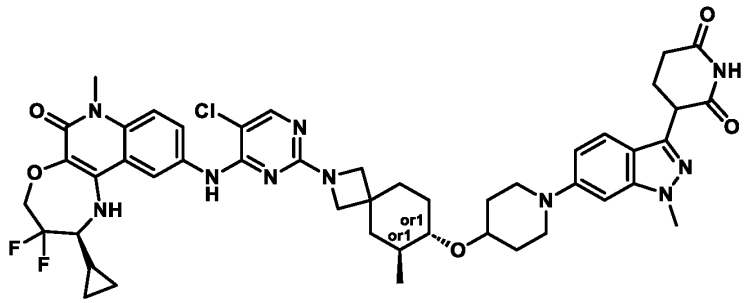
LC-MS (ESI): m/z: 873.2 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.88 (s, 1H), 8.78 (s, 1H), 8.20 (s, 1H), 8.03 (s, 1H), 7.73 (br d, *J* = 8.8 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.55 (s, 1H), 7.45 (d, *J* = 9.2 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 6.14 (s, 1H), 4.91 -4.67 (m, 1H), 4.53 -4.30 (m, 5H), 3.98 (s, 3H), 3.57 (s, 3H), 3.28 -3.21 (m, 2H), 2.94 -2.74 (m, 4H), 2.71 -2.58 (m, 2H), 2.39 -2.30 (m, 1H), 2.29 -2.11 (m, 3H), 2.09 -1.95 (m, 2H), 1.86 -1.68 (m, 5H), 1.40 -1.28 (m, 1H), 1.15 -0.94 (m, 2H), 0.78 -0.64 (m, 1H), 0.52 (d, J = 5.2 Hz, 2H), 0.43 -0.28 (m, 1H)

Example 115: 3-[6-[4-[[(6*S*,7*S*)-2-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-6-methyl-2-azaspiro[3.5]nonan-7-yl]oxy]-1-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione

[3-[6-[4-[[(6*S,7*S**)-2-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-6-methyl-2-azaspiro[3.5]nonan-7-yl]oxy]-1-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione]**

(Compound 116a)



Preparation of *tert*-butyl (6*S*,7*S*)-6-methyl-7-(4-pyridyloxy)-2-azaspiro[3.5]nonane-2-carboxylate

To a solution of *tert*-butyl (6*S*,7*S*)-7-hydroxy-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate (1.5 g, 5.87 mmol, 1 *equiv.*) and 4-chloropyridine (800.39 mg, 7.05 mmol, 1.2 *equiv.*) in DMSO (20 mL), t-BuOK (1.32 g, 11.75 mmol, 2 *equiv.*) was added. The mixture was stirred at 25 °C for 2 hours. The reaction mixture was diluted with H_2O (100 mL) and extracted with ethyl acetate (400 mL). The combined organic layers were washed with sodium chloride solution (200 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (petroleum ether/ethyl acetate=15/85 to 10/90) to afford *tert*-butyl (6*S*,7*S*)-6-methyl-7-(4-pyridyloxy)-2-azaspiro[3.5]nonane-2-carboxylate (1.45 g) as a yellow oil.

LC-MS (ESI): m/z = 333.2 $[M+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ = 8.38 - 8.23 (m, 2H), 6.70 (br dd, J = 1.2, 4.8 Hz, 2H), 5.38 - 5.11 (m, 1H), 3.78 (dt, J = 4.0, 10.0 Hz, 1H), 3.60 (d, J = 7.6 Hz, 1H), 3.56 - 3.49 (m, 2H), 3.48 - 3.43 (m, 1H), 2.02 (td, J = 3.6, 9.6 Hz, 1H), 1.94 (s, 2H), 1.49 (dt, J = 2.8, 13.2 Hz, 1H), 1.39 - 1.35 (m, 9H), 1.32 - 1.22 (m, 2H), 0.97 - 0.91 (m, 3H)

Preparation of *tert*-butyl (6*S*,7*S*)-7-(1-benzylpyridin-1-ium-4-yl)oxy-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate

To a solution of *tert*-butyl (6*S*,7*S*)-6-methyl-7-(4-pyridyloxy)-2-azaspiro[3.5]nonane-2-carboxylate (1.7 g, 5.11 mmol, 1 *equiv.*) in DCM (20 mL), bromomethylbenzene (1.05 g, 6.14 mmol, 728.86 μL, 1.2 *equiv.*) was added. The mixture was stirred at 25 °C for 2 hours and then concentrated under reduced pressure to afford *tert*-butyl (6*S*,7*S*)-7-(1-benzylpyridin-1-ium-4-yl)oxy-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate (2.0 g, crude) as a yellow oil.

LC-MS (ESI): m/z = 423.1 $[M+H]^+$

Preparation of *tert*-butyl (6*S*,7*S*)-7-[(1-benzyl-3,6-dihydro-2*H*-pyridin-4-yl)oxy]-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate

To a solution of *tert*-butyl (6*S*,7*S*)-7-(1-benzylpyridin-1-ium-4-yl)oxy-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate (2.0 g, 4.72 mmol, 1 *equiv.*) in MeOH (20 mL), $NaBH_4$ (535.88 mg, 14.17 mmol, 3 *equiv.*) was added. The mixture was stirred at 25 °C for 2 hours. The reaction mixture was quenched by the addition of ammonium chloride (15 mL) at 25 °C, then diluted with H_2O (30 mL) and extracted with ethyl acetate (90 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (DCM/methanol = 95/5 to 90/10) to afford *tert*-butyl (6*S*,7*S*)-7-[(1-benzyl-3,6-dihydro-2*H*-pyridin-4-yl)oxy]-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate (2.0 g) as a white solid.

LC-MS (ESI): m/z = 427.3 $[M+H]^+$

Preparation of *tert*-butyl (6*S*,7*S*)-6-methyl-7-(4-piperidyloxy)-2-azaspiro[3.5]nonane-2-carboxylate

To a solution of *tert*-butyl (6*S*,7*S*)-7-[(1-benzyl-3,6-dihydro-2*H*-pyridin-4-yl)oxy]-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate (2 g, 4.69 mmol, 1 *equiv.*) in *i*-PrOH (25 mL) was added Pd on carbon (9.98 g, 9.38 mmol, 10% purity, 2 *equiv.*). The mixture was stirred at 25 °C for 12 hours under a H_2 atmosphere. The reaction mixture was filtered through Celite and concentrated under reduced pressure to give *tert*-butyl (6*S*,7*S*)-6-methyl-7-(4-piperidyloxy)-2-azaspiro[3.5]nonane-2-carboxylate (1.1 g) as a white solid.

LC-MS (ESI): m/z = 339.2 $[M+H]^+$

Preparation of *tert*-butyl (6*S*,7*S*)-7-[[1-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-4-piperidyl]oxy]-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate

To a solution of *tert*-butyl (6*S*,7*S*)-6-methyl-7-(4-piperidyloxy)-2-azaspiro[3.5]nonane-2-carboxylate (1.05 g, 3.10 mmol, 1 *equiv.*) and 6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazole (1.71 g, 3.41 mmol, 1.1 *equiv.*) in 1,4-dioxane (13 mL) was added cesium carbonate (3.03 g, 9.31 mmol, 3 *equiv.*) and XPhos Pd G3 (262.57 mg, 310.21 μmol, 0.1 *equiv.*). The mixture was stirred at 100 °C for 2 hours. The reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (300 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 7/1 to 6/1) to give *tert*-butyl (6*S*,7*S*)-7-[[1-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-4-

piperidyl]oxy]-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate (1.1 g) as a white solid.

LC-MS (ESI): m/z = 758.8 $[M+H]^+$

^{1}H NMR(400 MHz, $CDCl_3$-*d*) δ = 7.93 - 7.88 (m, 1H), 7.57 (d, J = 9.2 Hz, 1H), 7.48 - 7.43 (m, 2H), 7.41 - 7.32 (m, 6H), 7.30 (d, J = 2.8 Hz, 1H), 7.25 (s, 1H), 6.80 (d, J = 8.8 Hz, 1H), 6.65 (s, 1H), 6.54 - 6.48 (m, 1H), 5.48 (s, 2H), 5.39 (s, 2H), 4.02 (s, 3H), 3.67 - 3.54 (m, 8H), 3.07 - 2.95 (m, 2H), 2.90 (dt, J = 3.6, 10.0 Hz, 1H), 2.01 - 1.91 (m, 4H), 1.82 - 1.74 (m, 2H), 1.57 (s, 4H), 1.45 (s, 12H), 1.07 - 1.00 (m, 3H)

Preparation of *tert*-butyl (6*S*,7*S*)-7-[[1-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-4-piperidyl]oxy]-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate

To a solution of *tert*-butyl (6*S*,7*S*)-7-[[1-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-4-piperidyl]oxy]-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate (1.0 g, 1.32 mmol, 1 *equiv.*) in CF_3CH_2OH (20 mL) was added Pd on carbon (500 mg, 469.84 μmol, 10% purity, 0.356 *equiv.*) and $Pd(OH)_2$ on carbon (500 mg, 712.07 μmol, 20% purity, 0.54 *equiv.*). The mixture was stirred at 25 °C for 12 hours under a H_2 atmosphere. The reaction mixture was filtered through celite and concentrated under reduced pressure to give *tert*-butyl (6*S*,7*S*)-7-[[1-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-4-piperidyl]oxy]-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate (400 mg) as a yellow solid.

LC-MS (ESI): m/z = 580.5 $[M+H]^+$

Preparation of 3-[1-methyl-6-[4-[[(6*S*,7*S*)-6-methyl-2-azaspiro[3.5]nonan-7-yl]oxy]-1-piperidyl]indazol-3-yl]piperidine-2,6-dione

To a solution of *tert*-butyl (6*S*,7*S*)-7-[[1-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-4-piperidyl]oxy]-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate (50 mg, 86.25 μmol, 1 *equiv.*) in DCM (0.3 mL) was added TFA (0.9 mL). The mixture was stirred at 25 °C for 1 hour and concentrated under reduced pressure to give 3-[1-methyl-6-[4-[[(6*S*,7*S*)-6-methyl-2-azaspiro[3.5]nonan-7-yl]oxy]-1-piperidyl]indazol-3-yl]piperidine-2,6-dione (35 mg) as a yellow solid.

LC-MS (ESI): m/z = 480.4 $[M+H]^+$

Preparation of 3-[6-[4-[[(6*S*,7*S*)-2-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-6-methyl-2-azaspiro[3.5]nonan-7-yl]oxy]-1-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione

[3-[6-[4-[[(6*S,7*S**)-2-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-6-methyl-2-azaspiro[3.5]nonan-7-yl]oxy]-1-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione]**

A solution of 3-[1-methyl-6-[4-[[(6*S*,7*S*)-6-methyl-2-azaspiro[3.5]nonan-7-yl]oxy]-1-piperidyl]indazol-3-yl]piperidine-2,6-dione (35 mg, 51.81 μmol, 1 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (19.41 mg, 41.45 μmol, 0.8 *equiv.*) in TEA (2 mL) and DMSO (1 mL) was stirred at 100 °C for 1 hour. After cooling, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to give a residue. This residue was purified by prep-HPLC to afford 3-[6-[4-[[(6*S*,7*S*)-2-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-6-methyl-2-azaspiro[3.5]nonan-7-yl]oxy]-1-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione [3-[6-[4-[[(6*S**,7*S**)-2-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-6-methyl-2-azaspiro[3.5]nonan-7-yl]oxy]-1-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione] (11 mg) as a yellow solid.

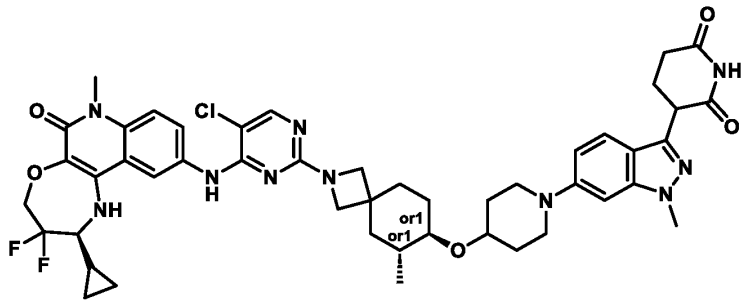
LC-MS (ESI): m/z = 911.4/913.5 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.84 (s, 1H), 8.72 (s, 1H), 8.20 (s, 1H), 8.01 (s, 1H), 7.93 - 7.81 (m, 1H), 7.45 (dd, J = 9.2, 14.4Hz, 2H), 6.98 - 6.76 (m, 2H), 6.10 (s, 1H), 4.53 - 4.31 (m, 2H), 4.28 - 4.20 (m, 1H), 3.88 (s, 3H), 3.67 (s, 2H), 3.62 - 3.48 (m, 7H), 3.00 (d, J = 4.4Hz, 3H), 2.61 (d, J = 5.2Hz, 2H), 2.37 - 2.24 (m, 2H), 2.20 - 2.09 (m, 1H), 1.99 - 1.78 (m, 5H), 1.65 - 1.07 (m, 8H), 0.94 (d, J = 6.0Hz, 3H), 0.79 - 0.64 (m, 1H), 0.53 (s, 2H), 0.37 (s, 1H)

Example 116: 3-[6-[4-[[(6*R*,7*R*)-2-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-6-methyl-2-azaspiro[3.5]nonan-7-yl]oxy]-1-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione

[3-[6-[4-[[(6*R,7*R**)-2-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-6-methyl-2-azaspiro[3.5]nonan-7-yl]oxy]-1-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione]**

(Compound 116c)



Preparation of *tert*-butyl (6*R*,7*R*)-6-methyl-7-(4-pyridyloxy)-2-azaspiro[3.5]nonane-2-carboxylate

To a solution of *tert*-butyl (6*R*,7*R*)-7-hydroxy-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate (2 g, 7.83 mmol, 1 *equiv.*) and 4-chloropyridine (1.07 g, 9.40 mmol, 1.2 *equiv.*) in DMSO (20 mL), 4-chloropyridine1 (1.76 g, 15.66 mmol, 2 *equiv.*) was added. The mixture was stirred at 25 °C for 3 hours. The reaction mixture was partitioned between water (20 mL) and ethyl acetate (60 mL). The organic phase was separated, washed with brine (60 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (0~38% ethyl acetate/petroleum ether) to give 4-chloropyridine2 (2.05 g) as a colorless oil.

LC-MS (ESI): m/z = 333.3 $[M+H]^+$

Preparation of *tert*-butyl (6*R*,7*R*)-7-(1-benzylpyridin-1-ium-4-yl)oxy-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate

To a solution of *tert*-butyl (6*R*,7*R*)-6-methyl-7-(4-pyridyloxy)-2-azaspiro[3.5]nonane-2-carboxylate (2 g, 6.02 mmol, 1 *equiv.*) in DCM (20 mL), BnBr (1.03 g, 6.02 mmol, 714.55 μL, 1 *equiv.*) was added. The mixture was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give *tert*-butyl (6*R*,7*R*)-7-(1-benzylpyridin-1-ium-4-yl)oxy-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate (2.55 g) as a brown crude solid.

LC-MS (ESI): m/z = 423.4 $[M+H]^+$

Preparation of *tert*-butyl (6*R*,7*R*)-7-[(1-benzyl-3,6-dihydro-2*H*-pyridin-4-yl)oxy]-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate

To a solution of *tert*-butyl (6*R*,7*R*)-7-(1-benzylpyridin-1-ium-4-yl)oxy-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate (2.55 g, 6.02 mmol, 1 *equiv.*) in MeOH (30 mL), $NaBH_4$ (683.24 mg, 18.06 mmol, 3 *equiv.*) was added at 0°C. The mixture was stirred at 25 °C for 2

hours. The reaction mixture was quenched by the addition of water (15 mL) at 0 °C, then diluted with water (30 mL), and extracted with ethyl acetate (90 mL). The combined organic layers were washed with brine (30 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give *tert*-butyl (6*R*,7*R*)-7-[(1-benzyl-3,6-dihydro-2*H*-pyridin-4-yl)oxy]-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate (2.57 g) as a yellow oil crude.

LC-MS (ESI): m/z = 427.4 $[M+H]^+$

Preparation of *tert*-butyl (6*R*,7*R*)-6-methyl-7-(4-piperidyloxy)-2-azaspiro[3.5]nonane-2-carboxylate

To a solution of *tert*-butyl (6*R*,7*R*)-7-[(1-benzyl-3,6-dihydro-2*H*-pyridin-4-yl)oxy]-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate (2.57 g, 6.02 mmol, 1 *equiv.*) in IPA (30 mL) was added Pd on carbon (1.28 g, 1.20 mmol, 10% purity, 0.2 *equiv.*) under a N_2 atmosphere. The suspension was degassed and purged with H_2 three times. The mixture was stirred under H_2 (50 psi) at 40 °C for 12 hours. The reaction mixture was filtered and concentrated under reduced pressure to give *tert*-butyl (6*R*,7*R*)-6-methyl-7-(4-piperidyloxy)-2-azaspiro[3.5]nonane-2-carboxylate (1.8 g) as a white solid.

LC-MS (ESI): m/z = 339.1 $[M+H]^+$

Preparation of *tert*-butyl (6*R*,7*R*)-7-[[1-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-4-piperidyl]oxy]-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate

A mixture of *tert*-butyl (6*R*,7*R*)-6-methyl-7-(4-piperidyloxy)-2-azaspiro[3.5]nonane-2-carboxylate (1.7 g, 5.02 mmol, 1 *equiv.*), 6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazole (2.01 g, 4.02 mmol, 0.8 *equiv.*), XPhos Pd G3 (425.12 mg, 502.24 μmol, 0.1 *equiv.*), cesium carbonate (4.91 g, 15.07 mmol, 3 *equiv.*) in dioxane (20 mL) was degassed and purged with N_2 three times. The mixture was stirred at 90 °C for 3 hours under a N_2 atmosphere. The reaction mixture was partitioned between water (30 mL) and ethyl acetate (90 mL). The organic phase was dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (0~46% ethyl acetate/petroleum ether) to afford *tert*-butyl (6*R*,7*R*)-7-[[1-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-4-piperidyl]oxy]-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate (1.2 g) as a white solid.

LC-MS (ESI): m/z = 758.4 $[M+H]^+$

Preparation of *tert*-butyl (6*R*,7*R*)-7-[[1-[3-(2,6-dioxo-3-piperidyl)-1-methyl-

indazol-6-yl]-4-piperidyl]oxy]-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate

A mixture of *tert*-butyl (6*R*,7*R*)-7-[[1-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-4-piperidyl]oxy]-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate (200 mg, 263.87 μmol, 1 *equiv.*), $Pd(OH)_2$ on carbon (92.64 mg, 131.93 μmol, 20% purity, 0.5 *equiv.*), Pd on carbon (140.40 mg, 131.93 μmol, 10% purity, 0.5 *equiv.*) in CF_3CH_2OH (4 mL) was degassed and purged with H_2 three times. The mixture was stirred at 25 °C for 12 hours under a H_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give *tert*-butyl (6*R*,7*R*)-7-[[1-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-4-piperidyl]oxy]-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate (100 mg) as a white solid.

LC-MS (ESI): m/z = 580.3 $[M+H]^+$

Preparation of 3-[1-methyl-6-[4-[[(6*R*,7*R*)-6-methyl-2-azaspiro[3.5]nonan-7-yl]oxy]-1-piperidyl]indazol-3-yl]piperidine-2,6-dione

A solution of *tert*-butyl (6*R*,7*R*)-7-[[1-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-4-piperidyl]oxy]-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate (100 mg, 172.49 μmol, 1 *equiv.*) in TFA (1 mL) and DCM (1 mL) was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to remove TFA and DCM. The pH was adjusted to 11-12 with saturated sodium carbonate. The residue was diluted with water (10 mL) and extracted with DCM/MeOH (30 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to give 3-[1-methyl-6-[4-[[(6*R*,7*R*)-6-methyl-2-azaspiro[3.5]nonan-7-yl]oxy]-1-piperidyl]indazol-3-yl]piperidine-2,6-dione (80 mg) as a brown solid.

LC-MS (ESI): m/z = 480.0 $[M+H]^+$.

Preparation of 3-[6-[4-[[(6*R*,7*R*)-2-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-6-methyl-2-azaspiro[3.5]nonan-7-yl]oxy]-1-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione

[3-[6-[4-[[(6*R,7*R**)-2-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-6-methyl-2-azaspiro[3.5]nonan-7-yl]oxy]-1-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione]**

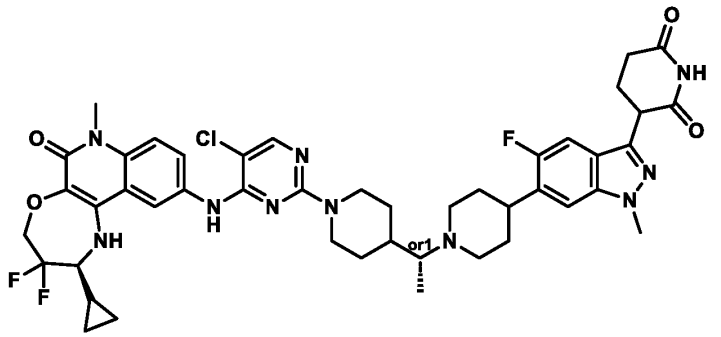
To a solution of 3-[1-methyl-6-[4-[[(6*R*,7*R*)-6-methyl-2-azaspiro[3.5]nonan-7-yl]oxy]-1-piperidyl]indazol-3-yl]piperidine-2,6-dione (80 mg, 166.80 μmol, 1 *equiv.*) and (*S*)-2-

cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (62.49 mg, 133.44 μmol, 0.8 *equiv.*) in DMSO (2 mL), TEA (67.51 mg, 667.20 μmol, 92.87 μL, 4 *equiv.*) was added. The mixture was stirred at 100 °C for 1 hour. The reaction mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give 3-[6-[4-[[(6*R*,7*R*)-2-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-6-methyl-2-azaspiro[3.5]nonan-7-yl]oxy]-1-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione [3-[6-[4-[[(6*R**,7*R**)-2-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-6-methyl-2-azaspiro[3.5]nonan-7-yl]oxy]-1-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione] (39.70 mg) as a yellow solid.

LC-MS (ESI): m/z = 911.4/912.4 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.91 - 10.75 (m, 1H), 8.86 - 8.66 (m, 1H), 8.28 - 8.14 (m, 1H), 8.03 (s, 1H), 7.88 (dd, J= 1.2, 2.4 Hz, 1H), 7.46 (dd, J = 9.2, 13.6 Hz, 2H), 6.93 - 6.78 (m, 2H), 6.15 - 6.01 (m, 1H), 4.51 - 4.31 (m, 2H), 4.25 (dd, J = 5.2, 9.2 Hz, 1H), 3.89 (s, 3H), 3.68 (s, 2H), 3.63 - 3.53 (m, 7H), 3.14 - 2.87 (m, 3H), 2.71 - 2.57 (m, 2H), 2.54 (s, 1H), 2.34 -2.24 (m, 2H), 2.21 - 2.12 (m, 1H), 1.98 - 1.78 (m, 5H), 1.61 - 1.47 (m, 2H), 1.41 - 1.27 (m, 2H), 1.27 - 1.07 (m, 3H), 0.94 (d, J = 6.0 Hz, 3H), 0.79 - 0.65 (m, 1H), 0.60 - 0.44 (m, 2H), 0.41 - 0.27 (m, 1H)

Example 117: 3-[6-[1-[(1*R*)-1-[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]ethyl]-4-piperidyl]-5-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione [3-[6-[1-[(1R*)-1-[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]ethyl]-4-piperidyl]-5-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione] (Compound 113b)



Preparation of *tert*-butyl 4-[(1*R*)-1-[4-[3-(2,6-dioxo-3-piperidyl)-5-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]ethyl]piperidine-1-carboxylate

A mixture of *tert*-butyl-4-[(1*R*)-1-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]ethyl]piperidine-1-carboxylate (250 mg, 341.58 μmol, 1 *equiv.*), Pd on carbon (90.88 mg, 85.39 μmol, 10% purity, 0.25 *equiv.*), $Pd(OH)_2$ on carbon (59.96 mg, 85.39 μmol, 20% purity, 0.25 *equiv.*) in CF_3CH_2OH (2 mL) was degassed and purged with H_2 three times. The mixture was stirred at 25 °C for 12 hours under a H_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give *tert*-butyl 4-[(1*R*)-1-[4-[3-(2,6-dioxo-3-piperidyl)-5-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]ethyl]piperidine-1-carboxylate (180 mg) as a yellow oil.

LC-MS (ESI): m/z = 556.3 $[M+H]^+$

Preparation of 3-[5-fluoro-1-methyl-6-[1-[(1*R*)-1-(4-piperidyl)ethyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione

To a solution of *tert*-butyl 4-[(1*R*)-1-[4-[3-(2,6-dioxo-3-piperidyl)-5-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]ethyl]piperidine-1-carboxylate (180.00 mg, 323.93 μmol, 1 *equiv.*) in DCM (1 mL), HCl/dioxane (4 M, 404.91 μL, 5 *equiv.*) was added. The mixture was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give 3-[5-fluoro-1-methyl-6-[1-[(1*R*)-1-(4-piperidyl)ethyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione (150 mg) as a yellow solid.

LC-MS (ESI): m/z = 456.2 $[M+H]^+$

Preparation of 3-[6-[1-[(1*R*)-1-[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]ethyl]-4-piperidyl]-5-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione

[3-[6-[1-[(1R*)-1-[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-

oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]ethyl]-4-piperidyl]-5-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione]

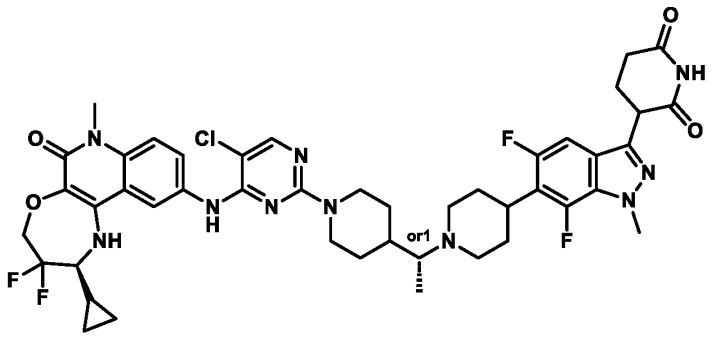
To a solution of 3-[5-fluoro-1-methyl-6-[1-[(1*R*)-1-(4-piperidyl)ethyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione (150 mg, 230.48 μmol, 1 *equiv.*) in DMSO (2 mL) was added TEA (69.97 mg, 691.45 μmol, 96.24 μL, 3 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (129.52 mg, 276.58 μmol, 1.2 *equiv.*). The mixture was stirred at 100 °C for 1 hour. The reaction mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to afford 3-[6-[1-[(1*R*)-1-[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]ethyl]-4-piperidyl]-5-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione [3-[6-[1-[(1R*)-1-[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]ethyl]-4-piperidyl]-5-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione] (58.68 mg) as a yellow solid.

LC-MS (ESI): m/z = 887.8 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.86 (s, 1H), 8.74 (s, 1H), 8.24 - 8.16 (m, 1H), 8.03 (s, 1H), 7.74 (dd, *J* = 1.6, 9.2 Hz, 1H),7.52 (d, *J* = 6.0 Hz, 1H), 7.48 - 7.42 (m, 2H), 6.16 (s, 1H), 4.51 - 4.29 (m, 5H), 3.99 (s, 3H), 3.57 (s, 3H), 2.83 - 2.56 (m, 9H),2.41 - 2.32 (m, 1H), 2.26 - 2.11 (m, 3H), 2.05 (d, *J* = 13.2 Hz, 1H), 1.81 - 1.66 (m, 5H), 1.57 - 1.50 (m, 1H), 1.37 - 1.28 (m, 1H),1.08 - 0.96 (m, 2H), 0.91 (d, *J* = 6.4 Hz, 3H), 0.76 - 0.67 (m, 1H), 0.58 - 0.48 (m, 2H), 0.41 - 0.32 (m, 1H)

Example 118: 3-[6-[1-[(1*R*)-1-[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]ethyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione

[3-[6-[1-[(1*R)-1-[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]ethyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione] (Compound 135b)**



Preparation of *tert*-butyl 4-[1-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]ethyl]piperidine-1-carboxylate

To a solution of 6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazole (1.95 g, 3.64 mmol, 1 *equiv.*) and *tert*-butyl-4-[1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2*H*-pyridin-1-yl]ethyl]piperidine-1-carboxylate (6.11 g, 14.54 mmol, 4 *equiv.*) in dioxane (40 mL) and water (10 mL) was added $Pd(dppf)Cl_2$ (266.02 mg, 363.56 μmol, 0.1 *equiv.*) and potassium carbonate (1.51 g, 10.91 mmol, 3 *equiv.*). The mixture was stirred at 100 °C for 12 hours under a N_2 atmosphere. The reaction mixture was filtered and concentrated to give a residue, which was purified by flash silica gel chromatography (0~10% methanol/DCM) to afford *tert*-butyl 4-[1-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]ethyl]piperidine-1-carboxylate (2.8 g) as a brown oil.

LC-MS (ESI): m/z = 750.1 $[M+H]^+$

Preparation of *tert*-butyl 4-[(1*R*)-1-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]ethyl]piperidine-1-carboxylate and *tert*-butyl 4-[(1*S*)-1-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]ethyl]piperidine-1-carboxylate

Enantiomers of *tert*-butyl 4-[1-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]ethyl]piperidine-1-carboxylate (2.8 g, 3.73 mmol, 1 *equiv.*) were separated by SFC to give *tert*-butyl 4-[(1*R*)-1-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]ethyl]piperidine-1-carboxylate (**Peak 1**) (0.62 g) as a brown oil and *tert*-butyl 4-[(1*S*)-1-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]ethyl]piperidine-1-carboxylate (**Peak 2**) (0.5 g) as a brown oil.

Preparation of *tert*-butyl 4-[(1*R*)-1-[4-[3-(2,6-dioxo-3-piperidyl)-5,7-difluoro-1-methyl-indazol-6-yl]-1-piperidyl]ethyl]piperidine-1-carboxylate

To a solution of *tert*-butyl 4-[(1*R*)-1-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]ethyl]piperidine-1-carboxylate (0.3 g, 400.06 μmol, 1 *equiv.*) in ethyl acetate (5 mL) was added $Pd(OH)_2$ on carbon (0.15 g, 106.81 μmol, 10% purity, 0.267 *equiv.*) and Pd on carbon (0.15 g, 140.95 μmol, 10% purity, 0.352 *equiv.*). The mixture was stirred at 25 °C for 3 days under a H_2 atmosphere. The reaction mixture was filtered and concentrated to give a residue, which was purified by flash silica gel chromatography (0~20% methanol/DCM) to afford *tert*-butyl 4-[(1*R*)-1-[4-[3-(2,6-dioxo-3-piperidyl)-5,7-difluoro-1-methyl-indazol-6-yl]-1-piperidyl]ethyl]piperidine-1-carboxylate (0.22 g) as a brown oil.

LC-MS (ESI): m/z = 574.1 $[M+H]^+$

Preparation of 3-[5,7-difluoro-1-methyl-6-[1-[(1*R*)-1-(4-piperidyl)ethyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione

A solution of *tert*-butyl 4-[(1*R*)-1-[4-[3-(2,6-dioxo-3-piperidyl)-5,7-difluoro-1-methyl-indazol-6-yl]-1-piperidyl]ethyl]piperidine-1-carboxylate (0.12 g, 209.18 μmol, 1 *equiv.*) in HCl/dioxane (2 M, 1.00 mL, 9.56 *equiv.*) was stirred at 25 °C for 1 hour. The reaction mixture was filtered and concentrated to give 3-[5,7-difluoro-1-methyl-6-[1-[(1*R*)-1-(4-piperidyl)ethyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione (0.12 g, crude) as a white solid.

LC-MS (ESI): m/z = 474.0 $[M+H]^+$

Preparation of 3-[6-[1-[(1*R*)-1-[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]ethyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione

[3-[6-[1-[(1*R)-1-[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]ethyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione]**

To a solution of 3-[5,7-difluoro-1-methyl-6-[1-[(1*R*)-1-(4-piperidyl)ethyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione (0.12 g, 253.40 μmol, 1 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (94.93 mg, 202.72 μmol, 0.8 *equiv.*) in DMSO (1 mL) was added TEA (102.57 mg, 1.01 mmol, 141.08 μL, 4 *equiv.*). The mixture was

stirred at 100 °C for 2 hours. The reaction mixture was filtered, and the collected filtrate was purified by prep-HPLC to afford 3-[6-[1-[(1*R*)-1-[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]ethyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione [3-[6-[1-[(1*R**)-1-[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]ethyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione] (84.71 mg) as a yellow solid.

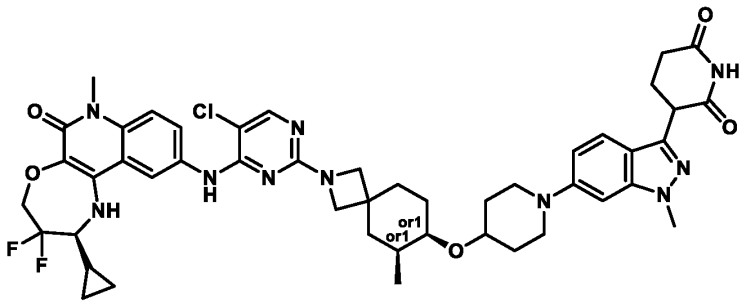
LC-MS (ESI): m/z = 905.1 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.92 (s, 1H), 8.93 (s, 1H), 8.81 - 8.67 (m, 1H), 8.20 (s, 1H), 8.07 (s, 1H), 7.72 (d, J = 8.8 Hz, 1H), 7.46 (t, J = 10.8 Hz, 2H), 6.30 - 6.18 (m, 1H), 4.59 - 4.31 (m, 5H), 4.13 (s, 3H), 3.58 (s, 3H), 3.27 - 3.15 (m, 4H), 2.89 - 2.71 (m, 3H), 2.64 - 2.56 (m, 3H), 2.43 - 2.39 (m, 3H), 2.20 - 2.07 (m, 2H), 2.04 - 1.90 (m, 2H), 1.77 - 1.53 (m, 2H), 1.42 - 1.10 (m, 7H), 0.80 - 0.63 (m, 1H), 0.60 - 0.45 (m, 2H), 0.41 - 0.26 (m, 1H).

Example 119: 3-[6-[4-[[(6*S*,7*R*)-2-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-6-methyl-2-azaspiro[3.5]nonan-7-yl]oxy]-1-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione

[3-[6-[4-[[(6*S,7*R**)-2-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-6-methyl-2-azaspiro[3.5]nonan-7-yl]oxy]-1-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione]**

(Compound 116b)



Preparation of *tert*-butyl (6*S*,7*R*)-6-methyl-7-(4-pyridyloxy)-2-azaspiro[3.5]nonane-2-carboxylate

To a solution of *tert*-butyl (6*S*,7*R*)-7-hydroxy-6-methyl-2-azaspiro[3.5]nonane-2-

carboxylate (1.3 g, 5.09 mmol, 1 *equiv.*) in DMSO (2 mL) was added t-BuOK (1.14 g, 10.18 mmol, 2 *equiv.*) and 4-chloropyridine (693.67 mg, 6.11 mmol, 1.2 *equiv.*). The mixture was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give *tert*-butyl (6*S*,7*R*)-6-methyl-7-(4-pyridyloxy)-2-azaspiro[3.5]nonane-2-carboxylate (1.5 g) as a yellow oil.

LC-MS (ESI): m/z = 333.1 $[M+H]^+$

Preparation of *tert*-butyl (6*S*,7*R*)-7-(1-benzylpyridin-1-ium-4-yl)oxy-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate

To a solution of *tert*-butyl (6*S*,7*R*)-6-methyl-7-(4-pyridyloxy)-2-azaspiro[3.5]nonane-2-carboxylate (1.5 g, 4.51 mmol, 1 *equiv.*) in DCM (2 mL) was added bromomethylbenzene (848.90 mg, 4.96 mmol, 589.52 μL, 1.1 *equiv.*). The mixture was stirred at 25 °C for 1 hour. The reaction mixture was filtered and concentrated under reduced pressure to give bromomethylbenzene2 (2.2 g) as a yellow oil.

LC-MS (ESI): m/z = 423.3 $[M+H]^+$

Preparation of *tert*-butyl (6*S*,7*R*)-7-[(1-benzyl-3,6-dihydro-2*H*-pyridin-4-yl)oxy]-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate

To a solution of *tert*-butyl (6*S*,7*R*)-7-(1-benzylpyridin-1-ium-4-yl)oxy-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate (2.2 g, 4.37 mmol, 1 *equiv.*) in methanol (20 mL) was added $NaBH_4$ (495.91 mg, 13.11 mmol, 3 *equiv.*). The mixture was stirred at 25 °C for 2 hours. The reaction mixture was quenched with ammonium chloride at 0 °C and then diluted with water (20 mL) and extracted with DCM (20 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (5% DCM/methanol) to afford *tert*-butyl (6*S*,7*R*)-7-[(1-benzyl-3,6-dihydro-2*H*-pyridin-4-yl)oxy]-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate (2.0 g) as a yellow oil.

LC-MS (ESI): m/z = 427.3 $[M+H]^+$

Preparation of *tert*-butyl (6*S*,7*R*)-6-methyl-7-(4-piperidyloxy)-2-azaspiro[3.5]nonane-2-carboxylate

A mixture of *tert*-butyl (6*S*,7*R*)-7-[(1-benzyl-3,6-dihydro-2*H*-pyridin-4-yl)oxy]-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate (1.8 g, 4.22 mmol, 1 *equiv.*) and Pd on carbon (1.12 g, 1.05 mmol, 10% purity, 0.25 *equiv.*) in isopropanol (2 mL) was degassed and purged

with N_2 three times. The mixture was stirred at 40 °C for 5 hours under H_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to afford *tert*-butyl (6*S*,7*R*)-6-methyl-7-(4-piperidyloxy)-2-azaspiro[3.5]nonane-2-carboxylate (1.3 g) as a crude yellow oil.

LC-MS (ESI): m/z = 339.2 $[M+H]^+$

Preparation of *tert*-butyl (6*S*,7*R*)-7-[[1-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-4-piperidyl]oxy]-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate

A mixture of *tert*-butyl (6*S*,7*R*)-6-methyl-7-(4-piperidyloxy)-2-azaspiro[3.5]nonane-2-carboxylate (1.25 g, 3.69 mmol, 1 *equiv.*), 6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazole (1.48 g, 2.95 mmol, 0.8 *equiv.*), cesium carbonate (3.61 g, 11.08 mmol, 3 *equiv.*), and XPhos Pd G3 (312.59 mg, 369.29 μmol, 0.1 *equiv.*) in dioxane (10 mL) was degassed and purged with N_2 three times. The mixture was stirred at 90 °C for 2 hours under a N_2 atmosphere. The mixture was diluted with water (50 mL) and extracted with ethyl acetate (100 mL). The combined organic layers were washed with brine (80 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (33% ethyl acetate/petroleum ether) to give *tert*-butyl (6*S*,7*R*)-7-[[1-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-4-piperidyl]oxy]-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate (830 mg) as a brown oil.

LC-MS (ESI): m/z = 758.9 $[M+H]^+$

Preparation of *tert*-butyl (6*S*,7*R*)-7-[[1-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-4-piperidyl]oxy]-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate

A mixture of *tert*-butyl (6*S*,7*R*)-7-[[1-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-4-piperidyl]oxy]-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate (400 mg, 527.73 μmol, 1 *equiv.*), Pd on carbon (280.81 mg, 263.87 μmol, 10% purity, 0.5 *equiv.*), $Pd(OH)_2$ on carbon (185.28 mg, 263.87 μmol, 20% purity, 0.5 *equiv.*), and AcOH (3.17 mg, 52.77 μmol, 3.02 μL, 0.1 *equiv.*) in CF_3CH_2OH (2 mL) was degassed and purged with H_2 three times. The mixture was stirred at 25 °C for 2 hours under H_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (83% ethyl acetate/petroleum ether) to afford *tert*-butyl (6*S*,7*R*)-7-[[1-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-4-piperidyl]oxy]-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate (300 mg) as a yellow oil.

LC-MS (ESI): m/z = 580.4 $[M+H]^+$

Preparation of 3-[1-methyl-6-[4-[[(6*S*,7*R*)-6-methyl-2-azaspiro[3.5]nonan-7-yl]oxy]-1-piperidyl]indazol-3-yl]piperidine-2,6-dione

To a solution of *tert*-butyl (6*S*,7*R*)-7-[[1-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-4-piperidyl]oxy]-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate (60 mg, 103.50 μmol, 1 *equiv.*) in DCM (1 mL) was added TFA (11.80 mg, 103.50 μmol, 7.69 μL, 1 *equiv.*). The mixture was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give 3-[1-methyl-6-[4-[[(6*S*,7*R*)-6-methyl-2-azaspiro[3.5]nonan-7-yl]oxy]-1-piperidyl]indazol-3-yl]piperidine-2,6-dione (50 mg) as a crude yellow oil.

LC-MS (ESI): m/z = 480.4 $[M+H]^+$

Preparation of 3-[6-[4-[[(6*S*,7*R*)-2-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-6-methyl-2-azaspiro[3.5]nonan-7-yl]oxy]-1-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione

[3-[6-[4-[[(6*S,7*R**)-2-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-6-methyl-2-azaspiro[3.5]nonan-7-yl]oxy]-1-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione]**

To a solution of 3-[1-methyl-6-[4-[[(6*S*,7*R*)-6-methyl-2-azaspiro[3.5]nonan-7-yl]oxy]-1-piperidyl]indazol-3-yl]piperidine-2,6-dione (50 mg, 104.25 μmol, 1 *equiv.*) in DMSO (0.5 mL) was added TEA (31.65 mg, 312.75 μmol, 43.53 μL, 3 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (39.06 mg, 83.40 μmol, 0.8 *equiv.*). The mixture was stirred at 100 °C for 1 hour. The reaction mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to afford 3-[6-[4-[[(6*S*,7*R*)-2-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-6-methyl-2-azaspiro[3.5]nonan-7-yl]oxy]-1-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione [3-[6-[4-[[(6*S**,7*R**)-2-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-6-methyl-2-azaspiro[3.5]nonan-7-yl]oxy]-1-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione] (10.68 mg) as a yellow solid.

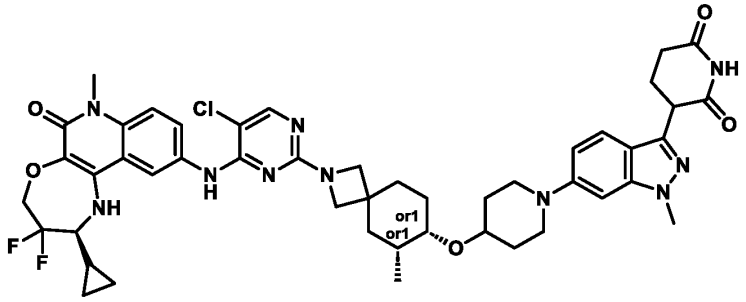
LC-MS (ESI): m/z = 911.8 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.84 (s, 1H), 8.72 (s, 1H), 8.31 - 8.20 (m, 1H), 8.01 (s, 1H), 7.87 - 7.79 (m, 1H), 7.45 (dd, J = 9.2, 18.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 1H), 6.83 (s, 1H), 6.08 (s, 1H), 4.50 - 4.31 (m, 2H), 4.24 (dd, J = 5.2, 9.2 Hz, 1H), 3.88 (s, 3H), 3.66 (s, 2H), 3.60 - 3.51 (m, 7H), 3.44 (s, 1H), 3.10 - 3.02 (m, 2H), 2.69 - 2.58 (m, 2H), 2.54 (s, 1H), 2.35 - 2.24 (m, 2H), 2.21 - 2.10 (m, 1H), 1.91 - 1.79 (m, 3H), 1.75 - 1.64 (m, 1H), 1.61 - 1.48 (m, 6H), 1.35 - 1.23 (m, 2H), 0.90 (d, J = 4.8 Hz, 3H), 0.75 - 0.66 (m, 1H), 0.52 (t, J = 6.0 Hz, 2H), 0.41 - 0.31 (m, 1H)

Example 120: 3-[6-[4-[[(6*R*,7*S*)-2-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-6-methyl-2-azaspiro[3.5]nonan-7-yl]oxy]-1-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione

[3-[6-[4-[[(6*R,7*S**)-2-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-6-methyl-2-azaspiro[3.5]nonan-7-yl]oxy]-1-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione]**

(Compound 116d)



Preparation of *tert*-butyl (6*R*,7*S*)-6-methyl-7-(4-pyridyloxy)-2-azaspiro[3.5]nonane-2-carboxylate

To a solution of *tert*-butyl (6*R*,7*S*)-7-hydroxy-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate (1.0 g, 3.92 mmol, 1.0 *equiv.*) in DMSO (10 mL) was added t-BuOK (1.32 g, 11.75 mmol, 3.0 *equiv.*) and 4-chloropyridine (489.13 mg, 4.31 mmol, 1.1 *equiv.*). The mixture was stirred at 25 °C for 1 hour. The reaction was diluted with water (100 mL) and extracted with DCM (200 mL). The combined organic layers were washed with brine (100 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give *tert*-butyl (6*R*,7*S*)-6-methyl-7-(4-pyridyloxy)-2-azaspiro[3.5]nonane-2-carboxylate (1.2 g) as a yellow oil.

LC-MS (ESI): m/z = 333.3 $[M+H]^+$

Preparation of *tert*-butyl (6*R*,7*S*)-7-(1-benzylpyridin-1-ium-4-yl)oxy-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate

To a solution of *tert*-butyl (6*R*,7*S*)-6-methyl-7-(4-pyridyloxy)-2-azaspiro[3.5]nonane-2-carboxylate (1.2 g, 3.61 mmol, 1.0 *equiv.*) in acetone (12 mL) was added bromomethylbenzene (740.86 mg, 4.33 mmol, 514.49 μL, 1.2 *equiv.*). The mixture was stirred at 80 °C for 1 hour. The reaction was diluted with water (100 mL) and extracted with ethyl acetate (200 mL). The combined organic layers were washed with brine (100 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give *tert*-butyl (6*R*,7*S*)-7-(1-benzylpyridin-1-ium-4-yl)oxy-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate (2.2 g) as a yellow oil.

LC-MS (ESI): m/z = 423.4 $[M+H]^+$

Preparation of *tert*-butyl (6*R*,7*S*)-7-[(1-benzyl-3,6-dihydro-2*H*-pyridin-4-yl)oxy]-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate

To a solution of *tert*-butyl (6*R*,7*S*)-7-(1-benzylpyridin-1-ium-4-yl)oxy-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate (2.2 g, 5.19 mmol, 1.0 *equiv.*) in methanol (22 mL) was added $NaBH_4$ (589.50 mg, 15.58 mmol, 3.0 *equiv.*). The mixture was stirred at 25 °C for 1 hour. The reaction mixture was quenched with saturated ammonium chloride (200 mL) at 0 °C and then extracted with ethyl acetate (300 mL). The combined organic layers were washed with saturated sodium chloride (200 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to afford *tert*-butyl (6*R*,7*S*)-7-[(1-benzyl-3,6-dihydro-2*H*-pyridin-4-yl)oxy]-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate (240 mg) as a colorless oil.

LC-MS (ESI): m/z = 427.4 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.52 - 7.34 (m, 5H), 4.21 (s, 1H), 3.78 (s, 2H), 3.62 (s, 2H), 3.56 (s, 3H), 3.50 (s, 2H), 2.91 (t, J = 6.0 Hz, 2H), 2.57 (t, J = 6.0 Hz, 2H), 1.59 (d, J = 18.8 Hz, 4H), 1.45 (s, 12H), 0.98 - 0.93 (m, 3H)

Preparation of *tert*-butyl (6*R*,7*S*)-6-methyl-7-(4-piperidyloxy)-2-azaspiro[3.5]nonane-2-carboxylate

To a solution of *tert*-butyl (6*R*,7*S*)-7-[(1-benzyl-3,6-dihydro-2*H*-pyridin-4-yl)oxy]-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate (240 mg, 562.60 μmol, 1.0 *equiv.*) in MeOH (4 mL), Pd on carbon (119.74 mg, 112.52 μmol, 10% purity, 0.2 *equiv.*) and $Pd(OH)_2$ on carbon

(79.01 mg, 112.52 μmol, 20% purity, 0.2 *equiv.*) were added under a N_2 atmosphere. The suspension was degassed and purged with H_2 three times. The mixture was stirred under H_2 (15 psi) at 40 °C for 12 hours. The reaction mixture was filtered and concentrated under reduced pressure to give *tert*-butyl (6*R*,7*S*)-6-methyl-7-(4-piperidyloxy)-2-azaspiro[3.5]nonane-2-carboxylate (190 mg) as a colorless oil.

LC-MS (ESI): m/z = 339.1 $[M+H]^+$

Preparation of *tert*-butyl (6*R*,7*S*)-7-[[1-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-4-piperidyl]oxy]-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate

To a solution of 6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazole (150 mg, 299.77 μmol, 1.0 *equiv.*), *tert*-butyl (6*R*,7*S*)-6-methyl-7-(4-piperidyloxy)-2-azaspiro[3.5]nonane-2-carboxylate (121.76 mg, 359.72 μmol, 1.2 *equiv.*) and Pd-PEPPSI-iHeptCl (29.16 mg, 29.98 μmol, 0.1 *equiv.*) in 2-methyl-2-butanol (5 mL) was added cesium carbonate (293.01 mg, 899.31 μmol, 3.0 *equiv.*) under a N_2 atmosphere. The mixture was stirred at 100 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give a residue, which was purified by column chromatography (SiO2, 20:1 to 1:1 petroleum ether/ethyl acetate) to afford *tert*-butyl (6*R*,7*S*)-7-[[1-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-4-piperidyl]oxy]-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate (55 mg) as a yellow oil.

LC-MS (ESI): m/z = 758.8 $[M+H]^+$

Preparation of *tert*-butyl (6*R*,7*S*)-7-[[1-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-4-piperidyl]oxy]-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate

To a solution of *tert*-butyl (6*R*,7*S*)-7-[[1-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-4-piperidyl]oxy]-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate (55 mg, 72.56 μmol, 1.0 *equiv.*) in THF (5 mL), Pd on carbon (15.44 mg, 14.51 μmol, 10% purity, 0.2 *equiv.*) and $Pd(OH)_2$ on carbon (10.19 mg, 14.51 μmol, 20% purity, 0.2 *equiv.*) were added under a N_2 atmosphere. The suspension was degassed and purged with H_2 three times. The mixture was stirred under H_2 (15 psi) at 25 °C for 12 hours. The reaction mixture was filtered and concentrated under reduced pressure to afford *tert*-butyl (6*R*,7*S*)-7-[[1-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-4-piperidyl]oxy]-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate (38 mg) as a yellow oil.

LC-MS (ESI): m/z = 580.4 $[M+H]^+$

Preparation of 3-[1-methyl-6-[4-[[(6*R*,7*S*)-6-methyl-2-azaspiro[3.5]nonan-7-yl]oxy]-1-piperidyl]indazol-3-yl]piperidine-2,6-dione

To a solution of *tert*-butyl (6*R*,7*S*)-7-[[1-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-4-piperidyl]oxy]-6-methyl-2-azaspiro[3.5]nonane-2-carboxylate (38 mg, 65.55 μmol, 1.0 *equiv.*) in DCM (1 mL) was added TFA (767.50 mg, 6.73 mmol, 0.5 mL, 102.69 *equiv.*). The mixture was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give 3-[1-methyl-6-[4-[[(6*R*,7*S*)-6-methyl-2-azaspiro[3.5]nonan-7-yl]oxy]-1-piperidyl]indazol-3-yl]piperidine-2,6-dione (30 mg) as a yellow oil.

LC-MS (ESI): m/z = 480.3 $[M+H]^+$

Preparation of 3-[6-[4-[[(6*R*,7*S*)-2-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-6-methyl-2-azaspiro[3.5]nonan-7-yl]oxy]-1-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione

[3-[6-[4-[[(6*R,7*S**)-2-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-6-methyl-2-azaspiro[3.5]nonan-7-yl]oxy]-1-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione]**

To a solution of 3-[1-methyl-6-[4-[[(6*R*,7*S*)-6-methyl-2-azaspiro[3.5]nonan-7-yl]oxy]-1-piperidyl]indazol-3-yl]piperidine-2,6-dione (20 mg, 41.70 μmol, 1.0 *equiv.*) in DMSO (1 mL) was added TEA (12.66 mg, 125.10 μmol, 17.41 μL, 3.0 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (19.53 mg, 41.70 μmol, 1.0 *equiv.*). The mixture was stirred at 80 °C for 12 hours. The reaction mixture was concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give 3-[6-[4-[[(6*R*,7*S*)-2-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-6-methyl-2-azaspiro[3.5]nonan-7-yl]oxy]-1-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione [3-[6-[4-[[(6*R**,7*S**)-2-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-6-methyl-2-azaspiro[3.5]nonan-7-yl]oxy]-1-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione]

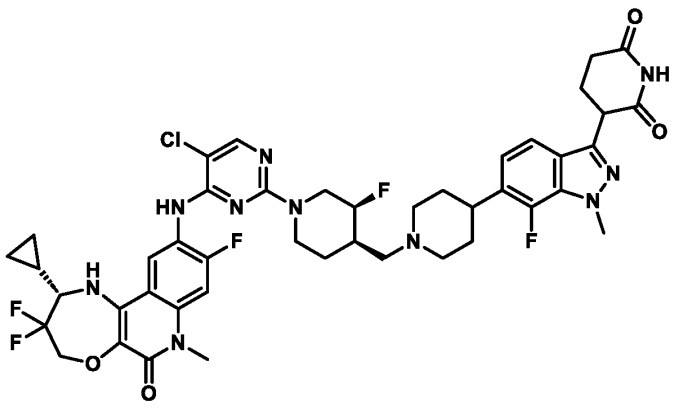
(11.55 mg) as a yellow solid.

LC-MS (ESI): m/z = 911.5 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.84 (s, 1H), 8.73 (s, 1H), 8.25 - 8.23 (m, 1H),

8.01 (s, 1H), 7.82 (d, *J* = 9.6 Hz, 1H), 7.48 - 7.41 (m, 2H), 6.90 (d, *J* = 8.8 Hz, 1H), 6.83 (s, 1H), 6.12 (s, 1H), 4.44 - 4.36 (m, 2H), 4.26 - 4.23 (m, 1H), 3.88 (s, 3H), 3.66 - 3.60 (m, 4H), 3.56 (s, 3H), 3.52 (s, 2H), 3.44 (s, 1H), 3.08 - 3.04 (m, 2H), 2.62 - 2.59 (m, 2H), 2.32 - 2.28 (m, 1H), 2.19 - 2.12 (m, 1H), 1.88 - 1.80 (m, 4H), 1.68 (d, *J* = 13.2 Hz, 1H), 1.59 - 1.52 (m, 7H), 1.34 - 1.28 (m, 2H), 0.90 (d, *J* = 5.2 Hz, 3H), 0.72 - 0.69 (m, 1H), 0.53 - 0.50 (m, 2H), 0.38 - 0.34 (m, 1H)

Example 121: 3-[6-[1-[[(3*S*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-7-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (Compound 169b)



Preparation of *tert*-butyl (3*S*,4*R*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3-fluoro-piperidine-1-carboxylate

To a solution of 3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)indazole (675.33 mg, 1.30 mmol, 1 *equiv.*) in DMSO (3 mL) was added AcOH (7.79 mg, 129.72 μmol, 7.43 μL, 0.1 *equiv.*), $NaBH(OAc)_3$ (412.40 mg, 1.95 mmol, 1.5 *equiv.*), and *tert*-butyl (3*S*,4*R*)-3-fluoro-4-formyl-piperidine-1-carboxylate (0.3 g, 1.30 mmol, 1 *equiv.*) at 25 °C. The mixture was stirred at 25 °C for 0.5 hours. The reaction mixture was extracted with ethyl acetate (30 mL). The combined organic layers were washed with brine (30 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (0~100% ethyl acetate/petroleum ether) to give *tert*-butyl (3*S*,4*R*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3-fluoro-piperidine-1-

carboxylate (385 mg) as a white solid.

LC-MS (ESI): m/z = 736.4 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.88 (d, J = 8.0 Hz, 1H), 7.49 - 7.28 (m, 11H), 6.88 (s, 1H), 6.53 (d, J = 8.0 Hz, 1H), 5.99 (s, 1H), 5.52 - 5.38 (m, 4H), 4.45 (s, 1H), 4.28 (s, 3H), 3.22 (s, 2H), 2.84 - 2.71 (m, 3H), 2.69 - 2.56 (m, 3H), 2.40 (s, 1H), 1.94 - 1.76 (m, 1H), 1.66 - 1.52 (m, 7H), 1.49 (s, 9H)

Preparation of *tert*-butyl (3*S*,4*R*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-7-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-fluoro-piperidine-1-carboxylate

To a solution of *tert*-butyl (3*S*,4*R*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3-fluoro-piperidine-1-carboxylate (385 mg, 523.20 μmol, 1 *equiv.*) in CF_3CH_2OH (5 mL) was added Pd on carbon (167.04 mg, 156.96 μmol, 10% purity, 0.3 *equiv.*) and $Pd(OH)_2$ on carbon (110.21 mg, 156.96 μmol, 20% purity, 0.3 *equiv.*) under a N_2 atmosphere. The suspension was degassed and purged with H_2 three times. The mixture was stirred under H_2 (15 psi) at 25 °C for 16 hours. The reaction mixture was filtered and concentrated under reduced pressure to give *tert*-butyl (3*S*,4*R*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-7-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-fluoro-piperidine-1-carboxylate (0.2 g) as a white solid.

Preparation of 3-[7-fluoro-6-[1-[[(3*S*,4*R*)-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione

To a solution of *tert*-butyl (3*S*,4*R*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-7-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-fluoro-piperidine-1-carboxylate (0.2 g, 357.37 μmol, 1 *equiv.*) in DCM (1 mL) was added HCl/dioxane (1 mL). The mixture was stirred at 25 °C for 1 hour. The reaction mixture was filtered and concentrated under reduced pressure to give 3-[7-fluoro-6-[1-[[(3*S*,4*R*)-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (0.16 g) as a white solid.

Preparation of 3-[6-[1-[[(3*S*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-7-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione

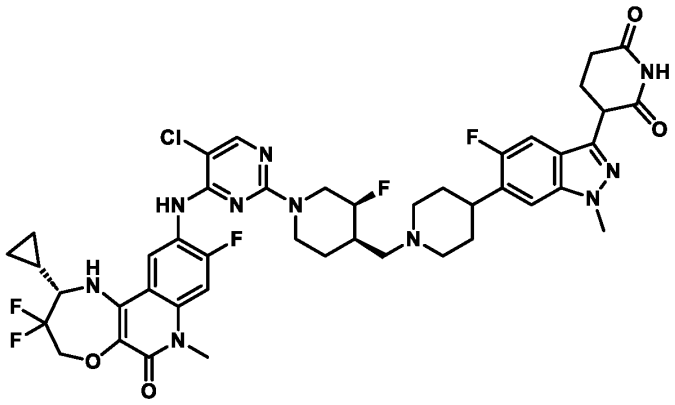
To a solution of 3-[7-fluoro-6-[1-[[(3*S*,4*R*)-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (141.75 mg, 308.47 μmol, 1 *equiv.*) in DMSO (2

mL) was added TEA (124.85 mg, 1.23 mmol, 171.74 μL, 4 *equiv.*) and (2*S*)-2-cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (0.15 g, 308.47 μmol, 1 *equiv.*). The mixture was stirred at 100 °C for 6 hours. The reaction mixture was quenched by the addition of H_2O (5 mL) and extracted with ethyl acetate (60 mL). The combined organic layers were washed with brine (60 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give 3-[6-[1-[[(3*S*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-7-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (46.83 mg) as a gray solid.

LC-MS (ESI): m/z = 909.4 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.91 (s, 1H), 8.87 - 8.81 (m, 1H), 8.29 (s, 1H), 8.19 (d, J = 8.0Hz, 1H), 8.05 - 7.98 (m, 1H), 7.48 - 7.41 (m, 2H), 7.37 - 7.37 (m, 1H), 7.05 (dd, J = 5.6, 8.4Hz, 1H), 6.50 - 6.32 (m, 1H), 4.87 - 4.61 (m, 2H), 4.48 - 4.30 (m, 4H), 4.11 (s, 3H), 3.56 (s, 3H), 3.08 - 2.74 (m, 5H), 2.73 - 2.58 (m, 2H), 2.44 - 2.28 (m, 3H), 2.15 (t, J = 4.0, 9.2Hz, 2H), 2.08 - 1.99 (m, 2H), 1.85 - 1.75 (m, 2H), 1.73 - 1.64 (m, 2H), 1.52 - 1.43 (m, 1H), 1.35 - 1.26 (m, 2H), 0.75 - 0.64 (m, 1H), 0.54 - 0.47 (m, 2H), 0.39 - 0.28 (m, 1H)

Example 122: 3-[6-[1-[[(3*S*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-5-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (Compound 151b)



Preparation of *tert*-butyl (3*S*,4*R*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3-fluoro-piperidine-1-carboxylate

To a solution of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indazole (500 mg, 960.44 μmol, 1 *equiv.*) in DMSO (6 mL) was added *tert*-butyl (3*S*,4*R*)-3-fluoro-4-formyl-piperidine-1-carboxylate (244.33 mg, 1.06 mmol, 1.1 *equiv.*), AcOH (5.77 mg, 96.04 μmol, 5.50 μL, 0.1 *equiv.*), and $NaBH(OAc)_3$ (305.33 mg, 1.44 mmol, 1.5 *equiv.*). The mixture was stirred at 25 °C for 2 hours. The reaction mixture was diluted with H_2O (30 mL) and extracted with ethyl acetate (30 mL). The combined organic layers were washed with brine (30 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (0~30% ethyl acetate/petroleum ether) to give *tert*-butyl (3*S*,4*R*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3-fluoro-piperidine-1-carboxylate (0.2 g) as a white solid.

LC-MS (ESI): m/z = 736.5 $[M+H]^+$

Preparation of *tert*-butyl (3*S*,4*R*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-fluoro-piperidine-1-carboxylate

To a solution of *tert*-butyl (3*S*,4*R*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3-fluoro-piperidine-1-carboxylate (250 mg, 339.74 μmol, 1 *equiv.*) in CF_3CH_2OH (5 mL) was added Pd on carbon (1.25 g, 1.17 mmol, 10% purity, 3.46 *equiv.*) and $Pd(OH)_2$ on carbon (625.00 mg, 890.09 μmol, 20% purity, 2.62 *equiv.*) under a N_2 atmosphere. The suspension was degassed under vacuum and purged with H_2 three times. The mixture was stirred under H_2 (15 psi) at 25 °C for 6 hours. The reaction mixture was filtered and concentrated under reduced pressure to give *tert*-butyl (3*S*,4*R*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-fluoro-piperidine-1-carboxylate (140 mg) as a blue oil and used in the next step without further purification.

LC-MS (ESI): m/z = 560.3 $[M+H]^+$

Preparation of 3-[5-fluoro-6-[1-[[(3*S*,4*R*)-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione

To a solution of *tert*-butyl (3*S*,4*R*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-fluoro-piperidine-1-carboxylate (0.14 g, 250.16 μmol, 1 *equiv.*) in DCM (2 mL) was added HCl/dioxane (2 M, 1 mL, 7.99 *equiv.*). The mixture was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give 3-[5-fluoro-6-[1-[[(3*S*,4*R*)-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-

3-yl]piperidine-2,6-dione (0.1 g) as a dark blue oil, which was used in the next step without further purification.

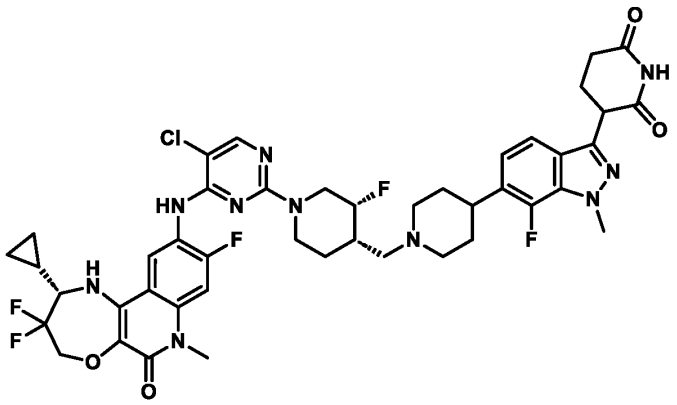
Preparation of 3-[6-[1-[[(3*S*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-5-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione

To a solution of 3-[5-fluoro-6-[1-[[(3*S*,4*R*)-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (0.1 g, 217.61 μmol, 1 *equiv.*) in DMSO (3 mL) was added TEA (88.08 mg, 870.45 μmol, 121.16 μL, 4 *equiv.*) and (2*S*)-2-cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (105.82 mg, 217.61 μmol, 1 *equiv.*). The mixture was stirred at 100 °C for 1 hour. The reaction mixture was filtered and the residue was purified by prep-HPLC to give 3-[6-[1-[[(3*S*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-5-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (40.28 mg) as a purple solid.

LC-MS (ESI): m/z = 909.5 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.87 (s, 1H), 8.85 (s, 1H), 8.18 (d, J = 8.0 Hz, 1H), 8.14 (s, 1H), 8.02 (s, 1H), 7.54 (d, J = 6.0 Hz, 1H), 7.50 - 7.38 (m, 2H), 6.41 (d, J = 2.0 Hz, 1H), 4.93 - 4.58 (m, 2H), 4.52 - 4.23 (m, 4H), 3.99 (s, 3H), 3.64 - 3.50(m, 3H), 3.06 - 2.80 (m, 4H), 2.76 - 2.59 (m, 3H), 2.58 - 2.53 (m, 1H), 2.36 (dt, J = 4.0, 9.2 Hz, 2H), 2.21 - 1.72 (m, 9H), 1.54 -1.41 (m, 1H), 1.39 - 1.20 (m, 2H), 0.80 - 0.63 (m, 1H), 0.59 - 0.42 (m, 2H), 0.39 - 0.26 (m, 1H)

Example 123: 3-[6-[1-[[(3*R*,4*S*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-7-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (Compound 169a)



Preparation of *tert*-butyl (3*R*,4*S*)-3-fluoro-4-formyl-piperidine-1-carboxylate

To a solution of *tert*-butyl (3*R*,4*S*)-3-fluoro-4-(hydroxymethyl)piperidine-1-carboxylate (1 g, 4.29 mmol, 1 *equiv.*) in DCM (10 mL) was added dropwise DMP (3.64 g, 8.57 mmol, 2.66 mL, 2 *equiv.*) at 0 °C. The resulting mixture was stirred at 0 °C for 2 hours. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (0~20% ethyl acetate/petroleum ether) to give *tert*-butyl (3*R*,4*S*)-3-fluoro-4-formyl-piperidine-1-carboxylate (670 mg) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ = 9.77 (s, 1H), 5.31 - 5.03 (m, 1H), 4.57 - 4.19 (m, 2H), 3.11 - 2.69 (m, 2H), 2.55 - 2.39 (m, 1H), 2.05 - 1.95 (m, 1H), 1.90 - 1.80 (m, 1H), 1.49 - 1.47 (m, 9H)

Preparation of *tert*-butyl (3*R*,4*S*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3-fluoro-piperidine-1-carboxylate

To a solution of *tert*-butyl (3*R*,4*S*)-3-fluoro-4-formyl-piperidine-1-carboxylate (230 mg, 994.54 μmol, 1 *equiv.*) and 3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)indazole (414.20 mg, 795.63 μmol, 0.8 *equiv.*) in DMSO (2 mL) was added AcOH (5.97 mg, 99.45 μmol, 5.69 μL, 0.1 *equiv.*) and $NaBH(OAc)_3$ (316.17 mg, 1.49 mmol, 1.5 *equiv.*). The mixture was stirred at 25 °C for 2 hours. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (0~40% ethyl acetate/petroleum ether) to give *tert*-butyl (3*R*,4*S*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3-fluoro-piperidine-1-carboxylate (480 mg) as a white solid.

LC-MS (ESI): m/z = 736.3 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.89 (d, *J* = 8.0 Hz, 1H), 7.52 - 7.44 (m, 2H), 7.43 - 7.25 (m, 9H), 6.93 (dd, *J* = 6.4, 8.4 Hz, 1H), 6.59 (d, *J* = 8.0 Hz, 1H), 5.99 (s, 1H), 5.44 (d, *J* = 8.8 Hz, 4H), 4.89 - 4.69 (m, 1H), 4.19 (s, 3H), 3.20 - 3.04 (m, 2H), 3.01 - 2.75 (m, 2H), 2.71 - 2.60 (m, 2H), 2.35 - 2.22 (m, 1H), 1.96 - 1.88 (m, 1H), 1.56 - 1.48 (m, 1H), 1.43 - 1.37 (m, 12H), 1.26 - 1.20 (m, 1H)

Preparation of *tert*-butyl (3*R*,4*S*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-7-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-fluoro-piperidine-1-carboxylate

To a solution of *tert*-butyl (3*R*,4*S*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3-fluoro-piperidine-1-carboxylate (480 mg, 652.30 μmol, 1 *equiv.*) in CF_3CH_2OH (10 mL) was added $Pd(OH)_2$ on carbon (229.02 mg, 163.07 μmol, 10% purity, 0.25 *equiv.*) and Pd on carbon (173.54 mg, 163.07 μmol, 10% purity, 0.25 *equiv.*) under a N_2 atmosphere. The suspension was degassed and purged with H_2 three times. The mixture was stirred under H_2 (15 psi) at 25 °C for 16 hours. The reaction mixture was filtered and concentrated under reduced pressure to give *tert*-butyl (3*R*,4*S*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-7-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-fluoro-piperidine-1-carboxylate (350 mg) as a yellow solid, which was used in the next step without further purification.

LC-MS (ESI): m/z = 560.2 $[M+H]^+$

Preparation of 3-[7-fluoro-6-[1-[[(3*R*,4*S*)-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione

A solution of *tert*-butyl (3*R*,4*S*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-7-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-fluoro-piperidine-1-carboxylate (350.00 mg, 481.55 μmol, 1 *equiv.*) in HCl/dioxane (2 mL) / DCM (2 mL) was stirred at 25 °C for 3 hours. The reaction mixture was concentrated under reduced pressure to give 3-[7-fluoro-6-[1-[[(3*R*,4*S*)-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (200 mg) as a purple solid, which was used in the next step without further purification.

LC-MS (ESI): m/z = 460.1 $[M+H]^+$

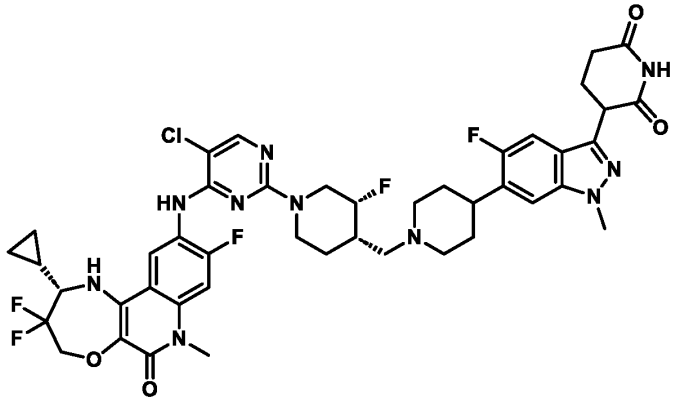
Preparation of 3-[6-[1-[[(3*R*,4*S*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-7-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione

To a solution of 3-[7-fluoro-6-[1-[[(3*R*,4*S*)-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (200 mg, 435.23 μmol, 1 *equiv.*) and (2*S*)-2-cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (190.48 mg, 391.70 μmol, 0.9 *equiv.*) in DMSO (2 mL) was added TEA (176.16 mg, 1.74 mmol, 242.31 μL, 4 *equiv.*). The mixture was stirred at 100 °C for 12 hours. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give 3-[6-[1-[[(3*R*,4*S*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-7-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (85.14 mg) as a white solid.

LC-MS (ESI): m/z = 909.3 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.91 (s, 1H), 8.87 - 8.81 (m, 1H), 8.29 (s, 1H), 8.19 (d, J = 8.0Hz, 1H), 8.05 - 7.98 (m, 1H), 7.48 - 7.41 (m, 2H), 7.37 - 7.37 (m, 1H), 7.05 (dd, J = 5.6, 8.4Hz, 1H), 6.50 - 6.32 (m, 1H), 4.87 - 4.61 (m, 2H), 4.48 - 4.30 (m, 4H), 4.11 (s, 3H), 3.56 (s, 3H), 3.08 - 2.74 (m, 5H), 2.73 - 2.58 (m, 2H), 2.44 - 2.28 (m, 3H), 2.15 (t, J = 4.0, 9.2Hz, 2H), 2.08 - 1.99 (m, 2H), 1.85 - 1.75 (m, 2H), 1.73 - 1.64 (m, 2H), 1.52 - 1.43 (m, 1H), 1.35 - 1.26 (m, 2H), 0.75 - 0.64 (m, 1H), 0.54 - 0.47 (m, 2H), 0.39 - 0.28 (m, 1H)

Example 124: 3-[6-[1-[[(3*R*,4*S*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-5-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (Compound 151a)



Preparation of *tert*-butyl (3*R*,4*S*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3-fluoro-piperidine-1-carboxylate

To a solution of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indazole (0.7 g, 1.34 mmol, 1 *equiv.*) and *tert*-butyl (3*R*,4*S*)-3-fluoro-4-formyl-piperidine-1-carboxylate (310.96 mg, 1.34 mmol, 1 *equiv.*) in DMSO (10 mL) was added AcOH (8.07 mg, 134.46 μmol, 7.70 μL, 0.1 *equiv.*) and $NaBH(OAc)_3$ (427.47 mg, 2.02 mmol, 1.5 *equiv.*). The mixture was stirred at 25 °C for 2 hours. The reaction mixture was diluted with H_2O (5 mL) and extracted with ethyl acetate (20 mL). The combined organic layers were washed with aqueous sodium chloride (15 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (80/20 to 70/30 petroleum ether/ethyl acetate) to give *tert*-butyl (3*R*,4*S*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3-fluoro-piperidine-1-carboxylate (0.46 g) as a yellow solid.

LC-MS (ESI): m/z = 736.3 $[M+H]^+$

Preparation of *tert*-butyl (3*R*,4*S*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-fluoro-piperidine-1-carboxylate

A mixture of *tert*-butyl (3*R*,4*S*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3-fluoro-piperidine-1-carboxylate (440 mg, 597.94 μmol, 1 *equiv.*), Pd on carbon (127.27 mg, 119.59 μmol, 10% purity, 0.2 *equiv.*), and $Pd(OH)_2$ on carbon (83.97 mg, 119.59 μmol, 20% purity, 0.2 *equiv.*) in CF_3CH_2OH (4 mL) was degassed and purged with H_2 three times. The mixture was stirred at 25 °C for 8 hours under a H_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give *tert*-butyl (3*R*,4*S*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-fluoro-piperidine-1-carboxylate (187 mg) as a brown oil.

LC-MS (ESI): m/z = 560.4 $[M+H]^+$

Preparation of 3-[5-fluoro-6-[1-[[(3*R*,4*S*)-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione

To a solution of *tert*-butyl (3*R*,4*S*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-fluoro-piperidine-1-carboxylate (187 mg, 334.14 μmol, 1 *equiv.*) in DCM (1 mL) was added HCl/dioxane (2 M, 1.67 mL, 10 *equiv.*). The mixture was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give 3-[5-fluoro-6-[1-[[(3*R*,4*S*)-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (153 mg) as a white solid.

LC-MS (ESI): m/z = 460.3 $[M+H]^+$

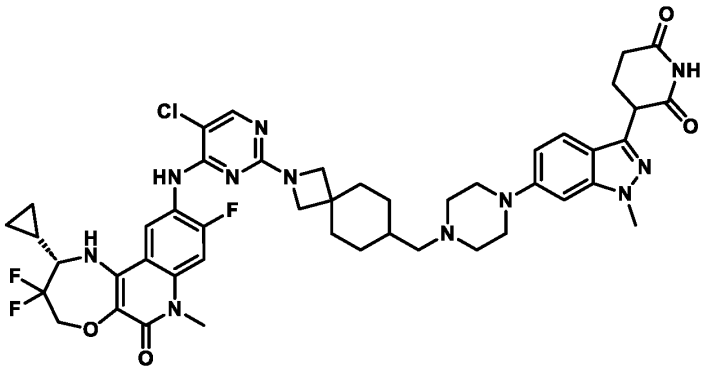
Preparation of 3-[6-[1-[[(3*R*,4*S*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-5-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione

To a solution of 3-[5-fluoro-6-[1-[[(3*R*,4*S*)-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (153 mg, 332.95 μmol, 1 *equiv.*) in DMSO (2 mL) was added TEA (134.76 mg, 1.33 mmol, 185.37 μL, 4 *equiv.*) and (2*S*)-2-cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (161.90 mg, 332.95 μmol, 1 *equiv.*). The mixture was stirred at 100 °C for 1 hour. The reaction mixture was filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give 3-[6-[1-[[(3*R*,4*S*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-5-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (58.36 mg) as a white solid.

LC-MS (ESI): m/z = 909.6 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.87 (s, 1H), 8.85 (s, 1H), 8.20 (br d, J = 8.0 Hz, 1H), 8.14 (s, 1H), 8.02 (s, 1H), 7.54 (d, J = 6.0 Hz, 1H), 7.49 - 7.40 (m, 2H), 6.46 (br d, J = 2.0 Hz, 1H), 4.85 - 4.64 (m, 2H), 4.50 - 4.29 (m, 4H), 3.99 (s, 3H), 3.55 (s, 3H), 3.05 - 2.80 (m, 5H), 2.74 - 2.59 (m, 3H), 2.40 - 2.31 (m, 2H), 2.20 - 1.95 (m, 5H), 1.85 - 1.72 (m, 4H), 1.46 (br d, J = 10.4 Hz, 1H), 1.36 - 1.20 (m, 2H), 0.76 - 0.65 (m, 1H), 0.61 - 0.42 (m, 2H), 0.39 - 0.23 (m, 1H)

Example 125: 3-[6-[4-[[2-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-2-azaspiro[3.5]nonan-7-yl]methyl]piperazin-1-yl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (Compound 193a)



Preparation of *tert*-butyl 7-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]piperazin-1-yl]methyl]-2-azaspiro[3.5]nonane-2-carboxylate

To a solution of 3-(1-methyl-6-(piperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (200 mg, 610.91 μmol, 1 *equiv.*) in DCM (5 mL) was added AcOH (3.67 mg, 61.09 μmol, 3.50 μL, 0.1 *equiv.*), $NaBH(OAc)_3$ (194.22 mg, 916.37 μmol, 1.5 *equiv.*), and *tert*-butyl 7-formyl-2-azaspiro[3.5]nonane-2-carboxylate (154.77 mg, 610.91 μmol, 1 *equiv.*). The mixture was stirred at 25 °C for 1 hour. The reaction mixture was partitioned between H_2O (5 mL) and ethyl acetate (15 mL). The organic phase was separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (0~10% DCM/MeOH) to give *tert*-butyl 7-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]piperazin-1-yl]methyl]-2-azaspiro[3.5]nonane-2-carboxylate (300 mg) as a white solid.

LC-MS (ESI): m/z = 565.3 $[M+H]^+$

Preparation of 3-[6-[4-(2-azaspiro[3.5]nonan-7-ylmethyl)piperazin-1-yl]-1-methyl-indazol-3-yl]piperidine-2,6-dione

To a solution of *tert*-butyl 7-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]piperazin-1-yl]methyl]-2-azaspiro[3.5]nonane-2-carboxylate (150 mg, 265.62 μmol, 1 *equiv.*) in DCM (1.5 mL) was added HCl/dioxane (1.5 mL). The mixture was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give 3-[6-[4-(2-azaspiro[3.5]nonan-7-ylmethyl)piperazin-1-yl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (100 mg) as a white solid.

LC-MS (ESI): m/z = 465.3 $[M+H]^+$

Preparation of 3-[6-[4-[[2-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-

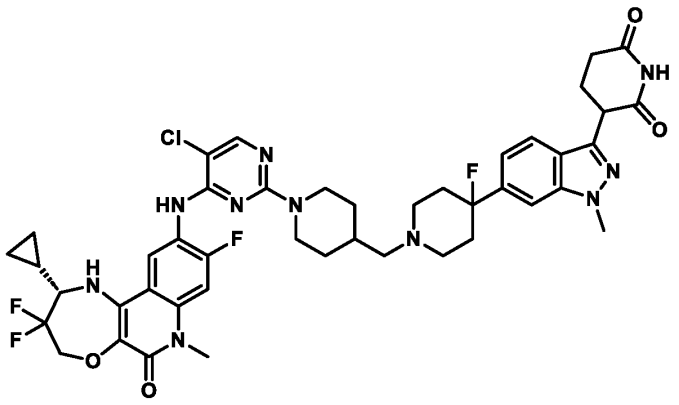
yl]-2-azaspiro[3.5]nonan-7-yl]methyl]piperazin-1-yl]-1-methyl-indazol-3-yl]piperidine-2,6-dione

To a solution of 3-[6-[4-(2-azaspiro[3.5]nonan-7-ylmethyl)piperazin-1-yl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (100 mg, 215.24 μmol, 1 *equiv.*) in DMSO (2 mL) was added TEA (87.12 mg, 860.95 μmol, 119.83 μL, 4 *equiv.*) and (2*S*)-2-cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (73.27 mg, 150.67 μmol, 0.7 *equiv.*). The mixture was stirred at 100 °C for 1 hour. The reaction mixture was filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give 3-[6-[4-[[2-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-2-azaspiro[3.5]nonan-7-yl]methyl]piperazin-1-yl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (0.035 g) as an off-white solid.

LC-MS (ESI): m/z = 914.3[M+H] $^{+}$.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.84 (s, 1H), 8.79 (s, 1H), 8.21 (d, *J* = 8.4 Hz, 1H), 8.00 (s, 1H), 7.54 - 7.36 (m, 2H), 6.90 (d, *J* = 8.8 Hz, 1H), 6.82 (s, 1H), 6.54 - 6.33 (m, 1H), 4.56 - 4.15 (m, 3H), 3.88 (s, 3H), 3.54 (s, 3H), 3.50 (d, *J* = 4.8 Hz, 3H), 3.19 (s, 5H), 2.71 - 2.58 (m, 3H), 2.37 - 2.22 (m, 3H), 2.19 - 2.03 (m, 4H), 1.84 - 1.73 (m, 2H), 1.72 - 1.59 (m, 2H), 1.56 - 1.23 (m, 5H), 0.99 - 0.79 (m, 2H), 0.77 - 0.66 (m, 1H), 0.51 (t, J = 5.6 Hz, 2H), 0.39 - 0.19 (m, 1H)

Example 126: 3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-4-fluoro-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (Compound 186a)



Preparation of *tert*-butyl 4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-

3,6-dihydro-2*H*-pyridine-1-carboxylate

To a solution of 6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazole (30 g, 59.95 mmol, 1 *equiv.*) in dioxane (400 mL) and H_2O (50 mL) was added cesium carbonate (48.84 g, 149.88 mmol, 2.5 *equiv.*), $Pd(dppf)Cl_2$ (4.39 g, 6.00 mmol, 0.1 *equiv.*), and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylate (22.25 g, 71.94 mmol, 1.2 *equiv.*). The mixture was stirred at 100 °C for 2 hours under a N_2 atmosphere. The reaction mixture was quenched by the addition of H_2O (50 mL) and extracted with ethyl acetate (150 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (0~50% ethyl acetate/petroleum ether) to give 6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazole0 (35 g) as a white solid.

LC-MS (ESI): m/z = 603.3 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.93 (d, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.48 - 7.25 (m, 10H), 7.12 (dd, *J* = 1.2, 8.4 Hz, 1H), 6.54 (d, *J* = 8.0 Hz, 1H), 6.23 - 6.08 (m, 1H), 5.53 - 5.37 (m, 4H), 4.11 - 4.05 (m, 3H), 3.71 (t, *J* = 5.2 Hz, 2H), 2.64 (s, 2H), 1.62 - 1.43 (m, 10H), 1.25 (s, 3H)

Preparation of *tert*-butyl 4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-4-hydroxy-piperidine-1-carboxylate

To a solution of *tert*-butyl 4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridine-1-carboxylate (35 g, 58.07 mmol, 1 *equiv.*) in *i*-PrOH (350 mL) and DCM (70 mL) was added phenylsilane (15.71 g, 145.18 mmol, 17.91 mL, 2.5 *equiv.*) and tris[(Z)-1-*tert*-butyl-4,4-dimethyl-3-oxo-pent-1-enoxy]manganese (3.51 g, 5.81 mmol, 0.1 *equiv.*). The mixture was stirred at 25 °C for 12 hours under an O_2 atmosphere. The reaction mixture was quenched by the addition of H_2O (50 mL) and extracted with ethyl acetate (120 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (0~50% ethyl acetate/petroleum ether) to give *tert*-butyl 4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-4-hydroxy-piperidine-1-carboxylate (9.5 g) as a white solid.

LC-MS (ESI): m/z = 621.3 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.90 (d, *J* = 8.0 Hz, 1H), 7.66 (s, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.52 - 7.44 (m, 2H), 7.41 - 7.33 (m, 5H), 7.32 - 7.25 (m, 3H), 7.20 (d, *J* = 1.2 Hz, 1H), 6.58 (d, *J* = 8.0 Hz, 1H), 5.44 (d, *J* = 16.4 Hz, 4H), 5.20 (s, 1H), 4.10 - 4.00 (m, 3H), 3.89

(d, J = 6.4 Hz, 2H), 3.27 - 3.06 (m, 2H), 1.97 - 1.84 (m, 2H), 1.64 (d, J = 12.4 Hz, 2H), 1.43 (s, 8H)

Preparation of *tert*-butyl 4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-4-hydroxy-piperidine-1-carboxylate

To a solution of *tert*-butyl 4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-4-hydroxy-piperidine-1-carboxylate (9.5 g, 15.30 mmol, 1 *equiv.*) in CF_3CH_2OH (100 mL) was added Pd on carbon (4.89 g, 4.59 mmol, 10% purity, 0.3 *equiv.*) and $Pd(OH)_2$ on carbon (3.22 g, 4.59 mmol, 20% purity, 0.3 *equiv.*) under a N_2 atmosphere. The suspension was degassed and purged with H_2 three times. The mixture was stirred under H_2 (15 psi) at 25 °C for 12 hours. The reaction mixture was filtered and concentrated under reduced pressure to give *tert*-butyl 4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-4-hydroxy-piperidine-1-carboxylate (7 g) as a white solid.

Preparation of *tert*-butyl 4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-4-fluoro-piperidine-1-carboxylate

To a solution of *tert*-butyl 4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-4-hydroxy-piperidine-1-carboxylate (7 g, 15.82 mmol, 1 *equiv.*) in DCM (10 mL) was added DAST (10.20 g, 63.28 mmol, 8.36 mL, 4 *equiv.*) at -78 °C under a N_2 atmosphere. The mixture was stirred at -78 °C for 3 hours under a N_2 atmosphere. The reaction mixture was quenched by the addition of H_2O (30 mL) and extracted with ethyl acetate (150 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (0~50% ethyl acetate/petroleum ether) to give *tert*-butyl 4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-4-fluoro-piperidine-1-carboxylate (3.3 g) as a white solid.

LC-MS (ESI): m/z = 445.2 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.90 (s, 1H), 7.75 - 7.66 (m, 2H), 7.22 (dd, J = 1.2, 8.4 Hz, 1H), 4.41 - 4.33 (m, 1H), 4.08 - 4.03 (m, 2H), 3.32 - 3.25 (m, 3H), 3.19 - 3.00 (m, 2H), 2.74 - 2.57 (m, 3H), 2.31 - 2.27 (m, 1H), 2.44 - 2.27 (m, 1H), 2.23 - 2.12 (m, 2H), 2.11 - 2.02 (m, 1H), 1.97 - 1.92 (m, 1H), 1.45 (s, 10H)

Preparation of 3-[6-(4-fluoro-4-piperidyl)-1-methyl-indazol-3-yl]piperidine-2,6-dione

A solution of *tert*-butyl 4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-4-fluoro-piperidine-1-carboxylate (3.30 g, 7.42 mmol, 1 *equiv.*) in HCl/dioxane (30 mL) was stirred at 25 °C for 1 hour. The reaction mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give 3-[6-(4-fluoro-4-piperidyl)-1-methyl-indazol-3-yl]piperidine-2,6-dione (2 g) as a white solid.

LC-MS (ESI): m/z = 345.2 $[M+H]^+$

Preparation of *tert*-butyl 4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-4-fluoro-1-piperidyl]methyl]piperidine-1-carboxylate

To a solution of 3-[6-(4-fluoro-4-piperidyl)-1-methyl-indazol-3-yl]piperidine-2,6-dione (1.50 g, 4.36 mmol, 1 *equiv.*) and *tert*-butyl 4-formylpiperidine-1-carboxylate (1.39 g, 6.53 mmol, 1.50 *equiv.*) in DCM (1 mL) was added dropwise AcOH (26.16 mg, 435.56 μmol, 24.93 μL, 0.1 *equiv.*) at 25 °C. After addition, the mixture was stirred at 25 °C for 30 minutes, and then $NaBH(OAc)_3$ (1.38 g, 6.53 mmol, 1.5 *equiv.*) was added. The resulting mixture was stirred at 25 °C for 1 hour. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (0~100% ethyl acetate/petroleum ether) to give *tert*-butyl 4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-4-fluoro-1-piperidyl]methyl]piperidine-1-carboxylate (1.60 g) as a white solid.

LC-MS (ESI): m/z = 542.2 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.91 (s, 1H), 7.74 - 7.52 (m, 2H), 7.20 (d, *J* = 8.4 Hz, 1H), 6.30 - 6.23 (m, 1H), 4.37 (dd, *J* = 5.2, 10.0 Hz, 1H), 4.04 - 3.98 (m, 3H), 3.94 (d, *J* = 10.8 Hz, 2H), 2.81 (d, *J* = 8.4 Hz, 2H), 2.76 - 2.54 (m, 5H), 2.41- 2.11 (m, 7H), 2.03 - 1.89 (m, 2H), 1.78 - 1.65 (m, 3H), 1.40 (s, 9H), 0.97 (d, *J* = 10.0 Hz, 2H)

Preparation of 3-[6-[4-fluoro-1-(4-piperidylmethyl)-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione

A solution of *tert*-butyl 4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-4-fluoro-1-piperidyl]methyl]piperidine-1-carboxylate (1.30 g, 2.40 mmol, 1 *equiv.*) in HCl/dioxane (10 mL) was stirred at 25 °C for 1 hour. The reaction mixture was filtered and concentrated under reduced pressure to give 3-[6-[4-fluoro-1-(4-piperidylmethyl)-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (1.06 g, crude) as a white solid.

Preparation of 3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-

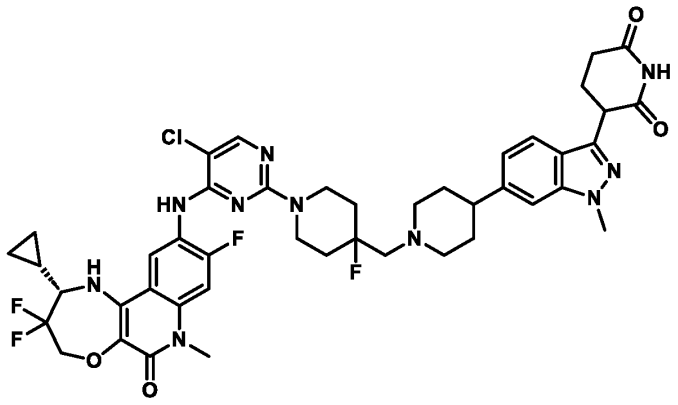
methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-4-fluoro-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione

To a solution of 3-[6-[4-fluoro-1-(4-piperidylmethyl)-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (179 mg, 405.40 μmol, 1 *equiv.*) in DMSO (2 mL) was added TEA (164.09 mg, 1.62 mmol, 225.71 μL, 4 *equiv.*) and (2*S*)-2-cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (197.13 mg, 405.40 μmol, 1 *equiv.*). The mixture was stirred at 100 °C for 1 hour. The reaction mixture was filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give 3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-4-fluoro-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (42.93 mg) as a white solid.

LC-MS (ESI): m/z = 891.3 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.89 (s, 1H), 8.82 (s, 1H), 8.21 (s, 1H), 8.19 (s, 1H), 8.01 (s, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.62 (s, 1H), 7.42 (d, *J* = 12.4 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 1H), 6.44 (d, *J* = 2.4 Hz, 1H), 4.50 - 4.28 (m, 5H), 4.00 (s, 3H), 3.55 (s, 3H), 2.81 - 2.59 (m, 7H), 2.42 - 2.33 (m, 1H), 2.25 (d, *J* = 8.4 Hz, 2H), 2.21 - 2.11 (m, 4H), 1.97 - 1.87 (m, 2H), 1.80 - 1.64 (m, 3H), 1.36 - 1.22 (m, 2H), 0.95 (d, *J* = 10.0 Hz, 2H), 0.75 - 0.66 (m, 1H), 0.57 - 0.47 (m, 2H), 0.37 - 0.27 (m, 1H)

Example 127: 3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-fluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (Compound 194a)



Preparation of 3-[1-methyl-6-(4-piperidyl)indazol-3-yl]piperidine-2,6-dione

To a solution of *tert*-butyl 4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]piperidine-1-carboxylate (1 g, 2.34 mmol, 1 *equiv.*) in DCM (2 mL) was added HCl/dioxane (2 M, 10 mL, 8.53 *equiv.*). The mixture was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give 3-[1-methyl-6-(4-piperidyl)indazol-3-yl]piperidine-2,6-dione (0.8 g, crude) as a violet solid.

LC-MS (ESI): m/z = 327.2 $[M+H]^+$

Preparation of *tert*-butyl 4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-4-fluoro-piperidine-1-carboxylate

To a solution of 3-[1-methyl-6-(4-piperidyl)indazol-3-yl]piperidine-2,6-dione (0.5 g, 1.53 mmol, 1 *equiv.*) in DMSO (6 mL) was added *tert*-butyl 4-fluoro-4-formyl-piperidine-1-carboxylate (425.13 mg, 1.84 mmol, 1.2 *equiv.*) and Ti(*i*-PrO)$_4$ (1.31 g, 4.60 mmol, 1.36 mL, 3 *equiv.*). The mixture was stirred for 12 hours, then $NaBH(OAc)_3$ (487.01 mg, 2.30 mmol, 1.5 *equiv.*) was added. The mixture was stirred at 25 °C for 4 hours. The reaction mixture was diluted with H_2O (10 mL) and extracted with ethyl acetate (15 mL × 3). The combined organic layers were washed with sodium chloride (20 mL × 3), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (5% methanol in DCM) to afford *tert*-butyl 4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-4-fluoro-piperidine-1-carboxylate (0.15 g) as a colorless oil.

LC-MS (ESI): m/z = 542.2 $[M+H]^+$

Preparation of 3-[6-[1-[(4-fluoro-4-piperidyl)methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione

To a solution of *tert*-butyl 4-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-4-fluoro-piperidine-1-carboxylate (0.15 g, 276.93 μmol, 1 *equiv.*) in DCM (2 mL) was added HCl/dioxane (2 M, 5 mL, 36.11 *equiv.*). The mixture was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give 3-[6-[1-[(4-fluoro-4-piperidyl)methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (0.15 g, crude) as a yellow oil.

LC-MS (ESI): m/z = 442.2 $[M+H]^+$

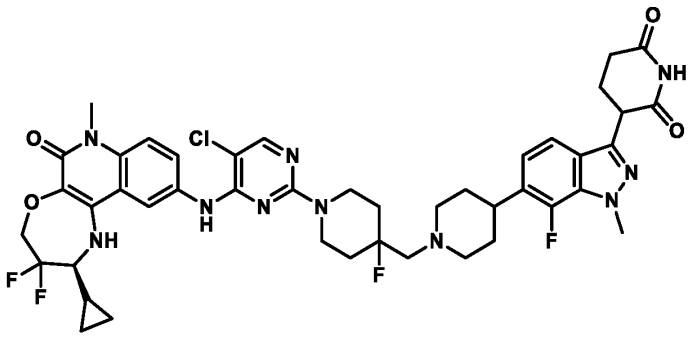
Preparation of 3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-fluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione

To a solution of 3-[6-[1-[(4-fluoro-4-piperidyl)methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (0.15 g, 339.72 μmol, 1 *equiv.*) in DMSO (2 mL) was added TEA (137.50 mg, 1.36 mmol, 189.14 μL, 4 *equiv.*) and (2*S*)-2-cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (148.68 mg, 305.75 μmol, 0.9 *equiv.*). The mixture was stirred at 100 °C for 1 hour. The reaction mixture was filtered and the crude product was purified by prep-HPLC to give 3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-fluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (0.0247 g) as a yellow solid.

LC-MS (ESI): m/z = 446.6 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.87 (s, 1H), 8.87 (s, 1H), 8.27 (s, 1H), 8.22 (d, J = 8.0 Hz, 1H), 8.05 (s, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.47 - 7.35 (m, 2H), 7.02 (s, 1H), 6.49 - 6.35 (m, 1H), 4.53 - 4.26 (m, 3H), 4.11 - 3.99 (m, 2H), 3.96 (s, 3H), 3.55 (s, 3H), 3.16 - 2.93 (m, 7H), 2.35 - 2.29 (m, 2H), 2.25 - 2.11 (m, 4H), 1.78 - 1.73 (m, 4H), 1.64 - 1.46 (m, 3H), 1.37 - 1.21 (m, 2H), 0.69 (s, 1H), 0.59 - 0.45 (m, 2H), 0.32 (d, J = 4.4 Hz, 1H).

Example 128: 3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-fluoro-4-piperidyl]methyl]-4-piperidyl]-7-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (Compound 191a)



Preparation of *tert*-butyl 4-[[4-[3-(2,6-dioxo-3-piperidyl)-7-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-4-fluoro-piperidine-1-carboxylate

A solution of 3-[7-fluoro-1-methyl-6-(4-piperidyl)indazol-3-yl]piperidine-2,6-dione (310 mg, 900.16 μmol, 1 *equiv.*), tetraisopropoxytitanium (767.52 mg, 2.70 mmol, 797.01 μL, 3 *equiv.*), and *tert*-butyl 4-fluoro-4-formyl-piperidine-1-carboxylate (312.26 mg, 1.35 mmol, 1.5 *equiv.*) in DMSO (14 mL) was stirred at 25 °C for 12 hours. To this mixture, $NaBH(OAc)_3$ (381.56 mg, 1.80 mmol, 2 *equiv.*) was added, and the resulting mixture was stirred at 25 °C for 5 hours. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (5% DCM/MeOH) to give *tert*-butyl 4-[[4-[3-(2,6-dioxo-3-piperidyl)-7-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-4-fluoro-piperidine-1-carboxylate (195 mg) as a yellow oil.

LC-MS (ESI): m/z = 560.2 $[M+H]^+$.

Preparation of 3-[7-fluoro-6-[1-[(4-fluoro-4-piperidyl)methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione

To a solution of *tert*-butyl 4-[[4-[3-(2,6-dioxo-3-piperidyl)-7-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-4-fluoro-piperidine-1-carboxylate (195 mg, 348.43 μmol, 1 *equiv.*) in DCM (1 mL) was added HCl/dioxane (2 M, 1.74 mL, 10 *equiv.*). The mixture was stirred at 25 °C for 0.5 hours. The reaction mixture was concentrated under reduced pressure to give 3-[7-fluoro-6-[1-[(4-fluoro-4-piperidyl)methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (160 mg) as a yellow solid.

LC-MS (ESI): m/z = 460.1 $[M+H]^+$.

Preparation of 3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-fluoro-4-piperidyl]methyl]-4-piperidyl]-7-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-

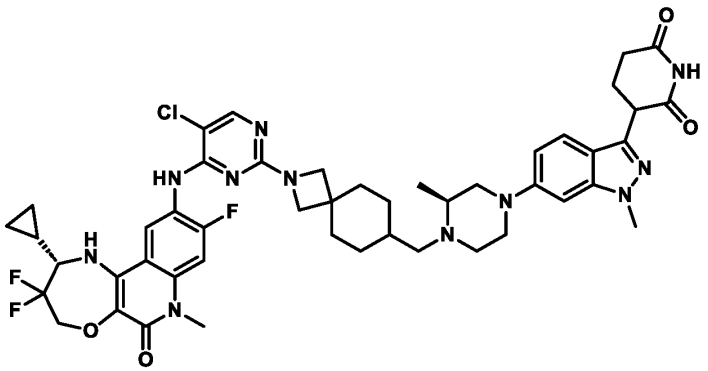
dione

To a solution of 3-[7-fluoro-6-[1-[(4-fluoro-4-piperidyl)methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (160 mg, 348.18 μmol, 1 *equiv.*) in DMSO (1 mL) was added TEA (140.93 mg, 1.39 mmol, 193.85 μL, 4 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (146.74 mg, 313.36 μmol, 0.9 *equiv.*). The mixture was stirred at 100 °C for 1 hour. The reaction mixture was filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give 3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-fluoro-4-piperidyl]methyl]-4-piperidyl]-7-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (44.06 mg) as a yellow solid.

LC-MS (ESI): m/z = 891.3 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.91 (s, 1H), 8.84 (s, 1H), 8.22 (d, *J* = 2.0 Hz, 1H), 8.20 (s, 1H), 8.06 (s, 1H), 7.71 (d, *J* = 2.0 Hz, 1H), 7.45 (d, *J* = 8.8 Hz, 2H), 7.04 (d, *J* = 6.0 Hz, 1H), 6.20 (s, 1H), 4.51 - 4.30 (m, 3H), 4.24 - 4.14 (m, 2H), 4.10 (s, 3H), 3.57 (s, 3H), 3.08 - 2.84 (m, 5H), 2.78 - 2.60 (m, 3H), 2.38 - 2.32 (m, 2H), 2.28 - 2.12 (m, 4H), 1.90 - 1.75 (m, 4H), 1.73 - 1.57 (m, 4H), 1.39 - 1.30 (m, 1H), 0.75 - 0.66 (m, 1H), 0.57 - 0.46 (m, 2H), 0.39 - 0.31 (m, 1H).

Example 129: 3-[6-[(3*S*)-4-[[2-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-2-azaspiro[3.5]nonan-7-yl]methyl]-3-methyl-piperazin-1-yl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (Compound 187a)



Preparation of *tert*-butyl (2*S*)-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-2-methyl-piperazine-1-carboxylate

A mixture of 6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazole (2.5 g, 5.00

mmol, 0.8 *equiv.*), *tert*-butyl (2*S*)-2-methylpiperazine-1-carboxylate (1.50 g, 7.49 mmol, 1.2 *equiv.*), Ruphos-Pd-G3 (522.33 mg, 624.52 μmol, 0.1 *equiv.*), t-BuONa (3.00 g, 31.23 mmol, 5 *equiv.*) in 1,4-dioxane (50 mL) was degassed and purged with N_2 three times. The mixture was then stirred at 95 °C for 12 hours under a N_2 atmosphere. The reaction mixture was concentrated under reduced pressure to remove the solvent. The residue was diluted with water (500 mL) and extracted with ethyl acetate (1500 mL). The combined organic layers were washed with brine (1000 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (0~20% ethyl acetate/petroleum ether) to give *tert*-butyl (2*S*)-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-2-methyl-piperazine-1-carboxylate (2.75 g) as a yellow oil.

LC-MS (ESI): m/z = 620.3 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.91 - 7.86 (m, 1H), 7.52 (d, *J* = 9.2 Hz, 1H), 7.48 - 7.44 (m, 2H), 7.42 - 7.25 (m, 8H), 6.87 - 6.83 (m, 1H), 6.83 - 6.77 (m, 1H), 6.56 (d, *J* = 8.0 Hz, 1H), 5.43 (d, *J* = 17.6 Hz, 4H), 4.29 - 4.18 (m, 1H), 3.83 (d, *J* = 13.2 Hz, 1H), 3.69 - 3.63 (m, 1H), 3.60 - 3.54 (m, 1H), 3.31 (s, 3H), 3.26 - 3.16 (m, 1H), 2.89 (d, *J* = 4.0 Hz, 1H), 2.70 (t, *J* = 3.2 Hz, 1H), 1.43 (s, 9H), 1.22 (d, *J* = 6.8 Hz, 3H).

Preparation of *tert*-butyl (2*S*)-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-2-methyl-piperazine-1-carboxylate

To a solution of *tert*-butyl (2*S*)-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-2-methyl-piperazine-1-carboxylate (2.75 g, 4.44 mmol, 1 *equiv.*) in CF_3CH_2OH (50 mL) was added Pd on carbon (1.42 g, 1.33 mmol, 10% purity, 0.3 *equiv.*) and $Pd(OH)_2$ on carbon (1.25 g, 887.45 μmol, 10% purity, 0.2 *equiv.*) under a N_2 atmosphere. The suspension was degassed and purged with H_2 three times. The mixture was stirred under H_2 (15 psi) at 25 °C for 12 hours. The reaction mixture was filtered and concentrated under reduced pressure to give *tert*-butyl (2*S*)-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-2-methyl-piperazine-1-carboxylate (1.8 g, crude) as a black solid, which was used in the next step without further purification.

LC-MS (ESI): m/z = 442.2 $[M+H]^+$

Preparation of 3-[1-methyl-6-[(3*S*)-3-methylpiperazin-1-yl]indazol-3-yl]piperidine-2,6-dione

A solution of *tert*-butyl (2*S*)-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-2-methyl-piperazine-1-carboxylate (500 mg, 1.13 mmol, 1 *equiv.*) in HCl/dioxane (10 mL) /

DCM (10 mL) was stirred at 25 °C for 3 hours. The reaction mixture was concentrated under reduced pressure to give 3-[1-methyl-6-[(3*S*)-3-methylpiperazin-1-yl]indazol-3-yl]piperidine-2,6-dione (350 mg, crude) as a pink solid, which was used in the next step without further purification.

LC-MS (ESI): m/z = 342.0 $[M+H]^+$

Preparation of *tert*-butyl 7-[[(2*S*)-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-2-methyl-piperazin-1-yl]methyl]-2-azaspiro[3.5]nonane-2-carboxylate

To a solution of 3-[1-methyl-6-[(3*S*)-3-methylpiperazin-1-yl]indazol-3-yl]piperidine-2,6-dione (500 mg, 1.32 mmol, 1 *equiv.*, HCl) and *tert*-butyl 7-formyl-2-azaspiro[3.5]nonane-2-carboxylate (402.26 mg, 1.59 mmol, 1.2 *equiv.*) in DCM (10 mL) was added AcOH (7.95 mg, 132.32 μmol, 7.57 μL, 0.1 *equiv.*) and $NaBH(OAc)_3$ (420.66 mg, 1.98 mmol, 1.5 *equiv.*). The mixture was stirred at 25 °C for 3 hours. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (0~100% ethyl acetate/petroleum ether) to give *tert*-butyl 7-[[(2*S*)-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-2-methyl-piperazin-1-yl]methyl]-2-azaspiro[3.5]nonane-2-carboxylate (400 mg) as a white solid.

LC-MS (ESI): m/z = 579.3 $[M+H]^+$

Preparation of 3-[6-[(3*S*)-4-(2-azaspiro[3.5]nonan-7-ylmethyl)-3-methyl-piperazin-1-yl]-1-methyl-indazol-3-yl]piperidine-2,6-dione

A solution of *tert*-butyl 7-[[(2*S*)-4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-2-methyl-piperazin-1-yl]methyl]-2-azaspiro[3.5]nonane-2-carboxylate (330 mg, 570.20 μmol, 1 *equiv.*) in HCl/dioxane (2 mL) / DCM (2 mL) was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give 3-[6-[(3*S*)-4-(2-azaspiro[3.5]nonan-7-ylmethyl)-3-methyl-piperazin-1-yl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (200 mg), which was used in the next step without further purification.

LC-MS (ESI): m/z = 479.3 $[M+H]^+$

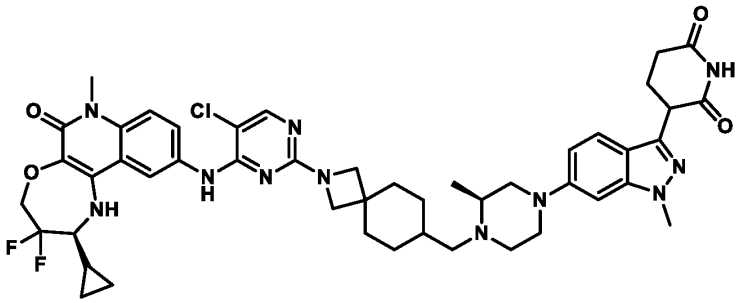
Preparation of 3-[6-[(3*S*)-4-[[2-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-2-azaspiro[3.5]nonan-7-yl]methyl]-3-methyl-piperazin-1-yl]-1-methyl-indazol-3-yl]piperidine-2,6-dione

To a solution of 3-[6-[(3*S*)-4-(2-azaspiro[3.5]nonan-7-ylmethyl)-3-methyl-piperazin-1-yl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (200 mg, 417.86 μmol, 1 *equiv.*) and (2*S*)-2-cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (60.96 mg, 125.36 μmol, 0.3 *equiv.*) in DMSO (3 mL) was added TEA (169.13 mg, 1.67 mmol, 232.64 μL, 4 *equiv.*). The mixture was stirred at 100 °C for 12 hours. The reaction mixture was filtered to give a residue. The residue was purified by prep-HPLC to give 3-[6-[(3*S*)-4-[[2-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-2-azaspiro[3.5]nonan-7-yl]methyl]-3-methyl-piperazin-1-yl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (31.92 mg) as a pink solid.

LC-MS (ESI): m/z = 928.2 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.83 (s, 1H), 8.77 (s, 1H), 8.26 - 8.21 (m, 1H), 8.20 (s, 1H), 8.00 (s, 1H), 7.51 - 7.45 (m, 1H), 7.41 (d, J = 12.4Hz, 1H), 6.93 - 6.86 (m, 1H), 6.84 - 6.77 (m, 1H), 6.50 - 6.40 (m, 1H), 4.50 - 4.30 (m, 2H), 4.28 - 4.21 (m, 1H), 3.88 (s, 3H), 3.54 (s, 3H), 3.49 (d, J = 10.0Hz, 6H), 2.95 - 2.80 (m, 3H), 2.67 (s, 1H), 2.35 - 2.10 (m, 5H), 1.96 - 1.85 (m, 1H), 1.83 - 1.72 (m, 3H), 1.62 - 1.51 (m, 1H), 1.46 - 1.26 (m, 5H), 1.08 - 1.00 (m, 3H), 0.97 - 0.76 (m, 3H), 0.75 - 0.66 (m, 1H), 0.56 - 0.46 (m, 2H), 0.36 - 0.27 (m, 1H).

Example 130: 3-[6-[(3*S*)-4-[[2-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-2-azaspiro[3.5]nonan-7-yl]methyl]-3-methyl-piperazin-1-yl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (Compound 188a)



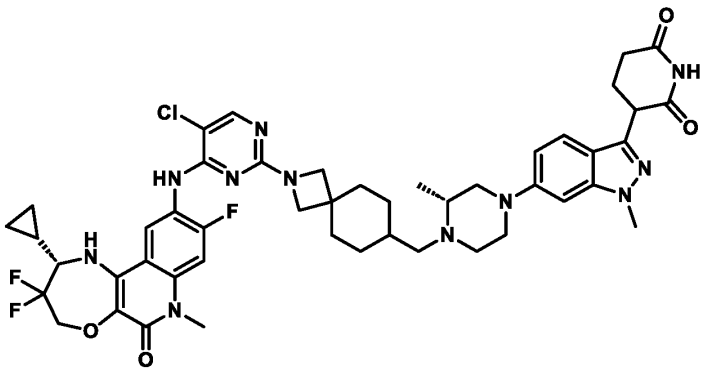
Preparation of 3-[6-[(3*S*)-4-[[2-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-2-azaspiro[3.5]nonan-7-yl]methyl]-3-methyl-piperazin-1-yl]-1-methyl-indazol-3-yl]piperidine-2,6-dione

To a solution of 3-[6-[(3*S*)-4-(2-azaspiro[3.5]nonan-7-ylmethyl)-3-methyl-piperazin-1-yl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (200 mg, 417.86 μmol, 1 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (156.54 mg, 334.29 μmol, 0.8 *equiv.*) in DMSO (3 mL) was added TEA (169.13 mg, 1.67 mmol, 232.65 μL, 4 *equiv.*). The mixture was stirred at 100 °C for 12 hours. The reaction mixture was filtered to give a residue. The residue was purified by prep-HPLC to give 3-[6-[(3*S*)-4-[[2-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-2-azaspiro[3.5]nonan-7-yl]methyl]-3-methyl-piperazin-1-yl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (188.07 mg) as a white solid.

LC-MS (ESI): m/z = 910.3 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.84 (s, 1H), 8.73 (s, 1H), 8.27 (s, 1H), 8.17 (s, 1H), 8.01 (s, 1H), 7.82 (d, J = 8.4Hz, 1H), 7.46 (d, J = 9.2Hz, 2H), 6.90 (d, J = 9.2Hz, 1H), 6.81 (s, 1H), 6.10 (s, 1H), 4.52 - 4.31 (m, 2H), 4.25 (d, J = 5.2Hz, 1H), 3.88 (s, 3H), 3.56 (s, 3H), 3.49 (d, J = 11.2Hz, 5H), 3.01 - 2.79 (m, 3H), 2.68 - 2.61 (m, 1H), 2.47 - 2.37 (m, 2H), 2.34 - 2.09 (m, 4H), 1.95 - 1.74 (m, 4H), 1.64 - 1.53 (m, 1H), 1.52 - 1.16 (m, 5H), 1.05 (d, J = 6.0Hz, 3H), 0.99 - 0.78 (m, 2H), 0.76 - 0.67 (m, 1H), 0.58 - 0.47 (m, 2H), 0.40 - 0.31 (m, 1H)

Example 131: 3-(6-((*R*)-4-((2-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-3-methylpiperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 187b)



Preparation of *tert*-butyl (*R*)-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)-2-methylpiperazine-1-carboxylate

To a mixture of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-1-methyl-1*H*-indazole (1 g, 2.00 mmol, 0.8 *equiv.*), *tert*-butyl (2R)-2-methylpiperazine-1-carboxylate (600.37 mg, 3.00

mmol, 1.2 *equiv.*), t-BuONa (1.20 g, 12.49 mmol, 5 *equiv.*) in dioxane (100 mL), RuPhos-Pd-G3 (208.93 mg, 249.81 μmol, 0.1 *equiv.*) was added under a N_2 atmosphere. The reaction mixture was degassed and purged with N_2 three times. The mixture was stirred at 95 °C for 3 hours under a N_2 atmosphere. The reaction mixture was poured into H_2O (200 mL) and extracted with ethyl acetate (300 mL). The combined organic layers were washed with brine (100 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 10/1 to 5/1) to give *tert*-butyl (*R*)-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)-2-methylpiperazine-1-carboxylate (5 g) as a yellow oil.

LC-MS (ESI): m/z = 620.4 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.89 (d, J = 8.0 Hz, 1H), 7.56 - 7.43 (m, 3H), 7.42 - 7.24 (m, 8H), 6.87 - 6.76 (m, 2H), 6.56 (d, J = 8.0 Hz, 1H), 5.43 (d, J = 17.2 Hz, 4H), 4.27 - 4.17 (m, 1H), 3.96 (s, 3H), 3.83 (d, J = 13.2 Hz, 1H), 3.58 (d, J = 12.4 Hz, 1H), 3.26 - 3.14 (m, 1H), 2.91 - 2.90 (m, 1H), 2.88 (d, J = 3.6 Hz, 1H), 2.70 (t, J = 3.2, 1H), 1.43 (s, 9H), 1.22 (d, J = 6.4 Hz, 3H).

Preparation of *tert*-butyl (2R)-4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)-2-methylpiperazine-1-carboxylate

To a solution of Pd on carbon (2.5 g, 2.35 mmol, 10% purity, 0.291 *equiv.*) and $Pd(OH)_2$/C (2.5 g, 3.56 mmol, 20% purity, 0.441 *equiv.*) in CF_3CH_2OH (100 mL) was added *tert*-butyl (*R*)-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)-2-methylpiperazine-1-carboxylate (5 g, 8.07 mmol, 1.0 *equiv.*) under a N_2 atmosphere. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 psi) at 25 °C for 18 hours. The reaction mixture was filtered and concentrated to give *tert*-butyl (2R)-4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)-2-methylpiperazine-1-carboxylate (3.2 g, crude) as a purple solid.

LC-MS (ESI): m/z = 442.1 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.84 (s, 1H), 7.51 (d, J = 8.8 Hz, 1H), 6.92 - 6.79 (m, 2H), 4.26 - 4.19 (m, 1H), 3.93 - 3.78 (m, 4H), 3.71 - 3.53 (m, 2H), 3.26 - 3.14 (m, 2H), 2.89 (d, J = 3.6 Hz, 1H), 2.76 - 2.56 (m, 3H), 2.36 - 2.24 (m, 1H), 2.21 - 2.07 (m, 1H), 1.43 (s, 9H), 1.22 (d, J = 6.4 Hz, 3H).

Preparation of 3-(1-methyl-6-((*R*)-3-methylpiperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione

A mixture of *tert*-butyl (2R)-4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)-2-methylpiperazine-1-carboxylate (2.2 g, 4.98 mmol, 1.0 *equiv.*) in HCl/dioxane (20 mL) and DCM (20 mL) was stirred at 25 °C for 2 hours. The reaction mixture was concentrated under reduced pressure to give 3-(1-methyl-6-((*R*)-3-methylpiperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (2.1 g, crude, HCl) as a brown solid.

LC-MS (ESI): m/z = 342.2 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.85 (s, 1H), 9.60 (d, J = 8.8 Hz, 1H), 9.47 - 9.21 (m, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.02 - 6.89 (m, 2H), 4.28 (d, J = 5.2 Hz, 1H), 3.92 (s, 3H), 3.46 - 3.32 (m, 2H), 3.18 - 3.05 (m, 2H), 2.88 (d, J = 10.8 Hz, 1H), 2.69 - 2.57 (m, 2H), 2.31 (t, J = 3.6 Hz, 1H), 2.24 - 2.09 (m, 1H), 1.34 (d, J = 6.4 Hz, 3H)

Preparation of *tert*-butyl 7-(((2R)-4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)-2-methylpiperazin-1-yl)methyl)-2-azaspiro[3.5]nonane-2-carboxylate

A mixture of 3-(1-methyl-6-((*R*)-3-methylpiperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (1 g, 2.65 mmol, 1 *equiv.*, HCl), *tert*-butyl 7-formyl-2-azaspiro[3.5]nonane-2-carboxylate (804.52 mg, 3.18 mmol, 1.2 *equiv.*), $NaBH(OAc)_3$ (841.33 mg, 3.97 mmol, 1.5 *equiv.*), AcOH (15.89 mg, 264.64 μmol, 15.15 μL, 0.1 *equiv.*) in DCM (10 mL) was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (DCM/methanol = 100/1 to 10/1) to give *tert*-butyl 7-(((2R)-4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)-2-methylpiperazin-1-yl)methyl)-2-azaspiro[3.5]nonane-2-carboxylate (0.85 g) as a yellow oil.

LC-MS (ESI): m/z = 579.3 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.84 (s, 1H), 7.48 (d, J = 8.8 Hz, 1H), 6.90 (d, J = 9.2 Hz, 1H), 6.81 (s, 1H), 4.25 (d, J = 5.2 Hz, 1H), 3.88 (s, 3H), 3.58 - 3.41 (m, 7H), 3.00 - 2.75 (m, 3H), 2.67 - 2.54 (m, 5H), 2.36 - 2.09 (m, 4H), 1.78 (d, J = 9.2 Hz, 4H), 1.63 - 1.52 (m, 1H), 1.37 (s, 9H), 1.05 (d, J = 5.6 Hz, 3H), 0.98 - 0.75 (m, 2H).

Preparation of 3-(6-((*R*)-4-((2-azaspiro[3.5]nonan-7-yl)methyl)-3-methylpiperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

A mixture of *tert*-butyl 7-(((2R)-4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)-2-methylpiperazin-1-yl)methyl)-2-azaspiro[3.5]nonane-2-carboxylate (0.4 g, 691.15 μmol, 1 *equiv.*) in DCM (3 mL) and HCl/dioxane (3 mL) was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give 3-(6-((*R*)-4-((2-

azaspiro[3.5]nonan-7-yl)methyl)-3-methylpiperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.35 g) as a yellow solid.

LC-MS (ESI): m/z = 479.2 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.85 (s, 1H), 10.73 - 10.40 (m, 1H), 9.32 - 9.02 (m, 2H), 7.61 - 7.49 (m, 1H), 7.04 - 6.90 (m, 2H), 4.28 (d, J = 5.2 Hz, 1H), 3.93 - 3.83 (m, 5H), 3.68 - 3.58 (m, 9H), 3.29 - 3.11 (m, 3H), 3.01 - 2.77 (m, 2H), 2.70 - 2.58 (m, 2H), 2.36 - 2.25 (m, 1H), 2.21 - 2.10 (m, 1H), 2.09 - 1.97 (m, 3H), 2.02 - 1.97 (m, 1H), 1.89 - 1.73 (m, 2H), 1.16 - 0.92 (m, 2H).

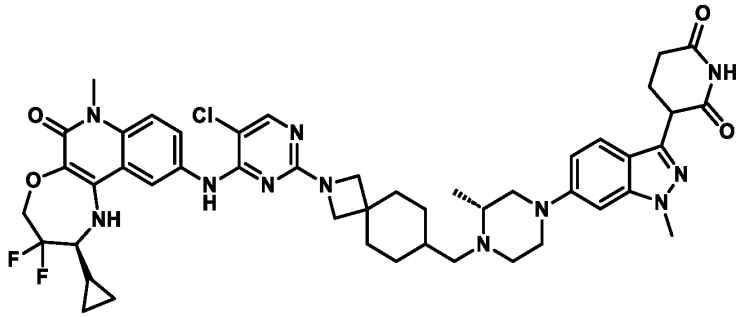
Preparation of 3-(6-((*R*)-4-((2-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-3-methylpiperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

A solution of 3-(6-((*R*)-4-((2-azaspiro[3.5]nonan-7-yl)methyl)-3-methylpiperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (150 mg, 291.21 μmol, 1.13 *equiv.*, HCl), (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3,9-trifluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (100 mg, 205.65 μmol, 0.8 *equiv.*), and TEA (104.05 mg, 1.03 mmol, 143.12 μL, 4 *equiv.*) in DMSO (2 mL) was stirred at 100 °C for 2 hours. The reaction mixture was concentrated under reduced pressure and purified by prep-HPLC to give 3-(6-((*R*)-4-((2-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-3-methylpiperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (25.39 mg) as a yellow solid.

LC-MS (ESI): m/z = 928.3 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.85 (s, 1H), 8.78 (s, 1H), 8.22 (d, J = 8.0Hz, 1H), 8.00 (s, 1H), 7.55 - 7.34 (m, 2H), 6.90 (d, J = 8.8Hz, 1H), 6.81 (s, 1H), 6.45 (s, 1H), 4.53 - 4.29 (m, 2H), 4.25 (d, J = 5.2Hz, 1H), 3.88 (s, 3H), 3.54 (s, 9H), 2.98 - 2.80 (m, 2H), 2.66 - 2.53 (m, 4H), 2.36 - 2.07 (m, 4H), 1.97 - 1.68 (m, 4H), 1.65 - 1.20 (m, 6H), 1.04 (d, J = 6.0Hz, 3H), 0.97 - 0.64 (m, 3H), 0.51 (t, J = 5.6Hz, 2H), 0.38 - 0.25 (m, 1H)

Example 132: 3-(6-((*R*)-4-((2-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-3-methylpiperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 188b)



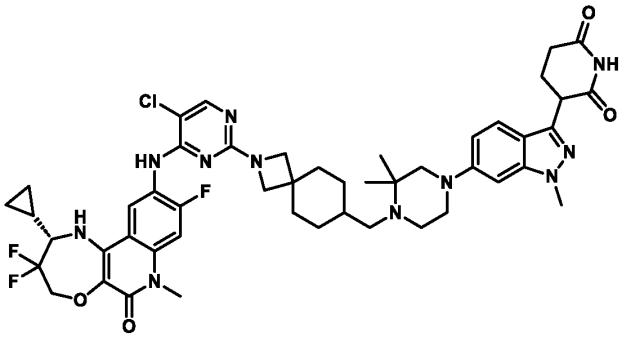
Preparation of 3-(6-((*R*)-4-((2-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-3-methylpiperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

A solution of 3-(6-((*R*)-4-((2-azaspiro[3.5]nonan-7-yl)methyl)-3-methylpiperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.2 g, 388.28 μmol, 1 *equiv.*, HCl), (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (145.46 mg, 310.63 μmol, 0.8 *equiv.*), and TEA (157.16 mg, 1.55 mmol, 216.18 μL, 4 *equiv.*) in DMSO (4 mL) was stirred at 100 °C for 2 hours. The reaction mixture was concentrated under reduced pressure and purified by prep-HPLC to give 3-(6-((*R*)-4-((2-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-3-methylpiperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (133.43 mg) as a yellow solid.

LC-MS (ESI): m/z = 910.3 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.85 (s, 1H), 8.73 (s, 1H), 8.27 (s, 1H), 8.01 (s, 1H), 7.82 (d, J = 9.2 Hz, 1H), 7.46 (J = 9.2 Hz, 2H), 6.90 (d, J = 8.8 Hz, 1H), 6.82 (s, 1H), 6.11 (s, 1H), 4.53 - 4.31 (m, 2H), 4.25 (J = 5.2 Hz, 1H), 3.88 (s, 3H), 3.56 (s, 9H), 3.00 - 2.80 (m, 2H), 2.71 - 2.53 (m, 4H), 2.36 - 2.09 (m, 4H), 1.97 - 1.73 (m, 4H), 1.69 - 1.19 (m, 6H), 1.05 (d, J = 6.0 Hz, 3H), 0.99 - 0.80 (m, 2H), 0.78 - 0.67 (m, 1H), 0.52 (t, J = 6.0 Hz, 2H), 0.42 - 0.31 (m, 1H).

Example 133: 3-[6-[4-[[2-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-2-azaspiro[3.5]nonan-7-yl]methyl]-3,3-dimethyl-piperazin-1-yl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (Compound 195a)



Preparation of *tert*-butyl 4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-2,2-dimethyl-piperazine-1-carboxylate

A mixture of 6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazole (3 g, 6.00 mmol, 1 *equiv.*), *tert*-butyl 2,2-dimethylpiperazine-1-carboxylate (1.54 g, 7.19 mmol, 1.2 *equiv.*), RuPhos-Pd-G3 (501.43 mg, 599.54 μmol, 0.1 *equiv.*), and t-BuONa (2.88 g, 29.98 mmol, 5 *equiv.*) in dioxane (30 mL) was degassed and purged with N_2 three times. The mixture was stirred at 95 °C for 3 hours under a N_2 atmosphere. The reaction mixture was diluted with water (40 mL) and extracted with EtOAc (120 mL). The combined organic layers were washed with brine (120 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (15-20% ethyl acetate/petroleum ether) to give *tert*-butyl 4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-2,2-dimethyl-piperazine-1-carboxylate (2.6 g) as a yellow oil.

LC-MS (ESI): m/z = 634.5 $[M+H]^+$

Preparation of *tert*-butyl 4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-2,2-dimethyl-piperazine-1-carboxylate

To a solution of *tert*-butyl 4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-2,2-dimethyl-piperazine-1-carboxylate (2.6 g, 4.10 mmol, 1 *equiv.*) in CF_3CH_2OH (26 mL) was added Pd on carbon (1.00 g, 943.55 μmol, 10% purity, 0.23 *equiv.*) and $Pd(OH)_2$ on carbon (1.01 g, 1.44 mmol, 20% purity, 0.35 *equiv.*) under a N_2 atmosphere. The suspension was degassed and purged with H_2 three times. The mixture was stirred under H_2 (15 psi) at 25 °C for 12 hours. The reaction mixture was filtered and concentrated under reduced pressure to give *tert*-butyl 4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-2,2-dimethyl-piperazine-1-carboxylate (1.8 g, crude) as a black solid.

LC-MS (ESI): m/z = 456.2 $[M+H]^+$

Preparation of 3-[6-(3,3-dimethylpiperazin-1-yl)-1-methyl-indazol-3-yl]piperidine-2,6-dione

To a solution of *tert*-butyl 4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-2,2-dimethyl-piperazine-1-carboxylate (1.8 g, 3.95 mmol, 1 *equiv.*) in DCM (9 mL) was added HCl/dioxane (2 M, 9 mL, 4.56 *equiv.*). The mixture was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give 3-[6-(3,3-dimethylpiperazin-1-yl)-1-methyl-indazol-3-yl]piperidine-2,6-dione (2.1 g, crude, HCl) as a black solid.

LC-MS (ESI): m/z = 356.1 $[M+H]^+$.

Preparation of *tert*-butyl 7-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-2,2-dimethyl-piperazin-1-yl]methyl]-2-azaspiro[3.5]nonane-2-carboxylate

To a solution of 3-[6-(3,3-dimethylpiperazin-1-yl)-1-methyl-indazol-3-yl]piperidine-2,6-dione (2.1 g, 5.36 mmol, 1 *equiv.*, HCl) and *tert*-butyl 7-formyl-2-azaspiro[3.5]nonane-2-carboxylate (1.63 g, 6.43 mmol, 1.2 *equiv.*) in DCM (21 mL), AcOH (321.79 mg, 5.36 mmol, 306.76 µL, 1 *equiv.*) was added. The mixture was stirred at 25 °C for 2 hours, followed by the addition of $NaBH(OAc)_3$ (1.70 g, 8.04 mmol, 1.5 *equiv.*). The resulting mixture was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure and purified by flash silica gel chromatography (4% DCM/methanol) to give *tert*-butyl 7-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-2,2-dimethyl-piperazin-1-yl]methyl]-2-azaspiro[3.5]nonane-2-carboxylate (220 mg) as a yellow solid.

LC-MS (ESI): m/z = 593.6 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.84 (s, 1H), 7.47 (d, *J* = 8.8 Hz, 1H), 6.88 (d, *J* = 9.2 Hz, 1H), 6.80 (s, 1H), 4.27 - 4.23 (s, 1H), 3.88 (s, 3H), 3.54 - 3.40 (m, 5H), 3.20 - 3.09 (m, 4H), 2.93 (s, 2H), 2.69 - 2.54 (m, 4H), 2.35 - 2.22 (m, 1H), 2.20 - 2.06 (m, 3H), 1.80 (d, *J* = 12.8 Hz, 2H), 1.73 - 1.64 (m, 2H), 1.37 (s, 10H), 1.03 (s, 6H), 0.90 - 0.78 (m, 2H).

Preparation of 3-[6-[4-(2-azaspiro[3.5]nonan-7-ylmethyl)-3,3-dimethyl-piperazin-1-yl]-1-methyl-indazol-3-yl]piperidine-2,6-dione

To a solution of *tert*-butyl 7-[[4-[3-(2,6-dioxo-3-piperidyl)-1-methyl-indazol-6-yl]-2,2-dimethyl-piperazin-1-yl]methyl]-2-azaspiro[3.5]nonane-2-carboxylate (220 mg, 371.14 µmol, 1 *equiv.*) in DCM (2 mL) was added HCl/dioxane (2 M, 185.57 µL, 1 *equiv.*). The mixture was stirred at 25 °C for 1 hour. The reaction mixture was filtered and concentrated under reduced pressure to give 3-[6-[4-(2-azaspiro[3.5]nonan-7-ylmethyl)-3,3-dimethyl-piperazin-1-yl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (200 mg) as a yellow solid.

LC-MS (ESI): m/z = 493.2 $[M+H]^+$

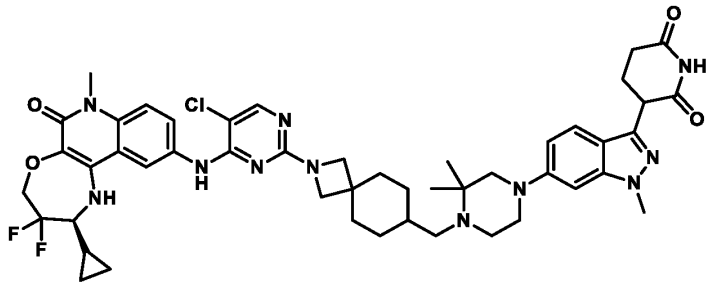
Preparation of 3-[6-[4-[[2-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-2-azaspiro[3.5]nonan-7-yl]methyl]-3,3-dimethyl-piperazin-1-yl]-1-methyl-indazol-3-yl]piperidine-2,6-dione

To a solution of 3-[6-[4-(2-azaspiro[3.5]nonan-7-ylmethyl)-3,3-dimethyl-piperazin-1-yl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (152.33 mg, 287.90 μmol, 1.4 *equiv.*, HCl) and (2*S*)-2-cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (100 mg, 205.65 μmol, 1 *equiv.*) in DMSO (1 mL) was added TEA (83.24 mg, 822.58 μmol, 114.49 μL, 4 *equiv.*). The mixture was stirred at 100 °C for 1 hour. After cooling, the reaction mixture was filtered to give a residue. This residue was purified by prep-HPLC to give 3-[6-[4-[[2-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-2-azaspiro[3.5]nonan-7-yl]methyl]-3,3-dimethyl-piperazin-1-yl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (38.22 mg) as a yellow solid.

LC-MS (ESI): m/z = 942.4 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.83 (s, 1H), 8.76 (s, 1H), 8.34 (s, 1H), 8.22 (d, *J* = 7.6 Hz, 1H), 8.00 (s, 1H), 7.51 - 7.35 (m, 2H), 6.87 (d, *J* = 8.8 Hz, 1H), 6.79 (s, 1H), 6.44 (s, 1H), 4.55 - 4.31 (m, 2H), 4.27 - 4.17 (m, 1H), 3.88 (s, 3H), 3.54 (s, 3H), 3.15 (s, 2H), 2.92 (s, 2H), 2.67 (s, 2H), 2.63 - 2.57 (m, 5H), 2.36 - 2.22 (m, 2H), 2.19 - 2.06 (m, 3H), 1.78 (d, *J* = 11.2 Hz, 2H), 1.72 - 1.62 (m, 2H), 1.45 - 1.24 (m, 5H), 1.01 (s, 6H), 0.91 - 0.77 (m, 2H), 0.74 - 0.65 (m, 1H), 0.55 - 0.45 (m, 2H), 0.38 - 0.26 (m, 1H).

Example 134: 3-[6-[4-[[2-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-2-azaspiro[3.5]nonan-7-yl]methyl]-3,3-dimethyl-piperazin-1-yl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (Compound 190a)



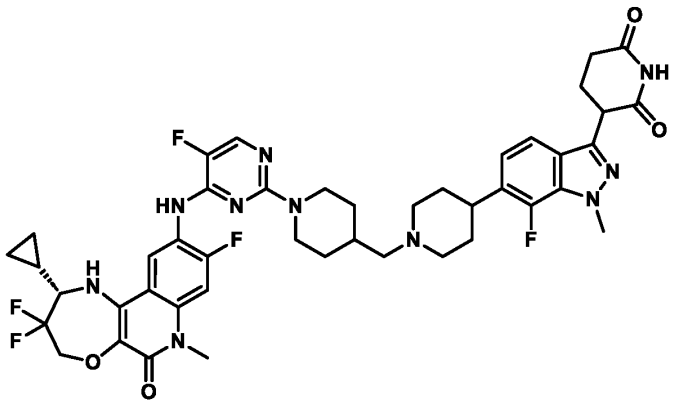
Preparation of 3-[6-[4-[[2-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-2-azaspiro[3.5]nonan-7-yl]methyl]-3,3-dimethyl-piperazin-1-yl]-1-methyl-indazol-3-yl]piperidine-2,6-dione

To a solution of 3-[6-[4-(2-azaspiro[3.5]nonan-7-ylmethyl)-3,3-dimethyl-piperazin-1-yl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (124.29 mg, 234.90 μmol, 1.1 *equiv.*, HCl) in DMSO (1 mL) was added TEA (86.43 mg, 854.18 μmol, 118.89 μL, 4 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (100 mg, 213.55 μmol, 1 *equiv.*). The mixture was stirred at 100 °C for 1 hour. The reaction mixture was filtered to give a residue, which was purified by prep-HPLC to afford 3-[6-[4-[[2-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-2-azaspiro[3.5]nonan-7-yl]methyl]-3,3-dimethyl-piperazin-1-yl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (86.42 mg) as a yellow solid.

LC-MS (ESI): m/z = 924.4 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.84 (s, 1H), 8.78 - 8.66 (m, 1H), 8.27 (s, 1H), 8.18 (s, 1H), 8.01 (s, 1H), 7.81 (d, *J* = 8.8 Hz, 1H), 7.49 – 7.38 (m, 2H), 6.93 - 6.85 (m, 1H), 6.80 (d, *J* = 0.8 Hz, 1H), 6.16 - 6.02 (m, 1H), 4.53 - 4.31 (m, 2H), 4.27 -4.23 (m, 1H), 3.88 (s, 3H), 3.64 (s, 2H), 3.59 (s, 2H), 3.56 (s, 3H), 3.16 (s, 3H), 2.93 (s, 2H), 2.68 - 2.55 (m, 4H), 2.35 - 2.22 (m, 1H), 2.19 - 2.07 (m, 3H), 1.90 - 1.78 (m, 2H), 1.71 (d, *J* = 11.2 Hz, 2H), 1.47 - 1.26 (m, 4H), 1.03 (s, 6H), 0.94 - 0.83 (m, 2H), 0.76 - 0.66 (m, 1H), 0.58 - 0.48 (m, 2H), 0.41 - 0.32 (m, 1H).

Example 135: 3-[6-[1-[[1-[4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]-5-fluoro-pyrimidin-2-yl]-4-piperidyl]methyl]-4-piperidyl]-7-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (Compound 207a)



Preparation of (2*S*)-10-[(2-chloro-5-fluoro-pyrimidin-4-yl)amino]-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one

To a solution of (2*S*)-10-amino-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (1 g, 2.95 mmol, 1 *equiv.*), 2,4-dichloro-5-fluoro-pyrimidine (984.16 mg, 5.89 mmol, 2 *equiv.*) and DIPEA (1.52 g, 11.79 mmol, 2.05 mL, 4 *equiv.*) in NMP (10 mL) under a N_2 atmosphere was heated at 140 °C for 3 hours in a sealed microwave tube. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (60 mL). The combined organic layers were washed with aqueous sodium chloride (60 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. This residue was purified by flash silica gel chromatography (50% ethyl acetate/petroleum ether) to afford (2*S*)-10-[(2-chloro-5-fluoro-pyrimidin-4-yl)amino]-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (223.88 mg) as a yellow solid.

LC-MS (ESI): m/z = 470.1 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.22 - 9.98 (m, 1H), 8.30 - 8.29 (m, 1H), 8.29 - 8.28 (m, 1H), 8.37 (d, *J* = 3.2 Hz, 1H), 8.22 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 12.4 Hz, 1H), 6.46 - 6.30 (m, 1H), 4.66 - 4.24 (m, 2H), 3.56 (s, 3H), 3.26 - 3.16 (m, 1H), 1.37 - 1.22 (m, 1H), 1.22 - 1.19 (m, 1H), 0.77 - 0.62 (m, 1H), 0.59 - 0.42 (m, 2H), 0.36 - 0.26 (m, 1H)

Preparation of 3-[6-[1-[[1-[4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]-5-fluoro-pyrimidin-2-yl]-4-piperidyl]methyl]-4-piperidyl]-7-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione

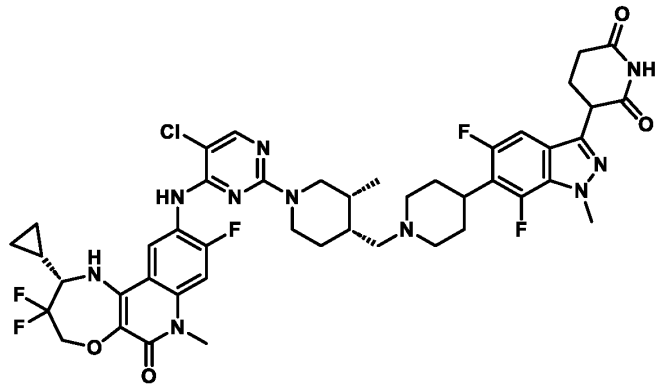
To a solution of (2*S*)-10-[(2-chloro-5-fluoro-pyrimidin-4-yl)amino]-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (100 mg,

212.85 μmol, 1 *equiv.*) and 3-(7-fluoro-1-methyl-6-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione, 2HCl (140.97 mg, 319.27 μmol, 1.5 *equiv.*) in DMSO (1 mL) was added TEA (86.15 mg, 851.39 μmol, 118.50 μL, 4 *equiv.*). The mixture was stirred at 100 °C for 1.5 hours. The reaction mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by reverse-phase HPLC to give 3-[6-[1-[[1-[4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]-5-fluoro-pyrimidin-2-yl]-4-piperidyl]methyl]-4-piperidyl]-7-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (31.98 mg) as a yellow solid.

LC-MS (ESI): m/z = 875.3 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.90 (s, 1H), 9.16 (s, 1H), 8.25 - 8.22 (m, 1H), 8.21 (s, 1H), 7.98 (d, J = 3.6 Hz, 1H), 7.50 - 7.36 (m, 2H), 7.11 - 6.99 (m, 1H), 6.45 - 6.39 (m, 1H), 4.51 - 4.29 (m, 5H), 4.10 (s, 3H), 3.58 - 3.53 (m, 3H), 3.00 - 2.87 (m, 4H), 2.75 - 2.64 (m, 4H), 2.21 - 2.10 (m, 3H), 2.04 - 1.93 (m, 2H), 1.85 - 1.60 (m, 8H), 1.38 - 1.25 (m, 1H), 1.02 - 0.86 (m, 2H), 0.75 - 0.65 (m, 1H), 0.55 - 0.47 (m, 2H), 0.36 - 0.26 (m, 1H).

Example 136: 3-[6-[1-[[(3*R*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (Compound 199a)



Preparation of *tert*-butyl 4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridine-1-carboxylate

A mixture of 6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazole (500 mg, 932.20 μmol, 1 *equiv.*), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylate (259.42 mg, 838.98 μmol, 0.9 *equiv.*), cesium carbonate (911.19 mg, 2.80 mmol, 3 *equiv.*), and $Pd(dppf)Cl_2$ (68.21 mg, 93.22 μmol, 0.1

equiv.) in dioxane (15 mL) and H_2O (5 mL) was degassed and purged with N_2 three times. The mixture was stirred at 90 °C for 12 hours under a N_2 atmosphere. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (100 mL). The combined organic layers were washed with brine (80 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (18% ethyl acetate/petroleum ether) to afford *tert*-butyl 4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridine-1-carboxylate (1.5 g) as a yellow oil.

LC-MS (ESI): m/z = 639.2 $[M+H]^+$

Preparation of 3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)indazole

To a solution of *tert*-butyl 4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridine-1-carboxylate (1.5 g, 2.35 mmol, 1 *equiv.*) in DCM (1 mL) was added HCl/dioxane (2 M, 11.74 mL, 10 *equiv.*). The mixture was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give 3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)indazole (1.3 g) as a yellow solid.

LC-MS (ESI): m/z = 539.2 $[M+H]^+$

Preparation of cis-*tert*-butyl 4-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridine-1-carbonyl]-3-methyl-piperidine-1-carboxylate

To a solution of 3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)indazole (1.3 g, 2.41 mmol, 1 *equiv.*) in DCM (10 mL) was added HATU (917.77 mg, 2.41 mmol, 1 *equiv.*), cis-1-*tert*-butoxycarbonyl-3-methyl-piperidine-4-carboxylic acid (587.26 mg, 2.41 mmol, 1 *equiv.*), and DIPEA (935.85 mg, 7.24 mmol, 1.26 mL, 3 *equiv.*). The mixture was stirred at 25 °C for 1 hour. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (100 mL). The combined organic layers were washed with brine (80 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (20% ethyl acetate/petroleum ether) to afford cis-*tert*-butyl 4-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridine-1-carbonyl]-3-methyl-piperidine-1-carboxylate (1.74 g) as a yellow solid.

LC-MS (ESI): m/z = 708.2 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.90 (d, J = 8.0 Hz, 1H), 7.49 - 7.47 (m, 1H), 7.41 - 7.35 (m, 4H), 7.35 - 7.26 (m, 5H), 6.60 (d, J = 8.0 Hz, 1H), 5.93 (s, 1H), 5.75 (s, 1H), 5.45 (d, J = 9.2 Hz, 4H), 4.27 (s, 1H), 4.17 (s, 3H), 3.78 - 3.68 (m, 3H), 3.16 - 3.01 (m, 2H), 2.69 (s, 5H), 2.45 - 2.28 (m, 2H), 2.02 - 1.96 (m, 1H), 1.40 (s, 9H), 0.79 (d, J = 7.2 Hz, 3H)

Preparation of cis-*tert*-butyl 4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3-methyl-piperidine-1-carboxylate

A mixture of LAH (2.5 M, 743.06 µL, 3 *equiv.*) and $AlCl_3$ (27.25 mg, 204.34 µmol, 11.17 µL, 0.33 *equiv.*) in THF (7 mL) was degassed and purged with N_2 three times at 0 °C. Cis-*tert*-butyl 4-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridine-1-carbonyl]-3-methyl-piperidine-1-carboxylate (473 mg, 619.22 µmol, 1 *equiv.*) was then added, and the resulting mixture was stirred at 25 °C for 12 hours under a N_2 atmosphere. The reaction mixture was quenched by the addition of water, 15% NaOH solution, and water again. The resulting mixture was extracted with ethyl acetate (60 mL). The combined organic layers were washed with brine (60 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (20% ethyl acetate/petroleum ether) to afford cis-*tert*-butyl 4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3-methyl-piperidine-1-carboxylate (300 mg) as a yellow oil.

LC-MS (ESI): m/z = 750.8 $[M+H]^+$

Preparation of *tert*-butyl (3*R*,4*R*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3-methyl-piperidine-1-carboxylate and *tert*-butyl (3*S*,4*S*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3-methyl-piperidine-1-carboxylate

Enantiomers of cis-*tert*-butyl 4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3-methyl-piperidine-1-carboxylate (930 mg, 1.24 mmol, 1 *equiv.*) were separated by SFC to afford *tert*-butyl (3*R*,4*R*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3-methyl-piperidine-1-carboxylate (**Peak 1**) (580 mg) as a yellow oil and *tert*-butyl (3*S*,4*S*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-

3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3-methyl-piperidine-1-carboxylate (**Peak 2**) (420 mg) as a yellow oil.

LC-MS (ESI): m/z = 750.3 $[M+H]^+$

LC-MS (ESI): m/z = 750.3 $[M+H]^+$

Preparation of *tert*-butyl (3*R*,4*R*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5,7-difluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-methyl-piperidine-1-carboxylate

To a solution of *tert*-butyl (3*R*,4*R*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3-methyl-piperidine-1-carboxylate (200 mg, 266.71 μmol, 1 *equiv.*) in CF_3CH_2OH (10 mL) under a N_2 atmosphere, Pd on carbon (141.91 mg, 133.35 μmol, 10 wt%, 0.5 *equiv.*) and $Pd(OH)_2$ on carbon (93.64 mg, 133.35 μmol, 20 wt%, 0.5 *equiv.*) were added. The suspension was degassed and purged with H_2 three times. The mixture was stirred under H_2 (15 psi) at 25 °C for 16 hours. The reaction mixture was filtered and concentrated under reduced pressure to give *tert*-butyl (3*R*,4*R*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5,7-difluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-methyl-piperidine-1-carboxylate (120 mg) as a colorless oil.

LC-MS (ESI): m/z = 574.3 $[M+H]^+$

Preparation of 3-[5,7-difluoro-1-methyl-6-[1-[[(3*R*,4*R*)-3-methyl-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione

To a solution of *tert*-butyl (3*R*,4*R*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5,7-difluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-methyl-piperidine-1-carboxylate (120 mg, 209.18 μmol, 1 *equiv.*) in DCM (3 mL) was added HCl/dioxane (3 mL). The mixture was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give 3-[5,7-difluoro-1-methyl-6-[1-[[(3*R*,4*R*)-3-methyl-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione (100 mg) as a colorless oil.

LC-MS (ESI): m/z = 474.4 $[M+H]^+$

Preparation of 3-[6-[1-[[(3*R*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione

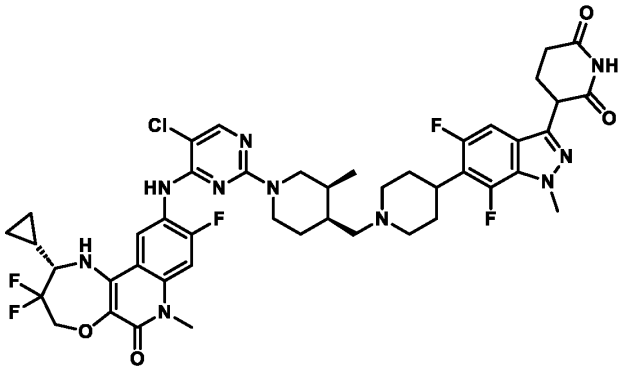
To a solution of 3-[5,7-difluoro-1-methyl-6-[1-[[(3*R*,4*R*)-3-methyl-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione (100 mg, 211.17 μmol, 1

equiv.) in DMSO (3 mL) was added TEA (85.47 mg, 844.67 μmol, 117.57 μL, 4 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3,9-trifluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (71.88 mg, 147.82 μmol, 0.7 *equiv.*). The mixture was stirred at 100 °C for 1 hour. The reaction mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to afford 3-[6-[1-[[(3*R*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (39.22 mg) as a pink solid.

LC-MS (ESI): m/z = 923.3 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.90 (s, 1H), 8.79 (s, 1H), 8.22 (s, 1H), 8.18 (m, 1H), 7.98 (s, 1H), 7.49 - 7.17 (m, 2H), 6.46 (s, 1H), 4.52 - 4.24 (m, 4H), 4.10 (s, 3H), 3.59 - 3.52 (m, 3H), 3.04 - 2.82 (m, 4H), 2.80 - 2.52 (m, 3H), 2.43 - 2.29 (m, 2H), 2.17 - 1.80 (m, 9H), 1.72 - 1.52 (m, 2H), 1.41 - 1.12 (m, 3H), 0.85 - 0.61 (m, 4H), 0.59 - 0.44 (m, 2H), 0.37 - 0.24 (m, 1H)

Example 137: 3-[6-[1-[[(3*S*,4*S*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (Compound 199b)



Preparation of *tert*-butyl (3*S*,4*S*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5,7-difluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-methyl-piperidine-1-carboxylate

To a solution of *tert*-butyl (3*S*,4*S*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3-methyl-piperidine-1-carboxylate (290 mg, 386.73 μmol, 1 *equiv.*) in CF_3CH_2OH (10 mL) was added Pd on carbon (205.78 mg, 193.36 μmol, 10 wt%, 0.5 *equiv.*) and $Pd(OH)_2$ on carbon (135.78 mg, 193.36

μmol, 20 wt%, 0.5 *equiv.*) under a N_2 atmosphere. The suspension was degassed and purged with H_2 three times. The mixture was stirred under H_2 (15 psi) at 25 °C for 16 hours. The reaction mixture was filtered and concentrated under reduced pressure to give *tert*-butyl (3*S*,4*S*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5,7-difluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-methyl-piperidine-1-carboxylate (180 mg) as a colorless oil.

LC-MS (ESI): m/z = 574.3 $[M+H]^+$

Preparation of 3-[5,7-difluoro-1-methyl-6-[1-[[(3*S*,4*S*)-3-methyl-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione

To a solution of *tert*-butyl (3*S*,4*S*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5,7-difluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-methyl-piperidine-1-carboxylate (180.00 mg, 313.77 μmol, 1 *equiv.*) in DCM (3 mL) was added HCl/dioxane (3 mL). The mixture was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give 3-[5,7-difluoro-1-methyl-6-[1-[[(3*S*,4*S*)-3-methyl-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione (120 mg) as a colorless oil.

LC-MS (ESI): m/z = 474.1 $[M+H]^+$

Preparation of 3-[6-[1-[[(3*S*,4*S*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione

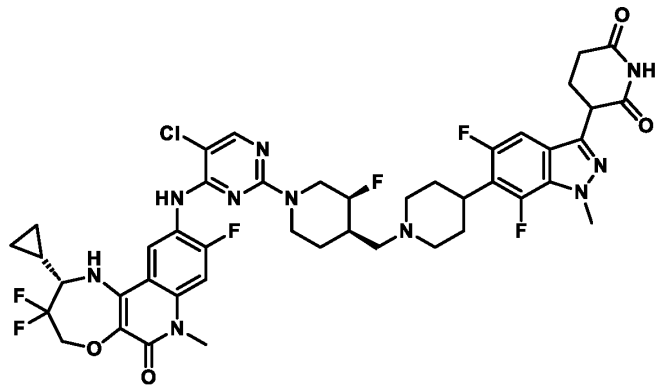
To a solution of 3-[5,7-difluoro-1-methyl-6-[1-[[(3*S*,4*S*)-3-methyl-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione (100.00 mg, 211.17 μmol, 1 *equiv.*) in DMSO (3 mL) was added TEA (85.47 mg, 844.67 μmol, 117.57 μL, 4 *equiv.*) and (2*S*)-2-cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (71.88 mg, 147.82 μmol, 0.7 *equiv.*). The mixture was stirred at 100 °C for 1 hour. The reaction mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to afford 3-[6-[1-[[(3*S*,4*S*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (51.36 mg) as a pink solid.

LC-MS (ESI): m/z = 923.3 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.90 (s, 1H), 8.78 (s, 1H), 8.30 (s, 1H), 8.19 (m, 1H), 8.01 - 7.94 (m, 1H), 7.44 - 7.33 (m, 2H), 6.46 (s, 1H), 4.51 - 4.21 (m, 4H), 4.10 (s, 3H),

3.57 - 3.52 (m, 3H), 3.05 - 2.82 (m, 5H), 2.80 - 2.53 (m, 3H), 2.42 - 2.31 (m, 2H), 2.14 - 1.94 (m, 6H), 1.90 - 1.77 (m, 2H), 1.66 (m, 2H), 1.38 - 1.19 (m, 3H), 0.74 - 0.59 (m, 4H), 0.56 - 0.44 (m, 2H), 0.37 - 0.24 (m, 1H)

Example 138: 3-[6-[1-[[(3*S*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (Compound 202a)



Preparation of *tert*-butyl (3*S*,4*R*)-3-fluoro-4-formyl-piperidine-1-carboxylate

To a solution of *tert*-butyl (3*S*,4*R*)-3-fluoro-4-(hydroxymethyl)piperidine-1-carboxylate (500 mg, 2.14 mmol, 1 *equiv.*) in DCM (10 mL) was added dropwise DMP (1.82 g, 4.29 mmol, 2 *equiv.*) at 0 °C over 30 minutes. The resulting mixture was stirred at 0 °C for 1.5 hours. The reaction mixture was concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (0~70% ethyl acetate/petroleum ether) to give *tert*-butyl (3*S*,4*R*)-3-fluoro-4-formyl-piperidine-1-carboxylate (500 mg) as a brown liquid.

LC-MS (ESI): m/z: 178.1.0 $[M-56]^+$.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.76 (s, 1H), 5.33 - 4.93 (m, 1H), 4.50 - 4.16 (m, 2H), 3.17 - 2.87 (m, 1H), 2.59 - 2.37 (m, 1H), 2.06 - 1.94 (m, 2H), 1.84 (d, *J* = 12.0 Hz, 2H), 1.49 - 1.46 (m, 10H)

Preparation of *tert*-butyl (3*S*,4*R*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5,7-difluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-fluoro-piperidine-1-carboxylate

To a solution of 3-(5,7-difluoro-1-methyl-6-(piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (150 mg, 376.10 μmol, 1 *equiv.*, HCl) in DCM (6 mL) was added

AcOH (2.26 mg, 37.61 μmol, 2.15 μL, 0.1 *equiv.*), *tert*-butyl (3*S*,4*R*)-3-fluoro-4-formyl-piperidine-1-carboxylate (173.95 mg, 752.19 μmol, 2 *equiv.*), and $NaBH(OAc)_3$ (119.57 mg, 564.14 μmol, 1.5 *equiv.*). The mixture was stirred at 25 °C for 2 hours. The reaction mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (0~70% ethyl acetate/petroleum ether) to give *tert*-butyl (3*S*,4*R*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5,7-difluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-fluoro-piperidine-1-carboxylate (120 mg) as a colorless oil.

LC-MS (ESI): m/z = 578.3 $[M+H]^+$

Preparation of 3-[5,7-difluoro-6-[1-[[(3*S*,4*R*)-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione

To a solution of *tert*-butyl (3*S*,4*R*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5,7-difluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-fluoro-piperidine-1-carboxylate (120 mg, 207.74 μmol, 1 *equiv.*) in DCM (1 mL) was added HCl/dioxane (3 mL). The mixture was stirred at 25 °C for 0.5 hour. The reaction mixture was concentrated under reduced pressure to give 3-[5,7-difluoro-6-[1-[[(3*S*,4*R*)-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (100 mg, crude) as a brown solid.

LC-MS (ESI): m/z = 478.2 $[M+H]^+$

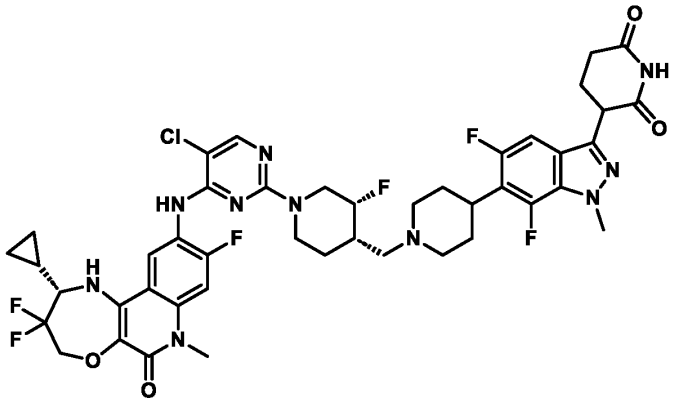
Preparation of 3-[6-[1-[[(3*S*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione

To a solution of 3-[5,7-difluoro-6-[1-[[(3*S*,4*R*)-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (100 mg, 209.41 μmol, 1 *equiv.*) in DMSO (2 mL) was added TEA (84.76 mg, 837.66 μmol, 116.59 μL, 4 *equiv.*) and (2*S*)-2-cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (71.28 mg, 146.59 μmol, 0.7 *equiv.*). The mixture was stirred at 100 °C for 1 hour. The reaction mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to afford 3-[6-[1-[[(3*S*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (50.98 mg) as a pink solid.

LC-MS (ESI): m/z = 927.4 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ= 11.03 - 10.80 (m, 1H), 8.89 - 8.78 (m, 1H), 8.22 - 8.11 (m, 1H), 8.04 - 7.96 (m, 1H), 7.48 - 7.34 (m, 2H), 6.48 - 6.37 (m, 1H), 4.79 - 4.59 (m, 1H), 4.55 - 4.25 (m, 4H), 4.10 (s, 3H), 3.56 (s, 3H), 3.03 - 2.83 (m, 4H), 2.73 - 2.56 (m, 3H), 2.41 - 2.24 (m, 4H), 2.16 - 1.79 (m, 7H), 1.72 - 1.61 (m, 2H), 1.53 - 1.40 (m, 1H), 1.37 - 1.21 (m, 2H), 0.76 - 0.61 (m, 1H), 0.58 - 0.43 (m, 2H), 0.39 - 0.21 (m, 1H)

Example 139: 3-(6-(1-(((3*R*,4*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-5,7-difluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 202b)



Preparation of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5,7-difluoro-1-methyl-1*H*-indazol-6-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate

A mixture of 6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazole (4 g, 7.46 mmol, 1.0 *equiv.*), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylate (3.00 g, 9.69 mmol, 1.3 *equiv.*), cesium carbonate (6.56 g, 20.14 mmol, 2.7 *equiv.*) in dioxane (80 mL) and H_2O (16 mL), and XantPhos Pd G2 (132.55 mg, 149.15 μmol, 0.02 *eq.*) was added under a N_2 atmosphere. The reaction mixture was degassed and purged with N_2 three times. The mixture was stirred at 90 °C for 3 hours under a N_2 atmosphere. The reaction mixture was poured into H_2O (200 mL) and extracted with ethyl acetate (300 mL). The combined organic layers were washed with brine (100 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate = 20:1 to 8:1) to give *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5,7-difluoro-1-methyl-1*H*-indazol-6-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (4.05 g) as a yellow solid.

LC-MS (ESI): m/z = 639.6 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.90 (d, J = 8.0 Hz, 1H), 7.54 - 7.19 (m, 11H), 6.59 (d, J = 8.0 Hz, 1H), 5.90 (s, 1H), 5.45 (d, J = 8.8 Hz, 4H), 4.16 (s, 3H), 4.02 (s, 2H), 3.56 (t, J = 5.2 Hz, 2H), 2.33 (s, 2H), 1.44 (s, 9H)

Preparation of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5,7-difluoro-1-methyl-1*H*-indazol-6-yl)piperidine-1-carboxylate

To a solution of Pd on carbon (10 wt%, 2.00 g, 1.88 mmol, 0.3 *equiv.*) and $Pd(OH)_2$ on carbon (20 wt%, 2.64 g, 3.76 mmol, 0.6 *equiv.*) in CF_3CH_2OH (80 mL) was added *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5,7-difluoro-1-methyl-1*H*-indazol-6-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (4 g, 6.26 mmol, 1.0 *equiv.*) under a N_2 atmosphere. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 psi) at 25 °C for 12 hours. The reaction mixture was filtered and the filtrate was concentrated to give *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5,7-difluoro-1-methyl-1*H*-indazol-6-yl)piperidine-1-carboxylate (2.85 g, crude) as a yellow solid.

LC-MS (ESI): m/z = 463.0 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.90 (s, 1H), 7.42 (d, J = 10.4 Hz, 1H), 4.34 (dd, J = 4.8, 10.4 Hz, 1H), 3.59 (td, J = 6.0, 14.4 Hz, 1H), 2.96 - 2.75 (m, 2H), 2.74 - 2.56 (m, 2H), 2.43 - 2.27 (m, 2H), 2.18 - 2.06 (m, 1H), 1.98 - 1.78 (m, 2H), 1.71 (d, J = 10.4 Hz, 2H), 1.43 (s, 9H).

Preparation of 3-(5,7-difluoro-1-methyl-6-(piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione

A mixture of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-5,7-difluoro-1-methyl-1*H*-indazol-6-yl)piperidine-1-carboxylate (0.8 g, 1.73 mmol, 1.0 *equiv.*) in DCM (10 mL) and HCl/dioxane (10 mL, 2 M) was stirred at 25 °C for 2 hours. The reaction mixture was concentrated under reduced pressure to give 3-(5,7-difluoro-1-methyl-6-(piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (650 mg, crude, HCl) as a yellow solid.

LC-MS (ESI): m/z = 363.0 $[M+H]^+$

Preparation of *tert*-butyl (3*R*,4*S*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-5,7-difluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate

A mixture of 3-(5,7-difluoro-1-methyl-6-(piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (0.2 g, 501.46 μmol, 1.0 *equiv.*, HCl), *tert*-butyl (3*R*,4*S*)-3-fluoro-4-formyl-piperidine-1-carboxylate (173.95 mg, 752.19 μmol, 1.5 *equiv.*), AcOH (3.01 mg, 50.15 μmol,

0.1 *equiv.*), and $NaBH(OAc)_3$ (159.42 mg, 752.19 μmol, 1.5 *equiv.*) in DCM (4 mL) was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give a residue, which was purified by silica gel chromatography (DCM: methanol 100:1 to 20:1) to give *tert*-butyl (3*R*,4*S*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-5,7-difluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (170 mg) as a yellow solid.

LC-MS (ESI): m/z = 578.4 $[M+H]^+$

Preparation of 3-(5,7-difluoro-6-(1-(((3*R*,4*S*)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

A mixture of *tert*-butyl (3*R*,4*S*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-5,7-difluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (150 mg, 259.68 μmol, 1.0 *equiv.*) in DCM (2 mL) and HCl/dioxane (2 mL, 2M) was stirred at 25 °C for 2 hours. The reaction mixture was concentrated under reduced pressure to give 3-(5,7-difluoro-6-(1-(((3*R*,4*S*)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (130 mg, crude, HCl) as a yellow solid.

LC-MS (ESI): m/z = 478.3 $[M+H]^+$

Preparation of 3-(6-(1-(((3*R*,4*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-5,7-difluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

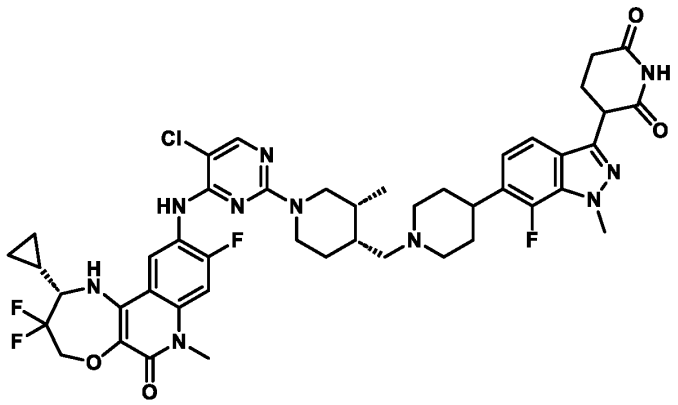
A solution of 3-(5,7-difluoro-6-(1-(((3*R*,4*S*)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (130 mg, 252.93 μmol, 1.0 *equiv.*, HCl), (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3,9-trifluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (122.99 mg, 252.93 μmol, 1.0 *equiv.*), and TEA (127.97 mg, 1.26 mmol, 176.02 μL, 5.0 *equiv.*) in DMSO (3 mL) was stirred at 100 °C for 2 hours. The reaction mixture was purified by prep-HPLC to give 3-(6-(1-(((3*R*,4*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-5,7-difluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (94.4 mg) as a pink solid.

LC-MS (ESI): m/z = 927.5 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.90 (s, 1H), 8.85 (s, 1H), 8.23 - 8.17 (m, 1H), 8.02 (s, 1H), 7.48 - 7.34 (m, 2H), 6.46 (d, J = 2.0 Hz, 1H), 4.95 - 4.57 (m, 2H), 4.53 - 4.24 (m,

4H), 4.10 (s, 3H), 3.56 (s, 3H), 3.07 - 2.79 (m, 5H), 2.75 - 2.55 (m, 3H), 2.45 - 2.25 (m, 2H), 2.21 - 1.81 (m, 7H), 1.67 (d, *J* = 10.0 Hz, 2H), 1.46 (d, *J* = 11.6 Hz, 1H), 1.36 - 1.20 (m, 2H), 0.76 - 0.65 (m, 1H), 0.60 - 0.42 (m, 2H), 0.39 - 0.26 (m, 1H)

Example 140: 3-[6-[1-[[(3*R*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]methyl]-4-piperidyl]-7-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (Compound 209a)



Preparation of *tert*-butyl (3*R*,4*R*)-4-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridine-1-carbonyl]-3-methyl-piperidine-1-carboxylate

To a solution of (3*R*,4*R*)-1-tert-butoxycarbonyl-3-methyl-piperidine-4-carboxylic acid (0.4 g, 1.64 mmol, 1 *equiv.*) in DMF (5 mL), HATU (750.15 mg, 1.97 mmol, 1.2 *equiv.*) and DIPEA (637.44 mg, 4.93 mmol, 859.08 μL, 3 *equiv.*) were added dropwise. The reaction was stirred at 0 °C for 10 minutes. Then 3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)indazole (941.49 mg, 1.81 mmol, 1.1 *equiv.*) was added dropwise at 0 °C. The mixture was then stirred at 25 °C for 1 hour. The reaction mixture was quenched by the addition of water (20 mL) and extracted with ethyl acetate (60 mL). The combined organic layers were washed with brine (60 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (0~50% ethyl acetate/petroleum ether) to give *tert*-butyl (3*R*,4*R*)-4-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridine-1-carbonyl]-3-methyl-piperidine-1-carboxylate (1.2 g) as a white solid.

LC-MS (ESI): m/z = 746.5 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.89 (d, *J* = 8.0 Hz, 1H), 7.47 - 7.26 (m, 11H),

6.98 - 6.85 (m, 1H), 6.60 (d, *J* = 8.0 Hz, 1H), 6.07 - 5.97 (m, 1H), 5.43 (d, *J* = 8.4 Hz, 4H), 4.27 (s, 1H), 4.19 (s, 3H), 4.12 (dd, *J* = 2.4, 8.4 Hz, 1H), 3.97 - 3.83 (m, 1H), 3.72 (t, *J* = 5.6 Hz, 3H), 3.12 - 2.98 (m, 2H), 2.94 - 2.72 (m, 1H), 2.68 (s, 1H), 2.55 (s, 1H), 2.45 (s, 1H), 2.06 - 2.00 (m, 1H), 1.87 - 1.72 (m, 1H), 1.39 (s, 9H), 0.78 (d, *J* = 6.4 Hz, 3H)

Preparation of *tert*-butyl (3*R*,4*R*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3-methyl-piperidine-1-carboxylate

To a solution of LAH (2.5 M, 836.60 μL, 1.3 *equiv.*) in THF (12 mL) was added dropwise $AlCl_3$ (70.79 mg, 530.92 μmol, 29.01 μL, 0.33 *equiv.*) at 0 °C. After 30 minutes, *tert*-butyl (3*R*,4*R*)-4-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridine-1-carbonyl]-3-methyl-piperidine-1-carboxylate (1.2 g, 1.61 mmol, 1 *equiv.*) in THF (12 mL) was added dropwise at 0 °C. The mixture was stirred at 0 °C for 2 hours. The reaction mixture was quenched by the addition of water (1 mL), 15% NaOH (1 mL), and water (3 mL). The mixture was dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (0~40% ethyl acetate/petroleum ether) to give *tert*-butyl (3*R*,4*R*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3-methyl-piperidine-1-carboxylate (0.86 g) as a white solid.

LC-MS (ESI): m/z = 732.3 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.89 (d, *J* = 8.0 Hz, 1H), 7.51 - 7.46 (m, 2H), 7.42 - 7.27 (m, 9H), 6.98 - 6.90 (m, 1H), 6.60 (d, *J* = 8.0 Hz, 1H), 6.02 - 5.96 (m, 1H), 5.44 (d, *J* = 8.0 Hz, 4H), 4.19 (s, 3H), 3.98 - 3.86 (m, 1H), 3.76 (d, *J* = 13.2 Hz, 1H), 3.12 - 3.07 (m, 2H), 2.95 - 2.84 (m, 1H), 2.70 - 2.57 (m, 5H), 2.38 - 2.16 (m, 3H), 1.96 - 1.83 (m, 2H), 1.40 (s, 9H), 1.31 - 1.22 (m, 1H), 0.79 (d, *J* = 6.8 Hz, 3H)

Preparation of *tert*-butyl (3*R*,4*R*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-7-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-methyl-piperidine-1-carboxylate

To a solution of *tert*-butyl (3*R*,4*R*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3-methyl-piperidine-1-carboxylate (1 g, 1.37 mmol, 1 *equiv.*) in CF_3CH_2OH (10 mL) was added Pd on carbon (1.45 g, 1.37 mmol, 10% purity, 1 *equiv.*) and $Pd(OH)_2$ on carbon (959.39 mg, 1.37 mmol, 20% purity, 1 *equiv.*) under a N_2 atmosphere. The suspension was degassed and purged with H_2 three times. The mixture was stirred under H_2 (15 psi) at 25 °C for 12 hours. The reaction

mixture was filtered and concentrated under reduced pressure to give *tert*-butyl (3*R*,4*R*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-7-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-methyl-piperidine-1-carboxylate (0.8 g, crude) as a white solid.

Preparation of 3-[7-fluoro-1-methyl-6-[1-[[(3*R*,4*R*)-3-methyl-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione

To a solution of *tert*-butyl (3*R*,4*R*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-7-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-methyl-piperidine-1-carboxylate (220 mg, 395.91 μmol, 1 *equiv.*) in DCM (1 mL), HCl/dioxane (1 mL) was added. The mixture was stirred at 25 °C for 1 hour. The reaction mixture was filtered and concentrated under reduced pressure to give 3-[7-fluoro-1-methyl-6-[1-[[(3*R*,4*R*)-3-methyl-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione (0.18 g, crude) as a white solid.

Preparation of 3-[6-[1-[[(3*R*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]methyl]-4-piperidyl]-7-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione

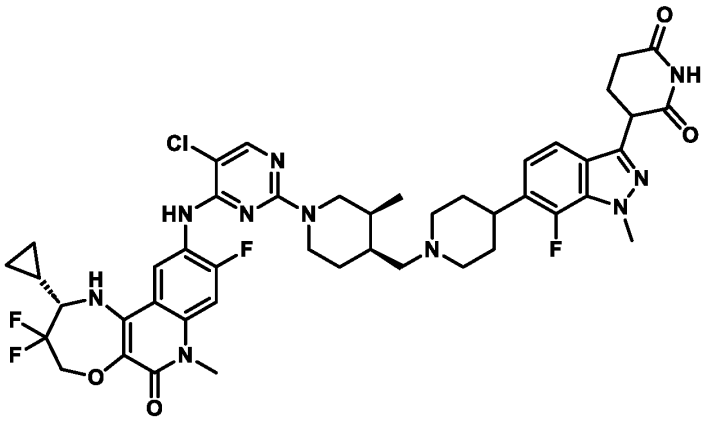
To a solution of 3-[7-fluoro-1-methyl-6-[1-[[(3*R*,4*R*)-3-methyl-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione (180 mg, 395.11 μmol, 1 *equiv.*) in DMSO (2 mL) were added TEA (159.92 mg, 1.58 mmol, 219.98 μL, 4 *equiv.*) and (2*S*)-2-cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (192.13 mg, 395.11 μmol, 1 *equiv.*). The mixture was stirred at 100 °C for 2 hours. The reaction mixture was quenched by the addition of water (5 mL) and extracted with ethyl acetate (60 mL). The combined organic layers were washed with brine (60 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give 3-[6-[1-[[(3*R*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]methyl]-4-piperidyl]-7-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (80.83 mg) as a pink solid.

LC-MS (ESI): m/z = 905.4 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.92 (s, 1H), 8.81 (s, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 7.99 (s, 1H), 7.56 - 7.33 (m, 2H), 7.06 (dd, *J* = 5.6, 8.4 Hz, 1H), 6.47 (s, 1H), 4.51 - 4.31 (m, 3H), 4.11 (s, 4H), 3.56 (s, 3H), 3.02 - 2.85 (m, 4H), 2.84 - 2.54 (m, 4H), 2.46 - 2.24 (m, 2H), 2.23 - 2.07 (m, 3H), 2.05 - 1.94 (m, 2H), 1.90 - 1.64 (m, 6H), 1.39 - 1.17 (m, 3H), 0.78 -

0.62 (m, 4H), 0.60 - 0.46 (m, 2H), 0.32 (d, *J* = 4.8 Hz, 1H)

Example 141: 3-[7-fluoro-1-methyl-6-[1-[[(3*S*,4*S*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione (Compound 209b)



Preparation of *tert*-butyl (3*S*,4*S*)-4-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridine-1-carbonyl]-3-methyl-piperidine-1-carboxylate

To a solution of (3*S*,4*S*)-1-*tert*-butoxycarbonyl-3-methyl-piperidine-4-carboxylic acid (192.17 mg, 789.87 μmol, 1 *equiv.*) in DMF (5 mL), HATU (450.50 mg, 1.18 mmol, 1.5 *equiv.*) and DIPEA (1.02 g, 7.90 mmol, 1.38 mL, 10 *equiv.*) were added. The mixture was stirred at 25 °C for 10 minutes. To this mixture 3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)indazole (0.44 g, 789.87 μmol, 1 *equiv.*, HCl) was added, and the resulting mixture was stirred for 2 hours. The reaction mixture was extracted with ethyl acetate (15 mL). The combined organic layers were washed with brine (15 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (0~50% ethyl acetate/petroleum ether) to give *tert*-butyl (3*S*,4*S*)-4-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridine-1-carbonyl]-3-methyl-piperidine-1-carboxylate (0.65 g) as a yellow gum.

LC-MS (ESI): m/z = 746.3 $[M+H]^+$

Preparation of *tert*-butyl (3*S*,4*S*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3-methyl-piperidine-1-carboxylate

To a solution of LAH (2.5 M, 425.27 μL, 1.3 *equiv.*) in THF (2 mL), $AlCl_3$ (141.76 mg, 1.06 mmol, 58.10 μL, 1.3 *equiv.*) in THF (2 mL) was added dropwise at 0 °C. The mixture was stirred at 0 °C for 30 minutes, and *tert*-butyl (3*S*,4*S*)-4-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridine-1-carbonyl]-3-methyl-piperidine-1-carboxylate (0.61 g, 817.83 μmol, 1 *equiv.*) in THF (2 mL) was then added at 0 °C. The reaction mixture was stirred at 25 °C for 1 hour under a N_2 atmosphere. The reaction was quenched by the sequential addition of water (0.04 mL), 15% aqueous NaOH (0.04 mL), and water (0.12 mL). Sodium sulfate was added. The resulting suspension was stirred for 10 minutes at 25 °C, filtered, and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether: ethyl acetate = 1:0 to 1:1) to give *tert*-butyl (3*S*,4*S*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3-methyl-piperidine-1-carboxylate (0.5 g) as a yellow oil.

LC-MS (ESI): m/z = 732.5 $[M+H]^+$

Preparation of *tert*-butyl (3*S*,4*S*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-7-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-methyl-piperidine-1-carboxylate

To a solution of *tert*-butyl (3*S*,4*S*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3-methyl-piperidine-1-carboxylate (0.35 g, 478.21 μmol, 1 *equiv.*) in CF_3CH_2OH (4 mL), Pd on carbon (0.125 g, 117.46 μmol, 10% purity, 0.246 *equiv.*) and $Pd(OH)_2$ on carbon (125.00 mg, 890.09 μmol, 1.86 *equiv.*) were added. The mixture was stirred at 25 °C for 12 hours under H_2 (15 psi). The reaction mixture was filtered and concentrated under reduced pressure to give *tert*-butyl (3*S*,4*S*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-7-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-methyl-piperidine-1-carboxylate (0.25 g, crude) as a brown oil.

LC-MS (ESI): m/z = 556.2 $[M+H]^+$

Preparation of 3-[7-fluoro-1-methyl-6-[1-[[(3*S*,4*S*)-3-methyl-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione

A solution of *tert*-butyl (3*S*,4*S*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-7-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-methyl-piperidine-1-carboxylate (0.1 g, 179.96 μmol, 1 *equiv.*) in HCl/dioxane (2 M, 2.00 mL, 22.23 *equiv.*) was stirred at 25 °C for 1 hour. The

reaction mixture was concentrated under reduced pressure to give 3-[7-fluoro-1-methyl-6-[1-[[(3*S*,4*S*)-3-methyl-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione (90 mg, crude, HCl) as a white solid.

LC-MS (ESI): m/z = 456.3 $[M+H]^+$

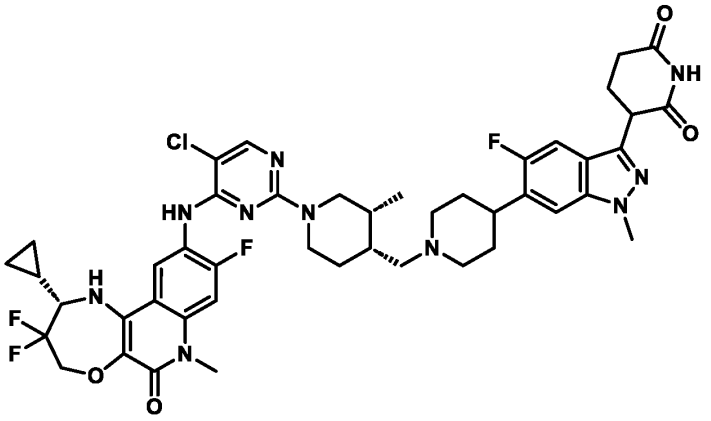
Preparation of 3-[7-fluoro-1-methyl-6-[1-[[(3*S*,4*S*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione

To a solution of 3-[7-fluoro-1-methyl-6-[1-[[(3*S*,4*S*)-3-methyl-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione (90 mg, 182.92 μmol, 1 *equiv.*, HCl) and (2*S*)-2-cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (88.95 mg, 182.92 μmol, 1 *equiv.*) in DMSO (2 mL), TEA (92.55 mg, 914.58 μmol, 127.30 μL, 5 *equiv.*) was added. The mixture was stirred at 100 °C for 2 hours. The reaction mixture was filtered, and the collected filtrate was purified by prep-HPLC to give 3-[7-fluoro-1-methyl-6-[1-[[(3*S*,4*S*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione (84.93 mg) as a yellow solid.

LC-MS (ESI): m/z = 905.3 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.91 (s, 1H), 8.79 (s, 1H), 8.19 (d, J = 8.0 Hz, 1H), 7.98 (s, 1H), 7.49 - 7.38 (m, 2H), 7.05 (dd, J = 5.6, 8.0 Hz, 1H), 6.46 (s, 1H), 4.54 - 4.31 (m, 3H), 4.10 (s, 3H), 3.55 (s, 3H), 3.26 - 3.17 (m, 1H), 3.04 - 2.84 (m, 4H), 2.80 - 2.58 (m, 3H), 2.39 - 2.31 (m, 1H), 2.21 - 2.09 (m, 3H), 2.05 - 1.93 (m, 2H), 1.91 - 1.63 (m, 7H), 1.42 - 1.16 (m, 4H), 0.77 - 0.61 (m, 4H), 0.51 (t, J = 5.6 Hz, 2H), 0.40 - 0.23 (m, 1H)

Example 142: 3-[5-fluoro-1-methyl-6-[1-[[(3*R*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione (Compound 210a)



Preparation of *tert*-butyl (3*R*,4*R*)-4-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridine-1-carbonyl]-3-methyl-piperidine-1-carboxylate

To a solution of (3*R*,4*R*)-1-tert-butoxycarbonyl-3-methyl-piperidine-4-carboxylic acid (0.5 g, 2.06 mmol, 1 *equiv.*) in DMF (5 mL), HATU (937.69 mg, 2.47 mmol, 1.2 *equiv.*) and DIPEA (796.80 mg, 6.17 mmol, 1.07 mL, 3 *equiv.*) were added dropwise. The mixture was stirred at 0°C for 10 minutes, then 3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indazole (1.07 g, 2.06 mmol, 1 *equiv.*) was added dropwise at 0 °C. The mixture was stirred at 25 °C for 1 hour. The reaction mixture was quenched by the addition of water (10 mL) and extracted with ethyl acetate (60 mL). The combined organic layers were washed with brine (60 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (0~50% ethyl acetate/petroleum ether) to give *tert*-butyl (3*R*,4*R*)-4-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridine-1-carbonyl]-3-methyl-piperidine-1-carboxylate (1.58 g) as a yellow solid.

LC-MS (ESI): m/z = 621.4 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.93 (d, *J* = 8.0 Hz, 1H), 7.59 (s, 1H), 7.53 - 7.23 (m, 9H), 6.60 (d, *J* = 8.0 Hz, 1H), 6.12 - 6.03 (m, 1H), 5.46 (d, *J* = 11.2 Hz, 4H), 4.32 - 4.23 (m, 1H), 4.18 - 4.10 (m, 1H), 4.09 - 4.06 (m, 3H), 3.96 - 3.83 (m, 1H), 3.80 - 3.61 (m, 3H), 3.16 - 3.01 (m, 2H), 2.89 (s, 1H), 2.86 - 2.77 (m, 1H), 2.58 - 2.55 (m, 1H), 2.47 (d, *J* = 5.6 Hz, 1H), 2.03 (d, *J* = 8.8 Hz, 1H), 1.88 - 1.72 (m, 1H), 1.40 (s, 9H), 0.78 (d, *J* = 6.4 Hz, 3H)

Preparation of *tert*-butyl (3*R*,4*R*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3-methyl-piperidine-1-

carboxylate

To a solution of LAH (2.5 M, 1.10 mL, 1.3 *equiv.*) in THF (12 mL), $AlCl_3$ (93.21 mg, 699.04 μmol, 38.20 μL, 0.33 *equiv.*) was added dropwise at 0 °C. After 30 minutes, *tert*-butyl (3*R*,4*R*)-4-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridine-1-carbonyl]-3-methyl-piperidine-1-carboxylate (1.58 g, 2.12 mmol, 1 *equiv.*) in THF (12 mL) was added dropwise at 0 °C. The mixture was stirred at 0 °C for 12 hours. The reaction mixture was quenched by the sequential addition of water (1 mL), 15% NaOH (1 mL), and water (3 mL). The mixture was extracted with ethyl acetate (30 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (0~40% ethyl acetate/petroleum ether) to give *tert*-butyl (3*R*,4*R*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3-methyl-piperidine-1-carboxylate (1.1 g) as a white solid.

LC-MS (ESI): m/z = 732.4 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.93 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 6.4 Hz, 1H), 7.49 (d, *J* = 7.2 Hz, 2H), 7.45 - 7.24 (m, 9H), 6.60 (d, *J* = 8.0 Hz, 1H), 6.01 (s, 1H), 5.46 (d, *J* = 11.6 Hz, 4H), 4.06 (s, 3H), 3.99 - 3.84 (m, 1H), 3.76 (d, *J* = 13.6 Hz, 1H), 3.10 (s, 2H), 3.00 - 2.84 (m, 1H), 2.74 - 2.56 (m, 6H), 2.34 - 2.16 (m, 2H), 1.98 - 1.79 (m, 2H), 1.40 (s, 10H), 1.34 - 1.24 (m, 1H), 0.79 (d, *J* = 6.8 Hz, 3H)

Preparation of *tert*-butyl (3*R*,4*R*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-methyl-piperidine-1-carboxylate

To a solution of *tert*-butyl (3*R*,4*R*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3-methyl-piperidine-1-carboxylate (1.1 g, 1.50 mmol, 1 *equiv.*) in CF_3CH_2OH (10 mL), Pd on carbon (479.83 mg, 450.88 μmol, 10% purity, 0.3 *equiv.*) and $Pd(OH)_2$ on carbon (316.61 mg, 450.88 μmol, 20% purity, 0.3 *equiv.*) were added under a N_2 atmosphere. The suspension was degassed and purged with H_2 three times. The mixture was stirred under H_2 (15 psi) at 25 °C for 12 hours. The reaction mixture was filtered and concentrated under reduced pressure to give *tert*-butyl (3*R*,4*R*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-methyl-piperidine-1-carboxylate (0.8 g, crude) as a white solid.

Preparation of 3-[5-fluoro-1-methyl-6-[1-[[(3*R*,4*R*)-3-methyl-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione

To a solution of *tert*-butyl (3*R*,4*R*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-methyl-piperidine-1-carboxylate (200 mg, 359.92 μmol, 1 *equiv.*) in DCM (1 mL), HCl/dioxane (1 mL) was added. The mixture was stirred at 25 °C for 0.5 hours. The reaction mixture was filtered and concentrated under reduced pressure to give 3-[5-fluoro-1-methyl-6-[1-[[(3*R*,4*R*)-3-methyl-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione (0.16 g, crude) as a white solid.

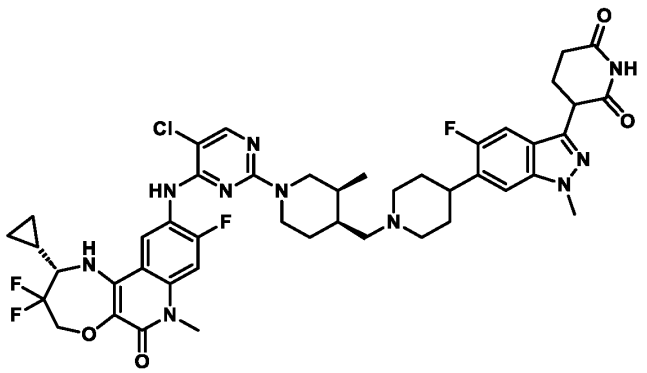
Preparation of 3-[5-fluoro-1-methyl-6-[1-[[(3*R*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione

To a solution of 3-[5-fluoro-1-methyl-6-[1-[[(3*R*,4*R*)-3-methyl-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione (0.16 g, 351.21 μmol, 1 *equiv.*) in DMSO (2 mL), TEA (142.16 mg, 1.40 mmol, 195.54 μL, 4 *equiv.*) and (2*S*)-2-cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (170.78 mg, 351.21 μmol, 1 *equiv.*) were added. The mixture was stirred at 100 °C for 2 hours. The reaction mixture was quenched by the addition of water (5 mL) and extracted with ethyl acetate (60 mL). The combined organic layers were washed with brine (60 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give 3-[5-fluoro-1-methyl-6-[1-[[(3*R*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione (111.12 mg) as a pink solid.

LC-MS (ESI): m/z = 905.5 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.88 (s, 1H), 8.81 (s, 1H), 8.19 (d, J = 8.0Hz, 1H), 7.99 (s, 1H), 7.56 (d, J = 6.0Hz, 1H), 7.50 - 7.39 (m, 2H), 6.47 (d, J = 2.0Hz, 1H), 4.49 - 4.30 (m, 5H), 4.00 (s, 3H), 3.56 (s, 3H), 3.29 (s, 1H), 3.02 - 2.57 (m, 7H), 2.44 - 2.30 (m, 1H), 2.21 - 2.05 (m, 3H), 2.02 - 1.64 (m, 8H), 1.41 - 1.20 (m, 3H), 0.77 - 0.65 (m, 4H), 0.52 (t, J = 6.0Hz, 2H), 0.39 - 0.26 (m, 1H)

Example 143: 3-[5-fluoro-1-methyl-6-[1-[[(3*S*,4*S*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione (Compound 210b)



Preparation of *tert*-butyl (3*S*,4*S*)-4-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridine-1-carbonyl]-3-methyl-piperidine-1-carboxylate

A mixture of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indazole (366.34 mg, 657.63 μmol, 1 *equiv.*, HCl), (3*S*,4*S*)-1-tert-butoxycarbonyl-3-methyl-piperidine-4-carboxylic acid (0.16 g, 657.63 μmol, 1 *equiv.*), HATU (375.07 mg, 986.44 μmol, 1.5 *equiv.*), and DIPEA (849.94 mg, 6.58 mmol, 1.15 mL, 10 *equiv.*) in DMF (8 mL) was stirred at 25 °C for 2 hours. Water (10 mL) was added to the mixture, and the resulting mixture was extracted with ethyl acetate (15 mL). The combined organic layers were washed with brine (15 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (0~50% ethyl acetate/petroleum ether) to give *tert*-butyl (3*S*,4*S*)-4-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridine-1-carbonyl]-3-methyl-piperidine-1-carboxylate (0.5 g) as a yellow gum.

LC-MS (ESI): m/z = 746.5 $[M+H]^+$

Preparation of *tert*-butyl (3*S*,4*S*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3-methyl-piperidine-1-carboxylate

To a solution of LAH (2.5 M, 348.58 μL, 1.3 *equiv.*) in THF (1 mL), $AlCl_3$ (116.20 mg, 871.46 μmol, 47.62 μL, 1.3 *equiv.*) in THF (2 mL) was added at 0 °C. The reaction mixture was stirred at 0 °C for 30 minutes. *tert*-Butyl (3*S*,4*S*)-4-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridine-1-carbonyl]-3-methyl-piperidine-1-carboxylate (0.5 g, 670.35 μmol, 1 *equiv.*) in THF (2 mL) was then added at 0 °C. The mixture was stirred at 0 °C for 1 hour under a N_2 atmosphere. The reaction mixture was quenched by the sequential addition of water (0.04 mL), 15% aqueous NaOH (0.04 mL), and water (0.12

mL). Sodium sulfate was added, and the suspension was stirred at 25 °C for 10 minutes, filtered, and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether: ethyl acetate = 1:0 to 1:1) to give *tert*-butyl (3*S*,4*S*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3-methyl-piperidine-1-carboxylate (0.4 g) as a yellow oil.

LC-MS (ESI): m/z = 732.6 $[M+H]^+$

Preparation of *tert*-butyl (3*S*,4*S*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-methyl-piperidine-1-carboxylate

To a solution of *tert*-butyl (3*S*,4*S*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3-methyl-piperidine-1-carboxylate (0.25 g, 341.58 μmol, 1 *equiv.*) in CF_3CH_2OH (3 mL), Pd on carbon (90 mg, 84.57 μmol, 10% purity, 0.248 *equiv.*) and $Pd(OH)_2$ on carbon (90 mg, 64.09 μmol, 10% purity, 0.188 *equiv.*) were added. The reaction mixture was filtered and concentrated under reduced pressure to give *tert*-butyl (3*S*,4*S*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-methyl-piperidine-1-carboxylate (150 mg, crude) as a brown oil.

LC-MS (ESI): m/z = 556.2 $[M+H]^+$

Preparation of 3-[5-fluoro-1-methyl-6-[1-[[(3*S*,4*S*)-3-methyl-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione

A solution of *tert*-butyl (3*S*,4*S*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-methyl-piperidine-1-carboxylate (100 mg, 179.96 μmol, 1 *equiv.*) in HCl/dioxane (2 M, 2 mL, 22.23 *equiv.*) was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give 3-[5-fluoro-1-methyl-6-[1-[[(3*S*,4*S*)-3-methyl-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione (90 mg, crude, HCl) as a white solid.

LC-MS (ESI): m/z = 456.3 $[M+H]^+$

Preparation of 3-[5-fluoro-1-methyl-6-[1-[[(3*S*,4*S*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione

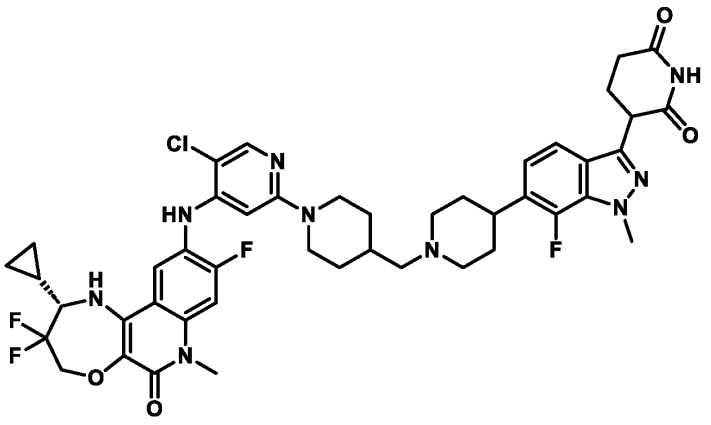
To a solution of 3-[5-fluoro-1-methyl-6-[1-[[(3*S*,4*S*)-3-methyl-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione (90.00 mg, 182.92 μmol, 1 *equiv.*, HCl) and (2*S*)-

2-cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (88.95 mg, 182.92 μmol, 1 *equiv.*) in DMSO (2 mL), TEA (92.55 mg, 914.58 μmol, 127.30 μL, 5 *equiv.*) was added. The mixture was stirred at 100 °C for 2 hours. The reaction mixture was filtered, and the collected filtrate was purified by prep-HPLC to give 3-[5-fluoro-1-methyl-6-[1-[[(3*S*,4*S*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione (69.74 mg) as a yellow solid.

LC-MS (ESI): m/z = 905.3 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.88 (s, 1H), 8.80 (s, 1H), 8.19 (d, J = 8.0 Hz, 1H), 7.99 (s, 1H), 7.56 (d, J = 6.0 Hz, 1H), 7.50 - 7.39 (m, 2H), 6.47 (s, 1H), 4.51 - 4.29 (m, 3H), 4.00 (s, 3H), 3.56 (s, 3H), 3.28 - 3.19 (m, 1H), 3.06 - 2.59 (m, 7H), 2.41 - 2.32 (m, 1H), 2.14 (dd, J = 5.6, 12.8 Hz, 3H), 2.06 - 1.69 (m, 9H), 1.43 - 1.19 (m, 4H), 0.77 - 0.60 (m, 4H), 0.51 (t, J = 5.6 Hz, 2H), 0.38 - 0.24 (m, 1H)

Example 144: 3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]-2-pyridyl]-4-piperidyl]methyl]-4-piperidyl]-7-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (Compound 211a)



Preparation of 5-chloro-2-[4-(1,3-dioxolan-2-yl)-1-piperidyl]-4-iodo-pyridine

To a solution of 5-chloro-2-fluoro-4-iodo-pyridine (2 g, 7.77 mmol, 1 *equiv.*) in NMP (20 mL), TEA (2.36 g, 23.31 mmol, 3.24 mL, 3 *equiv.*) and 4-(1,3-dioxolan-2-yl)piperidine (1.47 g, 9.32 mmol, 1.2 *equiv.*) were added. The mixture was stirred at 140 °C for 1 hour. The reaction mixture was partitioned between water (50 mL) and ethyl acetate (150 mL). The

organic phase was separated, washed with brine (150 mL), filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (0~3% ethyl acetate/petroleum ether) to give 5-chloro-2-[4-(1,3-dioxolan-2-yl)-1-piperidyl]-4-iodo-pyridine (3.5 g) as a brown liquid.

LC-MS (ESI): m/z = 395.0 $[M+H]^+$

Preparation of (2*S*)-10-[[5-chloro-2-[4-(1,3-dioxolan-2-yl)-1-piperidyl]-4-pyridyl]amino]-2-cyclopropyl-3,3,9-trifluoro7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one

A mixture of 5-chloro-2-[4-(1,3-dioxolan-2-yl)-1-piperidyl]-4-iodo-pyridine (1.74 g, 4.42 mmol, 1.5 *equiv.*), (2*S*)-10-amino-2-cyclopropyl-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (1 g, 2.95 mmol, 1 *equiv.*), t-BuONa (566.46 mg, 5.89 mmol, 2 *equiv.*), BINAP (367.02 mg, 589.43 μmol, 0.2 *equiv.*), and $Pd_2(dba)_3$ (269.87 mg, 294.71 μmol, 0.1 *equiv.*) in dioxane (50 mL) was degassed and purged with N_2 three times. The mixture was stirred at 95 °C for 12 hours under a N_2 atmosphere. The reaction mixture was partitioned between water (50 mL) and ethyl acetate (150 mL). The organic phase was separated, washed with brine (450 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give (2*S*)-10-[[5-chloro-2-[4-(1,3-dioxolan-2-yl)-1-piperidyl]-4-pyridyl]amino]-2-cyclopropyl-3,3,9-trifluoro7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (450 mg) as a brown oil.

LC-MS (ESI): m/z = 606.1 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ= 8.27 - 8.08 (m, 1H), 7.98 - 7.77 (m, 2H), 7.58 - 7.41 (m, 1H), 6.54 - 6.36 (m, 1H), 5.76 - 5.63 (m, 1H), 5.50 - 5.48 (m, 1H), 4.56 - 4.26 (m, 4H), 4.06 - 3.91 (m, 2H), 3.84 - 3.68 (m, 4H), 3.54 (d, *J* = 6.4 Hz, 3H), 1.70 - 1.54 (m, 3H), 1.32 - 1.11 (m, 4H), 1.04 (d, *J* = 7.2 Hz, 2H), 0.70 (d, *J* = 6.4 Hz, 1H), 0.55 - 0.43 (m, 2H), 0.29 (dd, *J* = 3.2, 8.0 Hz, 1H)

Preparation of 1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]-2-pyridyl]piperidine-4-carbaldehyde

To a solution of (2*S*)-10-[[5-chloro-2-[4-(1,3-dioxolan-2-yl)-1-piperidyl]-4-pyridyl]amino]-2-cyclopropyl-3,3,9-trifluoro7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (100 mg, 165.01 μmol, 1 *equiv.*) in 1,4-dioxane, formic acid (2 mL) was

added. The mixture was stirred at 70 °C for 16 hours. The mixture was treated with saturated aqueous $NaHCO_3$ to pH = 6-7 and partitioned between water (5 mL) and ethyl acetate (10 mL). The mixture was dried over sodium sulfate, filtered, and concentrated under reduced pressure to give 1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]-2-pyridyl]piperidine-4-carbaldehyde (100 mg) as a white solid.

LC-MS (ESI): m/z = 562.2 $[M+H]^+$

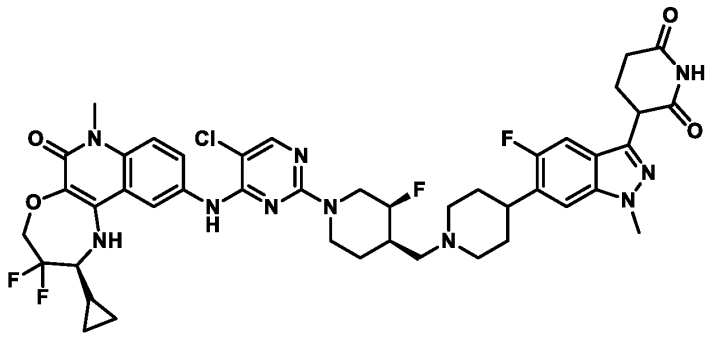
Preparation of 3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]-2-pyridyl]-4-piperidyl]methyl]-4-piperidyl]-7-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione

To a solution of 1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]-2-pyridyl]piperidine-4-carbaldehyde (80 mg, 142.35 μmol, 1 *equiv.*) in DMSO (4 mL), 3-(7-fluoro-1-methyl-6-(piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (49.02 mg, 142.35 μmol, 1 *equiv.*), Ti(*i*-PrO)$_4$ (40.46 mg, 142.35 μmol, 42.01 μL, 1 *equiv.*), and $NaBH(OAc)_3$ (45.26 mg, 213.53 μmol, 1.5 *equiv.*) were added. The mixture was stirred at 25 °C for 1 hour. The reaction mixture was filtered, and the filter cake was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give 3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]-2-pyridyl]-4-piperidyl]methyl]-4-piperidyl]-7-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (29.95 mg) as a white solid.

LC-MS (ESI): m/z = 890.4 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.05 - 10.79 (m, 1H), 8.21 (d, *J* = 8.0 Hz, 1H), 7.97 - 7.86 (m, 2H), 7.58 - 7.37 (m, 2H), 7.04 (dd, *J* = 5.6, 8.4 Hz, 1H), 6.58 - 6.45 (m, 1H), 5.68 (s, 1H), 4.48 - 4.29 (m, 3H), 4.10 (s, 3H), 4.00 - 3.89 (m, 2H), 3.56 (s, 3H), 2.98 - 2.87 (m, 4H), 2.70 - 2.64 (m, 3H), 2.35 - 2.31 (m, 2H), 2.18 - 2.10 (m, 3H), 2.03 - 1.95 (m, 2H), 1.73 - 1.62 (m, 6H), 1.38 - 1.16 (m, 2H), 1.10 - 1.08 (m, 1H), 1.10 - 0.95 (m, 2H), 0.75 - 0.64 (m, 1H), 0.50 (t, *J* = 5.2 Hz, 2H), 0.34 - 0.24 (m, 1H)

Example 145: 3-(6-(1-(((3*S*,4*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 111a)



Preparation of 6-bromo-5-fluoro-1*H*-indazole

To a stirred solution of 4-bromo-2,5-difluorobenzaldehyde (20.00 g, 90.50 mmol) in 1,2-dimethoxyethane (200.0 mL), methoxyamine Hydrochloride (8.012 g, 95.928 mmol), and potassium carbonate (12.007 g, 86.878 mmol, 0.96 *equiv.*) were added. The mixture was heated at 40 °C for 3 hours. The reaction mixture was diluted with DME (200 mL), filtered through a pad of celite, and washed with ethyl acetate (200 mL). The collected filtrate was concentrated under vacuum. To the resulting crude product, hydrazine 1.0 M in THF (80.0 mL) in 1,2-dimethoxyethane (200.0 mL) was added and heated to 90 °C for 18 hours. The reaction mixture was concentrated under vacuum and triturated with n-pentane (100 mL) to afford 6-bromo-5-fluoro-1*H*-indazole (7.20 g) as a pale yellow solid.

LC-MS (ESI): m/z = 215.10 $[M+H]^+$

Preparation of 6-bromo-5-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole and 6-bromo-5-fluoro-2-((2-(trimethylsilyl)ethoxy)methyl)-2*H*-indazole

To a solution of 6-bromo-5-fluoro-1*H*-indazole (20 g, 93.01 mmol) in THF (1 L) was added sodium hydride, 60% dispersion in mineral oil (6.70 g, 279.04 mmol), at 0 °C. The mixture was stirred for 15 minutes. Then, 2-(trimethylsilyl)ethoxymethyl chloride (50.0 mL, 279.04 mmol) was added at 0 °C and the mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with EtOAc (1 L) and quenched with ice-cold water (1 L). The separated organic layer was dried over anhydrous sodium sulfate, filtered, and dried under vacuum to give a mixture of 6-bromo-5-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole and 6-bromo-5-fluoro-2-((2-(trimethylsilyl)ethoxy)methyl)-2*H*-indazole (42.0 g) as a pale brown semi-solid.

LC-MS (ESI): m/z = 345.25 $[M+H]^+$

Preparation of *tert*-butyl 4-(5-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazol-6-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate and *tert*-butyl 4-(5-fluoro-2-((2-(trimethylsilyl)ethoxy)methyl)-2*H*-indazol-6-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate

To a stirred solution of 6-bromo-5-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole and 6-bromo-5-fluoro-2-((2-(trimethylsilyl)ethoxy)methyl)-2*H*-indazole (23 g, 66.61 mmol), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (30.90 g, 99.92 mmol), and tripotassium phosphate (42.42 g, 199.83 mmol) in 1,4-dioxane (184.0 mL) and water (46.0 mL) was degassed with argon for 10 minutes. $Pd(PPh_3)_4$ (7.70 g, 6.66 mmol) was added and the mixture was stirred under argon for 5 minutes, then heated to 100 °C for 14 hours. The reaction mixture was diluted with ethyl acetate (500 mL). The separated organic layer was dried over anhydrous sodium sulfate, filtered, and dried under vacuum to afford a crude product. The crude product was purified by flash silica gel chromatography (9% ethyl acetate/petroleum ether) to afford a mixture of *tert*-butyl 4-(5-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazol-6-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate and *tert*-butyl 4-(5-fluoro-2-((2-(trimethylsilyl)ethoxy)methyl)-2*H*-indazol-6-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (30 g) as a yellow semi-solid.

LC-MS (ESI): m/z = 448.50 $[M+H]^+$

Preparation of *tert*-butyl 4-(5-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazol-6-yl)piperidine-1-carboxylate and *tert*-butyl 4-(5-fluoro-2-((2-(trimethylsilyl)ethoxy)methyl)-2*H*-indazol-6-yl)piperidine-1-carboxylate

To a solution of a mixture of *tert*-butyl 4-(5-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazol-6-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate and *tert*-butyl 4-(5-fluoro-2-((2-(trimethylsilyl)ethoxy)methyl)-2*H*-indazol-6-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (20 g, 44.68 mmol) in THF (400 mL) was added Pd on carbon (10.0 g, 10 wt%). The mixture was stirred under hydrogen (H_2, Parr, 80 psi) at room temperature for 12 hours. The reaction mixture was diluted with THF (1 L) and filtered through a pad of celite. The collected filtrate was concentrated under vacuum to give a mixture of *tert*-butyl 4-(5-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazol-6-yl)piperidine-1-carboxylate and *tert*-butyl 4-(5-fluoro-2-((2-(trimethylsilyl)ethoxy)methyl)-2*H*-indazol-6-yl)piperidine-1-carboxylate (17.8 g) as a pale brown semi-solid.

LC-MS (ESI): m/z = 450.46 $[M+H]^+$

Preparation of *tert*-butyl 4-(5-fluoro-1*H*-indazol-6-yl)piperidine-1-carboxylate

To a solution of a mixture of *tert*-butyl 4-(5-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazol-6-yl)piperidine-1-carboxylate and *tert*-butyl 4-(5-fluoro-2-((2-(trimethylsilyl)ethoxy)methyl)-2*H*-indazol-6-yl)piperidine-1-carboxylate (17 g, 37.81 mmol) in THF (170 mL) was added TBAF, 1M solution in THF (340 mL), at 0 °C. The mixture was stirred at 60 °C for 16 hours. The reaction mixture was quenched with water and extracted into ethyl acetate. The combined organic layers were washed with brine solution and dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to obtain a crude product. The crude product was purified by flash silica gel chromatography (9% ethyl acetate/petroleum ether) to afford *tert*-butyl 4-(5-fluoro-1*H*-indazol-6-yl)piperidine-1-carboxylate (16 g) as a yellow semi-solid.

LC-MS (ESI): m/z = 320.44 $[M+H]^+$

Preparation of *tert*-butyl 4-(5-fluoro-3-iodo-1*H*-indazol-6-yl)piperidine-1-carboxylate

To a stirred solution of *tert*-butyl 4-(5-fluoro-1*H*-indazol-6-yl)piperidine-1-carboxylate (9.80 g, 30.68 mmol) in THF (78 mL), potassium hydroxide (5.17 g, 92.05 mmol) and Iodine (11.70 g, 46.02 mmol) were added at 0 °C. The mixture was stirred at room temperature for 2 hours. The reaction mixture was quenched with water (200 mL) and extracted with ethyl acetate (900 mL). The combined organic layers were washed with brine solution (200 mL) and dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to give *tert*-butyl 4-(5-fluoro-3-iodo-1*H*-indazol-6-yl)piperidine-1-carboxylate (9.75 g) as a brown semi-solid.

LC-MS (ESI): m/z = 444.32 $[M+H]^+$

Preparation of *tert*-butyl 4-(5-fluoro-3-iodo-1-methyl-1*H*-indazol-6-yl)piperidine-1-carboxylate

To a stirred solution of *tert*-butyl 4-(5-fluoro-3-iodo-1*H*-indazol-6-yl)piperidine-1-carboxylate (9.75 g, 21.90 mmol) in THF (100 mL), potassium tert-butoxide (9.83 g, 87.59 mmol) and iodomethane (10.0 mL) were added at 0 °C. The mixture was stirred at room temperature for 4 hours. The reaction mixture was quenched with water (100 mL) and extracted with ethyl acetate (400 mL). The combined organic layers were washed with brine solution, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to obtain crude product, which was purified by flash chromatography (10-15% ethyl acetate/petroleum ether) to yield *tert*-butyl 4-(5-fluoro-3-iodo-1-methyl-1*H*-indazol-6-yl)piperidine-1-carboxylate (3.70 g) as a pale yellow semi-solid.

LC-MS (ESI): m/z = 460.37 $[M+H]^+$

Preparation of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidine-1-carboxylate

A stirred solution of *tert*-butyl 4-(5-fluoro-3-iodo-1-methyl-1*H*-indazol-6-yl)piperidine-1-carboxylate (3.70 g, 8.06 mmol) and (2,6-bis(benzyloxy)pyridin-3-yl)boronic acid (3.79 g, 11.28 mmol) in 1,4-dioxane (30 mL) and water (7.4 mL), was purged with N_2 for 10 minutes. $Pd(PPh_3)_4$ (0.93 g, 0.80 mmol) and K_3PO_4 (5.15 g, 24.17 mmol) were added, and the mixture was further purged with N_2 for 15 minutes. The mixture was heated to 100 °C for 6 hours. The reaction mixture was quenched with water (50 mL) and extracted with ethyl acetate (100 mL). The combined organic layers were washed with brine solution, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to obtain a crude product. The crude product was purified by flash chromatography (10-15% ethyl acetate/petroleum ether) to afford *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidine-1-carboxylate (1.72 g) as a pale yellow solid.

LC-MS (ESI): m/z = 623.48 $[M+H]^+$

Preparation of 6-(benzyloxy)-5-(5-fluoro-1-methyl-6-(piperidin-4-yl)-1*H*-indazol-3-yl)pyridin-2-ol

To a stirred solution of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidine-1-carboxylate (1.50 g, 2.41 mmol) in DCM (30 mL) was added TFA (7.5 mL) at 0 °C. The mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated and co-distilled with DCM (60 mL) to obtain a crude product. The crude product was triturated with diethyl ether (15 mL) and dried to afford 6-(benzyloxy)-5-(5-fluoro-1-methyl-6-(piperidin-4-yl)-1*H*-indazol-3-yl)pyridin-2-ol (1.20 g) as a brown solid.

LC-MS (ESI): m/z = 433.30 $[M+H]^+$

Preparation of *tert*-butyl 4-(4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidine-1-carbonyl)-3-fluoropiperidine-1-carboxylate

To a solution of 6-(benzyloxy)-5-(5-fluoro-1-methyl-6-(piperidin-4-yl)-1*H*-indazol-3-yl)pyridin-2-ol (1.50 g, 3.47 mmol) and 1-(tert-butoxycarbonyl)-3-fluoropiperidine-4-carboxylic acid (0.89 g, 3.47 mmol) in DMF (15.0 mL) was added DIPEA (3.0 mL, 17.34

mmol). The mixture was stirred at room temperature for 5 minutes. Then, propylphosphonic anhydride solution (50% ethyl acetate) (2.21 g, 6.94 mmol) was added at 0 °C and the resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was poured into ice-cold water and stirred for 10 minutes. The precipitated solid was filtered and dried under vacuum to give *tert*-butyl 4-(4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidine-1-carbonyl)-3-fluoropiperidine-1-carboxylate (1.21 g) as an off white solid.

LC-MS (ESI): m/z = 662.60 $[M+H]^+$

Preparation of *tert*-butyl 4-((4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate

To a solution of *tert*-butyl 4-(4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidine-1-carbonyl)-3-fluoropiperidine-1-carboxylate (1.10 g, 1.66 mmol) in THF (20.0 mL) was added BH_3·DMS (neat) (4.4 mL) at 0 °C. The mixture was stirred at room temperature for 6 hours. The reaction mixture was quenched with MeOH (25 mL), concentrated, and co-distilled with methanol (40 mL) and petroleum ether (20 mL). The crude product was diluted with MeOH (20 mL), refluxed for 4 hours, cooled to room temperature, and concentrated. The dried crude product was purified by flash silica gel chromatography (50~100% ethyl acetate/petroleum ether) to afford *tert*-butyl 4-((4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (0.92 g) as an off white solid.

LC-MS (ESI): m/z = 648.35 $[M+H]^+$

Preparation of *tert*-butyl (3*S*,4*R*)-4-((4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate and *tert*-butyl (3*R*,4*S*)-4-((4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate

The diastereomers of *tert*-butyl 4-((4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate were separated by SFC to afford *tert*-butyl (3*S*,4*R*)-4-((4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (**Peak 1**) (0.25 g) as an off white solid and *tert*-butyl (3*R*,4*S*)-4-((4-(3-(2-

(benzyloxy)-6-hydroxypyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (**Peak 2**) (0.35 g) as an off white solid.

LC-MS (ESI): m/z = 648.8 $[M+H]^+$

LC-MS (ESI): m/z = 648.8 $[M+H]^+$

Preparation of *tert*-butyl (3*S*,4*R*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate

To a solution of *tert*-butyl (3*S*,4*R*)-4-((4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (0.28 g, 0.43 mmol) in THF (12 mL), DMF (0.6 mL), and acetic acid (0.1 mL) was added $Pd(OH)_2$ on carbon (0.36 g, 20 wt%). The mixture was stirred under hydrogen pressure (80 psi) at room temperature for 12 hours. The reaction mixture was diluted with ethyl acetate (50 mL), filtered through a pad of celite, and the filtrate was collected and concentrated to yield the crude product. The crude product was purified by trituration with diethyl ether to give *tert*-butyl (3*S*,4*R*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (0.25 g) as a pale brown semi-solid.

LC-MS (ESI): m/z = 560.56 $[M+H]^+$

Preparation of 3-(5-fluoro-6-(1-(((3*S*,4*R*)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

To a solution of *tert*-butyl (3*S*,4*R*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (0.09 g, 0.16 mmol) in DCM (4.5 mL) was added TFA (0.5 mL) at 0 °C. The mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated and co-distilled with DCM (60 mL) to yield the crude product. The crude product was triturated with diethyl ether (15 mL) and dried to afford 3-(5-fluoro-6-(1-(((3*S*,4*R*)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.25 g) as a brown solid.

LC-MS (ESI): m/z = 460.50 $[M+H]^+$

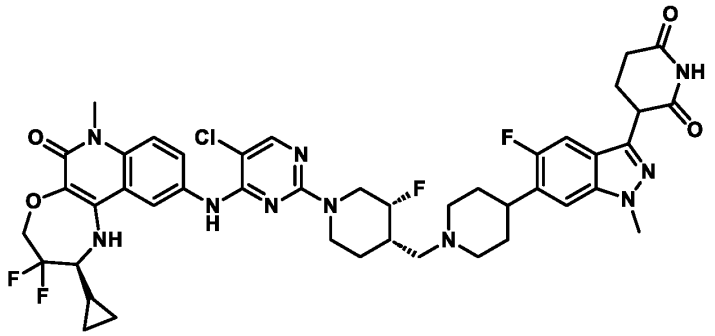
Preparation of 3-(6-(1-(((3*S*,4*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

To a solution of 3-(5-fluoro-6-(1-(((3*S*,4*R*)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.25 g, 0.54 mmol) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.10 g, 0.22 mmol) in DMSO (5.0 mL) was added DIPEA (2.0 mL). The mixture was stirred at 110 °C for 6 hours. The reaction mixture was poured into ice-cold water (20 mL), and the precipitated solid was filtered and dried to obtain the crude product, which was purified by prep-HPLC to give 3-(6-(1-(((3*S*,4*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.10 g) as an off-white solid.

LC-MS (ESI): m/z = 891.63 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.89 (s, 1H), 8.91 (s, 1H), 8.15 (s, 1H), 8.06 (s, 1H), 7.74 (d, J = 7.20 Hz, 1H), 7.67 (d, J = 6.00 Hz, 1H), 7.55 (d, J = 10.80 Hz, 1H), 7.52 (s, 1H), 4.83-4.79 (m, 2H), 4.35-4.34 (m, 2H), 4.32-4.01 (m, 2H), 3.70 (s, 3H), 3.67-3.54 (m, 1H), 3.57-3.54 (m, 4H), 3.17-3.14 (m, 7H), 3.00-2.88 (m, 1H), 2.62-2.60 (m, 3H), 2.38-2.37 (m, 2H), 2.07-2.07 (m, 5H), 1.72-1.69 (m, 1H), 1.52-1.49 (m, 1H), 1.39-1.34 (m, 1H), 0.71-0.69 (m, 1H), 0.53-0.52 (m, 2H), 0.35-0.34 (m, 1H).

Example 146: 3-(6-(1-(((3*R*,4*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 111b)



Preparation of *tert*-butyl (3*R*,4*S*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate

To a solution of *tert*-butyl (3*R*,4*S*)-4-((4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (0.32 g, 0.49 mmol) in THF (10 mL) was added $Pd(OH)_2$ on carbon (0.64 g, 20 wt%). The mixture was stirred under a H_2 atmosphere at room temperature for 12 hours. The reaction mixture was diluted with ethyl acetate (50 mL), filtered through a pad of celite, and the filtrate was collected and concentrated to yield the crude product. The crude product was purified by trituration with diethyl ether to give *tert*-butyl (3*R*,4*S*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (0.32 g) as a yellow semisolid.

LC-MS (ESI): m/z = 560.52 $[M+H]^+$

Preparation of 3-(5-fluoro-6-(1-(((3*R*,4*S*)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

To a solution of *tert*-butyl (3*R*,4*S*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (0.32 g, 0.57 mmol) in DCM (6.0 mL) was added TFA (1.5 mL) at 0 °C. The mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated and co-distilled with DCM (60 mL) to yield the crude product. The crude product was triturated with diethyl ether (15 mL) and dried under vacuum to afford 3-(5-fluoro-6-(1-(((3*R*,4*S*)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.35 g) as a brown semisolid.

LC-MS (ESI): m/z = 460.47 $[M+H]^+$

Preparation of 3-(6-(1-(((3*R*,4*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

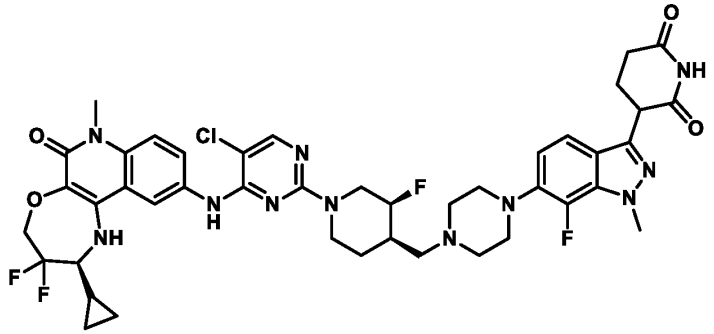
To a solution of 3-(5-fluoro-6-(1-(((3*R*,4*S*)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.34 g, 0.74 mmol) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.14 g, 0.29 mmol) in DMSO (6.80 mL) was added DIPEA (2.70 mL, 2.40 mmol). The mixture was stirred at 110 °C for 6 hours. The reaction mixture was poured into ice-cold water (20 mL), and the precipitated solid was filtered and dried to obtain the crude product. The crude product was purified by prep-HPLC to afford

3-(6-(1-(((3*R*,4*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.10 g) as an off-white solid.

LC-MS (ESI): m/z = 891.69 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.89 (s, 1H), 8.91 (s, 1H), 8.14 (d, *J* = 1.60 Hz, 1H), 8.06 (s, 1H), 7.75 (dd, *J* = 2.00, 9.00 Hz, 1H), 7.53 (d, *J* = 7.20 Hz, 1H), 7.45 (d, *J* = 4.80 Hz, 1H), 7.43 (s, 1H), 6.23 (brs, 1H), 4.82-4.80 (m, 2H), 4.42-4.35 (m, 2H), 4.33-4.32 (m, 2H), 4.01 (s, 3H), 3.70-3.68 (m, 1H), 3.58-3.51 (m, 3H), 3.42-3.39 (m, 6H), 3.21-3.19 (m, 1H), 2.87-2.80 (m, 1H), 2.66-2.60 (m, 3H), 2.38-2.387(m, 2H), 2.07-2.07 (m, 5H), 1.85-1.71 (m, 1H), 1.52-1.49 (m, 1H), 1.39-1.36 (m, 1H), 0.72-0.69 (m, 1H), 0.52-0.51 (m, 2H), 0.35-0.34 (m, 1H).

Example 147: 3-(6-(4-(((3*S*,4*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperazin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 189a)



Preparation of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-6-(piperazin-1-yl)-1*H*-indazole

To a solution of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-7-fluoro-1-methyl-1*H*-indazole (7.0 g, 13.5 mmol), piperazine (2.33 g, 2.01 mmol), and t-BuONa, (3.89 g, 6.05 mmol) in 1,4-dioxane (140 mL) was added RuPhos-Pd-G3 (0.56 g, 0.67 mmol). The mixture was degassed with argon for 5 minutes and then heated at 100 °C for 16 hours. The reaction mixture was quenched with ice-cold water (300 mL) and extracted with ethyl acetate (300 mL). The combined organic layers were washed with brine solution (300 mL), dried over anhydrous sodium sulfate, filtered, and dried under vacuum to give a residue. This residue was purified

by flash silica gel chromatography (40% ethyl acetate/petroleum ether) to give 3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-6-(piperazin-1-yl)-1*H*-indazole (4.25 g) as a pale brown semi-solid.

LC-MS (ESI): m/z = 524.52 $[M+H]^+$

Preparation of *tert*-butyl 4-(4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperazine-1-carbonyl)-3-fluoropiperidine-1-carboxylate

To a solution of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-6-(piperazin-1-yl)-1*H*-indazole (4.25 g, 8.12 mmol) and 1-(tert-butoxycarbonyl)-3-fluoropiperidine-4-carboxylic acid (2.0 g, 8.13 mmol) in DMF (42.5 mL) was added DIPEA (4.0 mL, 24.3 mmol). The mixture was stirred at room temperature for 5 minutes. Then, HATU (3.87 g, 12.1 mmol) was added at 0 °C and the mixture was stirred at room temperature for 2 hours. The reaction mixture was poured into ice-cold water and stirred for 10 minutes. The precipitated solid was filtered and dried to give *tert*-butyl 4-(4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperazine-1-carbonyl)-3-fluoropiperidine-1-carboxylate (5.21 g) as an off-white solid.

LC-MS (ESI): m/z = 753.81 $[M+H]^+$

Preparation of *tert*-butyl 4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate

To a solution of *tert*-butyl 4-(4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperazine-1-carbonyl)-3-fluoropiperidine-1-carboxylate (5.17 g, 6.87 mmol) in THF (103 mL) was added BH_3.DMS (neat) (51.7 mL) at 0 °C. The mixture was stirred at room temperature for 6 hours. The reaction mixture was quenched with MeOH (250 mL), concentrated, and co-distilled with methanol (200 mL). Additional methanol was then added and refluxed for 2 hours at 60 °C. The reaction mixture was concentrated under reduced pressure and co-distilled with petroleum ether to give *tert*-butyl 4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (4.72 g) as an off-white solid.

LC-MS (ESI): m/z = 739.86 $[M+H]^+$

Preparation of *tert*-butyl (3*S*,4*R*)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-3-fluoropiperidine-1-

carboxylate and *tert*-butyl (3*R*,4*S*)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate

The stereoisomers of *tert*-butyl 4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate were separated by SFC to afford *tert*-butyl (3*S*,4*R*)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (**Peak 1**) (0.90 g) as an off white solid and *tert*-butyl (3*R*,4*S*)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (**Peak 2**) (1.05 g) as an off white solid.

LC-MS (ESI): m/z = 739.68 $[M+H]^+$

LC-MS (ESI): m/z = 739.68 $[M+H]^+$

Preparation of *tert*-butyl (3*S*,4*R*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate

To a solution of *tert*-butyl (3*S*,4*R*)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (0.9 g, 1.21 mmol) in THF (90 mL), $Pd(OH)_2$ on carbon (1.35 g, 20 wt%) was added. The mixture was stirred under hydrogen pressure (80 psi) at room temperature for 4 hours. The reaction mixture was diluted with ethyl acetate (500 mL), filtered through a pad of celite, and the filtrate was collected and concentrated to give a residue. This residue was purified by trituration with diethyl ether to give *tert*-butyl (3*S*,4*R*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (0.65 g) as an off-white semi-solid.

LC-MS (ESI): m/z = 561.64 $[M+H]^+$

Preparation of 3-(7-fluoro-6-(4-(((3*S*,4*R*)-3-fluoropiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

To a solution of *tert*-butyl (3*S*,4*R*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (0.65 g, 1.16 mmol) in DCM (32.5 mL) was added TFA (5.2 mL) at 0 °C. The mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated and co-distilled with DCM (60 mL) to give a residue. This residue was triturated with diethyl ether (100 mL) and dried to give 3-(7-fluoro-6-(4-(((3*S*,4*R*)-3-fluoropiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.48 g) as a brown solid.

LC-MS (ESI): m/z = 461.41 $[M+H]^+$

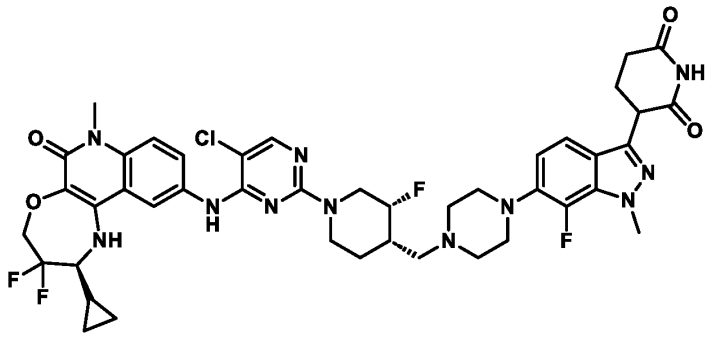
Preparation of 3-(6-(4-(((3*S*,4*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperazin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

To a solution of 3-(7-fluoro-6-(4-(((3*S*,4*R*)-3-fluoropiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.48 g, 1.04 mmol) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.097 g, 0.2 mmol) in DMSO (9.6 mL) was added DIPEA (4.8 mL). The mixture was stirred at 110 °C for 6 hours. The reaction mixture was poured into ice-cold water (20 mL), and the precipitated solid was filtered and dried to give a residue. This residue was purified by prep-HPLC to give 3-(6-(4-(((3*S*,4*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperazin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (53 mg) as an off-white solid.

LC-MS (ESI): m/z = 892.68 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.91 (s, 1H), 9.45 (br s, 1H), 8.92 (s, 1H), 8.14 (d, *J* = 2.00 Hz, 1H), 8.07 (s, 1H), 7.75 (dd, *J* = 2.00, 9.20 Hz, 1H), 7.45-7.42 (m, 2H), 6.98-6.96 (m, 1H), 6.23 (br s, 1H), 4.91-4.82 (m, 2H), 4.44-4.42 (m, 1H), 4.34-4.33 (m, 3H), 4.09 (s, 3H), 3.68-3.67 (m, 2H), 3.57 (s, 3H), 3.56-3.54 (m, 2H), 3.25-3.22 (m, 6H), 3.13-3.10 (m, 2H), 2.87-2.78 (m, 1H), 2.69-2.68 (m, 1H), 2.65-2.62 (m, 2H), 2.50-2.50 (m, 1H), 2.36-2.17 (m, 1H), 1.82-1.72 (m, 1H), 1.59-1.47 (m, 1H), 1.44-1.41 (m, 1H), 0.72-0.69 (m, 1H), 0.52-0.51 (m, 2H), 0.35-0.34 (m, 1H).

Example 148: 3-(6-(4-(((3*R*,4*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperazin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 189b)



Preparation of *tert*-butyl (3*R*,4*S*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate

To a solution of *tert*-butyl (3*R*,4*S*)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (0.75 g, 1.0 mmol) in THF (75 mL), $Pd(OH)_2$ on carbon (1.13 g, 20 wt%) was added. The mixture was stirred under hydrogen pressure (80 psi) at room temperature for 4 hours. The reaction mixture was diluted with ethyl acetate (200 mL), filtered through a pad of celite, and the filtrate was collected and concentrated to give a residue. This residue was purified by trituration with diethyl ether to give *tert*-butyl (3*R*,4*S*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (0.59 g) as a yellow semisolid.

LC-MS (ESI): m/z = 561.59 $[M+H]^+$

Preparation of 3-(7-fluoro-6-(4-(((3*R*,4*S*)-3-fluoropiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

To a solution of *tert*-butyl (3*R*,4*S*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (0.08 g, 0.14 mmol) in DCM (30 mL) was added TFA (4.7 mL) at 0 °C. The mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated and co-distilled with DCM (60 mL) to give a residue. This residue was triturated with diethyl ether (100 mL) and dried to give 3-(7-fluoro-6-(4-(((3*R*,4*S*)-3-fluoropiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.48 g) as a brown semisolid.

LC-MS (ESI): m/z = 461.58 $[M+H]^+$

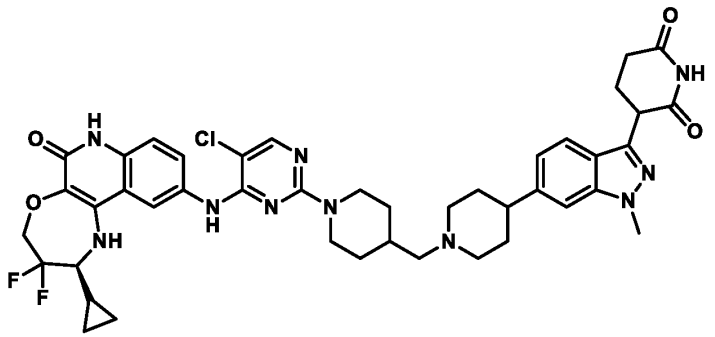
Preparation of 3-(6-(4-(((3*R*,4*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperazin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

To a solution of 3-(7-fluoro-6-(4-(((3*R*,4*S*)-3-fluoropiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.48 g, 1.0 mmol) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.097 g, 0.2 mmol) in DMSO (9.60 mL) was added DIPEA (4.80 mL). The mixture was stirred at 110 °C for 6 hours. The reaction mixture was poured into ice-cold water (20 mL), and the precipitated solid was filtered and dried to give a residue. This residue was purified by prep-HPLC to give 3-(6-(4-(((3*R*,4*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperazin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.066 g) as an off-white solid.

LC-MS (ESI): m/z = 892.67 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.91 (s, 1H), 8.91 (s, 1H), 8.14 (s, 1H), 8.06 (s, 1H), 7.75 (d, *J* = 8.80 Hz, 1H), 7.44-7.42 (m, 2H), 6.98-6.96 (m, 1H), 6.26 (br s, 1H), 4.94-4.82 (m, 2H), 4.34-4.33 (m, 4H), 4.09 (s, 3H), 3.68-3.66 (m, 2H), 3.56-3.54 (m, 5H), 3.25-3.23 (m, 6H), 3.13-3.10 (m, 2H), 2.99-2.87 (m, 1H), 2.61-2.58 (m, 2H), 2.17-2.15 (m, 2H), 1.75-1.65 (m, 2H), 1.56-1.50 (m, 1H), 1.44-1.35 (m, 1H), 0.70 (d, *J* = 9.60 Hz, 1H), 0.53 (t, *J* = 6.00 Hz, 2H), 0.35 (d, *J* = 4.80 Hz, 1H).

Example 149: 3-(6-(1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 182a)



Preparation of 3-(6-(1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

To a solution of 3-(1-methyl-6-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (0.30 g, 0.70 mmol) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.12 g, 0.28 mmol) in DMSO (6 mL) was added DIPEA (0.73 g, 5.66 mmol). The mixture was stirred at 100 °C for 8 hours. After completion, the reaction mixture was concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give 3-(6-(1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.041 g) as a brown solid.

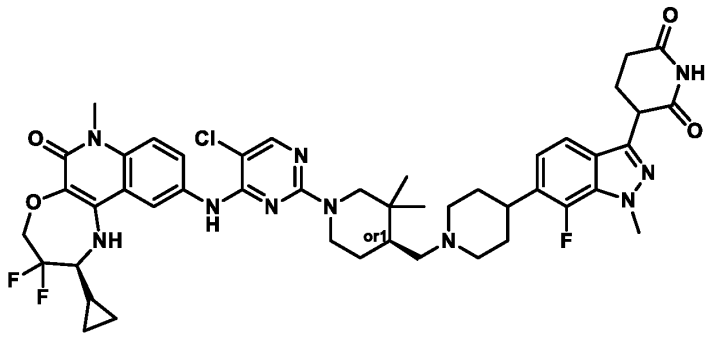
LC-MS (ESI): m/z = 841.63 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.35 (s, 1H), 10.89 (s, 1H), 8.89-8.83 (m, 1H), 8.05 (s, 1H), 8.03 (d, *J* = 1.60 Hz, 1H), 7.68 (d, *J* = 8.40 Hz, 1H), 7.62 (dd, *J* = 6.80, 8.80 Hz, 1H), 7.40 (s, 1H), 7.14-7.12 (m, 2H), 6.22 (s, 1H), 4.44-4.32 (m, 5H), 3.99 (s, 3H), 3.62 (d, *J* = 11.20 Hz, 2H), 3.28-3.18 (m, 1H), 3.09-2.97 (m, 5H), 2.85 (t, *J* = 12.40 Hz, 2H), 2.61-2.54 (m, 2H), 2.37-2.35 (m, 1H), 2.18-2.04 (m, 6H), 1.73-1.70 (m, 2H), 1.40-1.32 (m, 1H), 1.14-1.11 (m, 2H), 0.71-0.70 (m, 1H), 0.54-0.52 (m, 2H), 0.35-0.34 (m, 1H).

Example 150: 3-(6-(1-(((*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

[3-(6-(1-(((*S)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]**

(Compound 123a)



Preparation of *tert*-butyl 4-(4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidine-1-carbonyl)-3,3-dimethylpiperidine-1-carboxylate

To a solution of 6-(benzyloxy)-3-(7-fluoro-1-methyl-6-(piperidin-4-yl)-1*H*-indazol-3-yl)pyridin-2-ol (2.5 g, 5.78 mmol) and 1-(tert-butoxycarbonyl)-3,3-dimethylpiperidine-4-carboxylic acid (1.48 g, 5.78 mmol) in DMF (205 mL) was added DIPEA (5.03 g, 28.90 mmol). The mixture was stirred for 10 minutes. Then, HATU (3.29 g, 8.67 mmol) was added at 0 °C and the mixture was stirred at room temperature for 16 hours. The reaction mixture was diluted with ethyl acetate (40 mL) and washed with cold water (120 mL). The separated organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a residue. This residue was purified by flash silica gel chromatography (54% ethyl acetate/petroleum ether) to give *tert*-butyl 4-(4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidine-1-carbonyl)-3,3-dimethylpiperidine-1-carboxylate (1.1 g) as an off-white solid.

LC-MS (ESI): m/z = 672.37 $[M+H]^+$

Preparation of *tert*-butyl 4-((4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate

To a solution of *tert*-butyl 4-(4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidine-1-carbonyl)-3,3-dimethylpiperidine-1-carboxylate (1.1 g, 1.63 mmol) in THF (22 mL) was added a 10.0 M borane dimethyl sulfide solution in THF (11 mL). The mixture was stirred at room temperature for 16 hours. The mixture was quenched with methanol (20 mL) and concentrated under reduced pressure. The resulting residue was dissolved in methanol (20 mL) and refluxed at 80 °C for 2 hours. The reaction mixture was concentrated under reduced pressure to give a residue. This residue was purified by flash silica gel chromatography (30% ethyl acetate/petroleum ether) to give *tert*-butyl 4-((4-(3-(6-

(benzyloxy)-2-hydroxypyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate (0.75 g) as a yellow semi-solid.

LC-MS (ESI): m/z = 659.22 $[M+H]^+$

Preparation of *tert*-butyl (*S*)-4-((4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate and *tert*-butyl (*R*)-4-((4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate

The stereoisomers of *tert*-butyl 4-((4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate were separated by SFC to afford *tert*-butyl (*S*)-4-((4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate (**Peak 1**) (0.20 g) as a pink solid and *tert*-butyl (*R*)-4-((4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate (**Peak 2**) (0.20 g) as a pink solid.

Preparation of *tert*-butyl (4*S*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate

To a solution of *tert*-butyl (*S*)-4-((4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate (0.20 g, 0.30 mmol) in THF (6.0 mL) was added $Pd(OH)_2$ on carbon (0.20 g, 20 wt%). The mixture was stirred under hydrogen pressure (80 psi) at room temperature for 12 hours. The reaction mixture was diluted with THF (20 mL), filtered through a celite bed, and washed with DCM/IPA (20 mL, 20% DCM). The collected filtrate was concentrated under reduced pressure to give *tert*-butyl (4*S*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate (0.17 g) as a pink semi-solid.

LC-MS (ESI): m/z = 570.84 $[M+H]^+$

Preparation of 3-(6-(1-(((*S*)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

To a solution of *tert*-butyl (4*S*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate (0.17 g, 0.29

mmol) in DCM (3.4 mL) was added TFA (1.7 mL) at 0 °C. The mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure to obtain a crude product. The crude product was triturated with diethyl ether (10 mL) and dried to afford 3-(6-(1-(((*S*)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.14 g) as a brown solid.

LC-MS (ESI): m/z = 470.66 $[M+H]^+$

Preparation of 3-(6-(1-(((*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

[3-(6-(1-(((*S)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]**

To a stirred solution of 3-(6-(1-(((*S*)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.14 g, 0.29 mmol) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.03 g, 0.06 mmol) in DMSO (1.4 mL) was added DIPEA (1.40 mL). The mixture was stirred at 100 °C for 6 hours. The reaction mixture was quenched with ice-cold water and the precipitated solid was dried to obtain crude product. The crude product was purified by Prep-HPLC to afford 3-(6-(1-(((*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-(1-(((*S**)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (0.024 g) as a brown solid.

LC-MS (ESI): m/z = 901.66 $[M+H]^+$

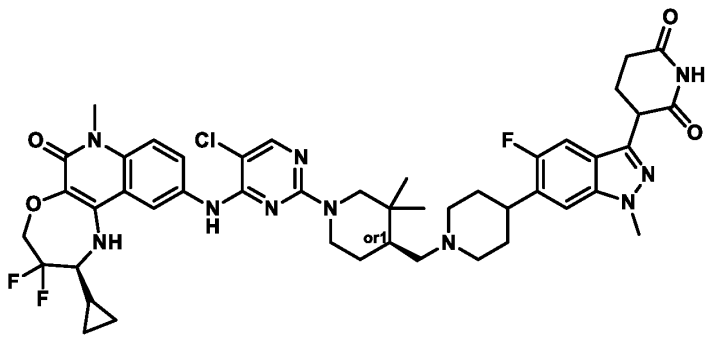
^{1}H NMR (400 MHz, DMSO-d_6): δ 10.91 (s, 1H), 8.76 (s, 1H), 8.24 (s, 1H), 8.00 (s, 1H), 7.75 (d, *J* = 8.80 Hz, 1H), 7.46 (d, *J* = 8.40 Hz, 2H), 7.07-7.03 (m, 1H), 6.16 (brs, 1H), 4.42-4.41 (m, 4H), 4.15 (s, 4H), 3.58 (s, 3H), 2.86-2.84 (m, 6H), 2.73-2.72 (m, 2H), 2.65-2.60 (m, 1H), 2.37-2.35 (m, 1H), 2.29-2.17 (m, 1H), 2.16-2.14 (m, 2H), 2.09-2.03 (m, 1H), 1.76-

1.71 (m, 5H), 1.51-1.48 (m, 1H), 1.41-1.31 (m, 1H), 1.24-1.15 (m, 1H), 0.93 (s, 3H), 0.89 (s, 3H), 0.71-0.70 (m, 1H), 0.54-0.52 (m, 2H), 0.43-0.41 (m, 1H).

Example 151: 3-(6-(1-(((*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

[3-(6-(1-(((*S)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]**

(Compound 160b)



Preparation of *tert*-butyl 4-(4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidine-1-carbonyl)-3,3-dimethylpiperidine-1-carboxylate

To a solution of 6-(benzyloxy)-5-(5-fluoro-1-methyl-6-(piperidin-4-yl)-1*H*-indazol-3-yl)pyridin-2-ol (1.0 g, 2.31 mmol), 1-(tert-butoxycarbonyl)-3,3-dimethylpiperidine-4-carboxylic acid (0.595 g, 2.31 mmol), and DIPEA (2.0 mL, 11.56 mmol) in DMF (10.00 mL), HATU (0.80 g, 2.31 mmol) was added at 0 °C. The mixture was stirred at room temperature for 2 hours. The reaction mixture was poured into ice-cold water and stirred for 10 minutes. The precipitated solid was filtered and dried to give *tert*-butyl 4-(4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidine-1-carbonyl)-3,3-dimethylpiperidine-1-carboxylate (1.10 g) as an off-white solid.

LC-MS (ESI): m/z = 672.560 $[M+H]^+$

Preparation of *tert*-butyl 4-((4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate

To a solution of *tert*-butyl 4-(4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidine-1-carbonyl)-3,3-dimethylpiperidine-1-carboxylate (1.2 g, 1.786 mmol) in THF (24.000 mL), borane dimethyl sulfide (Neat) (24.0 mL) was added. The mixture was stirred at room temperature for 22 hours. The mixture was then quenched with methanol (40 mL) and refluxed at 70 °C for 8 hours. The reaction mixture was concentrated under vacuum to obtain a crude product, which was purified by flash silica gel chromatography (50-100% ethyl acetate/petroleum ether) to afford *tert*-butyl 4-((4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate (0.92 g) as an off-white solid.

LC-MS (ESI): m/z = 658.88 $[M+H]^+$

Preparation of *tert*-butyl (*S*)-4-((4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate and *tert*-butyl (*R*)-4-((4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate

The stereoisomers of *tert*-butyl 4-((4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate were separated by SFC to afford *tert*-butyl (*S*)-4-((4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate (**Peak 1**) (0.25 g) as an off white solid and *tert*-butyl (*R*)-4-((4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate (**Peak 2**) (0.25 g) as an off white solid.

LC-MS (ESI): m/z = 658.79 $[M+H]^+$

LC-MS (ESI): m/z = 658.71 $[M+H]^+$

Preparation of *tert*-butyl (4*S*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate

To a solution of *tert*-butyl (*S*)-4-((4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate (0.25 g, 0.38 mmol) in THF (5.0 mL), $Pd(OH)_2$ on carbon (0.25 g, 20 wt%) was added. The mixture was stirred under H_2 (Parr, 80 psi pressure) for 16 hours at room temperature. The reaction mixture was diluted with ethyl acetate (50 mL), filtered through a pad of celite, and the filtrate was collected and concentrated to obtain a crude product. The

crude was purified by trituration with diethyl ether to afford *tert*-butyl (4*S*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate (0.23 g) as a pale brown semi-solid.

LC-MS (ESI): m/z = 570.75 $[M+H]^+$

Preparation of 3-(6-(1-(((*S*)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

To a solution of *tert*-butyl (4*S*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate (0.23 g, 0.40 mmol) in DCM (4.60 mL), Trifluoroacetic acid (2.76 mL) was added at 0 °C. The mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure to obtain a crude product. The crude product was triturated with diethyl ether (15 mL) and dried to afford 3-(6-(1-(((*S*)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.25 g) as a brown semisolid.

LC-MS (ESI): m/z = 470.61 $[M+H]^+$

Preparation of 3-(6-(1-(((*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

[3-(6-(1-(((*S)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]**

To a solution of 3-(6-(1-(((*S*)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.25 g, 0.53 mmol) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.075 g, 0.16 mmol) in DMSO (2.5 mL), DIPEA (2.5 mL) was added. The mixture was stirred at 100 °C for 16 hours. The reaction mixture was poured into ice-cold water (20 mL), and the precipitated solid was filtered and dried to obtain a crude product. The crude product was purified by prep-HPLC to afford 3-(6-(1-(((*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-

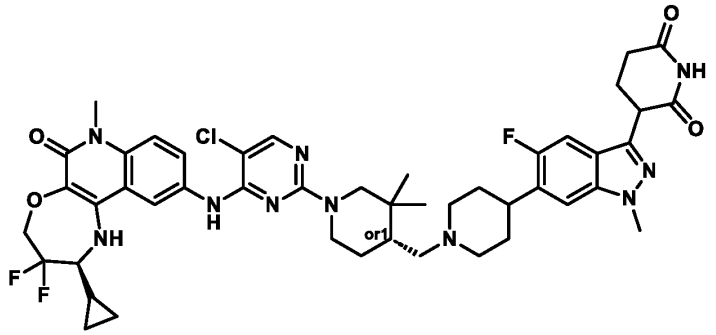
2,6-dione [3-(6-(1-(((*S**)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (0.03 g) as a pale yellow solid.

LC-MS (ESI): m/z = 901.75 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.87 (s, 1H), 8.76 (s, 1H), 8.17 (s, 1H), 8.00 (s, 1H), 7.75 (dd, *J* = 1.60, 9.00 Hz, 1H), 7.54 (d, *J* = 5.60 Hz, 1H), 7.47 (d, *J* = 6.00 Hz, 1H), 7.45 (d, *J* = 4.40 Hz, 1H), 6.15 (br s, 1H), 4.46-4.42 (m, 2H), 4.33-4.29 (m, 2H), 4.21-4.19 (m, 1H), 3.99 (s, 3H), 3.57 (s, 3H), 3.24-3.22 (m, 1H), 3.07 (d, *J* = 10.00 Hz, 1H), 2.88-2.86 (m, 2H), 2.74-2.64 (m, 1H), 2.62-2.56 (m, 3H), 2.39-2.36 (m, 1H), 2.30-2.18 (m, 1H), 2.16-2.15 (m, 2H), 2.13-2.04 (m, 1H), 1.87-1.77 (m, 6H), 1.52-1.49 (m, 1H), 1.36 (s, 3H), 1.29-1.28 (m, 1H), 0.93 (s, 3H), 0.70-0.62 (m, 2H), 0.54-0.51 (m, 2H), 0.36-0.35 (m, 1H).

Example 152: 3-(6-(1-(((*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

[3-(6-(1-(((*R)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (Compound 160a)**



Preparation of *tert*-butyl (4*R*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate

To a solution of *tert*-butyl (*R*)-4-((4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate (0.25 g, 0.38 mmol) in THF (5.0 mL), $Pd(OH)_2$ on carbon (0.25 g, 20 wt%) was

added. The mixture was stirred under H_2 (Parr, 80 psi) at room temperature for 16 hours. The reaction mixture was diluted with ethyl acetate (20 mL), filtered through a pad of celite, and concentrated under reduced pressure to give a residue. The residue was purified by trituration with diethyl ether to afford *tert*-butyl (4*R*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate (0.23 g) as a yellow semisolid.

LC-MS (ESI): m/z = 570.75 $[M+H]^+$

Preparation of 3-(6-(1-(((*R*)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

To a solution of *tert*-butyl (4*R*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate (0.23 g, 0.40 mmol) in DCM (4.60 mL) was added TFA (2.76 mL) at 0 °C. The mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated and co-distilled with DCM (60 mL) to give a residue. The residue was triturated with diethyl ether (15 mL) and dried to afford 3-(6-(1-(((*R*)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.21 g) as a brown semisolid.

LC-MS (ESI): m/z = 470.61 $[M+H]^+$

Preparation of 3-(6-(1-(((*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

[3-(6-(1-(((*R)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]**

To a solution of 3-(6-(1-(((*R*)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.19 g, 0.40 mmol), (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.045 g, 0.08 mmol) in DMSO (1.90 mL) was added DIPEA (1.90 mL). The mixture was stirred at 100 °C for 16 hours. The reaction mixture was poured into ice-cold water (20 mL) and the precipitated solid was filtered and dried to give a residue, which was purified by prep-HPLC to afford 3-(6-(1-(((*R*)-1-(5-chloro-4-(((*S*)-2-

cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-(1-(((*R**)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (0.04 g) as a pale brown solid.

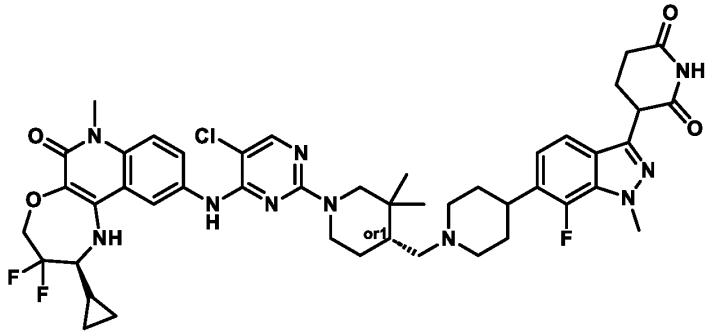
LC-MS (ESI): m/z = 901.75 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.87 (s, 1H), 8.74 (s, 1H), 8.00 (s, 1H), 7.76 (d, *J* = 7.60 Hz, 1H), 7.55 (d, *J* = 6.00 Hz, 1H), 7.47 (d, *J* = 5.20 Hz, 1H), 7.45-7.44 (m, 2H), 6.18 (br s, 1H), 4.46-4.43 (m, 4H), 4.30-4.29 (m, 1H), 3.99 (s, 3H), 3.57 (s, 3H), 3.33-2.29 (m, 1H), 3.07-3.05 (m, 1H), 2.90-2.87 (m, 2H), 2.67-2.67 (m, 1H), 2.61-2.59 (m, 2H), 2.39-2.36 (m, 2H), 2.29-2.18 (m, 1H), 2.16-2.15 (m, 2H), 2.11-2.04 (m, 1H), 1.79-1.77 (m, 6H), 1.52-1.49 (m, 1H), 1.36-1.23 (m, 3H), 0.91-0.89 (m, 3H), 0.72-0.69 (m, 3H), 0.52-0.50 (m, 2H), 0.36-0.34 (m, 1H).

Example 153: 3-(6-(1-(((*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

[3-(6-(1-(((*R)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]**

(Compound 123b)



Preparation of *tert*-butyl (4*R*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate

To a solution of *tert*-butyl (*R*)-4-((4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate (0.20 g, 0.30 mmol) in THF (6.0 mL), $Pd(OH)_2$ on carbon (0.20 g, 20 wt%) was added. The mixture was stirred under hydrogen pressure (80 psi) at room temperature for 12 hours. The reaction mixture was diluted with THF (20 mL), filtered through a celite bed, and washed with 20% DCM/IPA (20 mL). The filtrate was concentrated and dried under vacuum to afford *tert*-butyl (4*R*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate (0.17 g) as a pink semisolid.

LC-MS (ESI): m/z = 570.39 $[M+H]^+$

Preparation of 3-(6-(1-(((*R*)-3,3-dimethylpiperidin-4-yl)methyl) piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

To a solution of *tert*-butyl (4*R*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate (0.17 g, 0.29 mmol) in DCM (3.4 mL), TFA (1.7 mL) was added at 0 °C. The mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. The crude product was triturated with diethyl ether (10 mL) and dried under vacuum to afford 3-(6-(1-(((*R*)-3,3-dimethylpiperidin-4-yl)methyl) piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.14 g) as a brown solid.

LC-MS (ESI): m/z = 470.70 $[M+H]^+$

Preparation of 3-(6-(1-(((*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

[3-(6-(1-(((*R)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione]**

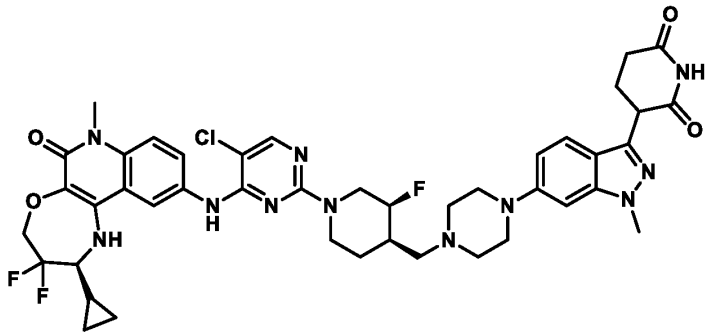
To a solution of 3-(6-(1-(((*R*)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.14 g, 0.29 mmol) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-

tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.03 g, 0.06 mmol) in DMSO (1.4 mL), DIPEA (1.40 mL) was added. The mixture was stirred at 100 °C for 6 hours. The reaction mixture was quenched with ice-cold water, and the resulting precipitate was filtered and dried to give a residue. The residue was purified by prep-HPLC to afford 3-(6-(1-(((*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione [3-(6-(1-(((*R**)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-dimethylpiperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione] (0.022 g) as a brown solid.

LC-MS (ESI): m/z = 901.70 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.9 (s, 1H), 8.90-9.10 (s, 1H), 8.14 (d, J = 6.80 Hz, 1H), 8.04 (s, 1H), 7.73 (d, J = 8.40 Hz, 1H), 7.53 (d, J = 8.40 Hz, 1H), 7.45 (d, J = 9.20 Hz, 1H), 6.97-6.96 (m, 1H), 6.22 (s, 1H), 4.36-4.35 (m, 4H), 4.13 (s, 4H), 3.66-3.58 (m, 3H), 3.19-3.22 (m, 4H), 3.11-3.01 (m, 1H), 2.80-2.71 (m, 4H), 2.61-2.58 (m, 3H), 2.39-2.36 (m, 1H), 2.12-2.09 (m, 5H), 1.85-1.82 (m, 2H), 1.34-1.31 (m, 2H), 0.93 (s, 3H), 0.73-0.69 (m, 4H), 0.54-0.51 (m, 2H), 0.35-0.33 (m, 1H).

Example 154: 3-(6-(4-(((3*S*,4*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 185a)



Preparation of *tert*-butyl 4-(4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperazine-1-carbonyl)-3-fluoropiperidine-1-carboxylate

To a stirred solution of 1-(tert-butoxycarbonyl)-3-fluoropiperidine-4-carboxylic acid (1.95 g, 8.0 mmol) and 3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-6-(piperazin-1-yl)-1*H*-indazole (5.0 g, 10.0 mmol) in DMF (50.0 mL), DIPEA (8.60 mL, 50.0 mmol) was added, followed by HATU (5.70 g, 15.0 mmol) at 0 °C. The mixture was stirred at room temperature for 16 hours. The reaction mixture was poured into cold water (50 mL), stirred for 10 minutes, and the precipitated solid was filtered and dried to afford *tert*-butyl 4-(4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperazine-1-carbonyl)-3-fluoropiperidine-1-carboxylate (6.10 g), which was used in the next step without further purification.

LC-MS (ESI): m/z = 735.65 $[M+H]^+$

Preparation of *tert*-butyl 4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate

To a solution of *tert*-butyl 4-(4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperazine-1-carbonyl)-3-fluoropiperidine-1-carboxylate (6.0 g, 8.17 mmol) in THF (120 mL), BH_3.DMS (neat) (60 mL) was added at 0 °C. The mixture was stirred at room temperature for 16 hours. The reaction mixture was quenched by methanol (200 mL) at 0 °C, concentrated under reduced pressure, and refluxed in methanol (300 mL) for 4 hours. The mixture was concentrated under reduced pressure to give a residue, which was purified by flash chromatography (60% ethyl acetate/petroleum ether to 5% methanol/DCM) to afford *tert*-butyl 4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate semi-solid (5.01 g) as an off-white solid.

LC-MS (ESI): m/z = 721.70 $[M+H]^+$

Preparation of *tert*-butyl (3*R*,4*S*)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate and *tert*-butyl (3*S*,4*R*)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate

The stereoisomers of *tert*-butyl 4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (3.5 g, 4.85 mmol) were separated by chiral SFC to afford *tert*-butyl (3*S*,4*R*)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (**Peak 1**) as an off white solid (1.02 g) and *tert*-butyl (3*R*,4*S*)-

4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (**Peak 2**) as an off white solid (0.96 g).

LC-MS (ESI): m/z = 721.80 $[M+H]^+$

LC-MS (ESI): m/z = 721.80 $[M+H]^+$

Preparation of *tert*-butyl (3*S*,4*R*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate

To a solution of *tert*-butyl (3*S*,4*R*)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate semi-solid (1.0 g, 1.38 mmol) in THF (80.0 mL) was added $Pd(OH)_2$ on carbon (2.0 g, 200 wt%). The mixture was stirred under H_2 atmosphere (80 psi) at room temperature for 16 hours. The reaction mixture was diluted with THF (60 mL), filtered through a celite bed, and washed with THF/DCM (1:1, 200 mL). The filtrate was concentrated to afford *tert*-butyl (3*S*,4*R*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (0.85 g), which was used in the next step without further purification.

LC-MS (ESI): m/z = 543.70 $[M+H]^+$

Preparation of 3-(6-(4-(((3*S*,4*R*)-3-fluoropiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

To a solution of *tert*-butyl (3*S*,4*R*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (0.85 g, 1.56 mmol) in DCM (25 mL), TFA (6.0 mL) was added at 0 °C. The mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated under vacuum and triturated with diethyl ether (60 mL). The solvent was decanted, and the residue was dried to afford 3-(6-(4-(((3*S*,4*R*)-3-fluoropiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.95 g).

LC-MS (ESI): m/z = 443.48 $[M+H]^+$

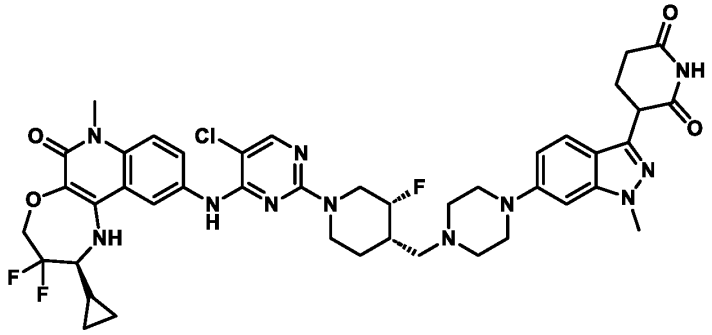
Preparation of 3-(6-(4-(((3*S*,4*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

To a solution of 3-(6-(4-(((3*S*,4*R*)-3-fluoropiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.30 g, 0.68 mmol) in DMSO (3.0 mL) and DIPEA (3.0 mL), (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.095 g, 0.20 mmol) was added. The mixture was stirred at 100 °C for 16 hours. The reaction mixture was quenched with cold water (8 mL), and the precipitated solid was filtered and dried to give a residue. The residue was purified by prep-HPLC to afford 3-(6-(4-(((3*S*,4*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (82 mg) as an off-white solid.

LC-MS (ESI): m/z = 874.70 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.84 (s, 1H), 8.91 (s, 1H), 8.14-8.13 (m, 1H), 8.06 (s, 1H), 7.76-7.73 (m, 1H), 7.57 (d, J = -12.00 Hz, 1H), 7.43 (d, J = -8.00 Hz, 1H), 7.21-6.95 (m, 2H), 6.23 (s, 1H), 5.01-4.77 (m, 2H), 4.47-4.38 (m, 4H), 3.96 (s, 5H), 3.57 (s, 4H), 3.27-3.11 (m, 8H), 2.66-2.55 (m, 5H), 2.49-2.16 (m, 2H), 1.78-1.68 (m, 1H), 1.56-1.48 (m, 1H), 1.38-1.24 (m, 1H), 0.71-0.69 (m, 1H), 0.52-0.50 (m, 2H), 0.35-0.34 (m, 1H).

Example 155: 3-(6-(4-(((3*R*,4*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 185b)



Preparation of *tert*-butyl (3*R*,4*S*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate

To a solution of *tert*-butyl (3*R*,4*S*)-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (0.95 g, 1.32 mmol)

in THF (76.0 mL), $Pd(OH)_2$ on carbon (1.90 g, 20 wt%) was added. The mixture was stirred under H_2 atmosphere (80 psi) at room temperature for 16 hours. The reaction mixture was diluted with THF (60 mL), filtered through a celite bed, and washed with THF/DCM (1:1, 200 mL). The filtrate was concentrated to afford *tert*-butyl (3*R*,4*S*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (0.75 g), which was used in the next step without further purification.

LC-MS (ESI): m/z = 543.58 $[M+H]^+$

Preparation of 3-(6-(4-(((3*R*,4*S*)-3-fluoropiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

To a solution of *tert*-butyl (3*R*,4*S*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (0.85 g, 1.38 mmol) in DCM (22 mL), TFA (7.50 mL) was added at 0 °C. The mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated under vacuum and triturated with diethyl ether (60 mL). The solvent was decanted, and the residue was dried to afford 3-(6-(4-(((3*R*,4*S*)-3-fluoropiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.62 g as a TFA salt).

LC-MS (ESI): m/z = 443.61 $[M+H]^+$

Preparation of 3-(6-(4-(((3*R*,4*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

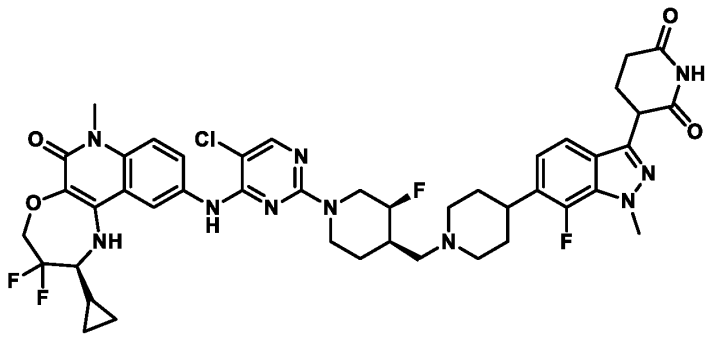
To a solution of 3-(6-(4-(((3*R*,4*S*)-3-fluoropiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.30 g, 0.68 mmol) in DMSO (3.0 mL) and DIPEA (3.0 mL), (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.095 g, 0.20 mmol) was added. The mixture was stirred at 100 °C for 16 hours. The reaction mixture was quenched with cold water (8 mL), and the precipitated solid was filtered and dried to give a residue. The residue was purified by prep-HPLC to afford 3-(6-(4-(((3*R*,4*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-

c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (59 mg) as an off-white solid.

LC-MS (ESI): m/z = 874.66 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.84 (s, 1H), 8.81 (s, 1H), 8.17 (s, 1H), 8.03 (s, 1H), 7.75 (d, J = 8.80 Hz, 1H), 7.50-7.44 (m, 2H), 6.93 (d, J = 1.20 Hz, 1H), 6.84 (s, 1H), 6.18 (s, 1H), 5.01-4.77 (m, 2H), 4.45-4.23 (m, 4H), 3.89 (s, 3H), 3.56 (s, 3H), 3.23 (br s, 5H), 2.81-2.60 (m, 2H), 2.57-2.50 (m, 6H), 2.42-2.29 (m, 4H), 2.19-2.16 (m, 1H), 1.75-1.73 (m, 1H), 1.35-1.32 (m, 2H), 0.71-0.69 (m, 1H), 0.52-0.50 (m, 2H), 0.35-0.34 (m, 1H).

Example 156: 3-(6-(1-(((3*S*,4*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 133b)



Preparation of 6-bromo-7-fluoro-1*H*-indazole

To a stirred solution of 4-bromo-2,3-difluorobenzaldehyde (50.0 g, 226.2 mmol) in DME (500.0 mL), O-methylhydroxylamine hydrochloride (34.01 g, 407.2 mmol) and potassium carbonate (46.90 g, 339.3 mmol) were added. The mixture was stirred at room temperature for 16 hours. Hydrazine monohydrate (250.0 mL) was then added at 0 °C. The resulting reaction mixture was stirred at 90 °C for 16 hours. The reaction mixture was diluted with water (500 mL) and extracted with ethyl acetate (2.1 L). The combined organic layer was concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (9-30% ethyl acetate/petroleum ether) to afford 6-bromo-7-fluoro-1*H*-indazole (20.0 g) as a pale yellow solid.

LC-MS (ESI): m/z = 215.06 $[M+H]^+$

Preparation of 6-bromo-7-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole and 6-bromo-7-fluoro-2-((2-(trimethylsilyl)ethoxy)methyl)-2*H*-indazole

To a solution of 6-bromo-7-fluoro-1*H*-indazole (18.0 g, 83.71 mmol) in THF (360.0 mL), sodium hydride (60% dispersion in mineral oil) (5.02 g, 125.5 mmol) was added at 0 °C. The mixture was stirred for 20 minutes. 2-(Trimethylsilyl)ethoxymethyl chloride (6.64 mL, 41.85 mmol) was then added to the mixture at the same temperature. The resulting mixture was stirred at room temperature for 6 hours. The reaction mixture was quenched with cold water (300 mL), extracted with EtOAc (800 mL), and the combined organic layer was concentrated and dried to give a crude product. The crude product was purified by flash silica gel chromatography (0-5% ethyl acetate/petroleum ether) to afford a mixture of 6-bromo-7-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole and 6-bromo-7-fluoro-2-((2-(trimethylsilyl)ethoxy)methyl)-2*H*-indazole (16.0 g) as a pale yellow solid.

LC-MS (ESI): m/z = 347.18 $[M+H]^+$

Preparation of *tert*-butyl 4-(7-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazol-6-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate and *tert*-butyl 4-(7-fluoro-2-((2-(trimethylsilyl)ethoxy)methyl)-2*H*-indazol-6-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate

To a stirred solution 6-bromo-7-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole and 6-bromo-7-fluoro-2-((2-(trimethylsilyl)ethoxy)methyl)-2*H*-indazole (16.0 g, 46.34 mmol), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (15.80 g, 50.98 mmol) in dioxane (220.0 mL) : water (50.0 mL), was added potassium phosphate (19.0 g, 136.08 mmol). The mixture was purged with N_2 gas for 15 minutes. To this mixture, $Pd(PPh_3)_4$ (5.35 g, 4.63 mmol) was added. The reaction mixture was stirred at 100 °C for 16 hours. The reaction mixture was diluted with EtOAc (500 mL), filtered through a celite bed, and washed with ethyl acetate (300 mL). The filtrate was concentrated under reduced pressure to obtain crude product, which was purified by flash column chromatography (5-20% ethyl acetate in petroleum ether) to afford *tert*-butyl 4-(7-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazol-6-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate and *tert*-butyl 4-(7-fluoro-2-((2-(trimethylsilyl)ethoxy)methyl)-2*H*-indazol-6-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (17.2 g).

LC-MS (ESI): m/z = 448.56 $[M+H]^+$

Preparation of *tert*-butyl 4-(7-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazol-6-yl)piperidine-1-carboxylate and *tert*-butyl 4-(7-fluoro-2-((2-(trimethylsilyl)ethoxy)methyl)-2*H*-indazol-6-yl)piperidine-1-carboxylate

To a solution of *tert*-butyl 4-(7-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazol-6-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate and *tert*-butyl 4-(7-fluoro-2-((2-(trimethylsilyl)ethoxy)methyl)-2*H*-indazol-6-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (16.0 g, 35.74 mmol) in THF (480.0 mL), was added Pd on carbon (8.0 g, 50 wt%). The mixture was stirred under hydrogen atmosphere (80 psi) at room temperature for 16 hours. The reaction mixture was diluted with EtOAc (200 mL), filtered through a celite bed, and washed with EtOAc:THF (1:1) (400 mL). The filtrate was concentrated and dried to afford *tert*-butyl 4-(7-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazol-6-yl)piperidine-1-carboxylate and *tert*-butyl 4-(7-fluoro-2-((2-(trimethylsilyl)ethoxy)methyl)-2*H*-indazol-6-yl)piperidine-1-carboxylate (12.01 g).

Preparation of *tert*-butyl 4-(7-fluoro-1*H*-indazol-6-yl)piperidine-1-carboxylate

To a solution of *tert*-butyl 4-(7-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazol-6-yl)piperidine-1-carboxylate and *tert*-butyl 4-(7-fluoro-2-((2-(trimethylsilyl)ethoxy)methyl)-2*H*-indazol-6-yl)piperidine-1-carboxylate (12.0 g, 26.68 mmol) in THF (180.0 mL), was added TBAF 1M in THF (144.0 mL) at 0 °C. The mixture was stirred at 70 °C for 16 hours. The reaction mixture was cooled to room temperature, diluted with EtOAc (200 mL), quenched with water (100 mL), and extracted with EtOAc (400 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered, concentrated under reduced pressure, and dried to afford *tert*-butyl 4-(7-fluoro-1*H*-indazol-6-yl)piperidine-1-carboxylate (9.50 g), which was used in the next step without further purification.

LC-MS (ESI): m/z = 318.39 $[M-H]^-$

Preparation of *tert*-butyl 4-(7-fluoro-3-iodo-1*H*-indazol-6-yl)piperidine-1-carboxylate

To a solution of *tert*-butyl 4-(7-fluoro-1*H*-indazol-6-yl)piperidine-1-carboxylate (8.50 g, 26.61 mmol, 1 *equiv.*) in THF (130 mL) was added potassium hydroxide (4.48 g, 79.84 mmol, 3 *equiv.*) followed by Iodine (10.13 g, 39.92 mmol, 1.5 *equiv.*) at 0 °C. The mixture was stirred at room temperature for 2 hours. The reaction mixture was quenched with water (150 mL) and then extracted with ethyl acetate (600 mL). The combined organic layer was dried

over anhydrous sodium sulfate, filtered, and concentrated to afford *tert*-butyl 4-(7-fluoro-3-iodo-1*H*-indazol-6-yl)piperidine-1-carboxylate (9.10 g).

LC-MS (ESI): m/z = 444.36 $[M-H]^-$

Preparation of *tert*-butyl 4-(7-fluoro-3-iodo-1-methyl-1*H*-indazol-6-yl)piperidine-1-carboxylate

To a solution of *tert*-butyl 4-(7-fluoro-3-iodo-1*H*-indazol-6-yl)piperidine-1-carboxylate (9.0 g, 20.21 mmol, 1 *equiv.*) in THF (180.0 mL) was added potassium tert-butoxide (9.07 g, 80.84 mmol, 4 *equiv.*) and iodomethane (9.0 mL, 1 *equiv.*) at 0 °C. The mixture was stirred at room temperature for 4 hours. The reaction mixture was quenched with water (150 mL) and extracted with ethyl acetate (400 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (6~15% ethyl acetate/petroleum ether) to give *tert*-butyl 4-(7-fluoro-3-iodo-1-methyl-1*H*-indazol-6-yl)piperidine-1-carboxylate (5.05 g).

LC-MS (ESI): m/z = 460.41 $[M+H]^+$

Preparation of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidine-1-carboxylate

To a stirred solution of *tert*-butyl 4-(7-fluoro-3-iodo-1-methyl-1*H*-indazol-6-yl)piperidine-1-carboxylate (5.0 g, 10.87 mmol) and (2,6-bis(benzyloxy)pyridin-3-yl)boronic acid (5.10 g, 15.24 mmol) in 1,4-dioxane (40 mL) and water (10 mL), K_3PO_4 (6.93 g, 32.65 mmol) was added. The mixture was purged with N_2 for 10 minutes. $Pd(PPh_3)_4$ (1.25 g, 1.08 mmol) was then added and the mixture was purged with N_2 for an additional 5 minutes. The reaction mixture was stirred at 100 °C for 16 hours under a N_2 atmosphere. The reaction mixture was diluted with EtOAc (150 mL), filtered through a celite bed, and the bed was washed with ethyl acetate (250 mL). The filtrate was concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (6 - 20% ethyl acetate/petroleum ether) to afford *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidine-1-carboxylate (5.52 g).

LC-MS (ESI): m/z = 63.36 $[M+H]^+$

Preparation of 6-(benzyloxy)-3-(7-fluoro-1-methyl-6-(piperidin-4-yl)-1*H*-indazol-3-yl)pyridin-2-ol

To a stirred solution of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidine-1-carboxylate (5.50 g, 8.83 mmol) in DCM (170.0 mL), TFA (55.0 mL) was added at 0 °C. The mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure and co-distilled with DCM (2 x 30 mL). The crude product was triturated with diethyl ether (2 x 40 mL), the solvent was decanted, and the product was dried to afford 6-(benzyloxy)-3-(7-fluoro-1-methyl-6-(piperidin-4-yl)-1*H*-indazol-3-yl)pyridin-2-ol (6.10 g) as a pale brown solid.

LC-MS (ESI): m/z = 433.54 $[M+H]^+$

Preparation of *tert*-butyl 4-(4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidine-1-carbonyl)-3-fluoropiperidine-1-carboxylate

To a stirred solution of 6-(benzyloxy)-3-(7-fluoro-1-methyl-6-(piperidin-4-yl)-1*H*-indazol-3-yl)pyridin-2-ol (2.50 g, 5.78 mmol) and 1-(tert-butoxycarbonyl)-3-fluoropiperidine-4-carboxylic acid (1.42 g, 5.78 mmol) in DMF (25.0 mL), DIPEA (5.03 mL, 28.90 mmol) was added followed by propanephosphonic acid anhydride 50% in EtOAc (5.20 mL, 17.34 mmol) at 0 °C. The mixture was stirred at room temperature for 16 hours. The reaction mixture was quenched with ice-cold water (50 mL), the precipitated solid was then filtered, and dried to afford *tert*-butyl 4-(4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidine-1-carbonyl)-3-fluoropiperidine-1-carboxylate (1.82 g) as an off-white solid.

LC-MS (ESI): m/z = 662.74 $[M+H]^+$

Preparation of *tert*-butyl 4-((4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate

To a stirred solution of *tert*-butyl 4-(4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidine-1-carbonyl)-3-fluoropiperidine-1-carboxylate (1.80 g, 2.72 mmol) in THF (36.0 mL), $BH_3 \cdot DMS$ (10 M in THF) (40.0 mL) was added at 0 °C. The mixture was stirred at room temperature for 16 hours. The reaction mixture was quenched with MeOH (80 mL), concentrated, and co-distilled with methanol (50 mL x 2). The crude product, as a borane complex, was obtained, and then refluxed in MeOH (150 mL) for 4

hours. The mixture was cooled to room temperature, and concentrated. The crude product was purified by flash silica gel chromatography (0 - 20% MeOH in DCM) to afford *tert*-butyl 4-((4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (1.01 g) as a white solid.

LC-MS (ESI): m/z = 648.32 $[M+H]^+$

Preparation of *tert*-butyl (3*R*,4*S*)-4-((4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate and *tert*-butyl (3*S*,4*R*)-4-((4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate

The stereoisomers of *tert*-butyl 4-((4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (1.01 g) were separated by chiral SFC to afford *tert*-butyl (3*R*,4*S*)-4-((4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (**Peak 1**) as an off white solid (0.41 g) and *tert*-butyl (3*S*,4*R*)-4-((4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (**Peak 2**) as an off white solid (0.40 g).

LC-MS (ESI): m/z = 648.71 $[M+H]^+$

LC-MS (ESI): m/z = 648.75 $[M+H]^+$

Preparation of *tert*-butyl (3*S*,4*R*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate

To a solution of *tert*-butyl (3*S*,4*R*)-4-((4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (0.40 g, 0.62 mmol) in THF (40.0 mL), $Pd(OH)_2$ on carbon (0.40 g, 20 wt%) was added. The mixture was stirred under a hydrogen atmosphere (80 psi) at room temperature for 16 hours. The reaction mixture was diluted with THF (50 mL), filtered through a celite bed, and washed with THF:DCM (1:1, 200 mL). The filtrate was concentrated to afford crude *tert*-butyl (3*S*,4*R*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (0.35 g).

LC-MS (ESI): m/z = 560.38$[M+H]^+$

Preparation of 3-(7-fluoro-6-(1-(((3*S*,4*R*)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

To a stirred solution of *tert*-butyl (3*S*,4*R*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (0.35 g, 0.62 mmol) in DCM (10.5 mL), TFA (3.50 mL) was added at 0 °C. The mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated under vacuum to obtain a crude product, which was then triturated with diethyl ether (15 mL x 3). The solvent was decanted and the product was dried to obtain 3-(7-fluoro-6-(1-(((3*S*,4*R*)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.34 g) as a brown solid.

LC-MS (ESI): m/z = 460.58 $[M+H]^+$

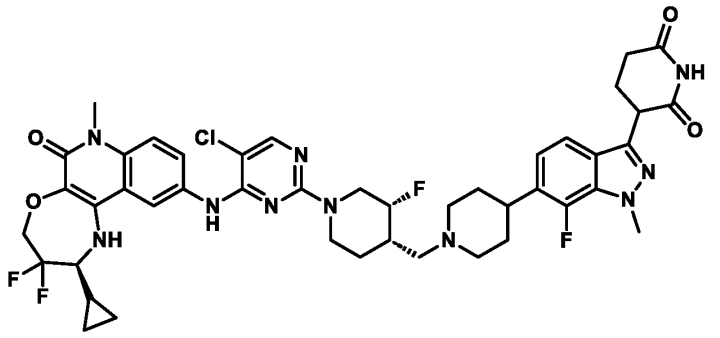
Preparation of 3-(6-(1-(((3*S*,4*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

To a stirred solution of 3-(7-fluoro-6-(1-(((3*S*,4*R*)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.33 g, 0.71 mmol) in DMSO (3.30 mL) and DIPEA (3.3 mL), (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.084 g, 0.18 mmol) was added. The mixture was stirred at 100 °C for 16 hours. The reaction mixture was quenched with cold water (10 mL) and the precipitated solid was filtered and dried to obtain a residue, which was purified by prep-HPLC to afford 3-(6-(1-(((3*S*,4*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (86 mg) as an off white solid.

LC-MS (ESI): m/z = 891.69 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.90 (s, 1H), 8.80 (s, 1H), 8.18 (br s, 2H), 8.03 (s, 1H), 7.75 (d, J = 8.00 Hz, 1H), 7.47-7.45 (m, 1H), 7.07-7.04 (m, 1H), 6.17 (br s, 1H), 5.01-4.77 (m, 2H), 4.42-4.33 (m, 4H), 4.11 (s, 3H), 3.57 (s, 3H), 3.05-2.91 (m, 5H), 2.80-2.50 (m, 4H), 2.37-2.34 (m, 2H), 2.17-2.03 (m, 4H), 1.78-1.69 (m, 4H), 1.69-1.24 (m, 3H), 0.70-0.68 (m, 1H), 0.53-0.51 (m, 2H), 0.34-0.31 (m, 1H).

Example 157: 3-(6-(1-(((3*R*,4*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 133a)



Preparation of *tert*-butyl (3*R*,4*S*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate

To a solution of *tert*-butyl (3*R*,4*S*)-4-((4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (0.40 g, 0.62 mmol) in THF (40.0 mL), $Pd(OH)_2$ on carbon (0.40 g, 20 wt%) was added. The mixture was stirred under a hydrogen atmosphere (80 psi) at room temperature for 5 hours. The reaction mixture was diluted with THF (50 mL), filtered through a celite bed, and washed with THF:DCM (200 mL). The filtrate was concentrated to afford crude *tert*-butyl (3*R*,4*S*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (0.34 g).

LC-MS (ESI): m/z = 560.31 $[M+H]^+$

Preparation of 3-(7-fluoro-6-(1-(((3*R*,4*S*)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

To a stirred solution of *tert*-butyl (3*R*,4*S*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate (0.34 g, 0.60 mmol) in DCM (10.20 mL), TFA (3.40 mL) was added at 0 °C. The mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated under vacuum and triturated with diethyl ether (15 mL x 3). The solvent was decanted and the product was dried to obtain 3-(7-fluoro-6-(1-(((3*R*,4*S*)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.32 g).

LC-MS (ESI): m/z = 460.47 $[M+H]^+$

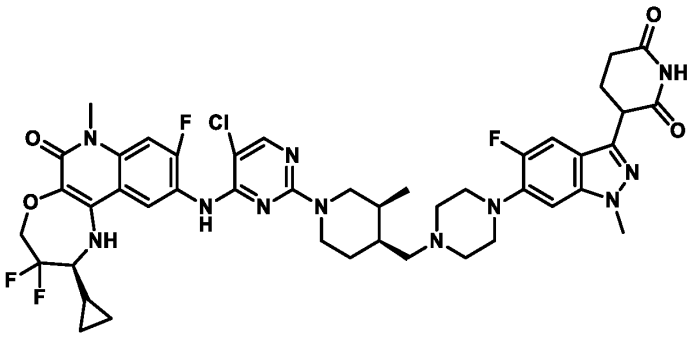
Preparation of 3-(6-(1-(((3*R*,4*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

To a stirred solution of 3-(7-fluoro-6-(1-(((3*R*,4*S*)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.31 g, 0.67 mmol) in DMSO (3.1 mL) and DIPEA (3.1 mL), (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.095 g, 0.20 mmol) was added. The mixture was stirred at 100 °C for 16 hours. The reaction mixture was quenched with cold water (10 mL) and the precipitated solid was filtered and dried to obtain a crude product. The crude product was purified by reverse phase purification to afford 3-(6-(1-(((3*R*,4*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-fluoropiperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (76 mg) as a pale brown solid.

LC-MS (ESI): m/z = 891.69 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.90 (s, 1H), 8.25 (br s, 1H), 8.16 (d, J = 1.60 Hz, 1H), 8.04 (s, 1H), 7.74-7.71 (m, 1H), 7.47-7.45 (m, 2H), 7.07-7.03 (m, 1H), 5.96 (br s, 1H), 5.01-4.81 (m, 2H), 4.46-4.33 (m, 4H), 4.11 (s, 3H), 3.58 (s, 3H), 3.07-2.61 (m, 8H), 2.39-2.35 (m, 2H), 2.17-2.06 (m, 5H), 1.87-1.71 (m, 2H), 1.68-1.37 (m, 5H), 0.71-0.69 (m, 1H), 0.52-0.50 (m, 2H), 0.35-0.34 (m, 1H).

Example 158: 3-(6-(4-(((3*S*,4*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-*c*]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperazin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 208a)



Preparation of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperazine-1-carboxylate

A mixture of *tert*-butyl piperazine-1-carboxylate (548 mg, 2.94 mmol), 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-5-fluoro-1-methyl-1*H*-indazole (1.00 g, 1.93 mmol), and RuPhos-Pd-G3 (170 mg, 203 μmol) in dioxane (12.00 mL) was sparged with N_2 for 5 minutes. The mixture was treated with NaOtBu (1.93 mL, 2.00 molar, 3.86 mmol) and sparged again with N_2 for another 5 minutes. The mixture was then warmed to 100 °C for 1 hour. The reaction mixture was purified directly by column chromatography (0-100% (3:1 ethyl acetate/EtOH)/heptane) to afford *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperazine-1-carboxylate (1.063 g) as an orange solid.

^{1}H NMR (400 MHz, DMSO) δ 7.91 (d, *J* = 8.1 Hz, 1H), 7.48 (d, *J* = 7.2 Hz, 3H), 7.39 (q, *J* = 7.0 Hz, 4H), 7.34 – 7.27 (m, 3H), 7.14 (d, *J* = 7.2 Hz, 1H), 6.58 (d, *J* = 8.1 Hz, 1H), 5.45 (d, *J* = 9.4 Hz, 4H), 4.01 (s, 3H), 3.52 (s, 5H), 3.00 (s, 5H), 1.43 (s, 11H).

LC-MS (ESI): m/z = 534.3 $[M\text{-}Bn+H]^+$.

Preparation of 6-(benzyloxy)-3-(5-fluoro-1-methyl-6-(piperazin-1-yl)-1*H*-indazol-3-yl)pyridin-2-ol bis(trifluoroacetate)

A solution of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperazine-1-carboxylate (330 mg, 29 μmol) in DCM (2.00 mL) was treated with a 1:1 solution of DCM (2.00 mL) and TFA (2.00 mL, 26.0 mmol). The mixture was stirred for 2 hours at room temperature. The reaction was concentrated under reduced pressure to afford 6-(benzyloxy)-3-(5-fluoro-1-methyl-6-(piperazin-1-yl)-1*H*-indazol-3-yl)pyridin-2-ol bis(trifluoroacetate) (351 mg), which was used as is in the next step.

LC-MS (ESI): m/z = 434.3 $[M+H]^+$

Preparation of *tert*-butyl (3*S*,4*S*)-4-(4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperazine-1-carbonyl)-3-methylpiperidine-1-carboxylate

A solution of (3*S*,4*S*)-1-(*tert*-butoxycarbonyl)-3-methylpiperidine-4-carboxylic acid (100 mg, 411 μmol), 6-(benzyloxy)-3-(5-fluoro-1-methyl-6-(piperazin-1-yl)-1*H*-indazol-3-yl)pyridin-2-ol bis(trifluoroacetate) (234 mg, 354 μmol), and HATU (174 mg, 458 μmol) in DMA (2.40 mL) was treated with DIPEA (368 μL, 2.11 mmol). The mixture was stirred at room temperature for 2 hours. The volatiles were removed under reduced pressure and purified by column chromatography (0-50% (3:1 Ethyl acetate/EtOH)/heptane) to afford *tert*-butyl (3*S*,4*S*)-4-(4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperazine-1-carbonyl)-3-methylpiperidine-1-carboxylate (181 mg).

LC-MS (ESI): m/z = 659.4 $[M+H]^+$

Preparation of *tert*-butyl (3*S*,4*S*)-4-((4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-3-methylpiperidine-1-carboxylate

A solution of *tert*-butyl (3*S*,4*S*)-4-(4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperazine-1-carbonyl)-3-methylpiperidine-1-carboxylate (180 mg, 273 μmol) in THF (1.50 mL) was treated dropwise with BH_3•DMS (259 μL, 2.73 mmol). The mixture was stirred at room temperature for 6 hours, warmed to 50 °C, and stirred for 2 hours. The reaction mixture was treated dropwise with MeOH (2 mL) and warmed to 70 °C. After 13 hours, the reaction mixture was cooled to room temperature. The volatiles were removed under reduced pressure to afford *tert*-butyl (3*S*,4*S*)-4-((4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-3-methylpiperidine-1-carboxylate (166 mg), which was used as is without further purification.

LC-MS (ESI): m/z = 645.4 $[M+H]^+$.

Preparation of *tert*-butyl (3*S*,4*S*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-3-methylpiperidine-1-carboxylate

A solution of *tert*-butyl (3*S*,4*S*)-4-((4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-3-methylpiperidine-1-carboxylate (164 mg, 223 μmol) in iPrOH (4.00 mL) and DMF (0.800 mL) was sparged with N_2 for 5 minutes. To this mixture was added $Pd(OH)_2$ on carbon (62.7 mg, 20 wt%, 89.3 μmol). The resulting mixture was sparged with H_2 for 5 minutes. The reaction mixture was warmed to 50

°C under an H_2 atmosphere for 5 hours. The reaction mixture was diluted with THF (1.60 mL), charged with additional $Pd(OH)_2$ on carbon (62.7 mg, 20 wt%, 89.3 μmol), and sparged with H_2 for 5 minutes. The mixture was stirred at 50 °C under H_2 atmosphere for 16 hours. The reaction mixture was filtered through a pad of celite and rinsed thoroughly with DMF, methanol, and DCM. The filtrate was concentrated under reduced pressure to afford *tert*-butyl (3*S*,4*S*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-3-methylpiperidine-1-carboxylate (159 mg).

LC-MS (ESI): m/z = 557.3 $[M+H]^+$.

Preparation of 3-(5-fluoro-1-methyl-6-(4-(((3*S*,4*S*)-3-methylpiperidin-4-yl)methyl)piperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione

A solution of *tert*-butyl (3*S*,4*S*)-4-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-3-methylpiperidine-1-carboxylate (124 mg, 223 μmol) and DCM (1.00 mL) was treated with a 1:1 solution of TFA (1.00 mL) and DCM (1.00 mL). The mixture was stirred at room temperature for 2 hours. The volatiles were removed under reduced pressure, and the residue was suspended in DCM (2 mL). The volatiles removed again under reduced pressure to afford 3-(5-fluoro-1-methyl-6-(4-(((3*S*,4*S*)-3-methylpiperidin-4-yl)methyl)piperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (102 mg).

LC-MS (ESI): m/z = 457.4 $[M+H]^+$.

Preparation of 3-(6-(4-(((3*S*,4*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-*c*]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperazin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

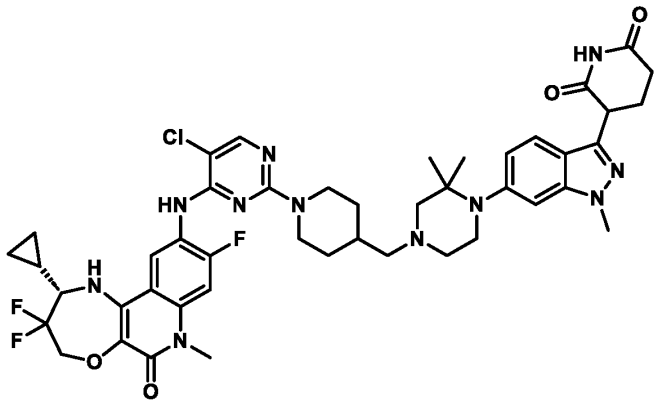
A mixture of (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3,9-trifluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-*c*]quinolin-6(7*H*)-one (110 mg, 226 μmol), 3-(5-fluoro-1-methyl-6-(4-(((3*S*,4*S*)-3-methylpiperidin-4-yl)methyl)piperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione hydrochloride (124 mg), CsF (88.0 mg, 579 μmol), and DIPEA (161 μL, 926 μmol) in DMSO (1.50 mL) was warmed to 80 °C under a N_2 atmosphere for 24 hours. The reaction mixture was then warmed to 100 °C and stirred for 4 days. The mixture was then cooled to room temperature. The reaction mixture was filtered, treated with formic acid (0.054 mL), and purified by Prep-HPLC to afford 3-(6-(4-(((3*S*,4*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-

[1,4]oxazepino[2,3-*c*]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperazin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (23.7 mg).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.84 (s, 1H), 8.78 (s, 1H), 8.18 (d, J = 8.0 Hz, 1H), 7.98 (s, 1H), 7.43 (dd, *J* = 12.5, 11.3 Hz, 2H), 7.09 (d, *J* = 7.1 Hz, 1H), 6.46 (s, 1H), 4.51 – 4.29 (m, 2H), 4.26 (dd, *J* = 9.7, 5.1 Hz, 1H), 4.13 – 4.08 (m, 1H), 3.93 (s, 3H), 3.54 (s, 3H), 3.29 – 3.17 (m, 2H), 3.12 – 2.97 (m, 4H), 2.91 (d, *J* = 12.5 Hz, 1H), 2.76 (s, 1H), 2.71 – 2.57 (m, 2H), 2.56 – 2.52 (m, 2H), 2.38 – 2.28 (m, 1H), 2.25 – 2.06 (m, 4H), 1.94 – 1.75 (m, 2H), 1.39 – 1.20 (m, 4H), 0.76 – 0.63 (m, 4H), 0.51 (t, *J* = 5.9 Hz, 2H), 0.36 – 0.26 (m, 1H).

LC-MS (ESI): m/z = 453.9 $[M+2H]^{2+}$.

Example 159: 3-(6-(4-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-*c*]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)-2,2-dimethylpiperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 204a)



Preparation of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)-3,3-dimethylpiperazine-1-carboxylate

To a solution of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-6-bromo-1-methyl-1*H*-indazole (15.0 g, 29.9 mmol, 1.00 *equiv.*), *tert*-butyl 3,3-dimethylpiperazine-1-carboxylate (12.8 g, 59.9 mmol, 2.00 *equiv.*) in dioxane (150 mL) was added *t*-BuONa (8.64 g, 89.9 mmol, 3.00 *equiv.*) and RuPhos (1.40 g, 3.00 mmol, 0.10 *equiv.*). The mixture was degassed and purged with N_2 three times. To this mixture was added $Pd_2(dba)_3$ (2.75 g, 3.00 mmol, 0.10 *equiv.*). The resulting mixture was stirred at 100 °C for 1 hour. The reaction mixture was diluted with H_2O (200 mL) and extracted with EtOAc (300 mL). The combined organic layers were washed with brine (200 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (petroleum ether:

EtOAc = 5: 1 to 1: 1) to give *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)-3,3-dimethylpiperazine-1-carboxylate (12.4 g) as a green solid.

LC-MS (ESI): m/z = 635.1 $[M+H]^+$

^{1}H NMR: (400 MHz, DMSO-d_6) δ 7.93 - 7.79 (m, 1H), 7.53 - 7.23 (m, 12H), 6.82 - 6.77 (m, 1H), 6.57 (d, J = 8.1 Hz, 1H), 5.43 (d, J = 3.4 Hz, 4H), 4.01 (s, 2H), 3.52 - 3.44 (m, 2H), 3.30 - 3.27 (m, 2H), 3.13 - 3.07 (m, 2H), 1.99 (s, 3H), 1.44 (s, 9H), 0.99 (s, 6H)

Preparation of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)-3,3-dimethylpiperazine-1-carboxylate

To a solution of *tert*-butyl 4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)-3,3-dimethylpiperazine-1-carboxylate (11.0 g, 17.3 mmol, 1.00 equiv.) in THF (110 mL), EtOH (110 mL), and AcOH (11.0 mL) were added Pd on carbon (2.75 g, 2.58 mmol, 10 wt%) and $Pd(OH)_2$ on carbon (2.75 g, 3.92 mmol, 20.0% purity) under a N_2 atmosphere. The suspension was degassed and purged with H_2 three times. The mixture was stirred under H_2 (50 Psi) at 50 °C for 4 hours. The reaction mixture was filtered and washed with THF (200 mL), then concentrated under reduced pressure to give *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)-3,3-dimethylpiperazine-1-carboxylate (5.40 g) as a white solid.

LC-MS (ESI): m/z = 456.5 $[M+H]^+$

Preparation of 3-(6-(2,2-dimethylpiperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

A mixture of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)-3,3-dimethylpiperazine-1-carboxylate (5.00 g, 10.9 mmol, 1.00 *equiv.*) in HCl/dioxane (60.0 mL) was stirred at 25 °C for 1 hour. The reaction mixture was filtered and concentrated under reduced pressure to give 3-(6-(2,2-dimethylpiperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (3.90 g) as a white solid.

LC-MS (ESI): m/z = 356.4 $[M+H]^+$

Preparation of *tert*-butyl 4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)-3,3-dimethylpiperazin-1-yl)methyl)piperidine-1-carboxylate

A mixture of 3-(6-(2,2-dimethylpiperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (323 mg, 824 μmol), *tert*-butyl 4-formylpiperidine-1-carboxylate (292 mg, 1.37 mmol), and potassium acetate (261 mg, 2.66 mmol) in THF (6.00 mL)/DMF (1.00 mL) was stirred at room temperature for 30 minutes. This mixture was then treated with sodium

triacetoxyborohydride (350 mg, 1.65 mmol). The resulting reaction mixture stirred at room temperature for 16 hours. The reaction mixture was treated with H_2O, stirred for 30 minutes, then diluted with DMSO and concentrated under reduced pressure. The residue was then purified by Prep-HPLC to afford *tert*-butyl 4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)-3,3-dimethylpiperazin-1-yl)methyl)piperidine-1-carboxylate (206 mg).

LC-MS (ESI): m/z = 553.5 $[M+H]^+$.

Preparation of 3-(6-(2,2-dimethyl-4-(piperidin-4-ylmethyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

A solution of *tert*-butyl 4-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl)-3,3-dimethylpiperazin-1-yl)methyl)piperidine-1-carboxylate (203.2 mg, 367.6 μmol) in dioxane (3.00 mL) was treated with HCl (4.0 M in dioxane, 3.40 mL, 13.6 mmol). The reaction mixture stirred at room temperature for 19 hours. The reaction mixture was concentrated under reduced pressure, suspended in DCM, and again concentrated under reduced pressure. The white solid was dissolved in MeOH, concentrated under reduced pressure, then once more suspended in DCM and concentrated under reduced pressure to afford 3-(6-(2,2-dimethyl-4-(piperidin-4-ylmethyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione dihydrochloride (196 mg).

LC-MS (ESI): m/z = 453.4 $[M+H]^+$.

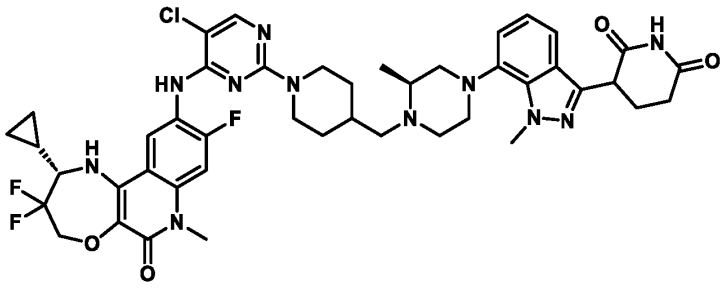
Preparation of 3-(6-(4-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-*c*]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)-2,2-dimethylpiperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

A mixture of (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3,9-trifluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-*c*]quinolin-6(7*H*)-one (96.2 mg, 198 μmol), 3-(6-(2,2-dimethyl-4-(piperidin-4-ylmethyl)piperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione dihydrochloride (80.0 mg, 152 μmol), and CsF (69.4 mg, 457 μmol) in DMSO (1.00 mL) was treated with DIPEA (133 μL, 761 μmol). The mixture was warmed to 80 °C for 30 hours, then cooled to room temperature. The reaction mixture was filtered with DMSO and purified by Prep-HPLC to afford 3-(6-(4-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-*c*]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)-2,2-dimethylpiperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (88.1 mg).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.86 (s, 1H), 8.80 (s, 1H), 8.20 (d, J = 8.1 Hz, 1H), 8.01 (s, 1H), 7.52 (d, J = 8.7 Hz, 1H), 7.42 (d, J = 12.4 Hz, 1H), 7.23 (s, 1H), 6.89 (d, J = 8.8 Hz, 1H), 6.46 (s, 1H), 4.51 – 4.34 (m, 1H), 4.33 – 4.27 (m, 2H), 3.93 (s, 3H), 3.55 (s, 3H), 3.29 – 3.18 (m, 2H), 3.17 – 3.00 (m, 2H), 2.79 – 2.59 (m, 4H), 2.49 – 2.39 (m, 2H), 2.38 – 2.31 (m, 1H), 2.31 – 2.21 (m, 2H), 2.21 – 2.13 (m, 1H), 2.10 (d, J = 6.9 Hz, 2H), 1.79 – 1.62 (m, 3H), 1.38 – 1.25 (m, 1H), 1.04 (s, 6H), 1.00 – 0.88 (m, 3H), 0.76 – 0.65 (m, 1H), 0.51 (t, J = 6.1 Hz, 2H), 0.39 – 0.26 (m, 1H).

LC-MS (ESI): m/z = 451.8 $[M+2H]^{2+}$.

Example 160: 3-(7-((*S*)-4-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-*c*]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 203a)



Preparation of *tert*-butyl (*S*)-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-7-yl)-2-methylpiperazine-1-carboxylate

A solution of *tert*-butyl (*S*)-2-methylpiperazine-1-carboxylate (2.161 g, 1.8 *equiv.*, 10.79 mmol), 3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-bromo-1-methyl-1*H*-indazole (3000 mg, 1 *equiv.*, 5.995 mmol), and RuPhos-Pd-G3 (351 mg, 0.0700 *equiv.*, 420 μmol) in THF (30.0 mL) was degassed with nitrogen. t-BuONa in THF (1.671 g, 8.693 mL, 2.0 M, 2.9 *equiv.*, 17.39 mmol) was added. The reaction mixture was warmed at 70 °C and stirred for 1.5 hours. The reaction mixture was filtered through celite and then purified via flash column (0-80% ethyl acetate/heptanes) to afford *tert*-butyl (*S*)-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-7-yl)-2-methylpiperazine-1-carboxylate.

LC-MS (ESI): m/z = 620.4 $[M+H]^+$.

Preparation of *tert*-butyl (2*S*)-4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-7-yl)-2-methylpiperazine-1-carboxylate

A solution of *tert*-butyl (*S*)-4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-7-yl)-2-methylpiperazine-1-carboxylate (3.500 g, 1 *equiv.*, 5.647 mmol) in isopropanol (6.00 mL)/DMF (1.20 mL)/ethyl acetate (1.20 mL) was treated with hydrogen and $Pd(OH)_2/C$ (0.99 g, 0.25 *equiv.*). After 2 hours, the reaction mixture was filtered through celite, and evaporated to dryness to afford *tert*-butyl (2*S*)-4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-7-yl)-2-methylpiperazine-1-carboxylate.

LC-MS (ESI): m/z = 442.3 $[M+H]^+$.

Preparation of 3-(1-methyl-7-((*S*)-3-methylpiperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione, 2HCl

tert-Butyl (2*S*)-4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-7-yl)-2-methylpiperazine-1-carboxylate (3.8595 g, 1 *equiv.*, 5.8406 mmol) was dissolved in DCM (40 mL) and treated with HCl in dioxane (1.704 g, 11.681 mL, 4 M, 8 *equiv.*, 46.724 mmol). The mixture was stirred at room temperature for 18 hours. The reaction mixture was concentrated, then triturated with hot ethyl acetate for 1 hour. The mixture was cooled to room temperature, filtered, and dried under vacuum to afford 3-(1-methyl-7-((*S*)-3-methylpiperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione, 2HCl.

LC-MS (ESI): m/z = 342.1 $[M+H]^+$.

Preparation of *tert*-butyl 4-(((2*S*)-4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-7-yl)-2-methylpiperazin-1-yl)methyl)piperidine-1-carboxylate

A mixture of 3-(1-methyl-7-((*S*)-3-methylpiperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione dihydrochloride (305 mg, 736 μmol), *tert*-butyl 4-formylpiperidine-1-carboxylate (252 mg, 1.18 mmol), and potassium acetate (241 mg, 2.46 mmol) in THF (6.00 mL)/DMF (1.00 mL) was stirred at room temperature for 30 minutes. This mixture was treated with sodium triacetoxyborohydride (342 mg, 1.61 mmol). The reaction mixture was stirred at room temperature for 16 hours. To this mixture was added additional *tert*-butyl 4-formylpiperidine-1-carboxylate (165 mg, 774 μmol) and sodium triacetoxyborohydride (165 mg, 779 μmol) and the resulting mixture was stirred at room temperature for 3 hours. The reaction mixture was then treated with water (1.0 mL), stirred for 30 minutes, then diluted with DMSO, and concentrated under reduced pressure. The DMSO mixture was then purified by reverse phase column chromatography (10-60% MeCN-H_2O [+0.1% formic acid]) to afford *tert*-butyl 4-(((2*S*)-4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-7-yl)-2-methylpiperazin-1-yl)methyl)piperidine-1-carboxylate (290 mg).

LC-MS (ESI): m/z = 539.4 $[M+H]^+$.

Preparation of 3-(1-methyl-7-((*S*)-3-methyl-4-(piperidin-4-ylmethyl)piperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione

A solution of *tert*-butyl 4-(((2*S*)-4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-7-yl)-2-methylpiperazin-1-yl)methyl)piperidine-1-carboxylate (289 mg, 536 μmol) in dioxane (3.00 mL) was treated with HCl (4.0 M in dioxane, 3.40 mL, 13.6 mmol). The reaction mixture was stirred at room temperature for 19 hours. The reaction mixture was concentrated under reduced pressure, the residue suspended in DCM, and the volatiles were again concentrated under reduced pressure to afford 3-(1-methyl-7-((*S*)-3-methyl-4-(piperidin-4-ylmethyl)piperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione dihydrochloride (278 mg).

LC-MS (ESI): m/z = 439.4 $[M+H]^+$.

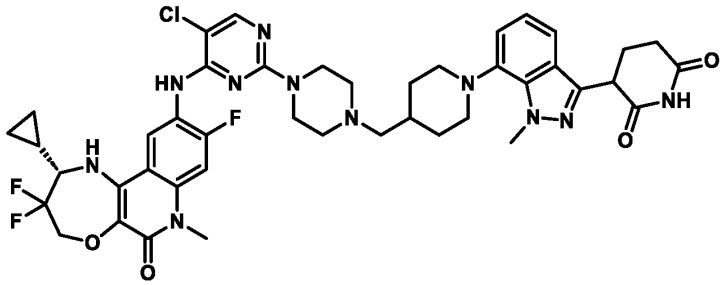
Preparation of 3-(7-((*S*)-4-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-*c*]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

A mixture of (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3,9-trifluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-*c*]quinolin-6(7*H*)-one (98.9 mg, 203 μmol), 3-(1-methyl-7-((*S*)-3-methyl-4-(piperidin-4-ylmethyl)piperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione dihydrochloride (80.0 mg, 156 μmol), and CsF (71.3 mg, 3469 μmol) in DMSO (1.00 mL) was treated with DIPEA (136 μL, 782 μmol) and warmed to 80 °C for 30 hours. The mixture was cooled to room temperature. The reaction mixture was filtered with DMSO and purified by Prep-HPLC to afford 3-(7-((*S*)-4-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-*c*]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (96.3 mg).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.87 (s, 1H), 8.81 (s, 1H), 8.20 (d, *J* = 8.1 Hz, 1H), 8.01 (s, 1H), 7.44 – 7.35 (m, 2H), 7.05 – 6.96 (m, 2H), 6.47 – 6.41 (m, 1H), 4.51 – 4.37 (m, 1H), 4.36 – 4.30 (m, 2H), 4.23 (s, 3H), 3.55 (s, 3H), 3.29 – 3.17 (m, 3H), 3.14 – 3.04 (m, 2H), 3.02 – 2.93 (m, 1H), 2.92 – 2.88 (m, 2H), 2.88 – 2.77 (m, 1H), 2.76 – 2.59 (m, 3H), 2.56 – 2.53 (m, 2H), 2.38 – 2.26 (m, 1H), 2.16 (dd, *J* = 13.2, 5.8 Hz, 1H), 1.99 – 1.85 (m, 1H), 1.83 – 1.62 (s, 1H), 1.60 – 1.46 (m, 1H), 1.43 – 1.21 (m, 1H), 1.08 – 0.96 (m, 6H), 0.95 – 0.83 (m, 1H), 0.71 (d, *J* = 8.6 Hz, 1H), 0.51 (t, *J* = 6.1 Hz, 2H), 0.32 (d, *J* = 5.7 Hz, 1H).

LC-MS (ESI): m/z = 444.9 $[M+2H]^{2+}$.

Example 161: 3-(7-(4-((4-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-*c*]quinolin-10-yl)amino)pyrimidin-2-yl)piperazin-1-yl)methyl)piperidin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 200a)



Preparation of *tert*-butyl 4-((1-((benzyloxy)carbonyl)piperidin-4-yl)methyl)piperazine-1-carboxylate

To a stirred solution of *tert*-butyl piperazine-1-carboxylate (25.0 g, 0.13 mmol), benzyl-4-formylpiperidine-1-carboxylate (39.60 g, 0.16 mmol), and acetic acid (7.80 g, 0.13 mmol) in DCM (500 mL) was added $NaBH(OAc)_3$ (42.5 g, 0.20 mmol) at 25 °C and the resulting mixture was stirred at 25 °C for 3 hours. Reaction mixture was quenched with water and extracted with DCM. The organic layers were separated, dried over anhydrous sodium sulfate, filtered, and concentrated. Crude material was purified by column chromatography (SiO_2, 100-200 mesh, 15% ethyl acetate in petroleum ether) to afford *tert*-butyl 4-((1-((benzyloxy)carbonyl)piperidin-4-yl)methyl)piperazine-1-carboxylate (25.0 g) as a pale-yellow solid.

LC-MS (ESI): m/z = 418.12 $[M+H]^+$.

Preparation of *tert*-butyl 4-(piperidin-4-ylmethyl)piperazine-1-carboxylate

To a stirred solution of *tert*-butyl 4-((1-((benzyloxy)carbonyl)piperidin-4-yl)methyl)piperazine-1-carboxylate (25 g, 0.06 mmol) in MeOH (500 mL) was added Pd on carbon (7.5 g) and the reaction mixture was stirred under hydrogen atmosphere. The resulting mixture was stirred at room temperature for 16 hours. The reaction mixture was diluted with 30% methanol in DCM, filtered through celite. The filtrate was collected and concentrated to afford the crude product. The crude product was purified by trituration using hexane and

diethyl ether to afford *tert*-butyl 4-(piperidin-4-ylmethyl)piperazine-1-carboxylate (7.0 g) as a yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 3.29 (s, 4H), 3.11-3.08 (m, 2H), 2.66 (t, J = 11.60 Hz, 2H), 2.27-2.25 (m, 4H), 2.11 (d, J = 6.80 Hz, 2H), 1.74-1.71 (m, 3H), 1.39 (s, 9H), 1.17-1.14 (m, 2H).

Preparation of 7-bromo-3-iodo-1-methyl-indazole

To a solution of 7-bromo-3-iodo-1*H*-indazole (20 g, 61.93 mmol, 1.0 *equiv.*) in THF (50 mL) was added *t*-BuOK (13.90 g, 123.87 mmol, 2.0 *equiv.*) at 0 °C for 1 hour. Iodomethane (26.37 g, 185.80 mmol, 11.57 mL, 3.0 *equiv.*) was added to the mixture at 0 °C. The mixture was stirred at 20 °C for 2 hours under N_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to obtain a residue. The crude product was purified by reverse-phase HPLC (20 - 100% 50 min; 100% 20 minutes, 0.1 % formic acid condition) to afford 7-bromo-3-iodo-1-methyl-indazole (15 g) as a yellow solid.

LC-MS (ESI): m/z = 336.6 $[M+H]^+$.

Preparation of 7-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazole

A mixture of 2,6-dibenzyloxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (17.34 g, 41.55 mmol, 1.0 *equiv.*), 7-bromo-3-iodo-1-methyl-indazole (14 g, 41.55 mmol, 1.0 *equiv.*), $PdCl_2$(dppf)•DCM (6.79 g, 8.31 mmol, 0.2 *equiv.*), and cesium carbonate (40.61 g, 124.65 mmol, 3.0 *equiv.*) in THF (200 mL) and water (40 mL) was degassed and purged with N_2 three times. The mixture was then stirred at 85 °C for 1 hour under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure to remove solvent. The resulting residue was purified by column chromatography (SiO_2, petroleum ether / ethyl acetate = 1/0 to 10/1) to afford 7-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazole (15.1 g) as a white solid.

LC-MS (ESI): m/z = 502.3 $[M+H]^+$.

Preparation of *tert*-butyl 4-((1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-7-yl)piperidin-4-yl)methyl)piperazine-1-carboxylate

To a stirred solution of *tert*-butyl 4-(piperidin-4-ylmethyl)piperazine-1-carboxylate (0.34 g, 1.20 mmol) in 1,4-dioxane (10 mL) was added 7-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazole (0.50 g, 1.00 mmol). The reaction was purged with argon for 15 minutes, cesium carbonate (0. 98 g, 3.00 mmol) and Pd-PEPPSI-iHeptCl (0.05 g, 0.05 mmol)

were added. The resulting reaction was heated to 120 °C for 3 hours. The reaction mixture was quenched with water and extracted into ethyl acetate. The combined organic layers were washed with a brine solution and dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to provide a crude product. The crude product was purified by flash column chromatography (SiO_2, 100-200 mesh, 27% ethyl acetate in petroleum ether) to afford *tert*-butyl 4-((1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-7-yl)piperidin-4-yl)methyl)piperazine-1-carboxylate (0.48 g) as a pale yellow solid.

LC-MS (ESI): m/z = 703.5 $[M+H]^+$.

Preparation of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-7-(4-(piperazin-1-ylmethyl)piperidin-1-yl)-1*H*-indazole hydrochloride

To a stirred solution of *tert*-butyl 4-((1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-7-yl)piperidin-4-yl)methyl)piperazine-1-carboxylate (0.48 g, 0.68 mmol) in DCM (4.8 mL) was added 4 M HCl in dioxane (2.8 mL) at 0 °C. The reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was then concentrated under vacuum to provide 3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-7-(4-(piperazin-1-ylmethyl)piperidin-1-yl)-1*H*-indazole hydrochloride (0.45 g) as an off-white semi-solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.84 (d, J = 8.00 Hz, 1H), 7.48 (d, J = 1.60 Hz, 2H), 7.41-7.42 (m, 9H), 7.30-7.31 (m, 1H), 6.57-6.59 (m, 1H), 5.43 (d, J = 5.60 Hz, 4H), 4.32 (s, 3H), 3.27-3.25 (m, 2H), 3.08 (s, 4H), 2.54-2.57 (m, 1H), 2.51-2.51 (m, 3H), 2.28-2.30 (m, 1H).

Preparation of 3-(1-methyl-7-(4-(piperazin-1-ylmethyl)piperidin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione

To a stirred solution of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-7-(4-(piperazin-1-ylmethyl)piperidin-1-yl)-1*H*-indazole hydrochloride (0.45 g, 0.75 mmol) in DMF (4.50 mL) was added Pd on carbon (0.45 g, 10 wt%). The reaction was stirred under hydrogen purging with balloon pressure at room temperature for 16 hours. The reaction mixture was diluted with DCM and filtered through celite and washed with excess of 30% THF in DCM. The filtrate was collected and concentrated under vacuum to provide a crude product as a pale yellow solid. The crude product was triturated with methanol and diethyl ether to provide 3-(1-methyl-7-(4-(piperazin-1-ylmethyl)piperidin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (0.45 g) as pale yellow solid.

LC-MS (ESI): m/z = 425 $[M+H]^+$.

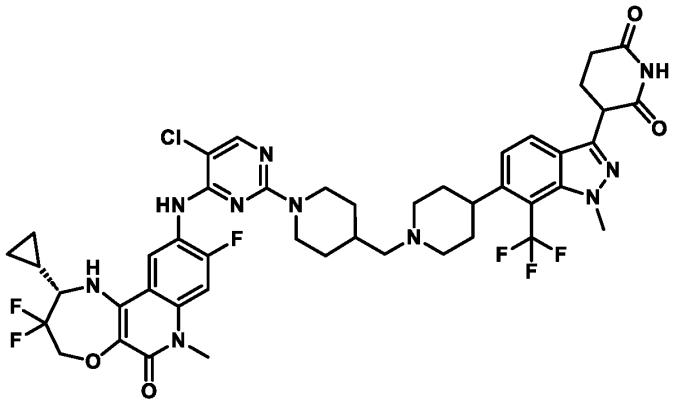
Preparation of 3-(7-(4-((4-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-*c*]quinolin-10-yl)amino)pyrimidin-2-yl)piperazin-1-yl)methyl)piperidin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

A mixture of (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3,9-trifluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-*c*]quinolin-6(7*H*)-one (130 mg, 267 μmol), 3-(1-methyl-7-(4-(piperazin-1-ylmethyl)piperidin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione dihydrochloride (111 mg, 223 μmol), CsF (104 mg, 685 μmol), and DIPEA (194 μL, 1.12 mmol) in DMSO (1.50 mL) was warmed to 80 °C under a N_2 atmosphere for 19 hours. The reaction mixture was cooled to room temperature, filtered, and purified by Prep-HPLC to afford 3-(7-(4-((4-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-*c*]quinolin-10-yl)amino)pyrimidin-2-yl)piperazin-1-yl)methyl)piperidin-1-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (89.7 mg).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.80 (s, 1H), 8.79 (s, 1H), 8.14 (d, J = 8.1 Hz, 1H), 8.02 (d, J = 41.3 Hz, 1H), 7.41 – 7.23 (m, 2H), 7.05 – 6.82 (m, 2H), 6.38 (s, 1H), 4.46 – 4.29 (m, 2H), 4.29 – 4.21 (m, 1H), 4.16 (s, 3H), 3.48 (s, 3H), 3.44 – 3.34 (m, 4H), 3.20 – 3.06 (m, 4H), 3.06 – 2.79 (m, 2H), 2.69 – 2.51 (m, 4H), 2.32 – 2.18 (m, 4H), 2.17 – 2.02 (m, 2H), 1.85 – 1.70 (m, 2H), 1.66 – 1.36 (m, 1H), 1.33 – 1.14 (m, 2H), 0.72 – 0.58 (m, 1H), 0.53 – 0.36 (m, 2H), 0.31 – 0.18 (m, 1H).

LC-MS (ESI): m/z = 874.5 $[M+H]^+$.

Example 162: 3-(6-(1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-7-(trifluoromethyl)-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 201a)



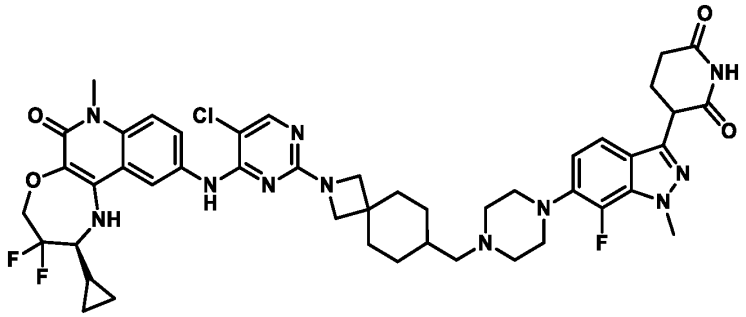
Preparation of 3-(6-(1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-7-(trifluoromethyl)-1*H*-indazol-3-yl)piperidine-2,6-dione

(*S*)-2-Cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3,9-trifluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (86 mg, 1 *equiv.*, 177 μmol) and 3-(1-methyl-6-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-7-(trifluoromethyl)-1*H*-indazol-3-yl)piperidine-2,6-dione dihydrochloride (100 mg, 1.0 *equiv.*, 177 μmol) were combined in DMSO (1.0 mL). To this mixture was added DIPEA (114 mg, 154 μL, 5.00 *equiv.*, 0.87 mmol) and CsF (135 mg, 5.00 *equiv.*, 0.87 mmol). The reaction was stirred at 90 °C for 12 hours. The resulting mixture was cooled to ambient temperature. The reaction was diluted with DMSO (1 mL), filtered, and directly purified by prep-HPLC (MeCN/water, each with 0.1% formic acid) to afford 3-(6-(1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-7-(trifluoromethyl)-1*H*-indazol-3-yl)piperidine-2,6-dione (78 mg).

LC-MS (ESI): m/z = 471.4 $[M+2H]^{2+}$.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.98 - 10.89 (m, 1H), 8.86 - 8.76 (m, 1H), 8.23 - 8.17 (m, 1H), 8.05 - 8.00 (m, 1H), 8.00 - 7.94 (m, 1H), 7.47 - 7.39 (m, 1H), 7.39 - 7.33 (m, 1H), 6.48 - 6.40 (m, 1H), 4.49 - 4.26 (m, 5H), 4.04 - 3.97 (m, 3H), 3.55 (s, 3H), 3.12 - 2.92 (m, 3H), 2.76 - 2.63 (m, 4H), 2.45 - 2.36 (m, 2H), 2.20 - 2.11 (m, 3H), 2.04 - 1.91 (m, 2H), 1.90 - 1.77 (m, 2H), 1.76 - 1.60 (m, 5H), 1.36 - 1.28 (m, 1H), 1.02 - 0.87 (m, 2H), 0.76 - 0.65 (m, 1H), 0.57 - 0.47 (m, 2H), 0.32 (br d, J = 2.1 Hz, 1H).

Example 163: 3-(6-(4-((2-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)piperazin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 196a)



Preparation of *tert*-butyl 7-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-2-azaspiro[3.5]nonane-2-carboxylate

A mixture of *tert*-butyl 7-formyl-2-azaspiro[3.5]nonane-2-carboxylate (177 mg, 1.0 *equiv.*, 0.70 mmol), 3-(7-fluoro-1-methyl-6-(piperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione hydrochloride (267 mg, 1.00 *equiv.*, 0.70 mmol), and potassium acetate (206 mg, 3.*0* *equiv.*, 2.10 mmol) in a mixture of THF (6 mL) and DMF (1.2 mL) was stirred at ambient temperature for 15 minutes. The reaction was then treated with $NaBH(OAc)_3$ (296 mg, 2.0 *equiv.*, 1.40 mmol). The resulting mixture was stirred overnight at ambient temperature. The THF was removed under a stream of nitrogen. The mixture was then filtered and purified by prep-HPLC (ACN/water, each with 0.1% formic acid) to afford *tert*-butyl 7-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-2-azaspiro[3.5]nonane-2-carboxylate (120 mg).

LC-MS (ESI): m/z = 583.4 $[M+H]^+$.

Preparation of 3-(6-(4-((2-azaspiro[3.5]nonan-7-yl)methyl)piperazin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione, hydrochloride

tert-Butyl 7-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-2-azaspiro[3.5]nonane-2-carboxylate (120 mg, 1 *equiv.*, 0.21 mmol) was dissolved in DCM (10 mL). To this mixture was added a solution of 4 N HCl in dioxane (225 mg, 1.54 mL, 30 *equiv.*, 6.18 mmol). The mixture was stirred overnight at ambient temperature. The mixture was then concentrated under reduced pressure to afford an oil that was triturated with diethyl ether/hexanes and then reconcentrated to afford 3-(6-(4-((2-azaspiro[3.5]nonan-7-yl)methyl)piperazin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione, hydrochloride (106 mg), which was used without further purification.

Preparation of 3-(6-(4-((2-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-

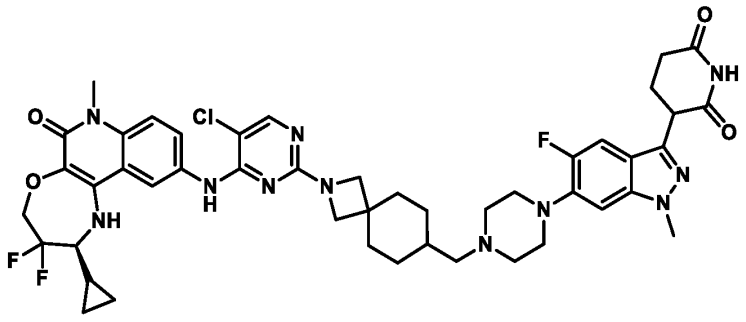
2-azaspiro[3.5]nonan-7-yl)methyl)piperazin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

To a solution of (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (49 mg, 1.0 *equiv.*, 0.10 mmol) and 3-(6-(4-((2-azaspiro[3.5]nonan-7-yl)methyl)piperazin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (50 mg, 1 *equiv.*, 0.10 mmol) in DMSO (1.0 mL) was added DIPEA (67 mg, 90 μL, 5.0 *equiv.*, 0.52 mmol) followed by CsF (79 mg, 5.0 *equiv.*, 0.52 mmol). The resulting mixture was stirred overnight at 90 °C. The reaction mixture was filtered and purified by prep-HPLC (ACN/water, both with 0.1% formic acid) to afford 3-(6-(4-((2-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)piperazin-1-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (57 mg).

LC-MS (ESI): m/z = 457.9 $[M+H]^{2+}$.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.88 (s, 1H), 8.72 (s, 1H), 8.25 (d, J = 2.0 Hz, 1H), 8.01 (s, 1H), 7.86 - 7.80 (m, 1H), 7.47 - 7.36 (m, 2H), 6.96 - 6.88 (m, 1H), 6.15 - 6.03 (m, 1H), 4.51 - 4.28 (m, 3H), 4.06 (s, 3H), 3.68 - 3.58 (m, 4H), 3.56 (s, 3H), 3.28 - 3.16 (m, 4H), 3.08 (br s, 4H), 2.54 (s, 3H), 2.39 - 2.27 (m, 1H), 2.25 - 2.04 (m, 3H), 1.84 (br d, J = 12.8 Hz, 2H), 1.76 - 1.62 (m, 2H), 1.42 (br s, 4H), 0.99 - 0.84 (m, 2H), 0.78 - 0.66 (m, 1H), 0.58 - 0.47 (m, 2H), 0.42 - 0.32 (m, 1H).

Example 164: 3-(6-(4-((2-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)piperazin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 192a)



Preparation of *tert*-butyl 7-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-2-azaspiro[3.5]nonane-2-carboxylate

A mixture of *tert*-butyl 7-formyl-2-azaspiro[3.5]nonane-2-carboxylate (309 mg, 2.0 *equiv.*, 1.22 mmol), 3-(5-fluoro-1-methyl-6-(piperazin-1-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione hydrochloride (233 mg, 1.0 *equiv.*, 0.61 mmol), and potassium acetate (180 mg, 3.*0* *equiv.*, 1.83 mmol) in THF (6 mL) and DMF (1.2 mL) was stirred at ambient temperature for 15 minutes. The reaction was then treated with $NaBH(OAc)_3$ (259 mg, 2.0 *equiv.*, 1.22 mmol). The resulting mixture was stirred overnight at ambient temperature. The THF was removed under a stream of nitrogen. The mixture was then filtered and purified by prep-HPLC (ACN/water, each with 0.1% formic acid) to afford *tert*-butyl 7-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-2-azaspiro[3.5]nonane-2-carboxylate (159 mg).

LC-MS (ESI): m/z = 583.4 $[M+H]^+$.

Preparation of 3-(6-(4-((2-azaspiro[3.5]nonan-7-yl)methyl)piperazin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione hydrochloride

tert-Butyl 7-((4-(3-(2,6-dioxopiperidin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-2-azaspiro[3.5]nonane-2-carboxylate (159 mg, 1 *equiv.*, 0.21 mmol) was dissolved in DCM (10 mL). To this solution was added 4 N HCl in dioxane (298 mg, 2.05 mL, 30 *equiv.*, 8.19 mmol). The mixture was stirred overnight at ambient temperature. The reaction was concentrated under reduced pressure to afford an oil that was triturated with diethyl ether/hexanes to afford 3-(6-(4-((2-azaspiro[3.5]nonan-7-yl)methyl)piperazin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione hydrochloride (100 mg), which was used without further purification.

LC-MS (ESI): m/z = 483.4 $[M+H]^+$.

Preparation of 3-(6-(4-((2-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)piperazin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

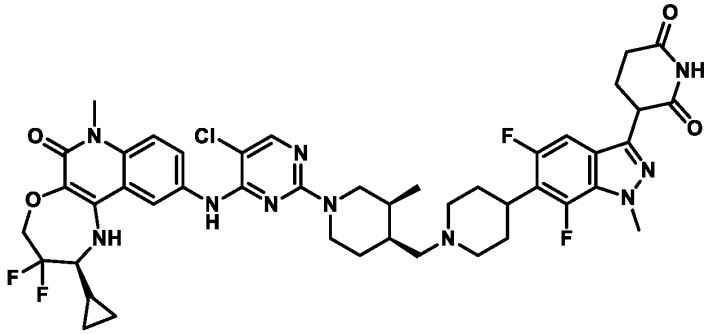
To A solution of (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (49 mg, 1.0 *equiv.*, 0.10 mmol) and 3-(6-(4-((2-azaspiro[3.5]nonan-7-yl)methyl)piperazin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (50 mg, 1 *equiv.*, 0.10 mmol) in DMSO (1.0 mL) was added DIPEA (67 mg, 90 µL, 5.0 *equiv.*, 0.52 mmol) followed by CsF (79 mg, 5.0 *equiv.*, 0.52 mmol) and the resulting mixture was stirred overnight at 90 °C. The reaction

mixture was filtered and purified by prep-HPLC (ACN/water, both with 0.1% formic acid) to afford 3-(6-(4-((2-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)piperazin-1-yl)-5-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (38 mg).

LC-MS (ESI): m/z = 457.9 $[M+2H]^{2+}$.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.84 (s, 1H), 8.80 - 8.64 (m, 1H), 8.30 - 8.19 (m, 1H), 8.01 (s, 1H), 7.91 - 7.79 (m, 1H), 7.51 - 7.36 (m, 2H), 7.20 - 7.02 (m, 1H), 6.22 - 6.03 (m, 1H), 4.55 - 4.32 (m, 2H), 4.32 - 4.20 (m, 1H), 3.94 (s, 3H), 3.56 (s, 8H), 3.27 - 3.17 (m, 1H), 3.12 - 3.00 (m, 4H), 2.70 - 2.54 (m, 3H), 2.40 - 2.08 (m, 5H), 1.90 - 1.66 (m, 4H), 1.56 - 1.25 (m, 5H), 1.01 - 0.84 (m, 2H), 0.75 - 0.62 (m, 1H), 0.53 (br t, J = 5.7 Hz, 2H), 0.37 (br d, J = 5.3 Hz, 1H).

Example 165: 3-[6-[1-[[(3*S*,4*S*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (Compound 219a)



Preparation of 3-[6-[1-[[(3*S*,4*S*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione

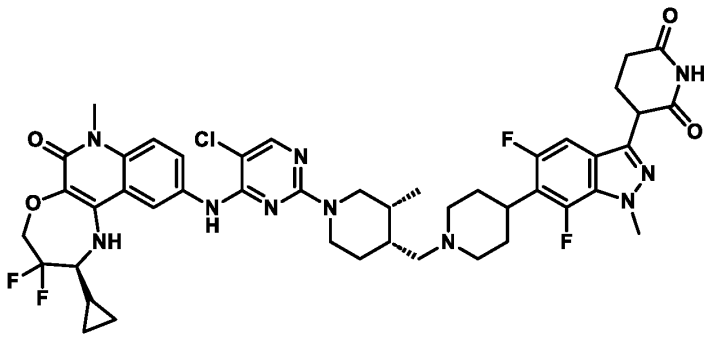
To a solution of 3-[5,7-difluoro-1-methyl-6-[1-[[(3S,4S)-3-methyl-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione (1 g, 2.11 mmol, 1 *equiv.*) in DMSO (10 mL), TEA (854.71 mg, 8.45 mmol, 1.18 mL, 4 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (988.86 mg, 2.11 mmol, 1 *equiv.*) were added. The

mixture was stirred at 100 °C for 2 hours. The reaction mixture was quenched by the addition of water (30 mL) and extracted with ethyl acetate (120 mL). The combined organic layers were washed with brine (120 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give 3-[6-[1-[[(3*S*,4*S*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione as a pink solid.

LC-MS (ESI): m/z = 905.4 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.92 (s, 1H), 8.74 (s, 1H), 8.16 (s, 2H), 8.01 (s, 1H), 7.78 (dd, J = 2.0, 9.2 Hz, 1H), 7.58 - 7.26 (m, 2H), 6.20 (s, 1H), 4.51 - 4.30 (m, 4H), 4.11 (s, 3H), 3.58 (s, 3H), 3.40 - 3.27 (m, 4H), 3.08 - 2.88 (m, 4H), 2.72 - 2.60 (m, 2H), 2.40 (d, J = 8.4 Hz, 1H), 2.25 - 1.90 (m, 8H), 1.69 (d, J = 10.4 Hz, 2H), 1.51 - 1.26 (m, 3H), 0.85 - 0.64 (m, 4H), 0.52 (t, J = 5.6 Hz, 2H), 0.36 (d, J = 5.2 Hz, 1H)

Example 166: 3-[6-[1-[[(3*R*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (Compound 219b)



Preparation of 3-[6-[1-[[(3*R*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione

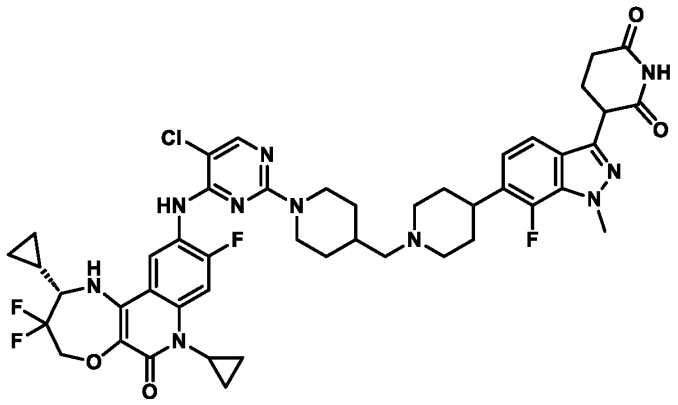
To a solution of 3-[5,7-difluoro-1-methyl-6-[1-[[(3*R*,4*R*)-3-methyl-4-piperidyl]methyl]-4-piperidyl]indazol-3-yl]piperidine-2,6-dione (1 g, 2.11 mmol, 1 *equiv.*) in DMSO (10 mL), TEA (854.71 mg, 8.45 mmol, 1.18 mL, 4 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-

[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (988.86 mg, 2.11 mmol, 1 *equiv.*) were added. The mixture was stirred at 100 °C for 2 hours. The reaction mixture was quenched by the addition of water (20 mL) and extracted with ethyl acetate (90 mL). The combined organic layers were washed with brine (90 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give 3-[6-[1-[[(3*R*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione as a yellow solid.

LC-MS (ESI): m/z = 905.4 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.90 (s, 1H), 8.73 (s, 1H), 8.17 (br d, J = 10.0 Hz, 1H), 8.00 (s, 1H), 7.77 (br d, J = 8.8 Hz, 1H), 7.51 - 7.33 (m, 2H), 6.18 (br s, 1H), 4.56 - 4.21 (m, 5H), 4.10 (s, 3H), 3.57 (s, 3H), 3.11 - 2.77 (m, 6H), 2.75 - 2.54 (m, 2H), 2.46 - 2.31 (m, 1H), 2.23 - 1.84 (m, 9H), 1.67 (br d, J = 10.0 Hz, 2H), 1.48 - 1.24 (m, 3H), 0.84 - 0.65 (m, 4H), 0.59 - 0.43 (m, 2H), 0.43 - 0.28 (m, 1H)

Example 167: 3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2,7-dicyclopropyl-3,3,9-trifluoro-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-4-piperidyl]-7-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (Compound 215a)



Preparation of 5-bromo-2-(cyclopropylamino)-4-fluoro-benzoic acid

To a solution of 2-amino-5-bromo-4-fluoro-benzoic acid (50 g, 213.65 mmol, 1 *equiv.*) and cyclopropylboronic acid (55.06 g, 640.96 mmol, 3 *equiv.*) in DCE (500 mL) were added $Cu(OAc)_2$ (38.81 g, 213.65 mmol, 1 *equiv.*) and 2-(2-pyridyl)pyridine (33.37 g, 213.65 mmol, 1 *equiv.*). The mixture was stirred at 70 °C for 12 hours. The reaction mixture was quenched

by the addition of water (100 mL) and extracted with DCM (300 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give 5-bromo-2-(cyclopropylamino)-4-fluoro-benzoic acid (15 g) as a white solid.

Preparation of 6-bromo-1-cyclopropyl-7-fluoro-3,1-benzoxazine-2,4-dione

A solution of 5-bromo-2-(cyclopropylamino)-4-fluoro-benzoic acid (15 g, 54.73 mmol, 1 *equiv.*) in THF (150 mL) was treated with bis(trichloromethyl)carbonate (16.24 g, 54.73 mmol, 1 *equiv.*). The mixture was stirred at 70 °C for 12 hours. The reaction mixture was quenched by the addition of water (10 mL) and extracted with ethyl acetate (90 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (0~10% ethyl acetate/petroleum ether) to give 6-bromo-1-cyclopropyl-7-fluoro-3,1-benzoxazine-2,4-dione (6 g) as a white solid.

LC-MS (ESI): m/z = 235.1 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.23 (d, J = 7.6 Hz, 1H), 7.67 (d, J = 10.4 Hz, 1H), 2.92 (t, J = 3.6, 6.8 Hz, 1H), 1.28 - 1.19 (m, 2H), 0.97 - 0.74 (m, 2H)

Preparation of ethyl 6-bromo-1-cyclopropyl-7-fluoro-4-hydroxy-2-oxo-quinoline-3-carboxylate

To a solution of diethylmalonate (1.39 g, 8.66 mmol, 1.32 mL, 2 *equiv.*) in DMA (10 mL) was dropwise added *t*-BuONa (832.67 mg, 8.66 mmol, 2 *equiv.*) at 0 °C. The mixture was stirred at 0 °C for 10 minutes, and then 6-bromo-1-cyclopropyl-7-fluoro-3,1-benzoxazine-2,4-dione (1.3 g, 4.33 mmol, 1 *equiv.*) was added. The resulting mixture was stirred at 100 °C for 2 hours. The reaction mixture was quenched by the addition of water (20 mL) and extracted with ethyl acetate (90 mL). The combined organic layers were washed with brine (90 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (0~100% ethyl acetate/petroleum ether) to give ethyl 6-bromo-1-cyclopropyl-7-fluoro-4-hydroxy-2-oxo-quinoline-3-carboxylate (1.3 g) as a white solid.

LC-MS (ESI): m/z = 369.9 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.21 (d, J = 7.8 Hz, 1H), 7.72 (d, J = 11.6 Hz, 1H), 4.29 (q, J = 7.2 Hz, 2H), 2.84 - 2.76 (m, 1H), 1.41 - 1.11 (m, 7H)

Preparation of ethyl 6-bromo-4-chloro-1-cyclopropyl-7-fluoro-2-oxo-quinoline-3-carboxylate

A solution of ethyl 6-bromo-1-cyclopropyl-7-fluoro-4-hydroxy-2-oxo-quinoline-3-carboxylate (1.3 g, 3.51 mmol, 1 *equiv.*) in DMF (10 mL) was treated with $(COCl)_2$ (1.34 g, 10.54 mmol, 922.25 μL, 3 *equiv.*). The mixture was stirred at 70 °C for 0.5 hour. The reaction mixture was quenched by the addition of water (5 mL), filtered, and concentrated under reduced pressure to give ethyl 6-bromo-4-chloro-1-cyclopropyl-7-fluoro-2-oxo-quinoline-3-carboxylate (1.3 g, crude) as a brown oil.

Preparation of 6-bromo-1-cyclopropyl-7-fluoro-4-[[1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]quinolin-2-one

A solution of ethyl 6-bromo-4-chloro-1-cyclopropyl-7-fluoro-2-oxo-quinoline-3-carboxylate (0.8 g, 2.06 mmol, 1 *equiv.*) in NMP (10 mL) was treated with LiCl (43.63 mg, 1.03 mmol, 21.10 μL, 0.5 *equiv.*) and 3-amino-3-cyclopropyl-2,2-difluoro-propan-1-ol (466.75 mg, 3.09 mmol, 1.5 *equiv.*). The mixture was stirred at 180 °C for 3 hours. The reaction mixture was quenched by the addition of water (10 mL) and extracted with ethyl acetate (90 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give 6-bromo-1-cyclopropyl-7-fluoro-4-[[1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]quinolin-2-one (0.8 g) as a white solid.

LC-MS (ESI): m/z = 433.1 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.65 (d, J = 7.6 Hz, 1H), 7.69 (d, J = 11.6 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 5.63 - 5.39 (m, 2H), 3.87 - 3.63 (m, 2H), 2.74 (d, J = 2.8 Hz, 1H), 1.33 - 1.13 (m, 5H), 0.78 - 0.40 (m, 6H), 0.33 - 0.12 (m, 1H)

Preparation of 3,6-dibromo-1-cyclopropyl-7-fluoro-4-[[1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]quinolin-2-one

A solution of 6-bromo-1-cyclopropyl-7-fluoro-4-[[1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]quinolin-2-one (800 mg, 1.78 mmol, 1 *equiv.*) in DMF (8 mL) was treated with NBS (285.27 mg, 1.60 mmol, 0.9 *equiv.*). The mixture was stirred at 0 °C for 20 minutes. The reaction mixture was quenched by the addition of water (20 mL) and extracted with ethyl acetate (90 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (0~100% ethyl acetate/petroleum ether) to give 3,6-dibromo-1-

cyclopropyl-7-fluoro-4-[[1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]quinolin-2-one (0.9 g) as a white solid.

LC-MS (ESI): m/z = 510.8 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.37 (d, J = 7.6 Hz, 1H), 7.79 (d, J = 11.2 Hz, 1H), 5.81 - 5.45 (m, 2H), 4.03 (q, J = 7.2 Hz, 2H), 3.90 - 3.73 (m, 2H), 3.01 - 2.92 (m, 1H), 1.33 - 1.20 (m, 3H), 0.74 (s, 2H), 0.69 - 0.46 (m, 3H), 0.42 - 0.23 (m, 1H)

Preparation of 10-bromo-2,7-dicyclopropyl-3,3,9-trifluoro-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one

A solution of 3,6-dibromo-1-cyclopropyl-7-fluoro-4-[[1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]quinolin-2-one (0.9 g, 1.76 mmol, 1 *equiv.*) in THF (10 mL) was treated with *t*-BuOK (197.97 mg, 1.76 mmol, 1 *equiv.*). The mixture was stirred at 60 °C for 1 hour. The reaction mixture was quenched by the addition of water (10 mL) and extracted with ethyl acetate (90 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (0~100% ethyl acetate/petroleum ether) to give 10-bromo-2,7-dicyclopropyl-3,3,9-trifluoro-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (0.5 g) as a white solid.

LC-MS (ESI): m/z = 429.1 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.51 (d, J = 7.2 Hz, 1H), 7.70 (d, J = 11.6 Hz, 1H), 6.51 (s, 1H), 4.57 - 4.19 (m, 2H), 2.93 - 2.74 (m, 1H), 1.39 - 1.17 (m, 3H), 0.87 - 0.18 (m, 6H)

Preparation of 10-(benzhydrylideneamino)-2,7-dicyclopropyl-3,3,9-trifluoro-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one

A solution of 10-bromo-2,7-dicyclopropyl-3,3,9-trifluoro-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (0.5 g, 1.16 mmol, 1 *equiv.*) in toluene (5 mL) was treated with $Pd_2(dba)_3$ (106.67 mg, 116.49 μmol, 0.1 *equiv.*), XantPhos (134.80 mg, 232.98 μmol, 0.2 *equiv.*), diphenylmethanimine (253.34 mg, 1.40 mmol, 234.57 μL, 1.2 *equiv.*), and cesium carbonate (948.85 mg, 2.91 mmol, 2.5 *equiv.*). The mixture was stirred at 90 °C for 12 hours under a N_2 atmosphere. The reaction mixture was quenched by the addition of water (10 mL) and extracted with ethyl acetate (90 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (0~100% ethyl acetate/petroleum ether) to give 10-(benzhydrylideneamino)-2,7-dicyclopropyl-3,3,9-trifluoro-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (0.67 g) as a white solid.

LC-MS (ESI): m/z = 530.3 $[M+H]^+$

Preparation of 10-amino-2,7-dicyclopropyl-3,3,9-trifluoro-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one

A solution of 10-(benzhydrylideneamino)-2,7-dicyclopropyl-3,3,9-trifluoro-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (0.67 g, 1.27 mmol, 1 *equiv.*) in DCM (5 mL) was treated with HCl/dioxane (2 M, 4.93 mL, 7.79 *equiv.*). The mixture was stirred at 25 °C for 1 hour. The reaction mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (0~10% DCM/methanol) to give 10-amino-2,7-dicyclopropyl-3,3,9-trifluoro-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (0.45 g) as a white solid.

LC-MS (ESI): m/z = 365.9 $[M+H]^+$

Preparation of (2*S*)-10-amino-2,7-dicyclopropyl-3,3,9-trifluoro-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one

The isomers of 10-amino-2,7-dicyclopropyl-3,3,9-trifluoro-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one were separated by SFC (column: DAICEL CHIRALCEL OD(250 mm × 30 mm,10 um);mobile phase: [CO_2-MeOH(0.1%NH_3H_2O)];B%:40%, isocratic elution mode) to give (2*S*)-10-amino-2,7-dicyclopropyl-3,3,9-trifluoro-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (240 mg) as a white solid.

LC-MS (ESI): m/z = 366.0 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.44 (d, J = 13.6 Hz, 1H), 7.32 (d, J = 9.2 Hz, 1H), 5.96 (d, J = 2.4 Hz, 1H), 4.99 (s, 2H), 4.51 - 4.20 (m, 2H), 3.20 (td, J = 4.8, 9.6 Hz, 1H), 2.80 - 2.69 (m, 1H), 1.35 - 1.25 (m, 1H), 1.21 - 1.17 (m, 2H), 0.78 - 0.66 (m, 2H), 0.63 - 0.57 (m, 1H), 0.54 - 0.42 (m, 2H), 0.38 - 0.24 (m, 1H)

Preparation of (2*S*)-2,7-dicyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3,9-trifluoro-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one

A solution of (2*S*)-10-amino-2,7-dicyclopropyl-3,3,9-trifluoro-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (50 mg, 136.86 μmol, 1 *equiv.*) in DMF (0.5 mL) was treated with DIPEA (53.06 mg, 410.57 μmol, 71.51 μL, 3 *equiv.*) and 2,4,5-trichloropyrimidine (37.65 mg, 205.28 μmol, 1.5 *equiv.*). The mixture was stirred at 80 °C for 12 hours. The reaction mixture was quenched by the addition of water (5 mL) and extracted with ethyl acetate (60 mL). The combined organic layers were washed with brine (60 mL), dried over sodium

sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (0~100% ethyl acetate/petroleum ether) to give (2*S*)-2,7-dicyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3,9-trifluoro-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (30 mg) as a white solid.

LC-MS (ESI): m/z = 512.1 $[M+H]^+$

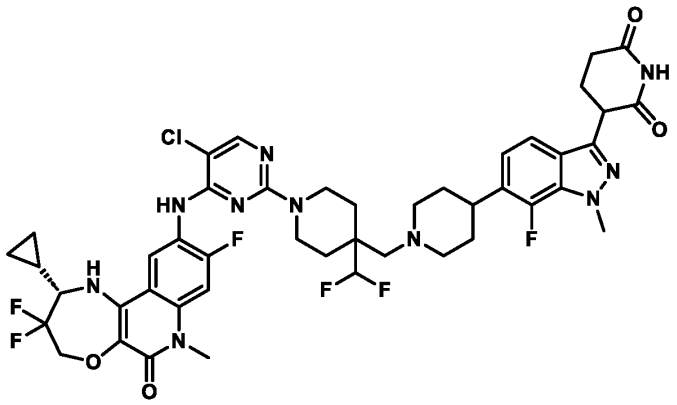
Preparation of 3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2,7-dicyclopropyl-3,3,9-trifluoro-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-4-piperidyl]-7-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione

A solution of 3-(7-fluoro-1-methyl-6-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (25.86 mg, 58.56 μmol, 1 *equiv.*) in DMSO (0.5 mL) was treated with DIPEA (22.70 mg, 175.67 μmol, 30.60 μL, 3 *equiv.*), CsF (17.79 mg, 117.12 μmol, 2 *equiv.*), and (2*S*)-2,7-dicyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3,9-trifluoro-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (30 mg, 58.56 μmol, 1 *equiv.*). The mixture was stirred at 80 °C for 12 hours. The reaction mixture was quenched by the addition of water (10 mL) and extracted with ethyl acetate (60 mL). The combined organic layers were washed with brine (60 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give 3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2,7-dicyclopropyl-3,3,9-trifluoro-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-4-piperidyl]-7-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (55 mg) as a pink solid.

LC-MS (ESI): m/z = 917.4 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.91 (s, 1H), 8.80 (s, 1H), 8.19 (s, 1H), 8.18 (s, 1H), 8.01 (s, 1H), 7.62 (d, J = 12.4 Hz, 1H), 7.45 (d, J = 8.4 Hz, 1H), 7.04 (d, J = 5.6, 8.4 Hz, 1H), 6.38 (s, 1H), 4.42 - 4.18 (m, 4H), 4.10 (s, 3H), 3.00 - 2.79 (m, 4H), 2.77 - 2.57 (m, 4H), 2.54 (s, 2H), 2.41 - 2.29 (m, 1H), 2.23 - 2.08 (m, 3H), 2.07 - 1.93 (m, 2H), 1.86 - 1.51 (m, 7H), 1.36 - 1.15 (m, 3H), 0.94 (d, J = 10.0 Hz, 2H), 0.84 - 0.58 (m, 3H), 0.56 - 0.42 (m, 2H), 0.32 (d, J = 5.2 Hz, 1H)

Example 168: 3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-(difluoromethyl)-4-piperidyl]methyl]-4-piperidyl]-7-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (Compound 216a)



Preparation of *tert*-butyl 4-(difluoromethyl)-4-formyl-piperidine-1-carboxylate

A mixture of 1-*tert*-butoxycarbonyl-4-(difluoromethyl)piperidine-4-carboxylic acid (0.27 g, 966.77 μmol, 1 *equiv.*) and DMAP (118.11 mg, 966.77 μmol, 1 *equiv.*) in DCM (5 mL) was treated with N,N-dimethyl-1-(trifluoromethylsulfonyl)pyridin-1-ium-4-amine (781.74 mg, 1.93 mmol, 2 *equiv.*, OTf) under a N_2 atmosphere. The reaction mixture was stirred at 25°C for 10 minutes, and then DMAP (118.11 mg, 966.77 μmol, 1 *equiv.*) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (123.72 mg, 966.77 μmol, 140.28 μL, 1 *equiv.*) were added. The reaction mixture was stirred at 25°C for another 10 minutes. The reaction mixture was quenched by the addition of water (5 mL) and extracted with DCM (15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by column chromatography (petroleum ether/ethyl acetate = 100/0 to 85/15) to give *tert*-butyl 4-(difluoromethyl)-4-formyl-piperidine-1-carboxylate (0.21 g) as a yellow oil.

Preparation of *tert*-butyl 4-(difluoromethyl)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-7-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]piperidine-1-carboxylate

To a solution of 3-[7-fluoro-1-methyl-6-(4-piperidyl)indazol-3-yl]piperidine-2,6-dione (0.3 g, 787.73 μmol, 1 *equiv.*, HCl) and *tert*-butyl 4-(difluoromethyl)-4-formyl-piperidine-1-carboxylate (207.39 mg, 787.73 μmol, 1 *equiv.*) in DCE (5 mL) was dropwise added $NaBH(OAc)_3$ (250.43 mg, 1.18 mmol, 1.5 *equiv.*) at 60°C. After addition, the mixture was stirred at this temperature for 13 hours, and then tetraisopropoxytitanium (335.83 mg, 1.18 mmol, 348.73 μL, 1.5 *equiv.*) and *tert*-butyl 4-(difluoromethyl)-4-formyl-piperidine-1-carboxylate (207.39 mg, 787.73 μmol, 1 *equiv.*) were added dropwise at 60°C. The resulting mixture was stirred at 60°C for 1 hour. The reaction mixture was quenched by the addition of water (10 mL) and extracted with DCM (15 mL). The combined organic layers were dried over

sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by column chromatography (DCM/methanol = 1/0 to 5/1) to give *tert*-butyl 4-(difluoromethyl)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-7-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]piperidine-1-carboxylate (0.25 g) as a brown oil.

LC-MS (ESI): m/z = 592.4 $[M+H]^+$

Preparation of 3-[6-[1-[[4-(difluoromethyl)-4-piperidyl]methyl]-4-piperidyl]-7-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione

A solution of *tert*-butyl 4-(difluoromethyl)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-7-fluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]piperidine-1-carboxylate (125 mg, 211.27 μmol, 1 *equiv.*) in DCM (1 mL) was treated with HCl/dioxane (1 mL). The mixture was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give 3-[6-[1-[[4-(difluoromethyl)-4-piperidyl]methyl]-4-piperidyl]-7-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (0.1 g, crude) as a brown solid.

LC-MS (ESI): m/z = 492.3 $[M+H]^+$

Preparation of 3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-(difluoromethyl)-4-piperidyl]methyl]-4-piperidyl]-7-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione

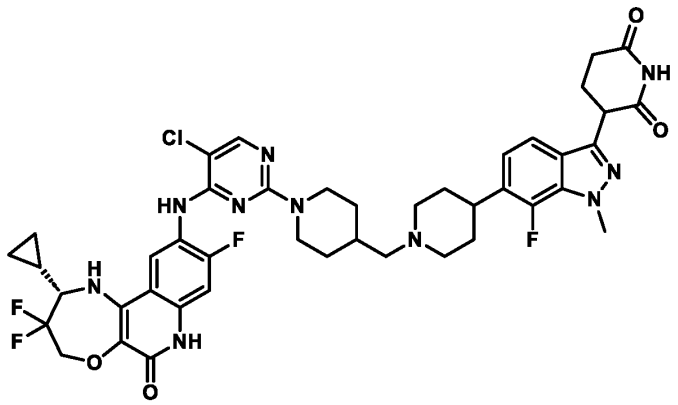
A solution of (2*S*)-2-cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (158.28 mg, 325.50 μmol, 0.8 *equiv.*) and 3-[6-[1-[[4-(difluoromethyl)-4-piperidyl]methyl]-4-piperidyl]-7-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (0.2 g, 406.88 μmol, 1 *equiv.*) in DMSO (3 mL) was treated with TEA (164.69 mg, 1.63 mmol, 226.53 μL, 4 *equiv.*). The mixture was stirred at 100°C for 1 hour. The reaction mixture was filtered, and the residue was purified by prep-HPLC to give 3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-(difluoromethyl)-4-piperidyl]methyl]-4-piperidyl]-7-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (25.09 mg) as a yellow solid.

LC-MS (ESI): m/z = 941.6 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.91 (s, 1H), 8.87 (s, 1H), 8.22 (d, J = 8.0 Hz, 1H), 8.13 (s, 1H), 8.04 (s, 1H), 7.52 - 7.33 (m, 2H), 7.02 (dd, J = 5.6, 8.4 Hz, 1H), 6.45 (s, 1H), 5.97 (m, 1H), 4.50 - 4.27 (m, 3H), 4.10 (s, 3H), 3.99 - 3.72 (m, 2H), 3.53 (s, 3H), 3.23 - 3.05

(m, 2H), 2.97 - 2.77 (m, 3H), 2.72 - 2.58 (m, 2H), 2.47 - 2.26 (m, 4H), 2.22 - 2.07 (m, 1H), 1.88 - 1.57 (m, 5H), 1.54 - 1.39 (m, 4H), 1.34 - 1.15 (m, 2H), 0.77 - 0.62 (m, 1H), 0.50 (t, *J* = 5.6 Hz, 2H), 0.38 - 0.20 (m, 1H)

Example 169: 3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-6-oxo-1,2,4,7-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-4-piperidyl]-7-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (Compound 218a)



Preparation of 6-bromo-7-fluoro-1*H*-3,1-benzoxazine-2,4-dione

To a solution of 2-amino-5-bromo-4-fluoro-benzoic acid (25 g, 106.83 mmol, 1 *equiv.*) in THF (300 mL) was added bis(trichloromethyl) carbonate (11.10 g, 37.39 mmol, 0.35 *equiv.*). The mixture was stirred at 70°C for 12 hours. The reaction mixture was filtered to give 6-bromo-7-fluoro-1*H*-3,1-benzoxazine-2,4-dione (23 g, crude) as a white solid.

Preparation of ethyl 6-bromo-7-fluoro-4-hydroxy-2-oxo-1*H*-quinoline-3-carboxylate

A solution of 6-bromo-7-fluoro-1*H*-3,1-benzoxazine-2,4-dione (6 g, 23.08 mmol, 1 *equiv.*) in DMA (70 mL) was treated with t-BuONa (4.44 g, 46.15 mmol, 2 *equiv.*) and diethyl propanedioate (7.39 g, 46.15 mmol, 7.01 mL, 2 *equiv.*). The mixture was stirred at 100°C for 16 hours. The pH of the mixture was adjusted to 4~5 with aqueous HCl, resulting in the formation of a solid. The mixture was filtered, and the filter cake was washed with water (2 mL). The cake was dried under vacuum to give ethyl 6-bromo-7-fluoro-4-hydroxy-2-oxo-1*H*-quinoline-3-carboxylate (3.5 g, crude) as a yellow solid.

LC-MS (ESI): m/z = 330.0 $[M+H]^+$

Preparation of ethyl 6-bromo-4-chloro-7-fluoro-2-oxo-1*H*-quinoline-3-carboxylate

A solution of ethyl 6-bromo-7-fluoro-4-hydroxy-2-oxo-1*H*-quinoline-3-carboxylate (3.5 g, 10.60 mmol, 1 *equiv.*) in DMF (40 mL) was treated with $(COCl)_2$ (2.02 g, 15.90 mmol, 1.39 mL, 1.5 *equiv.*). The mixture was stirred at 25°C for 10 minutes. The reaction mixture was quenched by the addition of water (50 mL) at 25°C, and then filtered to give ethyl 6-bromo-4-chloro-7-fluoro-2-oxo-1*H*-quinoline-3-carboxylate (3 g, crude) as a white solid.

LC-MS (ESI): m/z = 371.9 $[M+23]^+$

Preparation of 6-bromo-4-[[(1*S*)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-7-fluoro-1*H*-quinolin-2-one

A solution of ethyl 6-bromo-4-chloro-7-fluoro-2-oxo-1*H*-quinoline-3-carboxylate (3 g, 8.61 mmol, 1 *equiv.*) and (3*S*)-3-amino-3-cyclopropyl-2,2-difluoro-propan-1-ol (1.95 g, 12.91 mmol, 1.5 *equiv.*) in NMP (26 mL) was treated with LiCl (182.43 mg, 4.30 mmol, 88.21 µL, 0.5 *equiv.*). The mixture was stirred at 180°C for 2 hours. The reaction mixture was quenched by the addition of water (2 mL) at 25°C. The crude product was purified by reversed-phase HPLC to give 6-bromo-4-[[(1*S*)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-7-fluoro-1*H*-quinolin-2-one (1.5 g) as a brown solid.

LC-MS (ESI): m/z = 393.0 $[M+H]^+$

Preparation of 3,6-dibromo-4-[[(1*S*)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-7-fluoro-1*H*-quinolin-2-one

A solution of 6-bromo-4-[[(1*S*)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-7-fluoro-1*H*-quinolin-2-one (1.5 g, 3.83 mmol, 1 *equiv.*) in DMF (30 mL) was treated with NBS (614.24 mg, 3.45 mmol, 0.9 *equiv.*). The mixture was stirred at 0°C for 20 minutes. The reaction mixture was quenched by the addition of water (50 mL) at 25°C, and then filtered to obtain 3,6-dibromo-4-[[(1*S*)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-7-fluoro-1*H*-quinolin-2-one (1.2 g, crude) as a white solid.

LC-MS (ESI): m/z = 471.0 $[M+H]^+$

Preparation of (2*S*)-10-bromo-2-cyclopropyl-3,3,9-trifluoro-1,2,4,7-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6-one

A solution of 3,6-dibromo-4-[[(1*S*)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-7-fluoro-1*H*-quinolin-2-one (1.2 g, 2.55 mmol, 1 *equiv.*) in THF (7 mL) was

treated with *t*-BuOK (286.45 mg, 2.55 mmol, 1 *equiv.*). The mixture was stirred at 60°C for 1 hour. The reaction mixture was quenched by the addition of water (10 mL) at 25°C, and extracted with ethyl acetate (30 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was triturated with petroleum ether at 25°C for 20 minutes to give (2*S*)-10-bromo-2-cyclopropyl-3,3,9-trifluoro-1,2,4,7-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6-one (1.2 g, crude) as a white solid.

LC-MS (ESI): m/z = 391.0 $[M+H]^+$

Preparation of (2*S*)-10-(benzhydrylideneamino)-2-cyclopropyl-3,3,9-trifluoro-1,2,4,7-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6-one

A mixture of diphenylmethanimine (768.40 mg, 4.24 mmol, 711.48 μL, 1.5 *equiv.*), (2*S*)-10-bromo-2-cyclopropyl-3,3,9-trifluoro-1,2,4,7-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6-one (1.1 g, 2.83 mmol, 1 *equiv.*), *t*-BuONa (679.10 mg, 7.07 mmol, 2.5 *equiv.*), XantPhos (327.10 mg, 565.31 μmol, 0.2 *equiv.*), and $Pd_2(dba)_3$ (258.83 mg, 282.66 μmol, 0.1 *equiv.*) in dioxane (12 mL) was degassed and purged with N_2 three times. The mixture was stirred at 100°C for 1 hour under a N_2 atmosphere. The reaction mixture was quenched by the addition of water (10 mL) and extracted with ethyl acetate (30 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by column chromatography (DCM/methanol = 100/0 to 96/4) to give (2*S*)-10-(benzhydrylideneamino)-2-cyclopropyl-3,3,9-trifluoro-1,2,4,7-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6-one (0.9 g) as a yellow solid.

LC-MS (ESI): m/z = 490.3 $[M+H]^+$

Preparation of (2*S*)-10-amino-2-cyclopropyl-3,3,9-trifluoro-1,2,4,7-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6-one

A solution of (2*S*)-10-(benzhydrylideneamino)-2-cyclopropyl-3,3,9-trifluoro-1,2,4,7-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6-one (0.8 g, 1.63 mmol, 1 *equiv.*) in dioxane (5 mL) was treated with HCl/dioxane (5 mL). The mixture was stirred at 25°C for 1 hour. The reaction mixture was concentrated under reduced pressure to give a residue, which was purified by column chromatography (DCM/methanol = 100/0 to 85/15) to give (2*S*)-10-amino-2-cyclopropyl-3,3,9-trifluoro-1,2,4,7-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6-one (0.44 g) as a brown solid.

LC-MS (ESI): m/z = 326.1 $[M+H]^+$

Preparation of (2*S*)-10-amino-2-cyclopropyl-3,3,9-trifluoro-1,2,4,7-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6-one

(2*S*)-10-amino-2-cyclopropyl-3,3,9-trifluoro-1,2,4,7-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6-one (0.44 g, 1.35 mmol, 1 *equiv.*) was re-purification by SFC. The residue was purified by prep-HPLC (column: Daicel Chiralcel OD (250 mm × 30 mm, 10 um);mobile phase: [CO_2-MeOH(0.1% NH_3H_2O)]; B%:40%, isocratic elution mode) to give (2*S*)-10-amino-2-cyclopropyl-3,3,9-trifluoro-1,2,4,7-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6-one (0.23 g) as a brown solid.

LC-MS (ESI): m/z = 326.1 $[M+H]^+$

Preparation of (2*S*)-2-cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3,9-trifluoro-1,2,4,7-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6-one

A solution of (2*S*)-10-amino-2-cyclopropyl-3,3,9-trifluoro-1,2,4,7-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6-one (0.22 g, 676.33 μmol, 1 *equiv.*) and 2,4,5-trichloropyrimidine (148.87 mg, 811.60 μmol, 1.2 *equiv.*) in DMF (3 mL) was treated with DIPEA (262.23 mg, 2.03 mmol, 353.41 μL, 3 *equiv.*). The mixture was stirred at 70°C for 1 hour. The reaction mixture was quenched by the addition of water (7 mL) at 25°C and filtered to obtain (2*S*)-2-cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3,9-trifluoro-1,2,4,7-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6-one (0.3 g, crude) as a white solid.

LC-MS (ESI): m/z = 472.1 $[M+H]^+$

Preparation of 3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-6-oxo-1,2,4,7-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-4-piperidyl]-7-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione

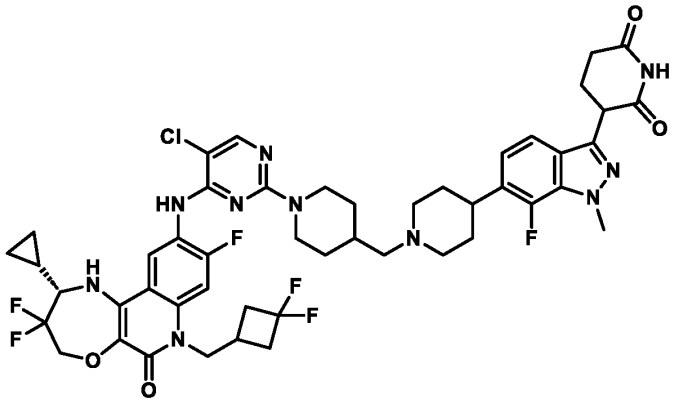
A solution of (2*S*)-2-cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3,9-trifluoro-1,2,4,7-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6-one (299.47 mg, 634.14 μmol, 0.8 *equiv.*) and 3-(7-fluoro-1-methyl-6-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (0.35 g, 792.68 μmol, 1 *equiv.*) in DMSO (5 mL) was treated with CsF (240.82 mg, 1.59 mmol, 2 *equiv.*) and DIPEA (307.34 mg, 2.38 mmol, 414.21 μL, 3 *equiv.*). The mixture was stirred at 100°C for 3 hours. The reaction mixture was filtered and the residue was purified by prep-HPLC to give 3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-6-oxo-1,2,4,7-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-

yl]-4-piperidyl]methyl]-4-piperidyl]-7-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (175.94 mg) as a yellow solid.

LC-MS (ESI): m/z = 877.4 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.39 (s, 1H), 10.91 (s, 1H), 8.78 (s, 1H), 8.15 (s, 1H), 8.11 (d, J = 7.6 Hz, 1H), 8.00 (s, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.12 - 6.99 (m, 2H), 6.41 (s, 1H), 4.53 - 4.23 (m, 5H), 4.11 (s, 3H), 3.33 - 3.15 (m, 2H), 3.04 - 2.88 (m, 3H), 2.73 - 2.60 (m, 3H), 2.44 - 2.28 (m, 1H), 2.24 - 1.95 (m, 5H), 1.90 - 1.56 (m, 7H), 1.38 - 1.25 (m, 1H), 0.94 (q, J = 10.4 Hz, 2H), 0.77 - 0.65 (m, 1H), 0.59 - 0.46 (m, 2H), 0.40 - 0.28 (m, 1H)

Example 170: 3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-7-[(3,3-difluorocyclobutyl)methyl]-3,3,9-trifluoro-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-4-piperidyl]-7-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (Compound 217a)



Preparation of 6-bromo-1-[(3,3-difluorocyclobutyl)methyl]-7-fluoro-3,1-benzoxazine-2,4-dione

To a solution of 6-bromo-7-fluoro-1*H*-3,1-benzoxazine-2,4-dione (3 g, 11.54 mmol, 1 *equiv.*) in DCM (30 mL) were added PPh_3 (3.33 g, 12.69 mmol, 1.1 *equiv.*), (3,3-difluorocyclobutyl)methanol (1.55 g, 12.69 mmol, 1.1 *equiv.*), and DIAD (2.57 g, 12.69 mmol, 2.46 mL, 1.1 *equiv.*). The mixture was stirred at 25°C for 12 hours. The reaction mixture was quenched by the addition of water (20 mL) and extracted with DCM (90 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (0~100% ethyl acetate/petroleum ether) to give 6-bromo-1-[(3,3-difluorocyclobutyl)methyl]-7-fluoro-3,1-benzoxazine-2,4-dione (2.8 g) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.27 (d, J = 7.2 Hz, 1H), 7.76 (d, J = 10.8 Hz, 1H), 4.19 (d, J = 5.8 Hz, 2H), 2.63 (s, 1H), 1.28 - 1.21 (m, 2H), 1.04 (d, J = 5.6 Hz, 2H)

Preparation of ethyl 6-bromo-1-[(3,3-difluorocyclobutyl)methyl]-7-fluoro-4-hydroxy-2-oxo-quinoline-3-carboxylate

Diethyl propanedioate (2.73 g, 17.03 mmol, 2.59 mL, 2 *equiv.*) in DMA (30 mL) was treated dropwise with t-BuONa (1.64 g, 17.03 mmol, 3 *equiv.*) at 0°C. After 10 minutes, 6-bromo-1-[(3,3-difluorocyclobutyl)methyl]-7-fluoro-3,1-benzoxazine-2,4-dione (3.1 g, 8.51 mmol, 1 *equiv.*) in DMA (30 mL) was added dropwise at 0°C. The resulting mixture was stirred at 100°C for 2 hours. The reaction mixture was quenched by the addition of water (40 mL) and extracted with ethyl acetate (120 mL). The combined organic layers were washed with brine (120 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (0~100% ethyl acetate/petroleum ether) to give ethyl 6-bromo-1-[(3,3-difluorocyclobutyl)methyl]-7-fluoro-4-hydroxy-2-oxo-quinoline-3-carboxylate (2.8 g) as a white solid.

LC-MS (ESI): m/z = 434.1 $[M+H]^+$

Preparation of ethyl 6-bromo-4-chloro-1-[(3,3-difluorocyclobutyl)methyl]-7-fluoro-2-oxo-quinoline-3-carboxylate

A solution of ethyl 6-bromo-1-[(3,3-difluorocyclobutyl)methyl]-7-fluoro-4-hydroxy-2-oxo-quinoline-3-carboxylate (2.2 g, 5.07 mmol, 1 *equiv.*) in DMF (20 mL) was treated with $(COCl)_2$ (1.93 g, 15.20 mmol, 1.33 mL, 3 *equiv.*). The mixture was stirred at 70°C for 0.5 hour. The reaction mixture was quenched by the addition of water (10 mL) and extracted with ethyl acetate (90 mL). The combined organic layers were washed with brine (90 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (0~20% ethyl acetate/petroleum ether) to give ethyl 6-bromo-4-chloro-1-[(3,3-difluorocyclobutyl)methyl]-7-fluoro-2-oxo-quinoline-3-carboxylate (2.2 g) as a white solid.

LC-MS (ESI): m/z = 454.0 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.26 (d, J = 7.2 Hz, 1H), 7.99 (s, 1H), 4.44 (d, J = 5.6 Hz, 2H), 4.37 (q, J = 7.2 Hz, 2H), 2.90 (s, 8H), 2.74 (s, 8H), 2.61 (s, 1H), 1.31 (t, J = 7.2 Hz, 3H), 1.18 (t, J = 7.2 Hz, 4H)

Preparation of 6-bromo-4-[[(1*S*)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-1-[(3,3-difluorocyclobutyl)methyl]-7-fluoro-quinolin-2-one

A solution of ethyl 6-bromo-4-chloro-1-[(3,3-difluorocyclobutyl)methyl]-7-fluoro-2-oxo-quinoline-3-carboxylate (1.2 g, 2.65 mmol, 1 *equiv.*) in NMP (10 mL) was treated with LiCl (56.19 mg, 1.33 mmol, 27.17 μL, 0.5 *equiv.*) and (3*S*)-3-amino-3-cyclopropyl-2,2-difluoro-propan-1-ol (601.08 mg, 3.98 mmol, 1.5 *equiv.*). The mixture was stirred at 180°C for 3 hours. The reaction mixture was quenched by the addition of water (20 mL) and extracted with ethyl acetate (120 mL). The combined organic layers were washed with brine (120 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (0~100% ethyl acetate/petroleum ether) to give 6-bromo-4-[[(1*S*)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-1-[(3,3-difluorocyclobutyl)methyl]-7-fluoro-quinolin-2-one (0.58 g) as a white solid.

LC-MS (ESI): m/z = 495.1 $[M+H]^+$

Preparation of 3,6-dibromo-4-[[(1*S*)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-1-[(3,3-difluorocyclobutyl)methyl]-7-fluoro-quinolin-2-one

A solution of 6-bromo-4-[[(1*S*)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-1-[(3,3-difluorocyclobutyl)methyl]-7-fluoro-quinolin-2-one (0.48 g, 920.69 μmol, 1 *equiv.*) in DMF (5 mL) was treated with NBS (147.48 mg, 828.62 μmol, 0.9 *equiv.*). The mixture was stirred at 0°C for 0.5 hour. The reaction mixture was quenched by the addition of water (10 mL) and extracted with ethyl acetate (90 mL). The combined organic layers were washed with brine (90 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (0~100% ethyl acetate/petroleum ether) to give 3,6-dibromo-4-[[(1*S*)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-1-[(3,3-difluorocyclobutyl)methyl]-7-fluoro-quinolin-2-one (0.43 g) as a white solid.

LC-MS (ESI): m/z = 575.0 $[M+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ = 8.27 (d, *J* = 7.2 Hz, 1H), 7.10 (d, *J* = 10.4 Hz, 1H), 4.89 (d, *J* = 11.6 Hz, 1H), 4.54 - 4.35 (m, 2H), 4.24 - 3.95 (m, 2H), 3.59 - 3.41 (m, 1H), 2.80 - 2.43 (m, 5H), 2.22 - 2.02 (m, 1H), 1.33 - 1.11 (m, 1H), 0.77 - 0.36 (m, 3H), -0.08 (d, *J* = 5.2, 9.6 Hz, 1H)

Preparation of (2*S*)-10-bromo-2-cyclopropyl-7-[(3,3-difluorocyclobutyl)methyl]-3,3,9-trifluoro-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one

A solution of 3,6-dibromo-4-[[(1*S*)-1-cyclopropyl-2,2-difluoro-3-hydroxy-propyl]amino]-1-[(3,3-difluorocyclobutyl)methyl]-7-fluoro-quinolin-2-one (0.43 g, 748.90 μmol, 1 *equiv.*) in THF (5 mL) was treated with *t*-BuOK (84.04 mg, 748.90 μmol, 1 *equiv.*). The mixture was stirred at 70°C for 1 hour. The reaction mixture was quenched by the addition of water (10 mL) and extracted with ethyl acetate (60 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (0~100% ethyl acetate/petroleum ether) to give (2*S*)-10-bromo-2-cyclopropyl-7-[(3,3-difluorocyclobutyl)methyl]-3,3,9-trifluoro-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (0.36 g) as a white solid.

LC-MS (ESI): m/z = 493.0 $[M+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ = 7.74 (d, *J* = 6.8 Hz, 1H), 7.20 - 7.07 (m, 1H), 4.68 (d, *J* = 13.2, 16.4 Hz, 1H), 4.62 - 4.31 (m, 4H), 4.24 (d, *J* = 10.4 Hz, 1H), 3.48 - 3.26 (m, 1H), 2.79 - 2.58 (m, 6H), 1.51 - 1.39 (m, 1H), 0.96 (t, *J* = 5.2, 8.4 Hz, 1H), 0.90 - 0.70 (m, 2H), 0.39 (d, *J* = 4.8, 9.6 Hz, 1H)

Preparation of (2*S*)-10-(benzhydrylideneamino)-2-cyclopropyl-7-[(3,3-difluorocyclobutyl)methyl]-3,3,9-trifluoro-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one

A solution of (2*S*)-10-bromo-2-cyclopropyl-7-[(3,3-difluorocyclobutyl)methyl]-3,3,9-trifluoro-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (0.36 g, 729.83 μmol, 1 *equiv.*) in toluene (4 mL) was treated with $Pd_2(dba)_3$ (66.83 mg, 72.98 μmol, 0.1 *equiv.*), cesium carbonate (594.48 mg, 1.82 mmol, 2.5 *equiv.*), XantPhos (84.46 mg, 145.97 μmol, 0.2 *equiv.*), and diphenylmethanimine (158.72 mg, 875.80 μmol, 146.97 μL, 1.2 *equiv.*). The mixture was stirred at 100°C for 12 hours. The reaction mixture was quenched by the addition of water (10 mL) and extracted with ethyl acetate (60 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (0~100% ethyl acetate/petroleum ether) to give (2*S*)-10-(benzhydrylideneamino)-2-cyclopropyl-7-[(3,3-difluorocyclobutyl)methyl]-3,3,9-trifluoro-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (0.3 g) as a white solid.

LC-MS (ESI): m/z = 594.2 $[M+H]^+$

Preparation of (2*S*)-10-amino-2-cyclopropyl-7-[(3,3-difluorocyclobutyl)methyl]-3,3,9-trifluoro-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one

A solution of (2*S*)-10-(benzhydrylideneamino)-2-cyclopropyl-7-[(3,3-difluorocyclobutyl)methyl]-3,3,9-trifluoro-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (0.3 g, 505.40 μmol, 1 *equiv.*) in DCM (2 mL) was treated with HCl/dioxane (2 M, 2 mL, 7.91 *equiv.*). The mixture was stirred at 25°C for 1 hour. The reaction mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (0~100% ethyl acetate/petroleum ether) to give (2*S*)-10-amino-2-cyclopropyl-7-[(3,3-difluorocyclobutyl)methyl]-3,3,9-trifluoro-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (0.2 g) as a white solid.

LC-MS (ESI): m/z = 430.3 $[M+H]^+$

Preparation of (2*S*)-10-amino-2-cyclopropyl-7-[(3,3-difluorocyclobutyl)methyl]-3,3,9-trifluoro-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one

(2*S*)-10-amino-2-cyclopropyl-7-[(3,3-difluorocyclobutyl)methyl]-3,3,9-trifluoro-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one was re-purified by SFC (column: DAICEL CHIRALPAK AD(250 mm × 30 mm,10 um);mobile phase: [CO_2-i-PrOH(0.1%NH_3H_2O)];B%:30%, isocratic elution mode) to give (2*S*)-10-amino-2-cyclopropyl-7-[(3,3-difluorocyclobutyl)methyl]-3,3,9-trifluoro-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (0.1 g) as a white solid.

LC-MS (ESI): m/z = 430.3 $[M+H]^+$

SFC: t_R = 1.481 min

Preparation of (2*S*)-2-cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-7-[(3,3-difluorocyclobutyl)methyl]-3,3,9-trifluoro-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one

A solution of (2*S*)-10-amino-2-cyclopropyl-7-[(3,3-difluorocyclobutyl)methyl]-3,3,9-trifluoro-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (0.1 g, 232.89 μmol, 1 *equiv.*) in DMF (1 mL) was treated with DIPEA (90.30 mg, 698.68 μmol, 121.70 μL, 3 *equiv.*) and 2,4,5-trichloropyrimidine (85.44 mg, 465.78 μmol, 2 *equiv.*). The mixture was stirred at 80°C for 12 hours. The reaction mixture was quenched by the addition of water (5 mL) and extracted with ethyl acetate (60 mL). The combined organic layers were washed with brine (60 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (0~100% ethyl acetate/petroleum ether) to give (2*S*)-2-cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-7-[(3,3-

difluorocyclobutyl)methyl]-3,3,9-trifluoro-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (0.1 g) as a red solid.

LC-MS (ESI): m/z = 576.1 $[M+H]^+$

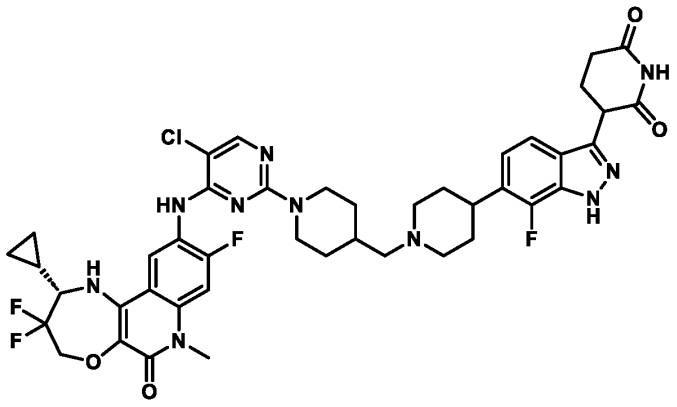
Preparation of 3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-7-[(3,3-difluorocyclobutyl)methyl]-3,3,9-trifluoro-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-4-piperidyl]-7-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione

A solution of 3-(7-fluoro-1-methyl-6-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (76.61 mg, 173.51 μmol, 1 *equiv.*) and (2*S*)-2-cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-7-[(3,3-difluorocyclobutyl)methyl]-3,3,9-trifluoro-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (0.1 g, 173.51 μmol, 1 *equiv.*) in DMSO (1 mL) was treated with CsF (52.71 mg, 347.01 μmol, 2 *equiv.*) and DIPEA (67.27 mg, 520.52 μmol, 90.67 μL, 3 *equiv.*). The mixture was stirred at 80°C for 12 hours. The reaction mixture was quenched by the addition of water (10 mL) and extracted with ethyl acetate (90 mL). The combined organic layers were washed with brine (90 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give 3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-7-[(3,3-difluorocyclobutyl)methyl]-3,3,9-trifluoro-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-4-piperidyl]-7-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (82.96 mg) as a pink solid.

LC-MS (ESI): m/z = 981.5 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.91 (s, 1H), 8.85 (s, 1H), 8.20 (d, J = 1.2 Hz, 1H), 8.19 (s, 1H), 8.02 (s, 1H), 7.60 (d, J = 12.4 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.10 - 6.98 (m, 1H), 6.44 (d, J = 2.4 Hz, 1H), 4.56 - 4.18 (m, 7H), 4.11 (s, 3H), 2.98 - 2.87 (m, 3H), 2.78 - 2.54 (m, 9H), 2.42 - 2.26 (m, 2H), 2.19 - 2.07 (m, 3H), 2.06 - 1.94 (m, 2H), 1.85 - 1.60 (m, 7H), 1.36 - 1.21 (m, 1H), 1.00 - 0.86 (m, 2H), 0.71 (d, J = 5.6 Hz, 1H), 0.52 (d, J = 5.6 Hz, 2H), 0.43 - 0.25 (m, 1H)

Example 171: 3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-4-piperidyl]-7-fluoro-1*H*-indazol-3-yl]piperidine-2,6-dione (Compound 214a)



Preparation of 6-bromo-7-fluoro-3-iodo-1*H*-indazole

To a solution of 6-bromo-7-fluoro-1*H*-indazole (9 g, 41.86 mmol, 1 *equiv.*) in DMF (90 mL) were added I_2 (15.94 g, 62.78 mmol, 12.65 mL, 1.5 *equiv.*) and KOH (3.52 g, 62.78 mmol, 1.5 *equiv.*). The mixture was stirred at 25°C for 3 hours. The reaction mixture was partitioned between water (200 mL) and ethyl acetate (600 mL). The organic phase was separated, washed with brine (600 mL) and sodium sulfite, dried over sodium sulfate, filtered, and concentrated under reduced pressure to give 6-bromo-7-fluoro-3-iodo-1*H*-indazole (12 g) as a yellow solid.

LC-MS (ESI): m/z = 340.7 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 14.24 (br s, 1H), 7.37 (dd, J = 5.6, 8.5 Hz, 1H), 7.22 (d, J = 8.8 Hz, 1H)

Preparation of 6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1*H*-indazole

A solution of 6-bromo-7-fluoro-3-iodo-1*H*-indazole (1 g, 2.93 mmol, 1 *equiv.*) in water (4 mL) and dioxane (16 mL) was treated with potassium carbonate (1.22 g, 8.80 mmol, 3 *equiv.*), 2,6-dibenzyloxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (1.10 g, 2.64 mmol, 0.9 *equiv.*), and Pd(dppf)Cl_2 (107.31 mg, 146.66 μmol, 0.05 *equiv.*). The mixture was stirred at 95°C for 5 hours. The reaction mixture was partitioned between water (20 mL) and ethyl acetate (60 mL). The organic phase was separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (0~15% ethyl acetate/petroleum ether) to give 6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1*H*-indazole (1.1 g) as a brown oil.

LC-MS (ESI): m/z = 506.1 $[M+H]^+$

Preparation of *tert*-butyl 4-[3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1*H*-indazol-6-yl]-3,6-dihydro-2*H*-pyridine-1-carboxylate

A mixture of 6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1*H*-indazole (1.1 g, 2.18 mmol, 1 *equiv.*), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylate (809.27 mg, 2.62 mmol, 1.2 *equiv.*), cesium carbonate (1.78 g, 5.45 mmol, 2.5 *equiv.*), $Pd(dppf)Cl_2$ (159.59 mg, 218.10 μmol, 0.1 *equiv.*), and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylate (809.27 mg, 2.62 mmol, 1.2 *equiv.*) in water (4 mL) and dioxane (16 mL) was degassed and purged with N_2 three times. The mixture was stirred at 95°C for 2 hours under a N_2 atmosphere. The reaction mixture was partitioned between water (10 mL) and ethyl acetate (30 mL). The combined organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (0~20% ethyl acetate/petroleum ether) to give *tert*-butyl 4-[3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1*H*-indazol-6-yl]-3,6-dihydro-2*H*-pyridine-1-carboxylate (1.5 g) as a yellow oil.

LC-MS (ESI): m/z = 607.3 $[M+H]^+$

Preparation of *tert*-butyl 4-[3-(2,6-dioxo-3-piperidyl)-7-fluoro-1*H*-indazol-6-yl]piperidine-1-carboxylate

To a solution of *tert*-butyl 4-[3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1*H*-indazol-6-yl]-3,6-dihydro-2*H*-pyridine-1-carboxylate (1.5 g, 2.47 mmol, 1 *equiv.*) in CF_3CH_2OH (20 mL) were added Pd on carbon (789.36 mg, 741.74 μmol, 10% purity, 0.3 *equiv.*) and $Pd(OH)_2$ on carbon (520.83 mg, 741.74 μmol, 20% purity, 0.3 *equiv.*) under a N_2 atmosphere. The suspension was degassed and purged with H_2 three times. The mixture was stirred under H_2 (15 Psi) at 25°C for 16 hours. The reaction mixture was filtered, and the filtrate was concentrated to give *tert*-butyl 4-[3-(2,6-dioxo-3-piperidyl)-7-fluoro-1*H*-indazol-6-yl]piperidine-1-carboxylate (0.9 g) as a brown solid crude.

LC-MS (ESI): m/z = 375.1 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 13.34 (br d, J = 1.2 Hz, 1H), 10.90 (s, 1H), 7.57 - 7.40 (m, 1H), 7.05 (dd, J = 6.0, 8.4 Hz, 1H), 6.10 - 5.98 (m, 1H), 4.10 - 3.97 (m, 5H), 3.63 - 3.53 (m, 1H), 2.99 - 2.78 (m, 2H), 2.39 - 2.29 (m, 2H), 1.80 - 1.57 (m, 3H), 1.45 - 1.42 (m, 9H)

Preparation of 3-[7-fluoro-6-(4-piperidyl)-1*H*-indazol-3-yl]piperidine-2,6-dione

To a solution of *tert*-butyl 4-[3-(2,6-dioxo-3-piperidyl)-7-fluoro-1*H*-indazol-6-yl]piperidine-1-carboxylate (0.9 g, 2.09 mmol, 1 *equiv.*) in HCl/dioxane (10 mL), the mixture

was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give 3-[7-fluoro-6-(4-piperidyl)-1*H*-indazol-3-yl]piperidine-2,6-dione (0.65 g) as a brown solid crude.

LC-MS (ESI): m/z = 331.1 $[M+H]^+$

Preparation of *tert*-butyl 4-[[4-[3-(2,6-dioxo-3-piperidyl)-7-fluoro-1*H*-indazol-6-yl]-1-piperidyl]methyl]piperidine-1-carboxylate

To a solution of 3-[7-fluoro-6-(4-piperidyl)-1*H*-indazol-3-yl]piperidine-2,6-dione (0.6 g, 1.82 mmol, 1 *equiv.*) in DCM (10 mL), AcOH (10.91 mg, 181.62 μmol, 10.40 μL, 0.1 *equiv.*) and *tert*-butyl 4-formylpiperidine-1-carboxylate (387.35 mg, 1.82 mmol, 1 *equiv.*) were added. $NaBH(OAc)_3$ (577.40 mg, 2.72 mmol, 1.5 *equiv.*) was added after 0.5 hours. The mixture was stirred at 25 °C for 1.5 hours. The reaction mixture was partitioned between water (10 mL) and DCM (30 mL). The organic phase was separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (0~5% DCM/MeOH) to give *tert*-butyl 4-[[4-[3-(2,6-dioxo-3-piperidyl)-7-fluoro-1*H*-indazol-6-yl]-1-piperidyl]methyl]piperidine-1-carboxylate (0.7 g) as a brown solid.

LC-MS (ESI): m/z = 528.2 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ = 13.45 - 13.17 (m, 1H), 10.99 - 10.76 (m, 1H), 7.69 - 7.39 (m, 1H), 7.14 - 6.97 (m, 1H), 3.99 - 3.80 (m, 3H), 3.26 - 3.15 (m, 3H), 2.75 - 2.57 (m, 4H), 2.43 - 2.23 (m, 2H), 2.22 - 2.05 (m, 1H), 1.98 - 1.88 (m, 3H), 1.84 - 1.56 (m, 5H), 1.54 - 1.46 (m, 1H), 1.39 (s, 13H)

Preparation of 3-[7-fluoro-6-[1-(4-piperidylmethyl)-4-piperidyl]-1*H*-indazol-3-yl]piperidine-2,6-dione

A solution of *tert*-butyl 4-[[4-[3-(2,6-dioxo-3-piperidyl)-7-fluoro-1*H*-indazol-6-yl]-1-piperidyl]methyl]piperidine1-carboxylate (300 mg, 568.58 μmol, 1 *equiv.*) in HCl/dioxane (5 mL) was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give 3-[7-fluoro-6-[1-(4-piperidylmethyl)-4-piperidyl]-1*H*-indazol-3-yl]piperidine-2,6-dione (200 mg) as a black solid crude.

LC-MS (ESI): m/z = 428.2 $[M+H]^+$

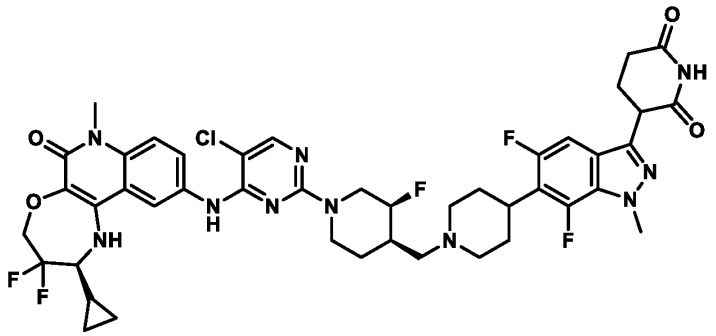
Preparation of 3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-4-piperidyl]-7-fluoro-1*H*-indazol-3-yl]piperidine-2,6-dione

To a solution of 3-[7-fluoro-6-[1-(4-piperidylmethyl)-4-piperidyl]-1*H*-indazol-3-yl]piperidine-2,6-dione (200 mg, 467.82 μmol, 1 *equiv.*) in DMSO (3 mL), TEA (189.35 mg, 1.87 mmol, 260.46 μL, 4 *equiv.*) and (2*S*)-2-cyclopropyl-10-[(2,5-dichloropyrimidin-4-yl)amino]-3,3,9-trifluoro-7-methyl-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-6-one (159.24 mg, 327.47 μmol, 0.7 *equiv.*) were added. The mixture was stirred at 100 °C for 2 hours. The reaction mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give 3-[6-[1-[[1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-4-piperidyl]methyl]-4-piperidyl]-7-fluoro-1*H*-indazol-3-yl]piperidine-2,6-dione (24.02 mg) as a white solid.

LC-MS (ESI): m/z = 877.4 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 13.27 (s, 1H), 10.87 (s, 1H), 8.78 (s, 1H), 8.25 (s, 1H), 8.19 - 8.09 (m, 1H), 7.97 (s, 1H), 7.49 - 7.31 (m, 2H), 7.00 (dd, *J* = 5.6, 8.6 Hz, 1H), 6.41 (d, *J* = 1.6 Hz, 1H), 4.54 - 4.16 (m, 5H), 3.53 - 3.48 (m, 3H), 2.97 - 2.81 (m, 3H), 2.72 - 2.59 (m, 3H), 2.56 (d, *J* = 2.8 Hz, 1H), 2.40 - 2.26 (m, 2H), 2.22 - 2.05 (m, 3H), 2.00 - 1.89 (m, 2H), 1.84 - 1.51 (m, 7H), 1.33 - 1.19 (m, 1H), 0.98 - 0.81 (m, 2H), 0.72 - 0.60 (m, 1H), 0.54 - 0.40 (m, 2H), 0.33 - 0.22 (m, 1H)

Example 172: 3-[6-[1-[[(3*S*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (Compound 220b)



Preparation of *tert*-butyl 4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2Hpyridin-1-yl]methyl]-3-fluoro-piperidine-1-carboxylate

To a solution of *tert*-butyl 3-fluoro-4-formyl-piperidine-1-carboxylate (858.78 mg, 3.71 mmol, 1 *equiv.*) and 3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)indazole (2 g, 3.71 mmol, 1 *equiv.*) in DMSO (20 mL), AcOH (22.30 mg, 371.34 μmol, 21.26 μL, 0.1 *equiv.*), and $NaBH(OAc)_3$ (1.18 g, 5.57 mmol, 1.5 *equiv.*) were added. The mixture was stirred at 25 °C for 1 hour. The reaction mixture was quenched by the addition of water (30 mL) and then extracted with DCM/MeOH (10:1, 60 mL in total). The combined organic layers were washed with sodium chloride solution (60 mL in total), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by column chromatography (DCM/MeOH = 1/0 to 5/1) to give *tert*-butyl 4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2Hpyridin-1-yl]methyl]-3-fluoro-piperidine-1-carboxylate (2 g) as a yellow oil.

LC-MS (ESI): m/z = 754.3 $[M+H]^+$

Preparation of *tert*-butyl (3*S*,4*R*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3-fluoro-piperidine-1-carboxylate and *tert*-butyl (3*R*,4*S*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3-fluoro-piperidine-1-carboxylate

The isomers of *tert*-butyl 4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*pyridin-1-yl]methyl]-3-fluoro-piperidine-1-carboxylate were separated by SFC to afford *tert*-butyl (3*S*,4*R*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3-fluoro-piperidine-1-carboxylate (2 g) (**Peak 1**) and *tert*-butyl (3*R*,4*S*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3-fluoro-piperidine-1-carboxylate (2.8 g) (**Peak 2**).

Peak 1:

LC-MS (ESI): m/z = 754.3 $[M+H]^+$

Peak 2:

LC-MS (ESI): m/z = 754.3 $[M+H]^+$

Preparation of *tert*-butyl (3*S*,4*R*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5,7-difluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-fluoro-piperidine-1-carboxylate

To a solution of *tert*-butyl (3*S*,4*R*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3-fluoro-piperidine-1-

carboxylate (2 g, 2.65 mmol, 1 *equiv.*) in CF_3CH_2OH (40 mL) under a N_2 atmosphere, Pd on carbon (847.01 mg, 795.91 μmol, 10 wt%, 0.3 *equiv.*) and $Pd(OH)_2$ on carbon (558.87 mg, 795.91 μmol, 20 wt%, 0.3 *equiv.*) were added. The suspension was degassed and purged with H_2 three times. The mixture was stirred under H_2 (15 psi) at 25 °C for 12 hours. The reaction mixture was filtered and concentrated under reduced pressure to give *tert*-butyl (3*S*,4*R*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5,7-difluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-fluoro-piperidine-1-carboxylate (1.5 g) as a yellow solid.

LC-MS (ESI): m/z = 578.3 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.91 (s, 1H), 7.41 (d, J = 10.4 Hz, 1H), 5.75 (s, 1H), 4.89 - 4.63 (m, 1H), 4.10 (s, 3H), 3.10 - 2.87 (m, 4H), 2.78 - 2.58 (m, 3H), 2.44 - 2.29 (m, 2H), 2.24 - 1.85 (m, 8H), 1.69 (d, J = 8.8 Hz, 2H), 1.49 (d, J = 11.2 Hz, 1H), 1.39 (s, 9H), 1.34 - 1.29 (m, 1H), 1.34 - 1.21 (m, 1H)

Preparation of 3-[5,7-difluoro-6-[1-[[(3*S*,4*R*)-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione

A solution of *tert*-butyl (3*S*,4*R*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5,7-difluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-fluoro-piperidine-1-carboxylate (1.5 g, 2.60 mmol, 1 *equiv.*) in HCl/dioxane (15 mL) was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give 3-[5,7-difluoro-6-[1-[[(3*S*,4*R*)-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (1.3 g) as a yellow solid.

LC-MS (ESI): m/z = 478.2 $[M+H]^+$

Preparation of 3-[6-[1-[[(3*S*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione

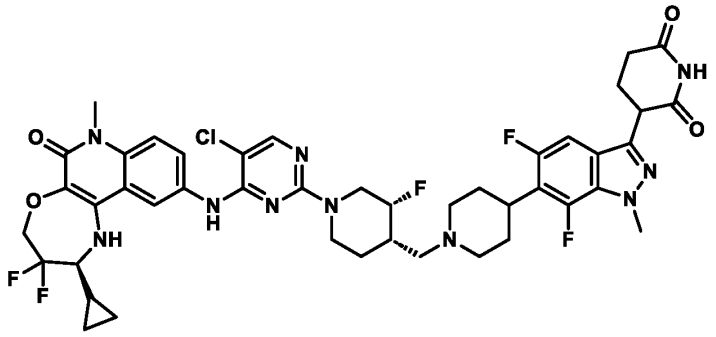
To a solution of 3-[5,7-difluoro-6-[1-[[(3*S*,4*R*)-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (1.3 g, 2.72 mmol, 1 *equiv.*) in DMSO (15 mL), TEA (826.43 mg, 8.17 mmol, 1.14 mL, 3 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (892.40 mg, 1.91 mmol, 0.7 *equiv.*) were added. The mixture was stirred at 100 °C for 1 hour. The reaction mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give 3-[6-[1-[[(3*S*,4*R*)-1-[5-chloro-4-

[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (1.18 g) as a pink solid.

LC-MS (ESI): m/z = 455.3 $[M/2+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.01 - 10.85 (m, 1H), 8.83 (s, 1H), 8.31 (s, 2H), 8.16 (s, 1H), 8.09 - 8.00 (m, 1H), 7.75 (dd, J = 1.6, 8.8 Hz, 1H), 7.54 - 7.32 (m, 2H), 6.23 - 5.68 (m, 1H), 4.97 - 4.75 (m, 2H), 4.67 - 4.53 (m, 1H), 4.49 - 4.27 (m, 3H), 4.11 (s, 3H), 3.58 (s, 3H), 3.30 - 3.14 (m, 2H), 3.07 - 2.98 (m, 2H), 2.94 - 2.87 (m, 1H), 2.84 - 2.75 (m, 1H), 2.44 - 2.31 (m, 3H), 2.17 - 1.90 (m, 7H), 1.68 (d, J = 10.8 Hz, 2H), 1.53 (d, J = 11.2 Hz, 1H), 1.43 - 1.32 (m, 2H), 0.76 - 0.67 (m, 1H), 0.59 - 0.46 (m, 2H), 0.41 - 0.26 (m, 1H)

Example 173: 3-[6-[1-[[(3*R*,4*S*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (Compound 220a)



Preparation of *tert*-butyl (3*R*,4*S*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5,7-difluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-fluoro-piperidine-1-carboxylate

To a solution of *tert*-butyl (3*R*,4*S*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3-fluoro-piperidine-1-carboxylate (2.5 g, 3.32 mmol, 1 *equiv.*) in CF_3CH_2OH (50 mL) under a N_2 atmosphere, Pd on carbon (1.06 g, 994.89 μmol, 10 wt%, 0.3 *equiv.*) and $Pd(OH)_2$ on carbon (698.59 mg, 994.89 μmol, 20 wt%, 0.3 *equiv.*) were added. The suspension was degassed and purged with H_2 three times. The mixture was stirred under H_2 (15 psi) at 25 °C for 12 hours. The reaction mixture was filtered and concentrated under reduced pressure to give *tert*-butyl (3*R*,4*S*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5,7-difluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-fluoro-piperidine-1-carboxylate (2 g) as a yellow solid.

LC-MS (ESI): m/z = 578.3 $[M+H]^+$

Preparation of 3-[5,7-difluoro-6-[1-[[(3*R*,4*S*)-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione

A solution of *tert*-butyl (3*R*,4*S*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5,7-difluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3-fluoro-piperidine-1-carboxylate (2 g, 3.46 mmol, 1 *equiv.*) in HCl/dioxane (20 mL) was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give 3-[5,7-difluoro-6-[1-[[(3*R*,4*S*)-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (1.7 g) as a yellow solid.

LC-MS (ESI): m/z = 478.2 $[M+H]^+$

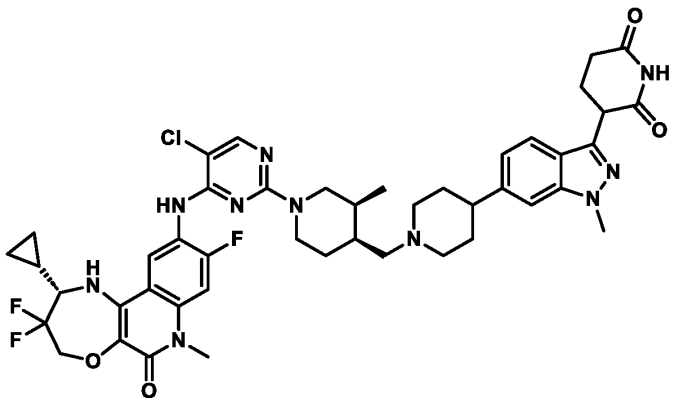
Preparation of 3-[6-[1-[[(3*R*,4*S*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione

To a solution of 3-[5,7-difluoro-6-[1-[[(3*R*,4*S*)-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indazol-3-yl]piperidine-2,6-dione (300 mg, 628.24 μmol, 1 *equiv.*) in DMSO (5 mL), TEA (254.29 mg, 2.51 mmol, 349.77 μL, 4 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (205.94 mg, 439.77 μmol, 0.7 *equiv.*) were added. The mixture was stirred at 100 °C for 1 hour. The reaction mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give 3-[6-[1-[[(3*R*,4*S*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-fluoro-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (114.74 mg) as a pink solid.

LC-MS (ESI): m/z = 909.1 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.91 (s, 1H), 8.81 (s, 1H), 8.31 (s, 1H), 8.17 (s, 1H), 8.03 (s, 1H), 7.82 - 7.70 (m, 1H), 7.55 - 7.37 (m, 2H), 6.28 - 6.14 (m, 1H), 4.91 - 4.70 (m, 2H), 4.61 - 4.24 (m, 4H), 4.11 (s, 3H), 3.58 (s, 3H), 3.03 (d, J = 13.6 Hz, 3H), 2.96 - 2.87 (m, 2H), 2.86 - 2.76 (m, 1H), 2.69 - 2.63 (m, 1H), 2.46 - 2.29 (m, 3H), 2.19 - 1.89 (m, 7H), 1.79 - 1.61 (m, 2H), 1.59 - 1.47 (m, 1H), 1.43 - 1.26 (m, 2H), 0.79 - 0.62 (m, 1H), 0.59 - 0.46 (m, 2H), 0.43 - 0.28 (m, 1H)

Example 174. 3-(6-(1-(((3*S*,4*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 105b)



Preparation of 3-(6-(1-(((3*S*,4*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

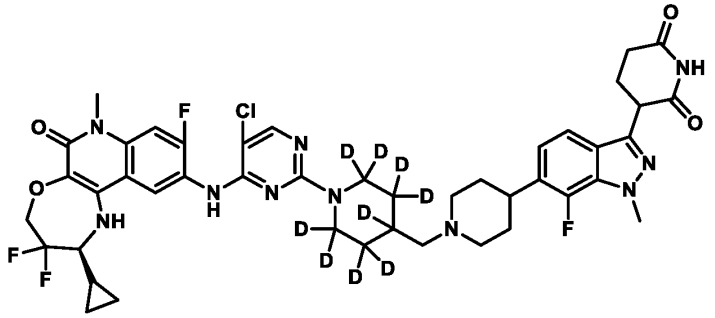
To a solution of (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3,9-trifluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (860 mg, 1.00 *equiv*., 1.77 mmol) in DMSO (6.0 mL) was added 3-(1-methyl-6-(1-(((3*S*,4*S*)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione (See Table P6) (967 mg, 1 *equiv*., 1.77 mmol) and DIPEA (1.14 g, 1.54 mL, 5.0 *equiv*., 8.84 mmol). The reaction mixture was stirred at 90 °C for 17 hours. The reaction mixture was diluted with DMSO to a total volume of 10.0 mL, filtered, and purified by reverse phase HPLC to give 3-(6-(1-(((3*S*,4*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (885 mg) as a light pink solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 10.88 (s, 1H), 8.80 (s, 1H), 8.19 (d, J = 8.1 Hz, 1H), 7.98 (s, 1H), 7.60 (d, J = 8.5 Hz, 1H), 7.42 (t, J = 6.3 Hz, 2H), 7.02 (d, J = 8.5 Hz, 1H), 6.47 (br d, J = 2.0 Hz, 1H), 4.52 - 4.17 (m, 4H), 3.96 (s, 3H), 3.55 (s, 3H), 3.29 - 3.17 (m, 2H), 3.06 - 2.85 (m, 3H), 2.82 - 2.72 (m, 1H), 2.73 - 2.55 (m, 3H), 2.42 - 2.28 (m, 1H), 2.25 -

2.11 (m, 3H), 2.09 - 1.96 (m, 2H), 1.94 - 1.67 (m, 6H), 1.42 - 1.20 (m, 3H), 0.78 - 0.60 (m, 4H), 0.51 (br t, J = 5.8 Hz, 2H), 0.37 - 0.26 (m, 1H).

LC-MS (ESI): m/z = 887.6 $[M+H]^+$

Example 175. 3-(6-(1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl-2,2,3,3,4,5,5,6,6-d9)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 213a)



Preparation of *tert*-butyl 4-(4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidine-1-carbonyl)piperidine-1-carboxylate-2,2,3,3,4,5,5,6,6-d9

HATU (184 mg, 1.08 *equiv.*, 483 μmol) was added to a solution of 1-(tert-butoxycarbonyl)piperidine-4-carboxylic-2,2,3,3,4,5,5,6,6-d9 acid (117 mg, 1.1 *equiv.*, 492 μmol), 3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-6-(piperidin-4-yl)-1*H*-indazole, HCl (0.250 g, 1 *equiv.*, 447 μmol), and DIPEA (231 mg, 312 μL, 4 *equiv.*, 1.79 mmol) in DMF (2.24 mL). The reaction mixture was stirred at ambient temperature for 18 hours. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was removed, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over sodium sulfate, and filtered. The filtrate was taken, and volatile organics were removed under reduced pressure to give a brown oil. The solid was taken up in DCM and purified by normal phase ISCO to give a white solid *tert*-butyl 4-(4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidine-1-carbonyl)piperidine-1-carboxylate-2,2,3,3,4,5,5,6,6-d9 (286 mg).

^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ (ppm) = 7.87 (d, J = 8.0 Hz, 1H), 7.48 - 7.26 (m, 11H), 6.79 (dd, J = 5.8, 8.5 Hz, 1H), 6.56 - 6.47 (m, 1H), 5.46 (d, J = 3.8 Hz, 2H), 5.40 (s, 2H), 4.86 (br d, J = 12.8 Hz, 1H), 4.27 (s, 3H), 4.07 (br d, J = 13.1 Hz, 1H), 3.35 - 3.13 (m, 2H), 2.77 - 2.61 (m, 1H), 2.00 - 1.84 (m, 2H), 1.81 - 1.71 (m, 2H), 1.48 (s, 9H).

LC-MS (ESI): m/z = 743 $[M+H]^+$

Preparation of *tert*-butyl 4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate-2,2,3,3,4,5,5,6,6-d9

Borane dimethylsulfide (351 mg, 401 μL, 12 *equiv.*, 4.62 mmol) was added to a solution of *tert*-butyl 4-(4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidine-1-carbonyl)piperidine-1-carboxylate-2,2,3,3,4,5,5,6,6-d9 (0.286 g, 1 *equiv.*, 385 μmol) in THF (7.70 mL). The reaction mixture was stirred at room temperature for 16 hours. The reaction was quenched by the slow addition of methanol (5 mL). The reaction mixture was warmed to 60 °C for 1 hour. Celite was added to the reaction mixture and concentrated *in vacuo*. The solid was taken up in DCM and purified by normal phase ISCO to give a white solid *tert*-butyl 4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate-2,2,3,3,4,5,5,6,6-d9 (142.3 mg) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ (ppm) = 7.87 (d, J = 8.0 Hz, 1H), 7.49 - 7.42 (m, 2H), 7.42 - 7.36 (m, 3H), 7.36 - 7.26 (m, 6H), 6.90 (dd, J = 5.8, 8.5 Hz, 1H), 6.52 (d, J = 8.1 Hz, 1H), 5.47 (s, 2H), 5.41 (s, 2H), 4.27 (s, 3H), 3.05 (br s, 3H), 2.27 (br s, 2H), 2.13 (br d, J = 11.3 Hz, 2H), 1.92 (br d, J = 11.0 Hz, 2H), 1.86 - 1.76 (m, 2H), 1.48 (s, 9H).

LC-MS (ESI): m/z = 729 $[M+H]^+$

Preparation of *tert*-butyl 4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate-2,2,3,3,4,5,5,6,6-d9

H_2 gas (1 *equiv.*, 1.434 mmol) was bubbled through a solution of *tert*-butyl 4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate-2,2,3,3,4,5,5,6,6-d9 (1.045 g, 1 *equiv.*, 1.434 mmol) and $Pd(OH)_2$ on carbon (201.3 mg, 1 *equiv.*, 1.434 mmol) in THF (49.86 mL) and DMF (7.479 mL) for 2 minutes. The reaction mixture was stirred at 60 °C for 20 hours. The reaction mixture was filtered through celite and concentrated *in vacuo*. The crude was then resuspended in ethyl acetate, washed with H_2O, brine, dried over sodium sulfate, and concentrated *in vacuo*. The solid was taken up in DMSO and purified by reverse phase HPLC to give *tert*-butyl 4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate-2,2,3,3,4,5,5,6,6-d9, formic Acid (270.3 mg) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 1.47 (s, 9 H) 1.89 (br d, *J*=13.13 Hz, 2 H) 2.21 (q, *J*=12.55 Hz, 2 H) 2.33 - 2.43 (m, 1 H) 2.44 - 2.57 (m, 3 H) 2.57 - 2.63 (m, 2 H) 2.64 - 2.75 (m, 1 H) 2.99 (ddd, *J*=17.67, 7.91, 4.94 Hz, 1 H) 3.09 - 3.21 (m, 1 H) 3.44 (br d, *J*=11.63 Hz, 2 H) 4.19 (s, 3 H) 4.25 (dd, *J*=7.69, 5.19 Hz, 1 H) 7.03 (dd, *J*=8.44, 5.69 Hz, 1 H) 7.40 (d, *J*=8.50 Hz, 1 H) 7.96 (br s, 1 H) 8.40 (s, 1 H).

LC-MS (ESI): m/z = 551.3 $[M+H]^+$

Preparation of 3-(7-fluoro-1-methyl-6-(1-((piperidin-4-yl-2,2,3,3,4,5,5,6,6-d9)methyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione, HCl, HCl

HCl (4.0 M in 1,4-dioxane) (179 mg, 1.23 mL, 4 M, 10 *equiv.*, 4.90 mmol) was added to a solution of *tert*-butyl 4-((4-(3-(2,6-dioxopiperidin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate-2,2,3,3,4,5,5,6,6-d9 (0.270 g, 1 *equiv.*, 490 μmol) in DCM (4.90 mL) at room temperature. The mixture was stirred for 18 hours. The reaction mixture was concentrated *in vacuo* to afford 3-(7-fluoro-1-methyl-6-(1-((piperidin-4-yl-2,2,3,3,4,5,5,6,6-d9)methyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione, HCl, HCl (289.1 mg) as a white solid, which was carried forward without further purification.

LC-MS (ESI): m/z = 451.4 $[M+H]^+$

Preparation of 3-(6-(1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl-2,2,3,3,4,5,5,6,6-d9)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

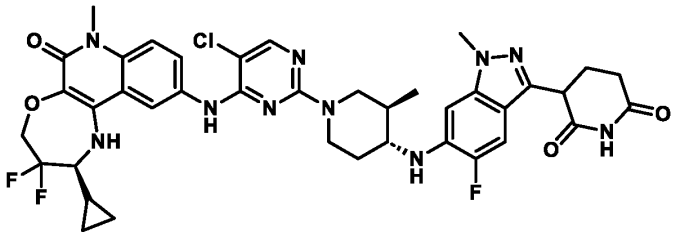
DIPEA (285.5 mg, 385 μL, 4 *equiv.*, 2.209 mmol) was added to a solution of 3-(7-fluoro-1-methyl-6-(1-((piperidin-4-yl-2,2,3,3,4,5,5,6,6-d9)methyl)piperidin-4-yl)-1*H*-indazol-3-yl)piperidine-2,6-dione, HCl, HCl (0.2891 g, 1 *equiv.*, 552.2 μmol), (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3,9-trifluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (282.0 mg, 1.05 *equiv.*, 579.8 μmol), and CsF (251.6 mg, 3 *equiv.*, 1.657 mmol) in DMSO (6.903 mL). The mixture was stirred at 85 °C for 16 hours. The reaction mixture was concentrated *in vacuo* followed by the addition of AcOH (0.05 mL). The solid was taken up in DMSO and purified by reverse phase HPLC to give 3-(6-(1-((1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)piperidin-4-yl-2,2,3,3,4,5,5,6,6-

d9)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (0.276 g) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.28 - 0.38 (m, 1 H) 0.45 - 0.58 (m, 2 H) 0.67 - 0.75 (m, 1 H) 1.26 - 1.38 (m, 1 H) 1.65 - 1.85 (m, 4 H) 2.00 (br d, J=2.75 Hz, 2 H) 2.07 - 2.22 (m, 3 H) 2.32 - 2.44 (m, 1 H) 2.55 - 2.76 (m, 2 H) 2.94 (br s, 3 H) 3.18 - 3.29 (m, 1 H) 3.55 (s, 3 H) 4.11 (s, 3 H) 4.29 - 4.52 (m, 3 H) 6.44 (br d, J=2.88 Hz, 1 H) 7.05 (dd, J=8.32, 5.82 Hz, 1 H) 7.37 - 7.52 (m, 2 H) 8.01 (s, 1 H) 8.20 (d, J=8.00 Hz, 1 H) 8.80 (s, 1 H) 10.90 (s, 1 H).

LC-MS (ESI): m/z = 450.8 $[M+H]^+/2$

Example 176. 3-[6-[[(3*R*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]amino]-5-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (Compound 229a)



Preparation of *tert*-butyl (3*R*,4*R*)-4-[[3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazol-6-yl]amino]-3-methylpiperidine-1-carboxylate

A mixture of *tert*-butyl (3*R*,4*R*)-4-amino-3-methyl-piperidine-1-carboxylate (248.05 mg, 1.16 mmol, 1.2 *equiv.*), 6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazole (0.5 g, 964.55 μmol, 1 *equiv.*), BINAP (120.12 mg, 192.91 μmol, 0.2 *equiv.*), t-BuONa (231.73 mg, 2.41 mmol, 2.5 *equiv.*), and $Pd_2(dba)_3$ (88.33 mg, 96.46 μmol, 0.1 *equiv.*) in dioxane (6 mL) was degassed and purged with N_2 three times. The mixture was stirred at 100 °C for 2 hours under a N_2 atmosphere. The reaction mixture was quenched by the addition of water (10 mL) and extracted with ethyl acetate (30 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by column chromatography (petroleum ether/ethyl acetate = 5/1 to 2/1) to give *tert*-butyl (3*R*,4*R*)-4-[[3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazol-6-yl]amino]-3-methylpiperidine-1-carboxylate (0.6 g) was obtained as a yellow oil.

LC-MS (ESI): m/z = 652.4 $[M+H]^+$

Preparation of *tert*-butyl (3*R*,4*R*)-4-[[3-(2,6-dioxo-3-piperidyl)-5-fluoro-1-methyl-indazol-6-yl]amino]-3-methylpiperidine-1-carboxylate

To a solution of *tert*-butyl (3*R*,4*R*)-4-[[3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazol-6-yl]amino]-3-methylpiperidine-1-carboxylate (613.20 mg, 940.82 μmol, 1 *equiv.*) in dioxane (10 mL) and DMF (0.5 mL) was added Pd on carbon (200.24 mg, 188.16 μmol, 10% purity, 0.2 *equiv.*) under a N_2 atmosphere. The suspension was degassed and purged with H_2 three times. The mixture was stirred under H_2 (20 psi) at 40 °C for 12 hours. The reaction mixture was filtered and concentrated under reduced pressure to give *tert*-butyl (3*R*,4*R*)-4-[[3-(2,6-dioxo-3-piperidyl)-5-fluoro-1-methyl-indazol-6-yl]amino]-3-methylpiperidine-1-carboxylate (0.44 g, crude) was obtained as a yellow oil.

LC-MS (ESI): m/z = 474.3 $[M+H]^+$

Preparation of 3-[5-fluoro-1-methyl-6-[[(3*R*,4*R*)-3-methyl-4-piperidyl]amino]indazol-3-yl]piperidine-2,6-dione

A solution of *tert*-butyl (3*R*,4*R*)-4-[[3-(2,6-dioxo-3-piperidyl)-5-fluoro-1-methyl-indazol-6-yl]amino]-3-methylpiperidine-1-carboxylate (0.4 g, 844.70 μmol, 1 *equiv.*) in DCM (2 mL) and HCl/dioxane (2 mL) was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give 3-[5-fluoro-1-methyl-6-[[(3*R*,4*R*)-3-methyl-4-piperidyl]amino]indazol-3-yl]piperidine-2,6-dione (0.4 g, crude) was obtained as a brown solid.

LC-MS (ESI): m/z = 374.1 $[M+H]^+$

Preparation of 3-[6-[[(3*R*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]amino]-5-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione

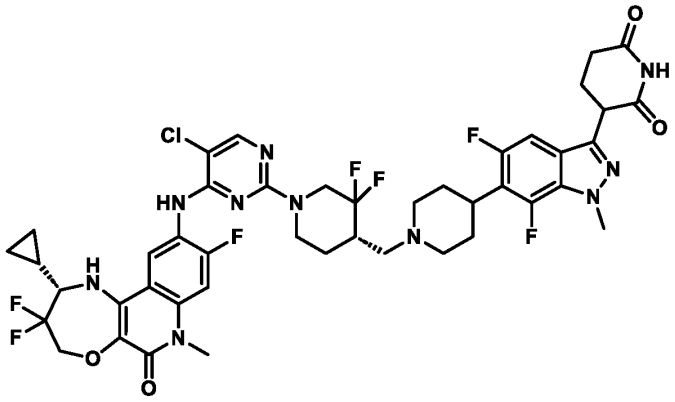
To a solution of 3-[5-fluoro-1-methyl-6-[[(3*R*,4*R*)-3-methyl-4-piperidyl]amino]indazol-3-yl]piperidine-2,6-dione (143.54 mg, 384.38 μmol, 1.2 *equiv.*) in DMSO (2 mL) was added TEA (129.65 mg, 1.28 mmol, 178.34 μL, 4 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3-difluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (0.15 g, 320.32 μmol, 1 *equiv.*). The mixture was stirred at 100 °C for 1 hour. The reaction mixture was filtered and the residue was purified by prep-HPLC to give 3-[6-[[(3*R*,4*R*)-1-[5-chloro-4-[[(2*S*)-2-cyclopropyl-3,3-difluoro-7-methyl-6-oxo-2,4-dihydro-1*H*-[1,4]oxazepino[2,3-c]quinolin-10-

yl]amino]pyrimidin-2-yl]-3-methyl-4-piperidyl]amino]-5-fluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (71.57 mg) as a pink solid.

LC-MS (ESI): m/z = 805.3 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.82 (s, 1H), 8.83 (s, 1H), 8.16 (d, J = 2.0 Hz, 1H), 8.06 (s, 1H), 7.76 (dd, J = 2.0, 9.2 Hz, 1H), 7.43 (d, J = 9.2 Hz, 1H), 7.30 (d, J = 11.6 Hz, 1H), 6.69 (d, J = 7.2 Hz, 1H), 6.17 (s, 1H), 5.35 (dd, J = 2.4, 9.2 Hz, 1H), 4.57 - 4.28 (m, 4H), 4.18 (dd, J = 5.2, 9.2 Hz, 1H), 3.86 (s, 3H), 3.54 (s, 3H), 3.29 - 3.15 (m, 2H), 2.98 (t, J = 12.0 Hz, 1H), 2.67 - 2.55 (m, 3H), 2.36 - 2.21 (m, 1H), 2.17 - 1.96 (m, 2H), 1.85 - 1.67 (m, 1H), 1.40 - 1.19 (m, 2H), 0.97 - 0.82 (m, 3H), 0.76 - 0.61 (m, 1H), 0.59 - 0.45 (m, 2H), 0.42 - 0.30 (m, 1H)

Example 212: 3-(6-(1-(((*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-5,7-difluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 239a)



Preparation of *tert*-butyl 4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridine-1-carboxylate

A mixture of 6-bromo-3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazole (5 g, 9.32 mmol, 1 *equiv.*), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylate (3.46 g, 11.19 mmol, 1.2 *equiv.*), cesium carbonate (7.59 g, 23.30 mmol, 2.5 *equiv.*), and $Pd(dppf)Cl_2$ (682.09 mg, 932.20 μmol, 0.1 *equiv.*) in dioxane (39 mL) and water (13 mL) was degassed and purged with N_2 three times. The mixture was stirred at 100 °C for 2 hours under a N_2 atmosphere. The reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (120 mL). The combined organic layers were washed with brine (120 mL), dried over sodium sulfate, filtered, and concentrated under

reduced pressure to give a residue, which was purified by flash silica gel chromatography (8-10% ethyl acetate/petroleum ether) to give *tert*-butyl 4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridine-1-carboxylate (5 g) as a yellow oil.

LC-MS (ESI): m/z = 639.7 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.90 (d, J = 8.0 Hz, 1H), 7.53 - 7.19 (m, 11H), 6.60 (d, J = 8.0 Hz, 1H), 5.45 (d, J = 8.8 Hz, 4H), 4.17 (s, 3H), 4.02 (s, 2H), 3.56 (s, 2H), 2.34 (s, 2H), 1.45 (s, 9H)

Preparation of *tert*-butyl 3,3-difluoro-4-formyl-piperidine-1-carboxylate

To a solution of *tert*-butyl 3,3-difluoro-4-(hydroxymethyl)piperidine-1-carboxylate (5 g, 19.90 mmol, 1 *equiv.*) in DCM (50 mL) was added DMP (16.88 g, 39.80 mmol, 12.33 mL, 2 *equiv.*). The mixture was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (12% ethyl acetate/petroleum ether) to give *tert*-butyl 3,3-difluoro-4-formyl-piperidine-1-carboxylate (4.2 g) as a yellow oil.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.94 (s, 1H), 9.80 (s, 1H), 4.04 (s, 1H), 3.83 (d, J = 12.8 Hz, 1H), 3.41 (d, J = 2.0 Hz, 2H), 2.99 (d, J = 1.2 Hz, 1H), 1.95 - 1.80 (m, 2H), 1.40 (s, 9H)

Preparation of 3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)indazole

To a solution of *tert*-butyl 4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridine-1-carboxylate (5 g, 7.83 mmol, 1 *equiv.*) in DCM (25 mL) was added HCl/dioxane (25 mL). The mixture was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give 3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)indazole (4.5 g, crude, HCl).

LC-MS (ESI): m/z = 539.3 $[M+H]^+$

Preparation of *tert*-butyl 4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3,3-difluoro-piperidine-1-carboxylate

To a solution of 3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-6-(1,2,3,6-tetrahydropyridin-4-yl)indazole (4.5 g, 7.83 mmol, 1 *equiv.*, HCl) and *tert*-butyl 3,3-difluoro-4-formyl-piperidine-1-carboxylate (2.15 g, 8.61 mmol, 1.1 *equiv.*) in DCM (50 mL) was added

AcOH (46.99 mg, 782.54 μmol, 44.80 μL, 0.1 *equiv.*) and $NaBH(OAc)_3$ (2.49 g, 11.74 mmol, 1.5 *equiv.*). The mixture was stirred at 25 °C for 12 hours. The reaction mixture was diluted with water (50 mL) and extracted with DCM (150 mL). The combined organic layers were washed with brine (150 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (5% DCM/MeOH) to give *tert*-butyl 4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3,3-difluoro-piperidine-1-carboxylate (4.5 g) as a yellow gum.

LC-MS (ESI): m/z = 772.5 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.91 (d, J = 8.0 Hz, 1H), 7.51 - 7.45 (m, 2H), 7.43 - 7.20 (m, 10H), 6.60 (d, J = 8.0 Hz, 1H), 5.45 (d, J = 8.8 Hz, 4H), 4.17 (s, 3H), 3.92 (d, J = 12.0 Hz, 2H), 3.24 - 3.12 (m, 2H), 3.09 - 3.01 (m, 1H), 2.94 - 2.73 (m, 2H), 2.65 (dd, J = 2.4, 12.8 Hz, 1H), 2.40 - 2.28 (m, 3H), 1.98 - 1.86 (m, 2H), 1.41 (s, 9H), 1.34 (d, J = 13.6 Hz, 2H)

Preparation of *tert*-butyl (4*R*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2Hpyridin-1-yl]methyl]-3,3-difluoro-piperidine-1-carboxylate and *tert*-butyl (4*S*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3,3-difluoro-piperidine-1-carboxylate

Isomers of *tert*-butyl 4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3,3-difluoro-piperidine-1-carboxylate (4.5 g, 5.83 mmol, 1 *equiv.*) were separated by SFC (column: Daicel Chiralpak IG (250 mm × 30 mm, 10 um); mobile phase: [CO_2-*i*-PrOH]; B%: 45%, isocratic elution mode) to afford *tert*-butyl (4*R*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2Hpyridin-1-yl]methyl]-3,3-difluoro-piperidine-1-carboxylate (**Peak 1**) (1.3 g) and *tert*-butyl (4*S*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3,3-difluoro-piperidine-1-carboxylate (**Peak 2**) (1.8 g).

LC-MS (ESI): m/z = 772.3 $[M+H]^+$

Peak 1 SFC: t_R = 1.168 min

LC-MS (ESI): m/z = 772.4 $[M+H]^+$

Peak 2 SFC: t_R = 1.470 min

Preparation of *tert*-butyl (4*S*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5,7-difluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3,3-difluoro-piperidine-1-carboxylate

To a solution of *tert*-butyl (4*S*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3,3-difluoro-piperidine-1-carboxylate (1.8 g, 2.33 mmol, 1 *equiv.*) in CF_3CH_2OH (18 mL) was added Pd on carbon (744.54 mg, 699.63 μmol, 10 wt%, 0.3 *equiv.*) and $Pd(OH)_2$ on carbon (491.26 mg, 699.63 μmol, 20 wt%, 0.3 *equiv.*) under a N_2 atmosphere. The suspension was degassed and purged with H_2 three times. The mixture was stirred under H_2 (15 psi.) at 25 °C for 12 hours. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (6% DCM/MeOH) to give *tert*-butyl (4*S*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5,7-difluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3,3-difluoro-piperidine-1-carboxylate (1.3 g) as a white solid.

LC-MS (ESI): m/z = 596.3 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.89 (s, 1H), 7.40 (d, J = 10.4 Hz, 1H), 4.71 (t, J = 5.6 Hz, 1H), 4.34 (dd, J = 5.2, 10.4 Hz, 1H), 4.10 (s, 3H), 3.99 - 3.85 (m, 2H), 3.24 - 3.12 (m, 2H), 3.02 (d, J = 8.0 Hz, 2H), 2.90 (d, J = 10.4 Hz, 2H), 2.70 - 2.58 (m, 2H), 2.42 - 2.29 (m, 3H), 2.22 - 1.85 (m, 8H), 1.40 (s, 9H)

Preparation of 3-[6-[1-[[(4*S*)-3,3-difluoro-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione

A solution of *tert*-butyl (4*S*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5,7-difluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3,3-difluoro-piperidine-1-carboxylate (1.3 g, 2.18 mmol, 1 *equiv.*) in HCl/dioxane (13 mL) was stirred at 25 °C for 12 hours. The reaction mixture was concentrated under reduced pressure to give 3-[6-[1-[[(4*S*)-3,3-difluoro-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (1.16 g, crude, HCl) as a white solid.

LC-MS (ESI): m/z = 496.2 $[M+H]^+$

Preparation of 3-(6-(1-(((*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-5,7-difluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

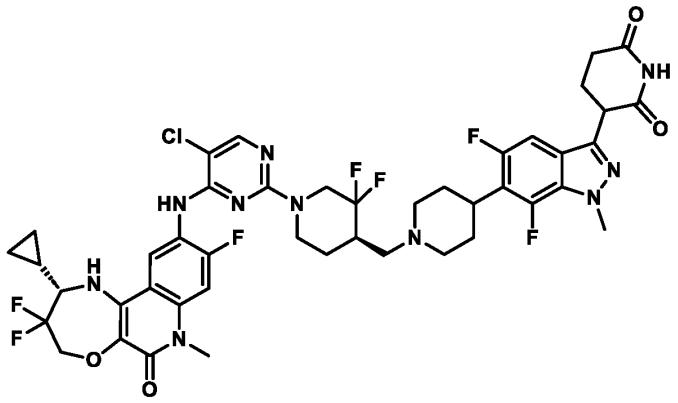
To a solution of 3-[6-[1-[[(4*S*)-3,3-difluoro-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (131.28 mg, 246.77 μmol, 1.2 *equiv.*, HCl) in DMSO (1 mL) was added TEA (83.24 mg, 822.58 μmol, 114.49 μL, 4 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3,9-trifluoro-7-methyl-1,2,3,4-

tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (100 mg, 205.65 μmol, 1 *equiv.*). The mixture was stirred at 100 °C for 1 hour. The reaction mixture was filtered to give a residue. The residue was purified by prep-HPLC to give 3-(6-(1-(((*S*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-5,7-difluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (47.38 mg) as a yellow solid.

LC-MS (ESI): m/z = 945.5 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.89 (s, 1H), 8.97 (s, 1H), 8.19 (d, J = 8.4 Hz, 1H), 8.06 (s, 1H), 7.50 - 7.36 (m, 2H), 6.46 (d, J = 2.4 Hz, 1H), 4.49 - 4.21 (m, 5H), 4.10 (s, 3H), 3.56 (s, 3H), 3.03 - 2.96 (m, 2H), 2.92 - 2.85 (m, 2H), 2.71 - 2.61 (m, 4H), 2.44 - 2.26 (m, 4H), 2.17 - 2.01 (m, 4H), 1.98 - 1.80 (m, 2H), 1.73 - 1.62 (m, 2H), 1.36 - 1.19 (m, 2H), 0.79 - 0.64 (m, 1H), 0.58 - 0.45 (m, 2H), 0.37 - 0.26 (m, 1H)

Example 213: 3-(6-(1-(((*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-5,7-difluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (Compound 239b)



Preparation of *tert*-butyl (4*R*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5,7-difluoro-1-methylindazol-6-yl]-1-piperidyl]methyl]-3,3-difluoro-piperidine-1-carboxylate

To a solution of *tert*-butyl (4*R*)-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3,3-difluoro-piperidine-1-carboxylate (1 g, 1.30 mmol, 1 *equiv.*) in CF_3CH_2OH (15 mL) was added Pd on carbon (413.63 mg, 388.68 μmol, 10% purity, 0.3 *equiv.*) and $Pd(OH)_2$ on carbon (272.92 mg, 388.68 μmol, 20 wt%, 0.3 *equiv.*) under a N_2 atmosphere. The suspension was degassed and purged with H_2

three times. The mixture was stirred under H_2 (15 psi) at 25 °C for 12 hours. The reaction mixture was filtered and concentrated to give *tert*-butyl (4*R*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5,7-difluoro-1-methylindazol-6-yl]-1-piperidyl]methyl]-3,3-difluoro-piperidine-1-carboxylate (650 mg) as a colorless oil.

LC-MS (ESI): m/z = 596.4 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.15 (d, J = 12.4 Hz, 1H), 7.10 (d, J = 10.0 Hz, 1H), 4.23 - 4.07 (m, 5H), 3.50 (s, 2H), 3.19 - 2.93 (m, 4H), 2.86 - 2.63 (m, 3H), 2.55 - 2.46 (m, 1H), 2.43 - 1.97 (m, 8H), 1.78 - 1.56 (m, 6H), 1.48 (s, 9H)

Preparation of 3-[6-[1-[[(4*R*)-3,3-difluoro-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione

A solution of *tert*-butyl (4*R*)-4-[[4-[3-(2,6-dioxo-3-piperidyl)-5,7-difluoro-1-methyl-indazol-6-yl]-1-piperidyl]methyl]-3,3-difluoro-piperidine-1-carboxylate (650 mg, 1.09 mmol, 1 *equiv.*) in HCl/dioxane (10 mL) was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give 3-[6-[1-[[(4*R*)-3,3-difluoro-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (600 mg) as a white solid crude.

LC-MS (ESI): m/z = 496.2 $[M+H]^+$

Preparation of 3-(6-(1-(((*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-5,7-difluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione

To a solution of 3-[6-[1-[[(4*R*)-3,3-difluoro-4-piperidyl]methyl]-4-piperidyl]-5,7-difluoro-1-methyl-indazol-3-yl]piperidine-2,6-dione (150 mg, 302.72 μmol, 1 *equiv.*) in DMSO (2 mL) was added TEA (122.53 mg, 1.21 mmol, 168.54 μL, 4 *equiv.*) and (*S*)-2-cyclopropyl-10-((2,5-dichloropyrimidin-4-yl)amino)-3,3,9-trifluoro-7-methyl-1,2,3,4-tetrahydro-[1,4]oxazepino[2,3-c]quinolin-6(7*H*)-one (117.76 mg, 242.17 μmol, 0.8 *equiv.*). The mixture was stirred at 100 °C for 1 hour. The reaction mixture was filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give 3-(6-(1-(((*R*)-1-(5-chloro-4-(((*S*)-2-cyclopropyl-3,3,9-trifluoro-7-methyl-6-oxo-1,2,3,4,6,7-hexahydro-[1,4]oxazepino[2,3-c]quinolin-10-yl)amino)pyrimidin-2-yl)-3,3-difluoropiperidin-4-yl)methyl)piperidin-4-yl)-5,7-difluoro-1-methyl-1*H*-indazol-3-yl)piperidine-2,6-dione (101.57 mg) as a pink solid.

LC-MS (ESI): m/z = 945.4 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.90 (s, 1H), 8.98 (s, 1H), 8.26 (s, 1H), 8.21 (d, J = 8.0 Hz, 1H), 8.06 (s, 1H), 7.48 - 7.34 (m, 2H), 6.52 - 6.41 (m, 1H), 4.63 - 4.20 (m, 5H), 4.10 (s, 3H), 3.55 (s, 3H), 3.23 - 3.08 (m, 2H), 3.06 - 2.96 (m, 2H), 2.94 - 2.80 (m, 2H), 2.75 - 2.53 (m, 3H), 2.44 - 2.22 (m, 3H), 2.20 - 1.81 (m, 6H), 1.67 (d, J = 10.8 Hz, 2H), 1.38 - 1.19 (m, 2H), 0.81 -0.66 (m, 1H), 0.62 - 0.43 (m, 2H), 0.38 - 0.27 (m, 1H)

The following examples were synthesized using methods similar to those described in the examples above:

Example No.	Compound No.	LC-MS (ESI)	^{1}H NMR
177	**212a**	m/z = 901.0 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d6) δ = 10.89 (s, 1H), 8.82 (s, 1H), 8.21 (d, J = 8.0 Hz, 1H), 8.02 (s, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.51 - 7.36 (m, 2H), 7.14 - 6.99 (m, 1H), 6.59 - 6.31 (m, 1H), 4.55 - 4.20 (m, 5H), 3.69 - 3.61 (m, 1H), 3.55 (s, 3H), 3.29 - 3.18 (m, 1H), 2.99 - 2.88 (m, 2H), 2.77 - 2.58 (m, 5H), 2.39 - 2.28 (m, 1H), 2.20 - 2.09 (m, 3H), 1.98 (, J = 10.0 Hz, 2H), 1.82 - 1.62 (m, 7H), 1.41 - 1.25 (m, 1H), 1.17 - 1.01 (m, 4H), 0.99 - 0.86 (m, 2H), 0.78 - 0.62 (m, 1H), 0.52 (t, J = 5.6 Hz, 2H), 0.33 (d, J = 4.8 Hz, 1H)
178	**225a**	m/z = 791.4 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d6) δ = 10.85 (s, 1H), 9.91 - 9.69 (m, 1H), 8.22 (dd, J = 2.4, 3.2 Hz, 1H), 8.17 - 8.05 (m, 1H), 7.56 - 7.37 (m, 2H), 7.04 - 6.66 (m, 2H), 6.45 (s, 1H), 4.52 - 4.14 (m, 4H), 3.89 (s, 3H), 3.54 (s, 3H), 3.35 - 3.14 (m, 3H), 3.00 - 2.76 (m, 1H), 2.70 - 2.55 (m, 3H), 2.38 - 2.24 (m, 2H), 2.18 - 2.10 (m, 1H), 2.00 - 1.78 (m, 2H), 1.73 - 1.47 (m, 2H), 1.38 - 1.21 (m, 1H), 0.74 - 0.67 (m, 1H), 0.51 (t, J = 5.2 Hz, 2H), 0.40 - 0.11 (m, 1H), -0.09 (s, 1H)
179	**226a**	m/z = 773.4 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d6) δ = 10.86 (s, 1H), 10.15 - 10.00 (m, 1H), 8.28 - 8.03 (m, 1H), 7.78 - 7.69 (m, 1H), 7.60 - 7.43 (m, 2H), 7.03 - 6.66 (m, 2H), 6.30 (s, 1H), 4.53 - 4.20 (m, 5H), 3.77 - 3.62 (m, 5H), 3.57 (s, 3H), 3.38 - 3.17 (m, 2H), 2.88 (s, 1H), 2.73 - 2.59 (m, 3H), 2.34 - 2.27 (m, 1H), 2.20 - 2.11 (m, 1H), 1.98 - 1.86 (m, 2H), 1.74 - 1.50 (m, 2H), 1.36 - 1.22 (m, 1H), 0.79 - 0.63 (m, 1H), 0.53 (d, J = 5.2 Hz, 2H), 0.40 - 0.23 (m, 1H)
180	**223a**	m/z = 823.4 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d6) δ = 10.87 (s, 1H), 9.01 - 8.84 (m, 1H), 8.17 (d, J = 8.0 Hz, 1H), 8.04 (s, 1H), 7.39 (d, J =12.4 Hz, 1H), 7.22 (d, J = 8.8 Hz, 1H), 6.75 (t, J = 8.0 Hz, 1H), 6.48 - 6.40 (m, 1H), 5.20 - 5.03 (m, 1H), 4.51 - 4.12 (m, 5H),4.06 - 3.84 (m, 3H), 3.51 (s, 3H), 3.26 (s, 2H), 2.89 - 2.74 (m, 1H), 2.61 (d, J = 6.8 Hz, 2H), 2.35 - 2.21 (m, 1H), 2.19 -2.04 (m, 1H), 1.88 - 1.72 (m, 1H), 1.68 - 1.53 (m, 1H), 1.46 - 1.15 (m, 3H), 0.97 - 0.77 (m, 3H), 0.75 - 0.61 (m, 1H), 0.59 - 0.44 (m, 2H), 0.36 - 0.26 (m, 1H)

181	**224a**	m/z = 823.3 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d6) δ = 10.83 (s, 1H), 8.92 (s, 1H), 8.18 (d, J = 8.0 Hz, 1H), 8.04 (s, 1H), 7.40 (d, J = 12.4 Hz, 1H), 7.29 (d, J = 11.6 Hz, 1H), 6.67 (d, J = 7.2 Hz, 1H), 6.46 (s, 1H), 5.37 (d, J = 2.8, 9.2 Hz, 1H), 4.50 - 4.25 (m, 4H), 4.17 (d, J = 5.2, 9.2 Hz, 1H), 3.87 - 3.81 (m, 3H), 3.56 - 3.49 (m, 3H), 3.24 (d, J = 5.2, 7.2 Hz, 2H), 2.97 - 2.82 (m, 1H), 2.62 - 2.57 (m, 2H), 2.33 - 2.22 (m, 1H), 2.16 - 2.05 (m, 1H), 1.93 (d, J = 11.2 Hz, 1H), 1.77 - 1.63 (m, 1H), 1.44 - 1.14 (m, 3H), 0.90 - 0.81 (m, 3H), 0.74 - 0.64 (m, 1H), 0.56 - 0.45 (m, 2H), 0.36 - 0.26 (m, 1H)
182	**228a**	m/z = 805.4 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d6) δ = 10.86 (s, 1H), 8.82 (s, 1H), 8.14 (d, J = 1.6 Hz, 1H), 8.05 (s, 1H), 7.76 (d, J = 9.6 Hz, 1H), 7.43 (d, J = 9.2 Hz, 1H), 7.24 (d, J = 8.8 Hz, 1H), 6.81 - 6.72 (m, 1H), 6.19 - 6.10 (m, 1H), 5.19 - 5.08 (m, 1H), 4.59 - 4.19 (m, 6H), 3.99 (s, 3H), 3.54 (s, 3H), 2.91 (t, J = 12.0 Hz, 1H), 2.68 - 2.55 (m, 4H), 2.36 - 2.22 (m, 1H), 2.19 - 2.07 (m, 1H), 1.93 - 1.80 (m, 1H), 1.75 - 1.57 (m, 1H), 1.35 - 1.24 (m, 2H), 0.91 (d, J = 6.0 Hz, 3H), 0.69 (d, J = 8.0 Hz, 1H), 0.56 - 0.45 (m, 2H), 0.41 - 0.27 (m, 1H)
183	**230a**	m/z = 855.4 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d6) δ = 10.88 (s, 1H), 8.84 (s, 1H), 8.14 (s, 1H), 8.06 (s, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.65 (d, J = 9.6 Hz, 1H), 7.43 (d, J = 9.2 Hz, 1H), 6.89 (d, J = 9.2 Hz, 1H), 6.18 - 6.08 (m, 1H), 5.51 - 5.35 (m, 1H), 4.51 - 4.36 (m, 3H), 4.29 (dd, J = 5.2, 9.6 Hz, 1H), 3.87 (d, J = 2.8 Hz, 3H), 3.55 (s, 3H), 3.51 - 3.42 (m, 1H), 3.27 - 3.17 (m, 1H), 3.04 - 2.89 (m, 1H), 2.69 - 2.69 (m, 1H), 2.71 - 2.58 (m, 3H), 2.35 - 2.24 (m, 2H), 2.19 - 2.09 (m, 1H), 1.95 - 1.86 (m, 1H), 1.82 - 1.71 (m, 1H), 1.47 - 1.21 (m, 3H), 0.89 (d, J = 5.6 Hz, 3H), 0.73 - 0.61 (m, 1H), 0.56 - 0.46 (m, 2H), 0.40 - 0.31 (m, 1H)
184	**231b**	m/z = 909.5 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d6) δ = 10.87 (s, 1H), 8.93 (s, 1H), 8.27 (s, 1H), 8.15 (d, J = 2.0 Hz, 1H), 8.07 (s, 1H), 7.71 (dd, J = 2.0, 9.2 Hz, 1H), 7.55 (d, J = 6.0 Hz, 1H), 7.51 - 7.43 (m, 2H), 6.25 (s, 1H), 4.69 - 4.56 (m, 1H), 4.51 - 4.28 (m, 4H), 3.99 (s, 3H), 3.57 (s, 3H), 3.07 - 2.80 (m, 4H), 2.71 - 2.58 (m, 2H), 2.44 - 2.28 (m, 4H), 2.27 - 2.05 (m, 3H), 2.04 - 1.84 (m, 3H), 1.79 (s, 4H), 1.44 - 1.28 (m, 2H), 0.77 - 0.65 (m, 1H), 0.58 - 0.45 (m, 2H), 0.42 - 0.30 (m, 1H)
185	**232a**	m/z = 909.5 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d6) δ = 10.91 (s, 1H), 8.93 (s, 1H), 8.20 (s, 1H), 8.16 (s, 1H), 8.07 (s, 1H), 7.75 - 7.65 (m, 1H), 7.46 (d, J = 8.8 Hz, 2H), 7.10 - 6.99 (m, 1H), 6.30 - 6.14 (m, 1H), 4.72 - 4.57 (m, 1H), 4.55 - 4.27 (m, 4H), 4.11 (s, 3H), 3.58 (s, 3H), 3.09 - 2.82 (m, 5H), 2.77 - 2.59 (m, 3H), 2.43 - 2.27 (m, 4H), 2.26 - 2.10 (m, 2H), 2.05 - 1.87 (m, 2H), 1.86 - 1.65 (m, 4H), 1.45 - 1.25 (m, 2H), 0.77 - 0.65 (m, 1H), 0.51 (t, J = 5.6 Hz, 2H), 0.42 - 0.29 (m, 1H)
186	**234a**	m/z = 927.3 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d6) δ = 10.91 (s, 1H), 8.93 (s, 1H), 8.16 (s, 1H), 8.08 (s, 1H), 7.73 (d, J = 9.2 Hz, 1H), 7.56 - 7.31 (m, 2H), 6.25 (d, J = 1.6 Hz, 1H), 4.75 - 4.53 (m, 1H), 4.52 - 4.27 (m, 4H),

			4.11 (s, 3H), 3.59 (s, 3H), 3.27 - 3.13 (m, 2H), 3.07 - 2.82 (m, 4H), 2.76 - 2.58 (m, 3H), 2.42 - 2.28 (m, 3H), 1.78 - 1.60 (m, 2H), 1.43 - 1.29 (m, 2H), 0.72 (d, J = 7.6 Hz, 1H), 0.53 (t, J = 5.6 Hz, 2H), 0.41 - 0.25 (m, 1H).
187	**231a**	m/z = 909.5 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d6) δ = 10.87 (s, 1H), 8.93 (s, 1H), 8.23 (d, J = 2.8 Hz, 1H), 8.19 (s, 1H), 8.07 (s, 1H), 7.70 (dd, J = 2.0, 8.8 Hz, 1H), 7.54 (d, J = 6.0 Hz, 1H), 7.51 - 7.40 (m, 2H), 6.19 (s, 1H), 4.73 - 4.53 (m, 1H), 4.52 - 4.23 (m, 4H), 3.99 (s, 3H), 3.60 - 3.53 (m, 3H), 3.07 - 2.94 (m, 2H), 2.93 - 2.80 (m, 2H), 2.72 - 2.58 (m, 2H), 2.41 - 2.27 (m, 4H), 2.26 - 2.07 (m, 3H), 2.06 - 1.86 (m, 3H), 1.84 - 1.72 (m, 4H), 1.41 - 1.29 (m, 2H), 0.76 - 0.66 (m, 1H), 0.57 - 0.49 (m, 2H), 0.40 - 0.30 (m, 1H)
188	**232b**	m/z = 909.5 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d6) δ = 10.95 - 10.85 (m, 1H), 8.93 (s, 1H), 8.26 (d, J = 3.2 Hz, 1H), 8.20 (s, 1H), 8.07 (s, 1H), 7.70 (d, J = 8.8 Hz, 1H), 7.52 - 7.42 (m, 2H), 7.09 - 6.99 (m, 1H), 6.29 - 6.09 (m, 1H), 4.74 - 4.57 (m, 1H), 4.52 - 4.30 (m, 4H), 4.11 (s, 3H), 3.57 (s, 3H), 3.10 - 2.83 (m, 5H), 2.61 (d, J = 4.4 Hz, 3H), 2.43 - 2.25 (m, 4H), 2.24 - 2.11 (m, 2H), 2.04 - 1.88 (m, 2H), 1.86 - 1.64 (m, 4H), 1.41 - 1.28 (m, 2H), 0.76 - 0.65 (m, 1H), 0.60 - 0.46 (m, 2H), 0.35 (d, J = 4.4 Hz, 1H)
189	**234b**	m/z = 926.3 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d6) δ = 10.92 (s, 1H), 9.47 - 9.18 (m, 1H), 9.03 (s, 1H), 8.16 (d, J = 1.6 Hz, 1H), 8.11 (s, 1H), 7.71 (dd, J = 2.0, 9.2 Hz, 1H), 7.54 - 7.31 (m, 2H), 6.30 (d, J = 1.2 Hz, 1H), 4.77 - 4.68 (m, 1H), 4.47 - 4.30 (m, 5H), 4.12 (s, 3H), 3.70 (d, J = 11.2 Hz, 1H), 3.61 (s, 3H), 3.38 (dd, J = 4.4, 11.2 Hz, 2H), 3.30 - 3.21 (m, 2H), 3.19 - 3.06 (m, 2H), 3.00 (t, J = 12.0 Hz, 1H), 2.88 - 2.74 (m, 1H), 2.71 - 2.57 (m, 2H), 2.43 - 2.31 (m, 3H), 2.16 - 1.96 (m, 4H), 1.57 - 1.41 (m, 1H), 1.39 - 1.27 (m, 1H), 0.81 - 0.67 (m, 1H), 0.59 - 0.43 (m, 2H), 0.42 - 0.27 (m, 1H)
190	**233a**	m/z = 909.3 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d6) δ = 10.88 (s, 1H), 8.99 (s, 1H), 8.24 (s, 1H), 8.22 - 8.17 (m, 1H), 8.13 - 7.98 (m, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.50 - 7.37 (m, 2H), 7.03 (d, J = 8.4 Hz, 1H), 6.47 (s, 1H), 4.54 - 4.21 (m, 5H), 3.97 (s, 3H), 3.57 - 3.54 (m, 3H), 3.09 - 2.82 (m, 4H), 2.69 - 2.57 (m, 3H), 2.42 - 2.23 (m, 4H), 2.21 - 2.10 (m, 2H), 2.04 - 1.83 (m, 3H), 1.82 - 1.66 (m, 4H), 1.41 - 1.16 (m, 3H), 0.80 - 0.68 (m, 1H), 0.52 (t, J = 5.6 Hz, 2H), 0.42 - 0.25 (m, 1H)
191	**233b**	m/z = 909.2 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d6) δ = 10.88 (s, 1H), 8.98 (s, 1H), 8.25 (s, 1H), 8.22 (d, J = 8.0 Hz, 1H), 8.13 - 7.97 (m, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.52 - 7.34 (m, 2H), 7.03 (d, J = 8.4 Hz, 1H), 6.45 (s, 1H), 4.54 - 4.21 (m, 2H), 3.97 (s, 3H), 3.56 (s, 3H), 3.09 - 3.00 (m, 1H), 2.97 - 2.75 (m, 3H), 2.69 - 2.58 (m, 3H), 2.41 - 2.23 (m, 4H), 2.22 - 2.14 (m, 2H), 1.90 (d, J = 10.0 Hz, 3H), 1.81 - 1.66 (m, 4H), 1.38 - 1.15 (m, 3H), 0.77 - 0.64 (m, 1H), 0.52 (d, J = 5.2 Hz, 2H), 0.38 - 0.27 (m, 1H)
192	**235a**	m/z = 892.3 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d6) δ = 10.62 (s, 1H), 8.84 (s, 1H), 8.18 (d, J = 1.6 Hz, 1H), 8.14 (s, 1H), 8.06 (s, 1H), 7.75 (dd, J = 2.0, 9.2 Hz, 1H), 7.45 (d,

			J = 9.2 Hz, 1H), 7.33 (d, J = 10.8 Hz, 1H), 6.24 (d, J = 1.6 Hz, 1H), 4.53 - 4.29 (m, 4H), 4.11 (s, 3H), 3.90 (t, J = 6.8 Hz, 2H), 3.58 (s, 3H), 3.30 - 3.17 (m, 2H), 3.08 (d, J = 7.2 Hz, 2H), 2.90 - 2.72 (m, 5H), 2.55 (s, 2H), 2.45 - 2.27 (m, 2H), 2.04 (s, 1H), 1.97 - 1.83 (m, 2H), 1.77 (d, J = 9.2 Hz, 2H), 1.33 (dd, J = 6.0, 9.2 Hz, 1H), 1.22 - 1.02 (m, 2H), 0.78 - 0.67 (m, 1H), 0.58 - 0.47 (m, 2H), 0.41 - 0.27 (m, 1H)
193	**236a**	m/z = 924.4 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d6) δ = 10.60 (s, 1H), 8.80 (s, 1H), 8.36 (s, 1H), 8.19 (d, J = 8.0 Hz, 1H), 7.99 (s, 1H), 7.43 (d, J = 12.4 Hz, 1H), 7.29 (d, J = 10.8 Hz, 1H), 6.53 - 6.38 (m, 1H), 4.54 - 4.21 (m, 3H), 4.10 (s, 3H), 3.89 (t, J = 6.8 Hz, 2H), 3.56 (s, 3H), 3.26 - 3.16 (m, 1H), 3.08 - 2.83 (m, 4H), 2.75 (t, J = 6.8 Hz, 3H), 2.23 - 1.77 (m, 8H), 1.77 - 1.58 (m, 2H), 1.41 - 1.14 (m, 3H), 0.70 (d, J = 6.4 Hz, 4H), 0.52 (t, J = 5.6 Hz, 2H), 0.40 - 0.22 (m, 1H)
194	**237a**	m/z = 928.6 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d6) δ = 10.65 - 10.46 (m, 1H), 8.89 - 8.80 (m, 1H), 8.37 (s, 1H), 8.20 (d, J = 7.2 Hz, 1H), 8.02 (s, 1H), 7.43 (d, J = 12.8 Hz, 1H), 7.28 (d, J = 10.8 Hz, 1H), 6.51 - 6.39 (m, 1H), 4.90 - 4.57 (m, 2H), 4.54 - 4.20 (m, 4H), 4.14 - 4.04 (m, 3H), 3.89 (t, J = 6.8 Hz, 2H), 3.56 (s, 3H), 3.05 - 2.88 (m, 3H), 2.78 - 2.66 (m, 3H), 2.36 - 2.30 (m, 2H), 2.18 - 1.91 (m, 6H), 1.75 - 1.62 (m, 2H), 1.52 - 1.40 (m, 1H), 1.31 (s, 4H), 1.28 (s, 2H), 0.76 - 0.64 (m, 1H), 0.59 - 0.45 (m, 2H), 0.39 - 0.25 (m, 1H)
195	**227a**	m/z = 394.9 [M+2H]2+	^{1}H NMR (400 MHz, DMSO-d6) δ 10.83 (s, 1H), 9.13 (s, 1H), 8.68 (d, J = 2.9 Hz, 2H), 8.10 (s, 1H), 7.30 (d, J = 8.8 Hz, 1H), 6.49 (dd, J = 9.1, 1.7 Hz, 1H), 6.43 (s, 1H), 6.39 (s, 1H), 5.68 (d, J = 8.8 Hz, 1H), 4.53 – 4.28 (m, 4H), 4.17 (dd, J = 8.7, 5.2 Hz, 1H), 3.80 (s, 3H), 3.60 (s, 3H), 3.31 – 3.17 (m, 3H), 3.01 (t, J = 12.6 Hz, 1H), 2.65 – 2.53 (m, 2H), 2.29 – 2.19 (m, 1H), 2.19 – 2.09 (m, 1H), 2.09 – 1.97 (m, 1H), 1.62 – 1.47 (m, 1H), 1.33 – 1.21 (m, 1H), 1.19 – 1.06 (m, 1H), 0.92 (d, J = 6.4 Hz, 3H), 0.75 – 0.65 (m, 1H), 0.61 – 0.46 (m, 2H), 0.41 – 0.32 (m, 1H).
196	**222a**	m/z = 403.4 [M+2H]2+	^{1}H NMR (400 MHz, DMSO-d6) δ 10.73 (s, 1H), 8.83 (s, 1H), 8.11 (d, J = 8.0 Hz, 1H), 7.97 (s, 1H), 7.32 (d, J = 12.5 Hz, 1H), 7.22 (d, J = 8.8 Hz, 1H), 6.48 – 6.39 (m, 1H), 6.37 (s, 1H), 6.31 (s, 1H), 5.57 (d, J = 9.0 Hz, 1H), 4.42 – 4.15 (m, 3H), 4.09 (dd, J = 8.7, 5.2 Hz, 1H), 3.72 (s, 3H), 3.45 (s, 3H), 3.20 – 3.06 (m, 4H), 2.90 – 2.76 (m, 1H), 2.55 – 2.45 (m, 2H), 2.23 – 2.11 (m, 1H), 2.06 (dd, J = 13.2, 6.2 Hz, 1H), 1.90 (d, J = 12.6 Hz, 1H), 1.48 – 1.35 (m, 1H), 1.29 – 1.16 (m, 1H), 1.08 – 0.95 (m, 1H), 0.80 (d, J = 6.4 Hz, 3H), 0.69 – 0.57 (m, 1H), 0.48 – 0.38 (m, 2H), 0.31 – 0.21 (m, 1H).
197	**221a**	m/z = 787.5 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d6) δ 10.80 (s, 1H), 8.81 (s, 1H), 8.15 (d, J = 2.3 Hz, 1H), 8.06 (s, 1H), 7.76 (dd, J = 9.1, 2.1 Hz, 1H), 7.42 (d, J = 9.2 Hz, 1H), 7.29 (d, J = 8.7 Hz, 1H), 6.53 – 6.46 (m, 1H), 6.40 (s, 1H), 6.15 (s, 1H), 5.65 (d, J = 8.9 Hz, 1H), 4.51 – 4.38 (m, 3H), 4.37 – 4.27 (m, 1H), 4.16 (dd, J = 8.7, 5.2 Hz, 1H), 3.80 (s, 3H), 3.54 (s, 3H), 3.30

			– 3.27 (m, 1H), 3.26 – 3.20 (m, 1H), 3.00 (t, J = 12.6 Hz, 1H), 2.70 – 2.62 (m, 1H), 2.59 (t, J = 7.4 Hz, 2H), 2.29 – 2.19 (m, 1H), 2.18 – 2.08 (m, 1H), 2.08 – 1.99 (m, 1H), 1.59 – 1.49 (m, 1H), 1.35 – 1.25 (m, 1H), 1.20 – 1.07 (m, 1H), 0.93 (d, J = 6.4 Hz, 3H), 0.72 – 0.64 (m, 1H), 0.60 – 0.44 (m, 2H), 0.41 – 0.30 (m, 1H).
198	**175b**	m/z = 891.2 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d6) δ 10.91 (s, 1H), 8.83 (s, 1H), 8.24 (m, 1H), 8.00 (s, 1H), 7.43 (m, 2H), 7.03 (m, 1H), 6.48 (s, 1H), 4.48 – 4.31 (m, 5 H), 4.12 (s, 3H), 3.54 (s, 3H), 3.24 (m, 2H), 2.83 (m, 2H), 2.75 – 2.60 (m, 3H), 2.22 (m, 1H), 2.41 – 1.83 (m, 5H), 1.76 – 1.68 (m, 7H), 1.32 – 1.30 (m, 2H), 0.99 – 0.89 (m, 2H), 0.74 (m, 1H), 0.50 (m, 2H), 0.29 – 0.25 (m, 1H)
199	**501a**	m/z = 888.9 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.81 (s, 1H), 8.20 (d, J = 8.1 Hz, 1H), 8.02 (s, 1H), 7.43 (d, J = 12.5 Hz, 1H), 7.08 (s, 1H), 7.00 (d, J = 8.1 Hz, 1H), 6.90 (d, J = 8.1 Hz, 1H), 6.44 (s, 1H), 5.34 (dd, J = 12.8, 5.4 Hz, 1H), 4.44 (d, J = 13.5 Hz, 1H), 4.33 (d, J = 9.9 Hz, 3H), 3.56 (s, 3H), 3.33 (s, 3H), 3.29 (s, 0H), 2.93 (d, J = 11.6 Hz, 3H), 2.72 (d, J = 4.7 Hz, 1H), 2.14 (s, 1H), 2.00 (d, J = 13.6 Hz, 3H), 1.73 – 1.62 (m, 6H), 0.94 (d, J = 12.9 Hz, 2H), 0.71 (d, J = 7.9 Hz, 1H), 0.56 – 0.49 (m, 2H), 0.33 (s, 1H).
200	**502a**	m/z = 855 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d6) δ 11.00 (s, 1H), 9.20 (s, 1H), 8.20 – 8.13 (m, 2H), 7.93 (d, J = 3.6 Hz, 1H), 7.71 (dd, J = 9.1, 2.1 Hz, 1H), 7.38 (d, J = 9.1 Hz, 1H), 7.01 (d, J = 1.5 Hz, 1H), 6.94 (d, J = 8.1 Hz, 1H), 6.84 (dd, J = 8.2, 1.5 Hz, 1H), 5.88 (d, J = 4.1 Hz, 1H), 5.27 (dd, J = 12.7, 5.4 Hz, 1H), 4.46 – 4.34 (m, 4H), 3.50 (s, 3H), 3.26 (s, 4H), 2.84 (d, J = 11.6 Hz, 2H), 2.71 (d, J = 12.6 Hz, 1H), 2.64 – 2.52 (m, 1H), 2.08 (d, J = 6.6 Hz, 2H), 1.97 – 1.87 (m, 3H), 1.71 – 1.62 (m, 7H), 1.28 (dd, J = 12.7, 9.0 Hz, 1H), 0.97 (d, J = 12.5 Hz, 2H), 0.64 (q, J = 5.9 Hz, 1H), 0.46 (t, J = 6.2 Hz, 2H), 0.30 (q, J = 5.9 Hz, 1H).
201	**503a**	m/z = 893 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d6) δ 10.87 (s, 1H), 10.35 (s, 1H), 9.13 (s, 1H), 8.45 (d, J = 7.1 Hz, 1H), 8.20 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 8.8 Hz, 1H), 7.42 (d, J = 12.5 Hz, 1H), 6.70 – 6.59 (m, 2H), 6.47 (d, J = 4.6 Hz, 1H), 4.70 (dt, J = 12.5, 6.4 Hz, 1H), 4.52 – 4.23 (m, 4H), 3.99 (d, J = 13.4 Hz, 2H), 3.93 (s, 3H), 3.54 (s, 3H), 3.34 – 3.18 (m, 1H), 3.09 (d, J = 10.8 Hz, 1H), 3.00 (d, J = 6.1 Hz, 2H), 2.85 – 2.70 (m, 1H), 2.18 – 1.99 (m, 3H), 1.77 (s, 2H), 1.38 – 1.21 (m, 1H), 1.09 (dd, J = 17.7, 7.6 Hz, 2H), 0.71 (q, J = 5.9 Hz, 1H), 0.52 (t, J = 6.1 Hz, 2H), 0.32 (q, J = 6.4 Hz, 1H), 0.07 (s, 1H).
202	**504a**	m/z = 910 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d6) δ 11.06 (s, 1H), 9.52 (s, 1H), 8.89 (s, 1H), 8.43 (d, J = 8.4 Hz, 1H), 8.16 – 8.02 (m, 2H), 7.99 (s, 1H), 7.86 – 7.78 (m, 1H), 7.38 – 7.23 (m, 2H), 7.07 (d, J = 7.5 Hz, 1H), 6.40 (s, 1H), 5.39 (dd, J = 12.8, 5.5 Hz, 1H), 4.45 – 4.22 (m, 3H), 3.55 (d, J = 11.4 Hz, 2H), 3.49 (s, 3H), 2.95 – 2.83 (m, 3H), 2.70 (t, J = 12.9 Hz, 2H), 2.18 (d, J = 13.0 Hz, 1H), 1.99 (dd, J = 24.9, 12.9 Hz, 3H), 1.70 (s, 2H), 1.24 (s, 1H), 1.19 – 1.08 (m,

			0H), 1.03 (d, J = 12.5 Hz, 1H), 0.65 (d, J = 7.9 Hz, 1H), 0.45 (t, J = 6.1 Hz, 2H), 0.28 – 0.21 (m, 1H).
203	**505a**	m/z = 890 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d6) δ 11.00 (s, 1H), 8.75 (s, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.94 (s, 1H), 7.63 (dd, J = 8.4, 7.2 Hz, 1H), 7.38 – 7.23 (m, 3H), 6.40 – 6.35 (m, 1H), 5.01 (dd, J = 12.8, 5.4 Hz, 1H), 4.44 – 4.21 (m, 2H), 3.47 (s, 3H), 3.19 (s, 5H), 2.80 (ddd, J = 17.1, 13.9, 5.5 Hz, 1H), 2.62 (t, J = 12.2 Hz, 2H), 2.48 (d, J = 8.7 Hz, 1H), 2.10 (s, 2H), 2.00 – 1.91 (m, 1H), 1.68 (s, 1H), 1.59 (d, J = 12.9 Hz, 2H), 1.22 (dt, J = 22.7, 7.5 Hz, 1H), 0.88 (q, J = 11.9 Hz, 2H), 0.63 (p, J = 6.4 Hz, 1H), 0.48 – 0.39 (m, 2H), 0.25 (q, J = 6.3 Hz, 1H).
204	**506a**	m/z = 881 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d6) δ 10.85 (s, 1H), 8.82 (s, 1H), 8.56 (dd, J = 8.3, 2.5 Hz, 1H), 8.19 (d, J = 8.1 Hz, 1H), 8.01 (s, 1H), 7.52 – 7.37 (m, 3H), 7.24 (t, J = 7.6 Hz, 1H), 6.44 (d, J = 4.6 Hz, 1H), 4.77 (ddd, J = 12.0, 8.2, 5.6 Hz, 1H), 4.52 – 4.28 (m, 2H), 3.55 (s, 3H), 3.25 (d, J = 32.5 Hz, 6H), 3.00 (s, 2H), 2.86 – 2.67 (m, 3H), 2.54 (s, 2H), 2.22 (s, 1H), 2.15 – 1.95 (m, 2H), 1.73 (s, 6H), 1.65 (d, J = 13.1 Hz, 2H), 1.38 – 1.21 (m, 1H), 0.94 (q, J = 12.1 Hz, 2H), 0.70 (q, J = 5.9 Hz, 1H), 0.55 – 0.46 (m, 2H), 0.32 (q, J = 6.1 Hz, 1H).
205	**507a**	m/z = 874.5 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d6) δ 10.91 (s, 1H), 8.75 (s, 1H), 8.16 – 8.09 (m, 1H), 7.94 (s, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.43 – 7.28 (m, 3H), 6.38 (s, 1H), 5.03 (dd, J = 13.3, 5.1 Hz, 1H), 4.44 – 4.17 (m, 5H), 3.48 (s, 3H), 3.18 (s, 2H), 2.91 – 2.77 (m, 3H), 2.60 – 2.45 (m, 2H), 2.37 – 2.28 (m, 1H), 2.05 (d, J = 6.9 Hz, 2H), 1.89 (t, J = 11.2 Hz, 3H), 1.66 (s, 4H), 1.61 (s, 1H), 1.24 (s, 1H), 0.86 (d, J = 12.3 Hz, 2H), 0.67 – 0.59 (m, 1H), 0.48 – 0.41 (m, 2H), 0.28 – 0.21 (m, 1H).
206	**181a**	m/z = 440.4 $[M+2H]^{2+}$	^{1}H NMR (400 MHz, DMSO-d6) δ 10.85 (s, 1H), 9.34 (d, J = 14.5 Hz, 1H), 8.40 (s, 1H), 8.21 – 8.02 (m, 1H), 7.67 (d, J = 8.9 Hz, 1H), 7.45 (d, J = 11.7 Hz, 2H), 7.10 (d, J = 6.9 Hz, 1H), 6.52 (s, 1H), 6.24 (d, J = 43.5 Hz, 1H), 4.73 – 4.55 (m, 1H), 4.54 – 4.31 (m, 4H), 4.27 (dd, J = 9.6, 5.0 Hz, 1H), 3.94 (s, 3H), 3.55 (s, 3H), 3.11 – 2.97 (m, 6H), 2.69 – 2.58 (m, 1H), 2.38 – 2.26 (m, 1H), 2.27 – 2.10 (m, 4H), 2.08 – 1.84 (m, 4H), 1.55 – 1.42 (m, 2H), 1.42 – 1.26 (m, 2H), 0.87 – 0.64 (m, 4H), 0.62 – 0.39 (m, 2H), 0.37 – 0.30 (m, 1H).
207	**197a**	m/z = 466.9 $[M+2H]^{2+}$	^{1}H NMR (400 MHz, CD3SOCD3, 300 K) δ (ppm) = 10.88 (s, 1H), 8.78 (s, 1H), 8.21 (d, J = 8.4 Hz, 1H), 8.00 (s, 1H), 7.49 - 7.32 (m, 2H), 6.91 (t, J = 7.9 Hz, 1H), 6.44 (br d, J = 1.5 Hz, 1H), 4.52 - 4.26 (m, 3H), 4.06 (s, 3H), 3.54 (s, 7H), 3.27 - 3.17 (m, 2H), 3.15 - 2.99 (m, 5H), 2.64 - 2.57 (m, 1H), 2.56 - 2.52 (m, 2H), 2.22 - 2.05 (m, 4H), 1.86 - 1.74 (m, 2H), 1.72 - 1.60 (m, 2H), 1.53 - 1.24 (m, 5H), 0.97 - 0.81 (m, 2H), 0.79 - 0.63 (m, 1H), 0.51 (br t, J = 5.6 Hz, 2H), 0.40 - 0.24 (m, 1H).
208	**198a**	m/z = 466.9 $[M+2H]^{2+}$	^{1}H NMR (400 MHz, CD3SOCD3, 300 K) δ (ppm) = 10.80 - 10.74 (m, 1H), 8.77 - 8.67 (m, 1H), 8.20 - 8.11 (m, 1H), 7.97 - 7.88 (m, 1H), 7.41 - 7.31 (m, 2H), 7.06 - 6.99 (m, 1H), 6.40 - 6.34 (m, 1H), 4.44 - 4.16 (m, 3H), 3.87 (s, 3H), 3.48 (s, 6H), 3.19 -

			3.10 (m, 2H), 2.98 (br s, 5H), 2.58 - 2.49 (m, 1H), 2.32 - 2.20 (m, 3H), 2.12 - 1.99 (m, 4H), 1.78 - 1.67 (m, 2H), 1.64 - 1.53 (m, 2H), 1.47 - 1.18 (m, 5H), 0.88 - 0.73 (m, 2H), 0.69 - 0.57 (m, 1H), 0.45 (br t, J = 5.7 Hz, 2H), 0.32 - 0.19 (m, 1H).
209	**203b**	m/z = 444.9 $[M+2H]^{2+}$	^{1}H NMR (400 MHz, DMSO) δ 10.87 (s, 1H), 8.81 (s, 1H), 8.19 (d, J = 8.1 Hz, 1H), 8.01 (s, 1H), 7.41 (d, J = 12.5 Hz, 1H), 7.01 (d, J = 6.7 Hz, 2H), 6.47 – 6.39 (m, 1H), 4.54 – 4.37 (m, 1H), 4.36 – 4.26 (m, 2H), 4.23 (s, 4H), 3.55 (s, 3H), 3.29 – 3.15 (m, 3H), 3.13 – 3.03 (m, 2H), 3.01 – 2.92 (m, 1H), 2.91 – 2.87 (m, 2H), 2.86 – 2.74 (m, 1H), 2.73 – 2.62 (m, 3H), 2.54 – 2.52 (m, 2H), 2.37 – 2.26 (m, 1H), 2.24 – 2.10 (m, 1H), 1.98 – 1.83 (m, 1H), 1.82 – 1.62 (s, 1H), 1.60 – 1.45 (m, 1H),1.37 – 1.27 (m, 1H), 1.08 – 0.91 (m, 6H), 0.93 – 0.82 (m, 1H), 0.73 – 0.69 (m, 1H), 0.59 – 0.46 (m, 2H), 0.34 – 0.24 (m, 1H).
210	**205a**	m/z = 438.3 $[M+2H]^{2+}$	^{1}H NMR (400 MHz, DMSO) δ 10.89 (s, 1H), 8.81 (s, 1H), 8.62 (s, 1H), 8.19 (d, J = 8.2 Hz, 1H), 8.01 (s, 1H), 7.41 (d, J = 12.4 Hz, 1H), 6.65 (s, 1H), 6.44 (s, 1H), 4.50 – 4.35 (m, 1H), 4.36 – 4.25 (m, 2H), 3.85 (s, 3H), 3.54 (s, 3H), 3.51 – 3.44 (m, 4H), 2.76 – 2.57 (m, 4H), 2.54 (s, 1H), 2.47 – 2.41 (m, 4H), 2.40 – 2.29 (m, 1H), 2.23 – 2.10 (m, 3H), 1.75 (s, 2H), 1.67 (d, J = 13.0 Hz, 2H), 1.27 (d, J = 27.6 Hz, 1H), 0.95 (d, J = 12.9 Hz, 3H), 0.71 (d, J = 7.8 Hz, 1H), 0.51 (t, J = 6.2 Hz, 2H), 0.32 (d, J = 5.5 Hz, 1H).
211	**206a**	m/z = 438.3 $[M+2H]^{2+}$	^{1}H NMR (400 MHz, DMSO) δ 10.85 (s, 1H), 8.82 (s, 1H), 8.20 (d, J = 8.0 Hz, 1H), 8.02 (s, 1H), 7.84 (d, J = 9.0 Hz, 1H), 7.42 (d, J = 12.5 Hz, 1H), 6.76 (d, J = 9.0 Hz, 1H), 6.44 (s, 1H), 4.53 – 4.37 (m, 1H), 4.38 – 4.26 (m, 2H), 4.21 (dd, J = 9.5, 5.1 Hz, 1H), 3.81 (s, 3H), 3.70 – 3.57 (m, 4H), 3.54 (s, 3H), 3.31 – 3.18 (m, 2H), 2.76 – 2.65 (m, 2H), 2.65 – 2.57 (m, 1H), 2.47 – 2.38 (m, 4H), 2.36 – 2.25 (m, 1H), 2.21 – 2.08 (m, 3H), 1.83 – 1.72 (m, 2H), 1.67 (d, J = 13.1 Hz, 2H), 1.37 – 1.22 (m, 1H), 1.03 – 0.86 (m, 2H), 0.71 (q, J = 6.1 Hz, 1H), 0.58 – 0.45 (m, 2H), 0.33 (q, J = 6.3 Hz, 1H).
214	**238d**	m/z = 462.4 $[M+H]^{+}$	^{1}H NMR (400 MHz, DMSO) δ 10.89 (s, 1H), 8.75 (s, 1H), 8.17 - 8.07 (m, 1H), 8.02 (s, 1H), 7.81 (dd, J = 1.6, 9.2 Hz, 1H), 7.53 - 7.33 (m, 2H), 6.16 (s, 1H), 4.87 - 4.71 (m, 1H), 4.51 - 4.31 (m, 3H), 4.11 (s, 3H), 3.58 (s, 3H), 3.09 - 2.92 (m, 5H), 2.70 - 2.58 (m, 3H), 2.42 - 2.30 (m, 3H), 2.16 - 1.85 (m, 7H), 1.77 - 1.63 (m, 2H), 1.50 - 1.21 (m, 3H), 0.85 (d, J = 3.6 Hz, 3H), 0.77 - 0.65 (m, 1H), 0.52 (d, J = 4.8 Hz, 2H), 0.41 - 0.27 (m, 1H).
215	**238c**	m/z = 923.1 $[M+H]^{+}$	^{1}H NMR (400 MHz, DMSO) δ 10.89 (s, 1H), 8.77 (s, 1H), 8.47 - 8.41 (m, 1H), 8.12 (s, 1H), 8.03 (s, 1H), 7.80 (s, 1H), 7.51 - 7.36 (m, 2H), 6.15 - 6.04 (m, 1H), 4.89 - 4.71 (m, 1H), 4.61 - 4.24 (m, 4H), 4.11 (s, 3H), 3.58 (s, 3H), 3.10 - 2.91 (m, 6H), 2.37 - 2.28 (m, 4H), 2.19 - 1.99 (m, 7H), 1.94 - 1.88 (m, 1H), 1.76 - 1.64 (m, 2H), 1.40 - 1.20 (m, 2H), 0.87 (d, J = 6.0 Hz, 3H), 0.76 - 0.66 (m, 1H), 0.56 - 0.46 (m, 2H), 0.41 - 0.28 (m, 1H).

216	**238a**	m/z = 923.4 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO) δ 7.96 (s, 1H), 7.80 (s, 2H), 7.61 (d, J = 9.2 Hz, 1H), 7.45 (s, 1H), 7.29 (d, J = 8.8 Hz, 1H), 7.07 - 6.91 (m, 2H), 4.80 - 4.64 (m, 1H), 4.62 - 4.51 (m, 1H), 4.44 - 4.33 (m, 1H), 4.25 (s, 1H), 4.10 (s, 3H), 3.97 - 3.82 (m, 2H), 3.67 (s, 3H), 3.49 - 3.38 (m, 1H), 3.28 - 3.18 (m, 1H), 3.02 - 2.90 (m, 3H), 2.84 (d, J = 10.4 Hz, 1H), 2.66 - 2.58 (m, 1H), 2.49 - 2.39 (m, 3H), 2.35 - 2.25 (m, 4H), 2.17 - 2.12 (m, 4H), 2.07 - 1.97 (m, 3H), 1.19 (s, 2H), 0.86 (d, J = 7.2 Hz, 3H), 0.79 (s, 1H), 0.61 (t, J = 5.6 Hz, 2H), 0.27 - 0.18 (m, 1H).
217	**238b**	m/z = 923.4 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$-d) δ = 7.96 (s, 1H), 7.80 (s, 2H), 7.61 (br d, J = 9.3 Hz, 1H), 7.45 (s, 1H), 7.29 (br d, J = 8.9 Hz, 1H), 7.07 - 6.91 (m, 2H), 4.80 - 4.64 (m, 1H), 4.62 - 4.51 (m, 1H), 4.44 - 4.33 (m, 1H), 4.25 (br s, 1H), 4.10 (s, 3H), 3.97 - 3.82 (m, 2H), 3.67 (s, 3H), 3.49 - 3.38 (m, 1H), 3.28 - 3.18 (m, 1H), 3.02 - 2.90 (m, 3H), 2.84 (br d, J = 10.5 Hz, 1H), 2.66 - 2.58 (m, 1H), 2.49 - 2.39 (m, 3H), 2.35 - 2.25 (m, 4H), 2.17 - 2.12 (m, 4H), 2.07 - 1.97 (m, 3H), 1.19 (br s, 2H), 0.86 (br d, J = 7.0 Hz, 3H), 0.79 (br s, 1H), 0.61 (br t, J = 5.5 Hz, 2H), 0.27 - 0.18 (m, 1H)
218	**179a**	m/z = 877.5 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.31 (s, 1H), 10.91 (s, 1H), 8.74 (s, 1H), 8.06 (d, J = 2.1 Hz, 1H), 8.01 (s, 1H), 7.58 (dd, J = 8.8, 2.0 Hz, 1H), 7.42 (d, J = 10.5 Hz, 1H), 7.20 (d, J = 8.8 Hz, 1H), 6.15 (s, 1H), 4.38 (ddd, J = 26.8, 11.7, 5.4 Hz, 5H), 4.11 (d, J = 1.1 Hz, 3H), 3.24 (d, J = 4.5 Hz, 0H), 3.04 (s, 3H), 2.80 – 2.56 (m, 4H), 2.42 – 2.32 (m, 0H), 2.23 (s, 1H), 2.17 – 2.08 (m, 1H), 1.71 (d, J = 12.3 Hz, 5H), 1.34 (s, 1H), 1.02 (d, J = 12.5 Hz, 2H), 0.70 (t, J = 7.5 Hz, 1H), 0.56 – 0.49 (m, 2H), 0.36 (q, J = 6.1 Hz, 1H).
219	**199c**	m/z = 923.2 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO) δ = 10.90 (s, 1H), 8.89 - 8.74 (m, 1H), 8.27 - 8.15 (m, 1H), 8.01 (s, 1H), 7.49 - 7.35 (m, 2H), 6.45 (d, J = 1.6 Hz, 1H), 4.56 - 4.21 (m, 4H), 4.10 (s, 3H), 3.55 (s, 3H), 2.89 (s, 4H), 2.60 (d, J = 4.8 Hz, 5H), 2.43 - 2.32 (m, 3H), 2.21 - 1.95 (m, 5H), 1.89 - 1.76 (m, 2H), 1.74 - 1.57 (m, 2H), 1.42 - 1.25 (m, 2H), 1.23 - 1.12 (m, 1H), 1.03 - 0.87 (m, 2H), 0.81 (d, J = 2.8 Hz, 2H), 0.74 - 0.65 (m, 1H), 0.51 (d, J = 5.6 Hz, 2H), 0.39 - 0.21 (m, 1H)
220	**199d**	m/z = 923.3 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO) δ = 10.91 (s, 1H), 8.85 (s, 1H), 8.22 - 8.14 (m, 1H), 8.01 (s, 1H), 7.46 - 7.34 (m, 2H), 6.46 (d, J = 2.4 Hz, 1H), 4.50 - 4.20 (m, 4H), 4.10 (s, 3H), 3.55 (s, 3H), 3.21 (s, 1H), 3.06 - 2.95 (m, 2H), 2.86 - 2.76 (m, 1H), 2.75 - 2.54 (m, 3H), 2.45 - 2.27 (m, 4H), 2.18 - 1.94 (m, 5H), 1.89 - 1.76 (m, 2H), 1.66 (d, J = 10.0 Hz, 2H), 1.41 - 1.27 (m, 2H), 1.20 - 1.11 (m, 1H), 0.93 (d, J = 10.8 Hz, 1H), 0.83 (d, J = 5.6 Hz, 3H), 0.74 - 0.65 (m, 1H), 0.55 - 0.44 (m, 2H), 0.36 - 0.27 (m, 1H)
221	**180a**	m/z = 877.4 [M+H]+	^{1}H NMR (400 MHz, DMSO-d6) δ = 13.53 - 13.14 (m, 1H), 11.04 - 10.80 (m, 1H), 8.72 (s, 1H), 8.26 (s, 1H), 8.14 (d, J = 1.8 Hz, 1H), 7.99 (s, 1H), 7.79 - 7.62 (m, 1H), 7.47 - 7.25 (m, 2H), 6.14 (br s, 1H), 4.59 - 4.25 (m, 5H), 3.55 - 3.52 (m, 3H), 3.03 -

			2.84 (m, 4H), 2.80 - 2.68 (m, 2H), 2.65 - 2.59 (m, 1H), 2.55 (br d, J = 5.3 Hz, 1H), 2.39 - 2.27 (m, 1H), 2.16 - 2.06 (m, 3H), 2.06 - 1.83 (m, 4H), 1.80 - 1.55 (m, 5H), 1.37 - 1.24 (m, 1H), 1.04 - 0.89 (m, 2H), 0.74 - 0.60 (m, 1H), 0.48 (br t, J = 6.0 Hz, 2H), 0.36 - 0.26 (m, 1H)

Resolution of stereoisomeric mixtures

Mixtures of stereoisomers were resolved using methods described in **Table S1**.

Table S1.

Reactant	Separation Method	Retention Time	Final Product
tert-butyl-4-((4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate	Column: Chiralpak AD-H (250 × 30mm, internal diameter: 5μm); mobile phase: Phase A (CO_2), and Phase B (0.2% 7N methanolic ammonia in MeCN:MeOH) (1:1)); isocratic elution B%: 45%; flow rate: 3mL/min; detector: PDA; wavelength: 325 nm; column temperature: 30°C; back pressure: 100 bar	R_T = 5.45 min	**110c** (Example 8)
		R_T = 6.80 min	**110e** (Example 9)
tert-butyl-4-((4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperazin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate	Column: Chiralpak AD-H (250 × 4.6mm, internal diameter: 5μm); mobile phase: Phase A (CO_2), and Phase B (i-PrOH with 0.2% isopropyl amine); isocratic elution B%: 50%; flow rate: 3mL/min; detector: PDA; wavelength: 260 nm; column temperature: 35°C; back pressure: 100 bar	R_T = 9.52 min	**131b** (Example 10)
		R_T = 7.21 min	**131a** (Example 11)
tert-butyl-9-((1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	Column: Chiralpak IC (250 × 4.6mm, internal diameter: 5μm); mobile phase: Phase A (CO_2), and Phase B (MeCN/i-PrOH (1:1) with 0.2% diethylamine); isocratic elution B%: 45%; flow rate: 3mL/min; detector: PDA; wavelength: 310 nm; column temperature: 35°C; back pressure: 100 bar	R_T = 5.92 min	**104a** (Example 12)
		R_T = 8.40 min	**104b** (Example 13)
tert-butyl-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)-3,6-dihydropyridin-1(2H)-yl)methyl)-3-methylpiperidine-1-carboxylate	Column: Lux i-Amylose-3 (250 × 4.6mm, internal diameter: 5μm); mobile phase: Phase A (CO_2), and Phase B (i-PrOH with 0.2% isopropyl amine); isocratic elution B%: 50%; flow rate: 3mL/min; detector: PDA; wavelength: 230 nm; column temperature: 30°C; back pressure: 100 bar	R_T = 9.60 min	**130a** (Example 18)
		R_T = 12.2 min	**130d** (Example 19)

tert-butyl-9-(1-(1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)piperidin-4-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	Column: Chiralpak AD-H (250 × 4.6mm, internal diameter: 5μm); mobile phase: Phase A (CO_2), and Phase B (i-PrOH with 0.2% isopropyl amine); isocratic elution B%: 50%; flow rate: 3mL/min; detector: PDA; wavelength: 260 nm; column temperature: 35°C; back pressure: 100 bar	R_T = 4.91 min	**142b** (Example 20)
		R_T = 6.48 min	**142a** (Example 22)
tert-butyl-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)-3,6-dihydropyridin-1(2H)-yl)methyl)-3-methylpiperidine-1-carboxylate	Column: Chiralpak IK (250 × 4.6mm, internal diameter: 5μm); mobile phase: Phase A (CO_2), and Phase B (0.2% 7N methanolic ammonia in MeCN:MeOH) (1:1)); isocratic elution B%: 35%; flow rate: 3mL/min; detector: PDA; wavelength: 287 nm; column temperature: 35°C; back pressure: 100 bar	R_T = 5.85 min	**121a** (Example 26)
		R_T = 6.24 min	**121d** (Example 27)
tert-butyl-4-[[(2R)-4-[3-(6-benzyloxy-2-oxo-3H-pyridin-3-yl)-1-methyl-indazol-6-yl]-2-methyl-1-piperidyl]methyl]piperidine-1-carboxylate	Column: Chiralcel OJ-3 (50 × 4.6mm, internal diameter: 3μm); mobile phase: Phase A (CO_2), and Phase B (EtOH with 0.05% diethylamine); isocratic elution B%: 40%; flow rate: 3mL/min; detector: PDA; wavelength: 220 nm; column temperature: 35°C; back pressure: 100 bar	R_T = 1.5 min	**153a** (Example 28)
		R_T = 0.71 min	
tert-butyl-4-(1-(4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)-3,6-dihydropyridin-1(2H)-yl)-2,2,2-trifluoroethyl)piperidine-1-carboxylate	Column: Chiralpak IK (250 × 30mm, internal diameter: 10μm); mobile phase: Phase A (CO_2), and Phase B (MeCN/i-PrOH with 0.1% NH_3H_2O); isocratic elution B%: 45%; flow rate: 3mL/min; detector: PDA; wavelength: 220 nm; column temperature: 35°C; back pressure: 100 bar	R_T = 1.27 min	**140a** (Example 30)
		R_T = 1.65 min	**140b** (Example 29)
tert-butyl-4-(hydroxylmethyl)-3-methyl-piperidine-1-carboxylate	Column: Chiralpak AD (250 × 30mm, internal diameter: 10μm); mobile phase: Phase A (CO_2), and Phase B (MeOH with 0.1% NH_3H_2O); isocratic elution B%: 15%; flow rate: 3mL/min; detector: PDA; wavelength: 220 nm; column temperature: 35°C; back pressure: 100 bar	R_T = 0.82 min	**101b** (Example 33)
		R_T = 0.64 min	**101a** (Example 34)
tert-butyl-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate	Column: Chiralpak AD-H (250 × 30mm, internal diameter: 5μm); mobile phase: Phase A (CO_2), and Phase B (i-PrOH with 0.1% isopropyl amine); isocratic elution B%: 15%; flow rate: 100mL/min; detector: PDA; wavelength: 320 nm;	R_T = 7.1 min	**129b** (Example 35)
		R_T = 8.2 min	**129a** (Example 36)

	column temperature: 30°C; back pressure: 100 bar		
tert-butyl-9-((1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	Column: Chiralpak AD-H (250 × 4.6mm, internal diameter: 5μm); mobile phase: Phase A (CO_2), and Phase B (i-PrOH with 0.1% isopropyl amine); isocratic elution B%: 15%; flow rate: 3mL/min; detector: PDA; wavelength: 260 nm; column temperature: 30°C; back pressure: 100 bar	R_T = 8.78 min	**107d** (Example 37)
		R_T = 11.77 min	**107b** (Example 38)
tert-butyl-9-((1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	Column: Chiralcel OX-H (250 × 4.6mm, internal diameter: 5μm); mobile phase: Phase A (CO_2), and Phase B (MeOH with 0.5% diethylamine); isocratic elution B%: 30%; flow rate: 3mL/min; detector: PDA; wavelength: 260 nm; column temperature: 30°C; back pressure: 100 bar	R_T = 7.1 min	**107a** (Example 39)
		R_T = 10.5 min	**107c** (Example 40)
tert-butyl-9-((1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	Column: Chiralpak IH (250 × 4.6mm, internal diameter: 5μm); mobile phase: Phase A (CO_2), and Phase B (MeOH with 0.5% diethylamine); isocratic elution B%: 30%; flow rate: 3mL/min; detector: PDA; wavelength: 311 nm; column temperature: 30°C; back pressure: 100 bar	R_T = 3.83 min	**119a** (Example 41)
		R_T = 5.00 min	**119d** (Example 42)
tert-butyl-9-((1-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)-3-methylpiperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate	Column: LUX Cellulose-4 (250 × 4.6mm, internal diameter: 5μm); mobile phase: Phase A (CO_2), and Phase B (i-PrOH with 0.2% isopropyl amine); isocratic elution B%: 45%; flow rate: 3mL/min; detector: PDA; wavelength: 230 nm; column temperature: 35°C; back pressure: 100 bar	R_T = 5.73 min	**119c** (Example 43)
		R_T = 7.57 min	**119b** (Example 44)
tert-butyl-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-6-fluoro-1-methyl-indazol-7-yl]piperazin-1-yl]methyl]-3-methyl-piperidine-1-carboxylate	Column: Chiralcel OD-3 (50 × 4.6mm, internal diameter: 3μm); mobile phase: Phase A (CO_2), and Phase B (MeOH with 0.05% diethylamine); isocratic elution B%: 40%; flow rate: 3mL/min; detector: PDA; wavelength: 220 nm; column temperature: 35°C; back pressure: 100 bar	R_T = 1.71 min	**148a** (Example 48)
		R_T = 2.10 min	**148b** (Example 49)
tert-butyl-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-2,2-dimethyl-piperidine-1-carboxylate	Column: Chiralcel AS-3 (50 × 4.6mm, internal diameter: 3μm); mobile phase: Phase A (CO_2), and Phase B (MeOH with 0.05% diethylamine); gradient elution B%: 5 to 40%; flow rate: 3mL/min; detector: PDA; wavelength: 220 nm;	R_T = 1.50 min	**112a** (Example 50)
		R_T = 1.63 min	**112b** (Example 52)

	column temperature: 35°C; back pressure: 100 bar		
tert-butyl-4-[1-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-7-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridin-1-yl]ethyl]piperidine-1-carboxylate	Column: Chiralpak AD (250 × 30mm, internal diameter: 10μm); mobile phase: Phase A (CO_2), and Phase B (MeCN/i-PrOH with 0.1% NH_3H_2O); isocratic elution B%: 55%; flow rate: 3mL/min	R_T = 2.39 min	**124b** (Example 53)
		R_T = 2.99 min	**124a** (Example 57)
tert-butyl-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-3-fluoro-1-piperidyl]methyl]piperidine-1-carboxylate	Column: Chiralcel OJ-3 (50 × 4.6mm, internal diameter: 3μm); mobile phase: Phase A (CO_2), and Phase B (EtOH with 0.05% diethylamine); isocratic elution B%: 40%; flow rate: 3mL/min; detector: PDA; wavelength: 220 nm; column temperature: 35°C; back pressure: 100 bar	R_T = 0.823 min	**127c** (Example 61)
		R_T = 1.48 min	**127d** (Example 114)
tert-butyl-4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridin-1-yl]methyl]-3-(trifluoromethyl)piperidine-1-carboxylate	Column: Chiralcel AD-3 (50 × 4.6mm, internal diameter: 3μm); mobile phase: Phase A (CO_2), and Phase B (MeCN/i-PrOH with 0.05% diethylamine); isocratic elution B%: 40%; flow rate: 3mL/min; detector: PDA; wavelength: 220 nm; column temperature: 35°C; back pressure: 100 bar	R_T = 1.24 min	**139b** (Example 68)
		R_T = 1.43 min	**139a** (Example 76)
tert-butyl-4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-indazol-6-yl]-3-fluoro-piperidine-1-carboxylate	Column: Chiralcel AD-3 (50 × 4.6mm, internal diameter: 3μm); mobile phase: Phase A (CO_2), and Phase B (EtOH with 0.05% diethylamine); isocratic elution B%: 40%; flow rate: 3mL/min; detector: PDA; wavelength: 220 nm; column temperature: 35°C; back pressure: 100 bar	R_T = 1.13 min	**127a** (Example 70)
		R_T = 1.69 min	**127b** (Example 71)
tert-butyl-4-[1-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-1-methyl-7-(trifluoromethyl)indazol-6-yl]-3,6-dihydro-2H-pyridin-1-yl]ethyl]piperidine-1-carboxylate	Column: Chiralcel AD-3 (50 × 4.6mm, internal diameter: 3μm); mobile phase: Phase A (CO_2), and Phase B (i-PrOH with 0.05% diethylamine); isocratic elution B%: 40%; flow rate: 3mL/min; detector: PDA; wavelength: 220 nm; column temperature: 35°C; back pressure: 100 bar	R_T = 0.794 min	**109b** (Example 75)
		R_T = 1.299 min	**109a** (Example 77)
tert-butyl-4-[1-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5-fluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2H-pyridin-1-yl]ethyl]piperidine-1-carboxylate	Column: Chiralcel IG-3 (50 × 4.6mm, internal diameter: 3μm); mobile phase: Phase A (CO_2), and Phase B (MeCN/i-PrOH with 0.05% diethylamine); isocratic elution B%: 50%; flow rate: 3mL/min; detector: PDA; wavelength: 220 nm; column temperature: 35°C; back pressure: 100 bar	R_T = 0.879 min	**113a** (Example 54)
		R_T = 1.51 min	**113b**

tert-butyl-4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate	Column: Chiralpak AD-H (250 × 4.6mm, internal diameter: 5μm); mobile phase: Phase A (CO_2), and Phase B (i-PrOH with 0.2% isopropyl amine); isocratic elution B%: 15%; flow rate: 3mL/min; detector: PDA; wavelength: 310 nm; column temperature: 35°C; back pressure: 100 bar	R_T = 9.62 min	**110a** (Example 78)
		R_T = 11.5 min	**110f** (Example 46)
tert-butyl 4-[1-[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]ethyl]piperidine-1-carboxylate	Column: Chiralpak AD-H (250 × 30 mm, internal diameter: 10 μm); mobile phase: Phase A (CO_2), and Phase B (i-PrOH/MeCN with 0.1% NH_3H_2O); isocratic elution B%: 65%; flow rate: 100mL/min; detector: PDA; wavelength: 220 nm; column temperature: 25°C; back pressure: 100 bar	R_T = 0.83 min	**135b** (Example 118)
		R_T = 2.11 min	**135a** (Example 65)
tert-butyl 4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*-pyridin-1-yl]methyl]-3-methyl-piperidine-1-carboxylate	Column: Chiralpak AD-3 (50 × 4.6mm, internal diameter: 3μm); mobile phase: Phase A (CO_2), and Phase B (i-PrOH with 0.2% diethylamine); isocratic elution B%: 40%; flow rate: 3mL/min; detector: PDA; wavelength: 220 nm; column temperature: 35°C; back pressure: 100 bar	R_T = 1.26 min	**199a** (Example 136)
		R_T = 1.90 min	**199b** (Example 137)
tert-butyl 4-((4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate	Column: Chiralpak AD-H (250 × 4.6mm, internal diameter: 5μm); mobile phase: Phase A (CO_2), and Phase B (i-PrOH with 0.2% isopropyl amine); isocratic elution B%: 50%; flow rate: 100mL/min; detector: PDA; wavelength: 322 nm; column temperature: 30°C; back pressure: 100 bar	R_T = 4.64 min	**111a** (Example 145)
		R_T = 5.59 min	**111b** (Example 146)
tert-butyl 4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate	Column: LUX Cellulose-4 (250 × 4.6mm, internal diameter: 5μm); mobile phase: Phase A (CO_2), and Phase B (MeOH with 0.2% diethylamine); isocratic elution B%: 50%; flow rate: 3mL/min; detector: PDA; wavelength: 322 nm; column temperature: 35°C; back pressure: 100 bar	R_T = 7.25 min	**189a** (Example 147)
		R_T = 7.26 min	**189b** (Example 148)
tert-butyl 4-((4-(3-(6-(benzyloxy)-2-hydroxypyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate	Column: LUX-i-Amylose-3 (250 × 4.6mm, internal diameter: 5μm); mobile phase: Phase A (CO_2), and Phase B (i-PrOH with 0.2% isopropyl amine); isocratic elution B%: 50%; flow rate: 3mL/min; detector: PDA; wavelength: 322 nm; column temperature: 35°C; back pressure: 100 bar	R_T = 7.97 min	**123a** (Example 150)
		R_T = 9.91 min	**123b** (Example 153)

tert-butyl 4-((4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-5-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3,3-dimethylpiperidine-1-carboxylate	Column: Chiralpak AD-H (250 × 30mm, internal diameter: 5μm); mobile phase: Phase A (CO_2), and Phase B (i-PrOH with 0.1% isopropyl amine); isocratic elution B%: 50%; flow rate: 100mL/min; detector: PDA; wavelength: 322 nm; column temperature: 30°C; back pressure: 100 bar	R_T = 3.91 min	**160b** (Example 151)
		R_T = 5.09 min	**160a** (Example 152)
tert-butyl 4-((4-(3-(2,6-bis(benzyloxy)pyridin-3-yl)-1-methyl-1*H*-indazol-6-yl)piperazin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate	Column: Chiralpak IC (250 × 4.6mm, internal diameter: 5μm); mobile phase: Phase A (CO_2), and Phase B (MeCN:i-PrOH (1:1) with 0.2% isopropyl amine); isocratic elution B%: 40%; flow rate: 3mL/min; detector: PDA; wavelength: 322 nm; column temperature: 50°C; back pressure: 100 bar	R_T = 7.51 min	**185a** (Example 154)
		R_T = 8.47 min	**185b** (Example 155)
tert-butyl 4-((4-(3-(2-(benzyloxy)-6-hydroxypyridin-3-yl)-7-fluoro-1-methyl-1*H*-indazol-6-yl)piperidin-1-yl)methyl)-3-fluoropiperidine-1-carboxylate	Column: Chiralpak OJ-H (250 × 4.6mm, internal diameter: 5μm); mobile phase: Phase A (CO_2), and Phase B (MeOH with 0.5% diethylamine); isocratic elution B%: 40%; flow rate: 3mL/min; detector: PDA; wavelength: 321 nm; column temperature: 30°C; back pressure: 100 bar	R_T = 4.31 min	**133b** (Example 156)
		R_T = 5.30 min	**133a** (Example 157)
tert-butyl 4-[[4-[3-(2,6-dibenzyloxy-3-pyridyl)-5,7-difluoro-1-methyl-indazol-6-yl]-3,6-dihydro-2*H*pyridin-1-yl]methyl]-3-fluoro-piperidine-1-carboxylate	Column: Chiralcel IG-3 (50 × 4.6mm, internal diameter: 3μm); mobile phase: Phase A (CO_2), and Phase B (EtOH with 0.05% diethylamine); isocratic elution B%: 40%; flow rate: 3mL/min; detector: PDA; wavelength: 220 nm; column temperature: 35°C; back pressure: 100 bar	R_T = 1.56 min	**220b** (Example 172)
		R_T = 1.9 min	**220a** (Example 173)

Example B1

HiBiT Based Degradation Assay

Human BCL6 protein coding open reading frame fused with N-terminal HiBiT coding sequence was synthesized from Integrated DNA Technologies (IDT). Next, the N-HiBiT-BCL6 sequence was cloned into pLV-UBC-PGK-Puro, a lentivirus plasmid purchased from Vectorbuilder, to generate pLV-UBC-N-HiBiT-BCL6-PGK-puro. Lentiviral particles were generated from Lenti-X™ 293T cells (Clontech) by co-transfection of pLV-UBC-N-HiBiT-BCL6-PGK-puro plasmids and lentiviral packaging plasmid mix (Cellecta). HT1080 [HT1080] (ATCC CCL-121™) cells were infected with the lentivirus, and HT1080 cells stably integrated

with the lentiviral vectors were established by incubation with 1 μg/mL puromycin (ThermoFisher).

HT1080 cells expressing N-terminal HiBiT tagged BCL6 were dispensed into a 384-well plate pre-spotted with compounds at varying concentrations. Five thousand cells were seeded into each well in 40 μL of RPMI 1640 media plus 10% Fetal Bovine Serum (10082-147, ThermoFisher). After 5 hours of incubation at 37°C with 5% CO_2, 30 μL of the NANO-GLO® HiBiT Lytic Detection System working solution (Promega) was added to each well and incubated at room temperature for 15 min. After incubation, luminescence was read on a PHERAstar FSX Plate Reader (BMG). BCL6 degradation at each indicated concentration was normalized with DMSO control. The BCL6 degradation curves were plotted using a four-parameter logistic model.

Table B1 provides the Y_{min} and EC_{50} values for certain compounds of this disclosure.

Table B1.

Compound No.	EC_{50} (5 h)	Y_{min} (5 h)
101a	+++	+++
101b	+++	+++
101c	+++	+++
101d	+++	+++
102a	+++	++
102b	+++	+++
103a	++	+
103b	+++	++
104a	+++	+++
104b	+++	+++
105a	+++	++
105b	+++	+++
106a	+++	+
107a	+++	+++
107b	+++	+++
107c	+++	+++
107d	+++	+++
108a	+++	++
109a	+++	+++
109b	+++	+++
110a	+++	+++
110b	+++	+++
110c	+++	+++

Compound No.	EC_{50} (5 h)	Y_{min} (5 h)
110d	+++	+++
110e	+++	+++
110f	+++	+++
111a	+++	+++
111b	+++	+++
112a	+++	+++
112b	+++	+++
113a	+++	+++
113b	+++	+++
114a	+++	+++
114b	+++	+++
115a	+++	++
116a	+++	++
116b	++	++
116c	+++	++
116d	++	+
117a	+++	+++
117b	+++	+++
118a	+++	+++
118b	+++	+++
119a	+++	+++
119b	+++	+++
119c	+++	+++
119d	+++	+++
120a	+++	+++
120b	+++	+++
121a	+++	+++
121b	+++	+++
121c	+++	+++
121d	+++	+++
121e	+++	+++
122a	+++	+++
123a	+++	+++
123b	+++	+++
124a	+++	+++
124b	+++	+++
125a	+++	+++
126a	+++	+++
127a	+++	+++
127b	+++	++
127c	+++	+++
127d	+++	+++

Compound No.	EC_{50} (5 h)	Y_{min} (5 h)
128a	+++	++
129a	+++	+++
129b	+++	+++
130a	+++	+++
130b	+++	+++
130c	+++	+++
130d	+++	+++
130e	+++	+++
131a	+++	++
131b	+++	++
132a	+++	+++
133a	+++	+++
133b	+++	+++
134a	+++	++
135a	+++	+++
135b	+++	+++
136a	+++	+++
137a	+++	+++
138a	+++	+++
139a	+++	+++
139b	+++	+++
140a	+	++
140b	+	+
141a	+++	+++
142a	+++	+++
142b	+++	+++
143a	+++	++
144a	+++	+++
145a	+++	+++
146a	+++	+++
146b	+++	+++
147a	+++	+++
148a	+++	+++
148b	+++	++
149a	+++	+++
150a	+++	+++
151a	+++	+++
151b	+++	+++
152a	+++	+++
153a	+++	++
154a	+++	+++
155a	+++	++

Compound No.	EC_{50} (5 h)	Y_{min} (5 h)
156a	+++	+++
157a	+++	+++
158a	+++	+++
159a	+++	+++
160a	+++	+++
160b	+++	++
161a	+++	+++
162a	+++	+++
163a	+++	+++
164a	+++	++
165a	+++	++
166a	+++	++
166b	+++	++
167a	+++	+++
168a	+++	++
169a	+++	+++
169b	+++	+++
170a	+++	++
171a	+++	+++
172a	+++	++
173a	+++	+++
174a	+++	+++
175a	+++	+++
176a	+++	+++
177a	+++	+++
178a	+++	++
181a	+++	++
182a	+++	+++
185a	+++	++
185b	+++	++
186a	+++	+++
187a	+++	+++
187b	+++	++
188a	+++	+++
188b	+++	++
189a	+++	++
189b	+++	+++
190a	+++	+++
191a	+++	+++
192a	+++	+++
193a	++	+++
194a	+++	+++

Compound No.	EC_{50} (5 h)	Y_{min} (5 h)
195a	++	++
196a	+++	+++
197a	++	++
198a	++	++
199a	+++	+++
199b	+++	+++
200a	+++	+++
201a	+++	+++
202a	+++	+++
202b	+++	+++
203a	+++	+++
203b	++	++
204a	+++	+++
205a	+++	++
206a	+++	++
207a	+++	+++
208a	+++	+++
209a	+++	+++
209b	+++	+++
210a	+++	+++
210b	+++	+++
211a	+++	+++
212a	+++	+++
213a	+++	+++
214a	+++	+++
215a	+++	+++
216a	++	+
217a	+++	+++
218a	+++	+++
219a	+++	+++
219b	+++	+++
220a	+++	+++
220b	+++	+++
221a	+++	+++
222a	+++	+++
223a	+++	++
224a	+++	+++
225a	+++	++
226a	+++	++
227a	+++	+++
228a	+++	+++
229a	+++	+++

Compound No.	EC_{50} (5 h)	Y_{min} (5 h)
230a	+++	+
231a	+++	+++
231b	+++	+++
232a	+++	+++
232b	+++	+++
233a	+++	+++
233b	+++	+++
234a	+++	+++
234b	+++	+++
235a	+++	+++
236a	+++	+++
237a	+++	+++
238a	+++	+++
238b	+++	+++
238c	+++	+++
238d	+++	+++
239a	+++	+++
239b	+++	+++
501a	+++	+++
502a	+++	+++
503a	++	++
504a	+++	+++
505a	+++	++
506a	++	+
507a	+++	+++

Notes:

$Y_{min} \leq 30\%$: "+++"; $30\% < Y_{min} \leq 50\%$: "++"; $50\% < Y_{min} \leq 70\%$: "+".

$EC_{50} \leq 25$ nM: "+++"; 25 nM $< EC_{50} \leq 100$ nM: "++"; 100 nM $< EC_{50} \leq 1000$ nM: "+".

5

Example B2

Cell Proliferation Assay

OCI-Ly1 (DSMZ: ACC 722), SU-DHL-5 (ATCC CRL-2958™), Toledo (ATCC CRL-2631™), and WSU-DLCL2 (DSMZ: ACC 575) cells are seeded at 1,000 cells per well in 50 µL RPMI 1640 media plus 10% Fetal Bovine Serum (10082-147, Thermofisher) in black 384-well plates. The plates are pre-spotted with compounds at varying concentrations. After 5 days of incubation at 37°C with 5% CO_2, cell viabilities are assessed using CELLTITER-GLO®

Cell Viability Assay kit according to manufacturer's instructions (Promega). Relative cell proliferation at each concentration is normalized against DMSO control.

References:

OCI-Ly1 cells:

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WSU-DLCL2 cells:

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Example B3

Pharmacokinetic Assessment

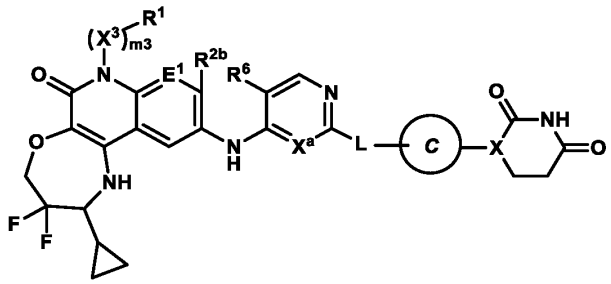
Pharmacokinetics (PK) studies are conducted on male CD-1 mice by two delivery routes: intravenous (IV) injection and oral gavage (PO). Mice for the IV group (n = 3) are allowed free access to food and water and mice for the PO group (n = 3) are fasted 6-8 hours prior to dosing. The test articles are formulated in solution for the IV route (commonly 5% DMSO/10%Solutol HS15/85% water (pH 5)) and solution or suspension for the PO route (commonly 100% PEG 400). On the day of the experiment, test article is administered via vein injection (commonly 1 mg/kg) for IV route or via oral gavage (commonly 10 mg/kg) for PO route, respectively. Blood samples are collected via the saphenous vein using a needle

(commonly 20 G) at 0.83 to 24 hours post dose. Approximately 30 μL of blood per timepoint is collected into pre-chilled tubes using K_2EDTA as the anti-coagulant. After collection of blood samples at each time point, the blood samples are stored on ice. Blood samples are centrifuged within 0.5 hour of collection to separate plasma. Centrifugation is conducted at 2500 x g for 15 minutes at 4 °C. Plasma samples are immediately acidified (commonly 0.1 M sodium citrate (pH=5) buffer). The samples are then submitted to LC-MS/MS for sample analysis. Pharmacokinetics parameters, including clearance (IV), area under the curve (AUC), and oral bioavailability (%F) are calculated by non-compartmental model.

EXEMPLARY EMBODIMENTS

P01 Embodiments

Embodiment 1. A compound of Formula (**I**):



Formula (**I**)

or a pharmaceutically acceptable salt thereof, wherein:

$\mathbf{E^1}$ is $C\mathbf{R^{2a}}$ or N;

$\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are independently selected from the group consisting of: H, halo, cyano, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, and C_{1-3} haloalkoxy;

m3 is 0 or 1;

$\mathbf{X^3}$ is C_{1-3} alkylene optionally substituted with 1-3 $\mathbf{R^c}$;

$\mathbf{R^1}$ is selected from the group consisting of: H and halo;

$\mathbf{X^a}$ is selected from the group consisting of: N and $C\mathbf{R^{Xa}}$;

$\mathbf{R^6}$ and $\mathbf{R^{Xa}}$ are independently selected from the group consisting of: H, halo, C_{1-2} alkyl, C_{1-2} haloalkyl, C_{1-2} alkoxy, CN, and -C≡CH;

L is $-(\mathbf{L^A})_{n1}-$, wherein:

n1 is an integer from 1 to 5; and

each $\mathbf{L^A}$ is independently selected from the group consisting of: $\mathbf{L^{A1}}$, $\mathbf{L^{A3}}$, and $\mathbf{L^{A4}}$, wherein:

0-2 of $\mathbf{L^A}$ is $\mathbf{L^{A1}}$;

0-2 of $\mathbf{L^A}$ is $\mathbf{L^{A3}}$; and

1-3 of $\mathbf{L^A}$ is $\mathbf{L^{A4}}$,

each $\mathbf{L^{A1}}$ is independently selected from the group consisting of: $-CH_2-$, $-CH\mathbf{R^L}-$, and $-C(\mathbf{R^L})_2-$, wherein:

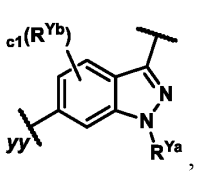
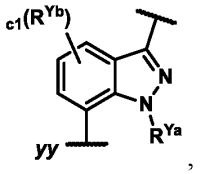
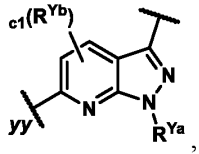
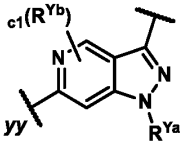
each $\mathbf{R^L}$ is independently selected from the group consisting of: halo, cyano, -OH, -C_{1-6} alkoxy, -C_{1-6} haloalkoxy, -(C_{0-3} alkylene)-(C_{3-5} cycloalkyl), -(C_{0-3} alkylene)-(4-6 membered heterocyclyl), and C_{1-6} alkyl optionally substituted with 1-6 $\mathbf{R^c}$;

each $\mathbf{L^{A3}}$ is independently selected from the group consisting of: -N($\mathbf{R^d}$)-, -N($\mathbf{R^b}$)-, -O-, -$S(O)_{0-2}$-, and C(=O);

each $\mathbf{L^{A4}}$ is independently selected from the group consisting of:

(a) C_{3-15} cycloalkylene or 4-15 membered heterocyclylene, each of which is optionally substituted with 1-6 substituents independently selected from the group consisting of: $\mathbf{R^a}$ and $\mathbf{R^b}$; and

(b) phenylene or 5-6 membered heteroarylene, each of which is optionally substituted with 1-3 substituents independently selected from the group consisting of: $\mathbf{R^a}$ and $\mathbf{R^b}$;

Ring C is selected from the group consisting of: , , , and , wherein:

c1 is 0, 1, or 2;

each $\mathbf{R^{Ya}}$ and $\mathbf{R^{Yb}}$ is independently selected from the group consisting of $\mathbf{R^a}$ and $\mathbf{R^b}$; and

yy represents the point of attachment to **L**;

X is CH or N;

each $\mathbf{R^a}$ is independently selected from the group consisting of:

(a) halo;

(b) cyano;

(c) -OH;

(d) oxo;

(e) C_{1-6} alkoxy optionally substituted with 1-6 $\mathbf{R^c}$;

(f) $-N\mathbf{R^d}\mathbf{R^e}$;

(g) $C(=O)C_{1-6}$ alkyl;

(h) $C(=O)OC_{1-6}$ alkyl;

(i) $C(=O)N(\mathbf{R^f})_2$;

(j) $S(O)_{0-2}(C_{1-6}$ alkyl);

(k) $S(O)_{0-2}(C_{1-6}$ haloalkyl); and

(l) C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, each optionally substituted with 1-6 $\mathbf{R^c}$;

each $\mathbf{R^b}$ is independently selected from the group consisting of: $-(\mathbf{L^b})_b-\mathbf{R^{b1}}$ and $-\mathbf{R^{b1}}$, wherein:

each **b** is independently 1, 2, or 3;

each $\mathbf{L^b}$ is independently selected from the group consisting of: -O-, -N(H)-, $-N(C_{1-3}$ alkyl)-, $-S(O)_{0-2}-$, C(=O), and C_{1-3} alkylene; and

each $\mathbf{R^{b1}}$ is independently selected from the group consisting of: C_{3-6} cycloalkyl and 4-8 membered heterocyclyl, each of which is optionally substituted with 1-3 $\mathbf{R^g}$;

each $\mathbf{R^c}$ is independently selected from the group consisting of: halo, cyano, -OH, $-C_{1-6}$ alkoxy, $-C_{1-6}$ haloalkoxy, $-N\mathbf{R^d}\mathbf{R^e}$, $C(=O)C_{1-6}$ alkyl, $C(=O)OC_{1-6}$ alkyl, $C(=O)N(\mathbf{R^f})_2$, $S(O)_{0-2}(C_{1-6}$ alkyl), and $S(O)_{0-2}(C_{1-6}$ haloalkyl);

each $\mathbf{R^d}$ and $\mathbf{R^e}$ is independently selected from the group consisting of: H, $C(=O)C_{1-6}$ alkyl, $C(=O)C_{1-6}$ haloalkyl, $C(=O)OC_{1-6}$ alkyl, $C(=O)OC_{1-6}$ haloalkyl, $C(=O)N(\mathbf{R^f})_2$, $S(O)_{1-2}(C_{1-6}$ alkyl), $S(O)_{1-2}(C_{1-6}$ haloalkyl), $S(O)_{1-2}N(\mathbf{R^f})_2$, and C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^h}$;

each $\mathbf{R^f}$ is independently selected from the group consisting of: H and C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^h}$;

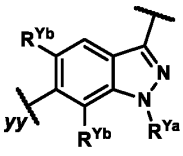
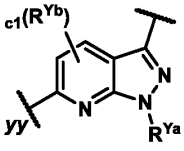
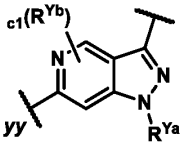
each $\mathbf{R^g}$ is independently selected from the group consisting of: $\mathbf{R^h}$, oxo, C_{1-3} alkyl, and C_{1-3} haloalkyl; and

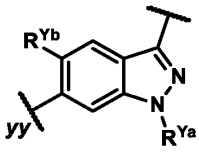
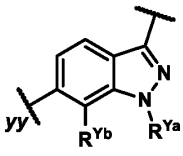
each $\mathbf{R^h}$ is independently selected from the group consisting of: halo, cyano, -OH, $-(C_{0-3}$ alkylene)-C_{1-6} alkoxy, $-(C_{0-3}$ alkylene)-C_{1-6} haloalkoxy, $-(C_{0-3}$ alkylene)-NH_2, $-(C_{0-3}$ alkylene)-N(H)(C_{1-3} alkyl), and $-(C_{0-3}$ alkylene)-$N(C_{1-3}$ alkyl)$_2$.

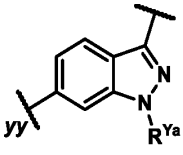
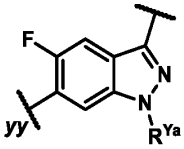
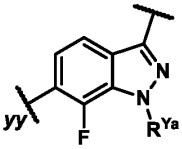
Embodiment 2. The compound of Embodiment 1, wherein one or more of **(1)-(5)** applies:

(1) $\mathbf{R^{2b}}$ is selected from the group consisting of: halo, cyano, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, and C_{1-3} haloalkoxy;

(2) $\mathbf{E^1}$ is N;

(3) Ring Cis selected from the group consisting of: , , , and ;

(4) Ring C is selected from the group consisting of:  and , wherein $\mathbf{R^{Yb}}$ is C_{1-3} alkyl optionally substituted with 1-3 F; and/or

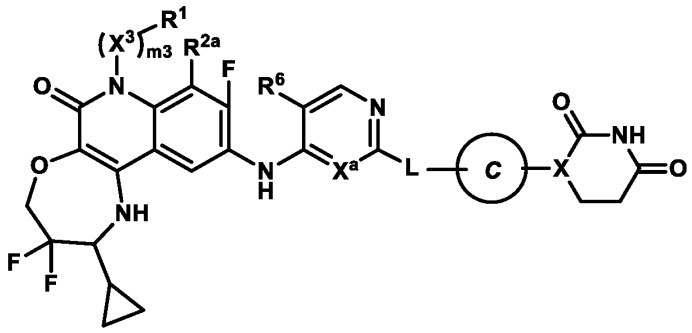
(5) Ring C is selected from the group consisting of: , , , and , wherein $\mathbf{R^{Ya}}$ is $-(C_{0-3}$ alkylene)-$\mathbf{R^{b1}}$ or C_{2-4} alkyl optionally substituted with 1-3 $\mathbf{R^c}$.

Embodiment 3. The compound of Embodiment 1 or 2, wherein $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are each independently H or F.

Embodiment 4. The compound of any one of Embodiments 1-3, wherein $\mathbf{E^1}$ is $C\mathbf{R^{2a}}$; and each of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ is H.

Embodiment 5. The compound of any one of Embodiments 1-3, wherein $\mathbf{E^1}$ is $C\mathbf{R^{2a}}$; one of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ is F; and the other of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ is H.

Embodiment 6. The compound of Embodiment 1, wherein the compound of Formula (**I**) is a compound of Formula (**I-1**):

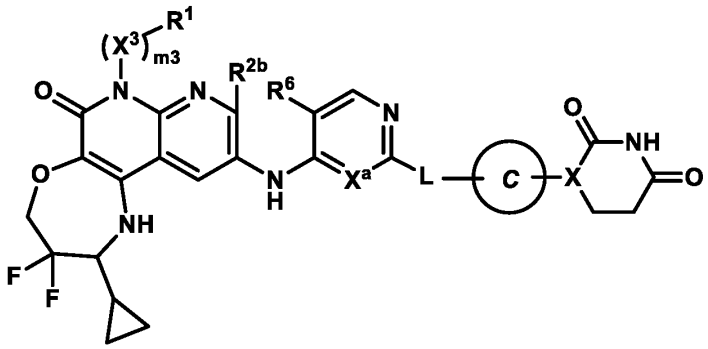


Formula (**I-1**)

or a pharmaceutically acceptable salt thereof.

Embodiment 7. The compound of Embodiment 6, wherein $\mathbf{R^{2a}}$ is H.

Embodiment 8. The compound of Embodiment 1, wherein the compound of Formula (**I**) is a compound of Formula (**I-2**):



Formula (**I-2**)

or a pharmaceutically acceptable salt thereof.

Embodiment 9. The compound of Embodiment 8, wherein $\mathbf{R^{2b}}$ is H.

Embodiment 10. The compound of any one of Embodiments 1-9, wherein **m3** is 1; and $\mathbf{R^1}$ is H.

Embodiment 11. The compound of any one of Embodiments 1-10, wherein $-(\mathbf{X^3})_{m3}\text{-}\mathbf{R^1}$ is $C_{1\text{-}3}$ alkyl.

Embodiment 12. The compound of any one of Embodiments 1-11, wherein $-(\mathbf{X^3})_{m3}\text{-}\mathbf{R^1}$ is methyl.

Embodiment 13. The compound of any one of Embodiments 1-12, wherein $\mathbf{R^6}$ is -Cl or -F.

Embodiment 14. The compound of any one of Embodiments 1-13, wherein $\mathbf{R^6}$ is -Cl.

Embodiment 15. The compound of any one of Embodiments 1-14, wherein $\mathbf{X^a}$ is N.

Embodiment 16. The compound of any one of Embodiments 1-15, wherein **L** is $-(\mathbf{L^A})_{n1}-$, wherein:

n1 is an integer from 2 to 4; and

each $\mathbf{L^A}$ is independently selected from the group consisting of: $\mathbf{L^{A1}}$, $\mathbf{L^{A3}}$, and $\mathbf{L^{A4}}$, wherein:

0-2 of $\mathbf{L^A}$ is $\mathbf{L^{A1}}$;

0-2 of $\mathbf{L^A}$ is $\mathbf{L^{A3}}$; and

2-3 of $\mathbf{L^A}$ are $\mathbf{L^{A4}}$, wherein:

each $\mathbf{L^{A4}}$ is independently a $C_{3\text{-}10}$ cycloalkylene or a 4-12 membered heterocyclylene, each of which is optionally substituted with 1-3 $\mathbf{R^a}$, wherein:

each $\mathbf{R^a}$ present on $\mathbf{L^{A4}}$ is independently selected from the group consisting of: -F, CN, $C_{1\text{-}3}$ alkoxy, OH, and $C_{1\text{-}3}$ alkyl optionally substituted with 1-3 F; and

each $\mathbf{R^L}$ is independently selected from the group consisting of: -F, -OH, and $C_{1\text{-}3}$ alkyl optionally substituted with 1-3 $\mathbf{R^c}$ (e.g., $C_{1\text{-}3}$ alkyl optionally substituted with 1-3 -F).

Embodiment 17. The compound of any one of Embodiments 1-15, wherein **L** is selected from the group consisting of:

-$\mathbf{L}^{A4a}$-$\mathbf{L}^{A1}$-$\mathbf{L}^{A4b}$-*bb*;

-$\mathbf{L}^{A4a}$-$\mathbf{L}^{A3}$-$\mathbf{L}^{A4b}$-*bb*;

-$\mathbf{L}^{A4a}$-$\mathbf{L}^{A4b}$-*bb*;

-$\mathbf{L}^{A4a}$-$\mathbf{L}^{A3}$-$\mathbf{L}^{A4c}$- $\mathbf{L}^{A4b}$-*bb*; and

-$\mathbf{L}^{A4a}$-$\mathbf{L}^{A4c}$-$\mathbf{L}^{A3}$-$\mathbf{L}^{A4b}$-*bb*, wherein:

$\mathbf{L}^{A4a}$, $\mathbf{L}^{A4b}$, and $\mathbf{L}^{A4c}$ are each an independently selected $\mathbf{L}^{A4}$,

$\mathbf{L}^{A3}$ is selected from the group consisting of: -O- and -N($\mathbf{R}^{d}$)-, and

bb represents the point of attachment to **Ring C**.

Embodiment 18. The compound of any one of Embodiments 1-15, wherein **L** is selected from the group consisting of:

-$\mathbf{L}^{A4a}$-$\mathbf{L}^{A1}$-$\mathbf{L}^{A4b}$-*bb*;

-$\mathbf{L}^{A4a}$-$\mathbf{L}^{A3}$-$\mathbf{L}^{A4b}$-*bb*; and

-$\mathbf{L}^{A4a}$-$\mathbf{L}^{A4b}$-*bb*; wherein:

$\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ are each an independently selected $\mathbf{L}^{A4}$,

$\mathbf{L}^{A3}$ is selected from the group consisting of: -O- and -N($\mathbf{R}^{d}$)-, and

bb represents the point of attachment to **Ring C**.

Embodiment 19. The compound of Embodiment 17 or 18, wherein:

$\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ are independently 4-12 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R}^{a}$;

$\mathbf{L}^{A4c}$ when present is a C_{3-10} cycloalkylene optionally substituted with 1-3 $\mathbf{R}^{a}$; and

each $\mathbf{R}^{L}$ is independently selected from the group consisting of: -F, -OH, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R}^{c}$ (e.g., C_{1-3} alkyl optionally substituted with 1-3 -F).

Embodiment 20. The compound of any one of Embodiments 1-15 or 17-19, wherein **L** is:

-$\mathbf{L}^{A4a}$-$\mathbf{L}^{A1}$-$\mathbf{L}^{A4b}$-*bb*, wherein:

$\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ are independently 4-12 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R}^{a}$; and

each $\mathbf{R}^{L}$ is independently selected from the group consisting of: -F, -OH, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R}^{c}$ (e.g., C_{1-3} alkyl optionally substituted with 1-3 -F).

Embodiment 21. The compound of any one of Embodiments 17-20, wherein $\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ are independently monocyclic 4-6 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R}^{a}$.

Embodiment 22. The compound of any one of Embodiments 17-21, wherein one of $\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ is a 1,4-piperidinylene; and

the other of $\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ is independently selected from the group consisting of: 1,4-piperidinylene and 1,4-piperazinylene,

wherein each of the 1,4-piperidinylene or 1,4-piperazinylene is optionally substituted with 1-2 $\mathbf{R}^{a}$.

Embodiment 23. The compound of any one of Embodiments 17-20, wherein one of $\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ is a monocyclic 4-6 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R}^{a}$; and

the other of $\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ is a bicyclic spirocyclic 6-12 (e.g., 10-12) membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R}^{a}$.

Embodiment 24. The compound of any one of Embodiments 17-20 or 23, wherein $\mathbf{L}^{A4b}$ is a monocyclic 4-6 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R}^{a}$; and

$\mathbf{L}^{A4a}$ is a bicyclic spirocyclic 6-12 (e.g., 10-12) membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R}^{a}$.

Embodiment 25. The compound of any one of Embodiments 17-20 or 23-24, wherein $\mathbf{L}^{A4b}$ is 1,4-piperidinylene optionally substituted with 1-2 $\mathbf{R}^{a}$; and

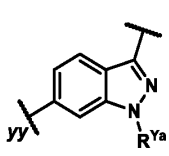
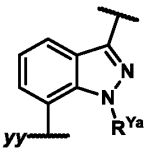
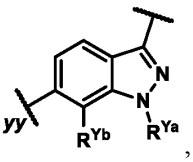
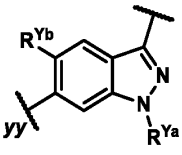
$\mathbf{L}^{A4a}$ is a bicyclic spirocyclic 10-12 membered nitrogen-containing heterocyclylene optionally substituted with 1-2 $\mathbf{R}^{a}$.

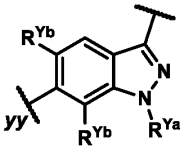
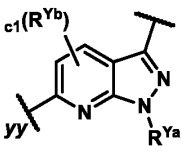
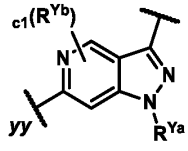
Embodiment 26. The compound of any one of Embodiments 17-25, wherein $\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ each contain 1-2 ring nitrogen atoms and no additional ring heteroatoms.

Embodiment 27. The compound of any one of Embodiments 17-26, wherein each R^a present on L^{A4a}, L^{A4b}, and/or L^{A4c} is independently selected from the group consisting of: -F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F.

Embodiment 28. The compound of any one of Embodiments 17-27, wherein L^{A1} is $-CH_2-$.

Embodiment 29. The compound of any one of Embodiments 17-27, wherein L^{A1} is $-CHR^L-$, wherein R^L is C_{1-3} alkyl optionally substituted with 1-3 F (e.g., R^L is methyl or CF_3).

Embodiment 30. The compound of any one of Embodiments 1-29, wherein **Ring C** is selected from the group consisting of: , , ,  and .

Embodiment 31. The compound of any one of Embodiments 1-29, wherein **Ring C** is selected from the group consisting of: , , and .

Embodiment 32. The compound of Embodiment 30 or 31, wherein:

R^{Ya} is selected from the group consisting of:

(a) C_{1-6} alkyl optionally substituted with 1-3 R^c, and

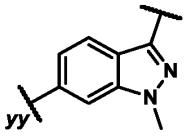
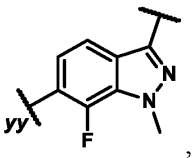
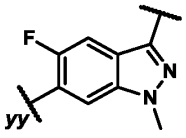
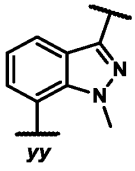
(b) –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^{g}}$; and

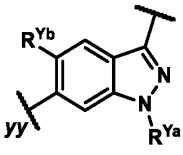
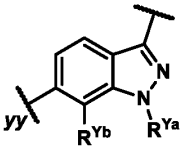
each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^{c}}$ (e.g., C_{1-3} alkyl optionally substituted with 1-3 -F).

Embodiment 33. The compound of any one of Embodiments 30-32, wherein:

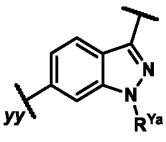
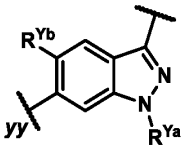
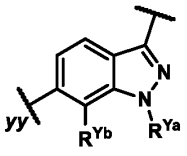
$\mathbf{R^{Ya}}$ is C_{1-3} alkyl optionally substituted with 1-3 -F; and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: -F and C_{1-3} alkyl optionally substituted with 1-3 -F.

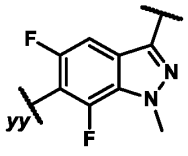
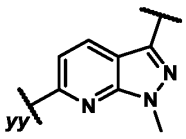
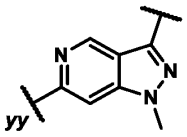
Embodiment 34. The compound of any one of Embodiments 1-30, wherein **Ring C** is selected from the group consisting of: , , , and .

Embodiment 35. The compound of any one of Embodiments 1-30, wherein **Ring C** is selected from the group consisting of:  and , wherein $\mathbf{R^{Yb}}$ is C_{1-3} alkyl optionally substituted with 1-3 F.

Embodiment 36. The compound of Embodiment 35, wherein $\mathbf{R^{Ya}}$ is methyl.

Embodiment 37. The compound of any one of Embodiments 1-30, wherein **Ring C** is selected from the group consisting of: ,  and , wherein $\mathbf{R^{Ya}}$ is –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$ or C_{2-4} alkyl optionally substituted with 1-3 $\mathbf{R^{c}}$.

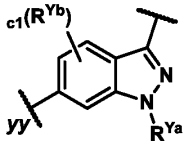
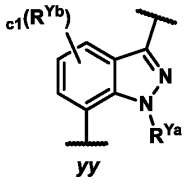
Embodiment 38. The compound of Embodiment 37, wherein $\mathbf{R^{Yb}}$ is independently -F or C_{1-3} alkyl optionally substituted with 1-3 -F.

Embodiment 39. The compound of any one of Embodiments 1-29 or 31, wherein **Ring C** is selected from the group consisting of: , , and .

Embodiment 40. The compound of any one of Embodiments 1-39, wherein **X** is CH.

Embodiment 41. The compound of any one of Embodiments 1-29, wherein:

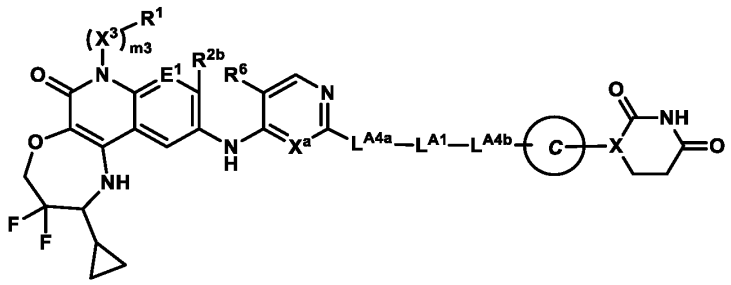
X is CH; and

Ring C is selected from the group consisting of:  and , wherein:

$\mathbf{R^{Ya}}$ is C_{1-3} alkyl optionally substituted with 1-3 -F, and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: -F and C_{1-3} alkyl optionally substituted with 1-3 -F.

Embodiment 42. The compound of Embodiment 1, wherein the compound of Formula (**I**) is a compound of Formula (**I-a**):



Formula (**I-a**)

or a pharmaceutically acceptable salt thereof, wherein:

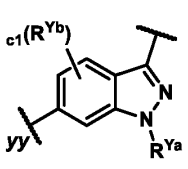
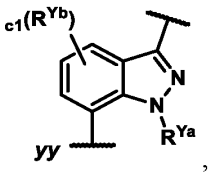
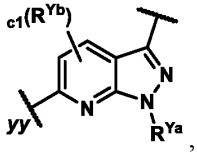
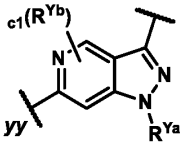
$\mathbf{E^1}$ is $C\mathbf{R^{2a}}$ or N;

$\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are each independently selected from the group consisting of: H and F;

$\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ are independently 4-12 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R^a}$;

$\mathbf{L^{A1}}$ is CH_2 or $CH\mathbf{R^L}$, and

$\mathbf{R^L}$ is selected from the group consisting of: -F, -OH, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$; and

Ring C is selected from the group consisting of: , , , and , wherein:

c1 is 0, 1, or 2;

$\mathbf{R^{Ya}}$ is selected from the group consisting of:

(a) C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$, and

(b) –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^{g}}$;

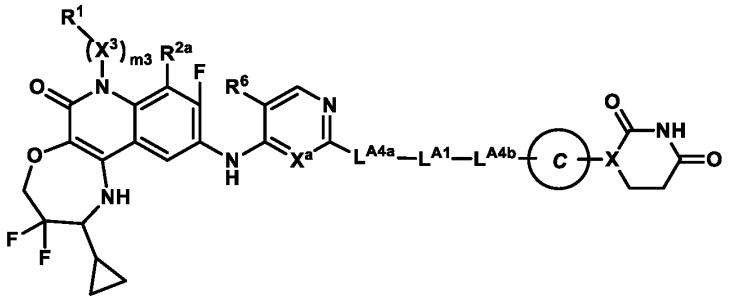
each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^{c}}$ (e.g., C_{1-3} alkyl optionally substituted with 1-3 -F); and

yy represents the point of attachment to $\mathbf{L^{A4b}}$.

Embodiment 43. The compound of Embodiment 42, wherein $\mathbf{E^1}$ is $C\mathbf{R^{2a}}$; and each of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ is H.

Embodiment 44. The compound of Embodiment 42, wherein $\mathbf{E^1}$ is $C\mathbf{R^{2a}}$; one of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ is F; and the other of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ is H.

Embodiment 45. The compound of Embodiment 42, wherein the compound of Formula (**I-a**) is a compound of Formula (**I-a-1**):

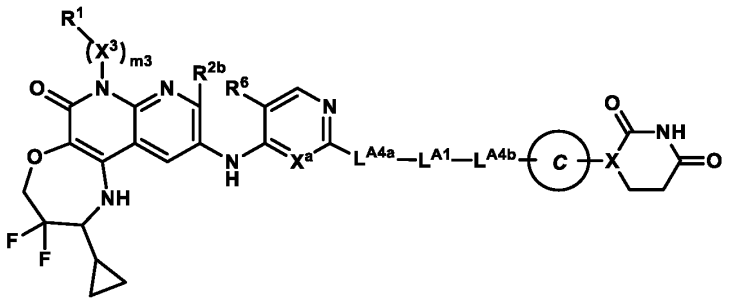


Formula (**I-a-1**)

or a pharmaceutically acceptable salt thereof.

Embodiment 46. The compound of Embodiment 45, wherein $\mathbf{R^{2a}}$ is H.

Embodiment 47. The compound of Embodiment 42, wherein the compound of Formula (**I-a**) is a compound of Formula (**I-a-2**):



Formula (**I-a-2**)

or a pharmaceutically acceptable salt thereof.

Embodiment 48. The compound of Embodiment 47, wherein $\mathbf{R^{2b}}$ is H.

Embodiment 49. The compound of any one of Embodiments 42-48, wherein $\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ are independently monocyclic 4-6 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R^a}$.

Embodiment 50. The compound of any one of Embodiments 42-48, wherein $\mathbf{L^{A4b}}$ is a monocyclic 4-6 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R^a}$; and

$\mathbf{L^{A4a}}$ is a bicyclic spirocyclic 10-12 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R^a}$.

Embodiment 51. The compound of any one of Embodiments 42-50, wherein:

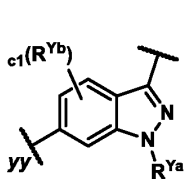
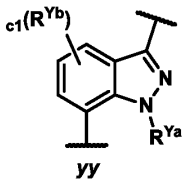
$\mathbf{R^L}$ is $C_{1\text{-}3}$ methyl optionally substituted with 1-3 F;

each $\mathbf{R^a}$ present on $\mathbf{L^{A4a}}$ and/or $\mathbf{L^{A4b}}$ is independently selected from the group consisting of: -F, CN, $C_{1\text{-}3}$ alkoxy, OH, and $C_{1\text{-}3}$ alkyl optionally substituted with 1-3 F; and

$\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ each contain 1-2 ring nitrogen atoms and no additional ring heteroatoms.

Embodiment 52. The compound of any one of Embodiments 42-51, wherein:

X is CH; and

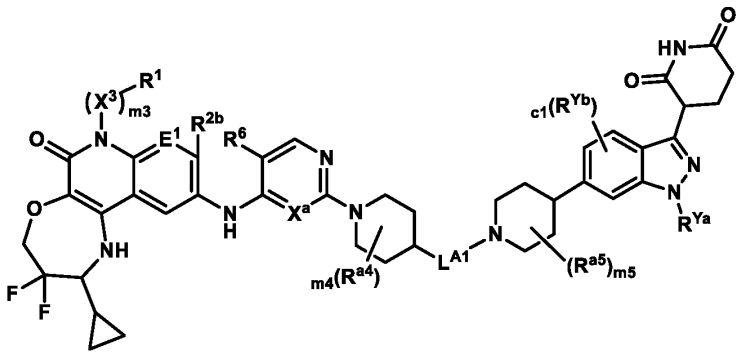
Ring C is selected from the group consisting of:  and , wherein:

c1 is 0, 1, or 2;

$\mathbf{R^{Ya}}$ is C_{1-3} alkyl optionally substituted with 1-3 -F; and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: -F and C_{1-3} alkyl optionally substituted with 1-3 -F.

Embodiment 53. The compound of Embodiment 1 or 42, wherein the compound is a compound of Formula (**I-b**):



Formula (**I-b**)

or a pharmaceutically acceptable salt thereof, wherein:

$\mathbf{E^1}$ is $C\mathbf{R^{2a}}$ or N;

$\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are each independently selected from the group consisting of: H and F;

m4 and **m5** are independently 0, 1, or 2;

each $\mathbf{R^{a4}}$ and $\mathbf{R^{a5}}$ is independently selected from the group consisting of: -F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F;

$\mathbf{L^{A1}}$ is CH_2 or $CH\mathbf{R^L}$, and

$\mathbf{R^L}$ is C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$;

c1 is 0, 1, or 2;

$\mathbf{R^{Ya}}$ is selected from the group consisting of:

(a) C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$, and

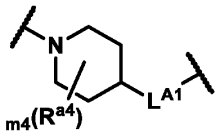
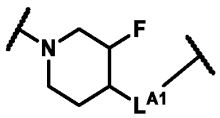
(b) –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$; and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$.

Embodiment 54. The compound of Embodiment 53, wherein one or more of **(1)-(6)** applies:

(1) $\mathbf{R^{2b}}$ is -F;

(2) $\mathbf{E^1}$ is N;

(3) the  moiety is: ;

(4) $\mathbf{R^{Ya}}$ is selected from the group consisting of: C_{2-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$, and –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$;

(5) c1 is 2; and/or

(6) c1 is 1, and $\mathbf{R^{Yb}}$ is C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$ (e.g., C_{1-3} alkyl optionally substituted with 1-3 F).

Embodiment 55. The compound of Embodiment 53, wherein two or more of **(1)-(4)** apply:

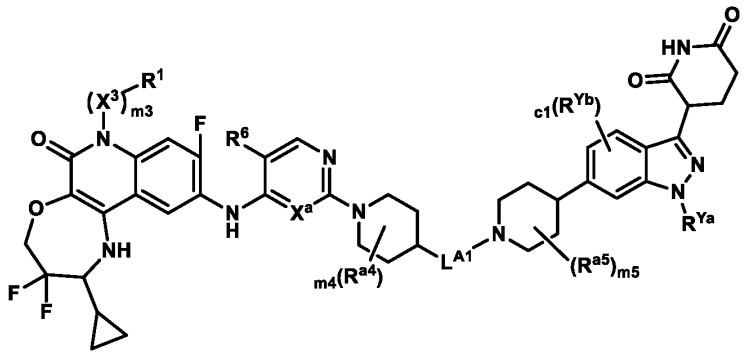
(1) m4 is 1 or 2;

(2) m5 is 1 or 2;

(3) $\mathbf{L^{A1}}$ is $CH\mathbf{R^L}$; and/or

(4) c1 is 1 or 2.

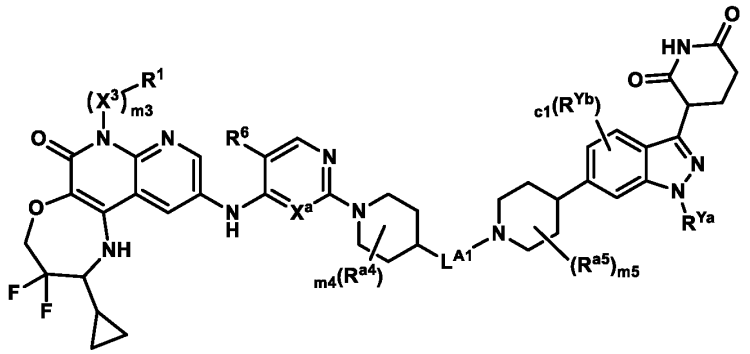
Embodiment 56. The compound of Embodiment 53, wherein the compound of Formula (**I-b**) is a compound of Formula (**I-b-1**):



Formula (**I-b-1**)

or a pharmaceutically acceptable salt thereof.

Embodiment 57. The compound of Embodiment 53, wherein the compound of Formula (**I-b**) is a compound of Formula (**I-b-2**):



Formula (**I-b-2**)

or a pharmaceutically acceptable salt thereof.

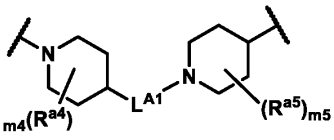
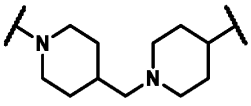
Embodiment 58. The compound of any one of Embodiments 53-57, wherein:

$\mathbf{R^{Ya}}$ is $C_{1\text{-}3}$ alkyl optionally substituted with 1-3 -F, and

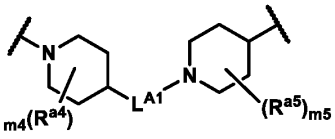
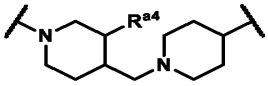
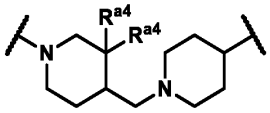
each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: -F and $C_{1\text{-}3}$ alkyl optionally substituted with 1-3 -F.

Embodiment 59. The compound of any one of Embodiments 53-58, wherein $\mathbf{L^{A1}}$ is CH_2.

Embodiment 60. The compound of any one of Embodiments 53-59, wherein **m4** is 0; and **m5** is 0.

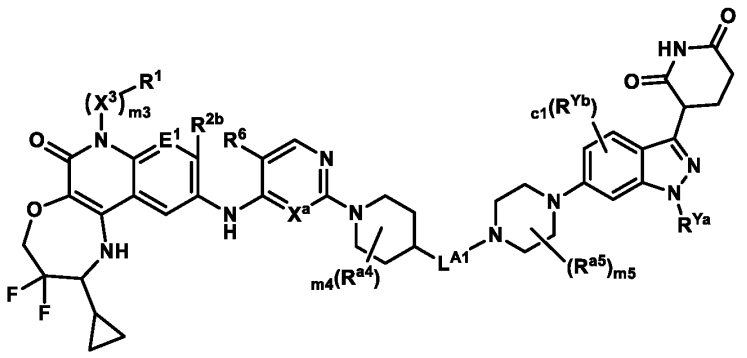
Embodiment 61. The compound of any one of Embodiments 53-60, wherein the  moiety is .

Embodiment 62. The compound of any one of Embodiments 53-59, wherein **m4** is 1 or 2; and **m5** is 0, wherein each R^{a4} is independently selected from the group consisting of: -F, Me, and CF_3.

Embodiment 63. The compound of any one of Embodiments 53-59 or 62, wherein the  moiety is  or .

Embodiment 64. The compound of any one of Embodiments 53-59, wherein **m4** is 0; and **m5** is 1 or 2, wherein each R^{a5} is independently selected from the group consisting of: -F, Me, and CF_3.

Embodiment 65. The compound of Embodiment 1 or 42, wherein the compound is a compound of Formula (**I-c**):



Formula (**I-c**)

or a pharmaceutically acceptable salt thereof, wherein:

$\mathbf{E^1}$ is $C\mathbf{R^{2a}}$ or N;

$\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are each independently selected from the group consisting of: H and F;

m4 and **m5** are independently 0, 1, or 2;

each $\mathbf{R^{a4}}$ is independently selected from the group consisting of: -F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F;

each $\mathbf{R^{a5}}$ is independently C_{1-3} alkyl optionally substituted with 1-3 F;

$\mathbf{L^{A1}}$ is CH_2 or $CH\mathbf{R^L}$, and

$\mathbf{R^L}$ is C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$;

c1 is 0, 1, or 2;

$\mathbf{R^{Ya}}$ is selected from the group consisting of:

(a) C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$, and

(b) –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$; and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$.

Embodiment 66. The compound of Embodiment 65, wherein one or more of **(1)-(4)** applies:

(1) $\mathbf{R^{2b}}$ is -F;

(2) $\mathbf{E^1}$ is N;

(3) $\mathbf{R^{Ya}}$ is selected from the group consisting of: C_{2-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$, and –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$; and/or

(4) c1 is 2.

Embodiment 67. The compound of Embodiment 65, wherein two or more of **(1)-(4)** apply:

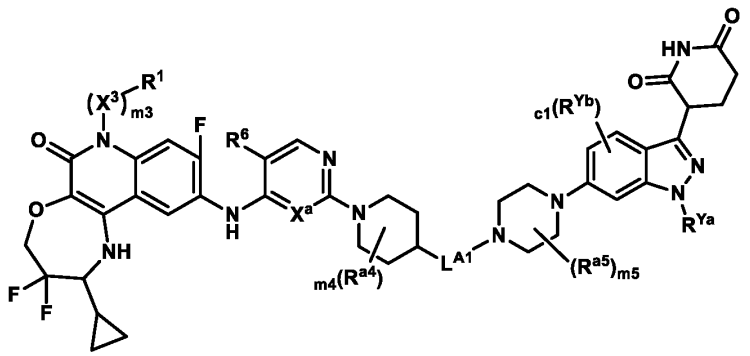
(1) m4 is 2;

(2) m5 is 1 or 2;

(3) $\mathbf{L^{A1}}$ is $CH\mathbf{R^L}$; and/or

(4) c1 is 1 or 2.

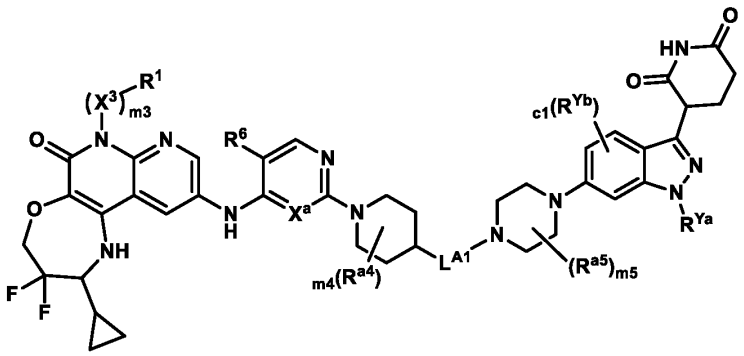
Embodiment 68. The compound of Embodiment 65, wherein the compound of Formula (**I-c**) is a compound of Formula (**I-c-1**):



Formula (**I-c-1**)

or a pharmaceutically acceptable salt thereof.

Embodiment 69. The compound of Embodiment 65, wherein the compound of Formula (**I-c**) is a compound of Formula (**I-c-2**):



Formula (**I-c-2**)

or a pharmaceutically acceptable salt thereof.

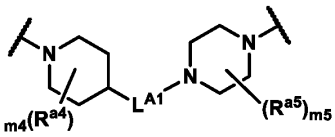
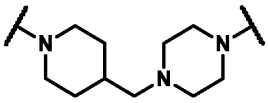
Embodiment 70. The compound of any one of Embodiments 65-69, wherein:

$\mathbf{R^{Ya}}$ is C_{1-3} alkyl optionally substituted with 1-3 -F, and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: -F and C_{1-3} alkyl optionally substituted with 1-3 -F.

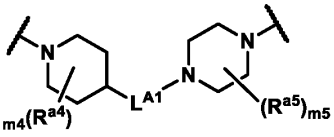
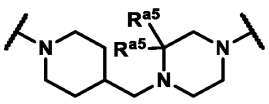
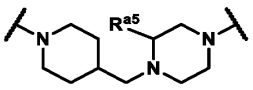
Embodiment 71. The compound of any one of Embodiments 65-70, wherein L^{A1} is CH_2.

Embodiment 72. The compound of any one of Embodiments 65-71, wherein **m4** is 0; and **m5** is 0.

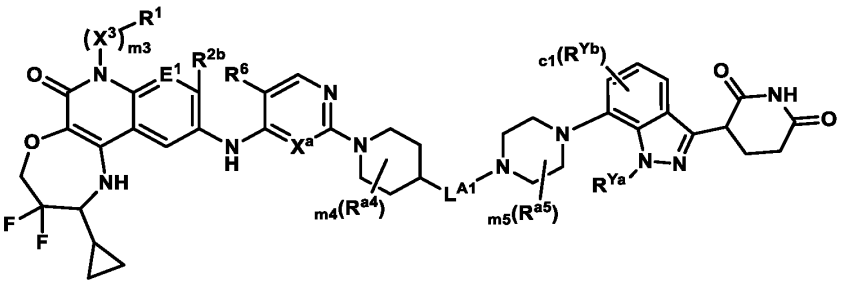
Embodiment 73. The compound of Embodiment 72, wherein the  moiety is .

Embodiment 74. The compound of any one of Embodiments 65-71, wherein **m4** is 1 or 2; and **m5** is 0, wherein each R^{a4} is independently selected from the group consisting of: -F, Me, and CF_3.

Embodiment 75. The compound of any one of Embodiments 65-71, wherein **m4** is 0; and **m5** is 1 or 2, wherein each R^{a5} is independently selected from the group consisting of Me and CF_3.

Embodiment 76. The compound of any one of Embodiments 65-71 or 75, wherein the  moiety is  or .

Embodiment 77. The compound of Embodiment 1 or 42, wherein the compound is a compound of Formula (**I-d**):



Formula (**I-d**)

or a pharmaceutically acceptable salt thereof, wherein:

$\mathbf{E^1}$ is $C\mathbf{R^{2a}}$ or N;

$\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are each independently selected from the group consisting of: H and F;

m4 and **m5** are independently 0, 1, or 2;

each $\mathbf{R^{a4}}$ is independently selected from the group consisting of: -F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F;

each $\mathbf{R^{a5}}$ is independently C_{1-3} alkyl optionally substituted with 1-3 F;

$\mathbf{L^{A1}}$ is CH_2 or $CH\mathbf{R^L}$, and

$\mathbf{R^L}$ is C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$;

c1 is 0, 1, or 2;

$\mathbf{R^{Ya}}$ is selected from the group consisting of:

(a) C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$, and

(b) –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$; and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$.

Embodiment 78. The compound of Embodiment 77, wherein one or more of **(1)-(4)** applies:

(1) $\mathbf{R^{2b}}$ is -F;

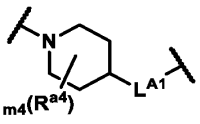
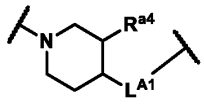
(2) $\mathbf{E^1}$ is N;

(3) $\mathbf{R^{Ya}}$ is selected from the group consisting of: C_{2-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$, and –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$; and/or

(4) c1 is 2.

Embodiment 79. The compound of Embodiment 77, wherein two or more of **(1)-(5)** apply:

(1) m4 is 2;

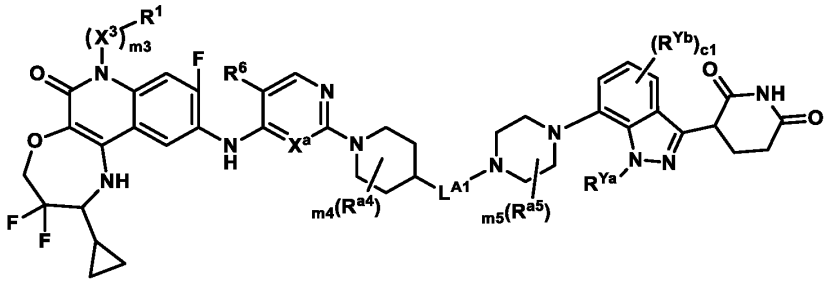
(2) m4 is 1, and the  moiety is: ;

(3) m5 is 1 or 2;

(4) L^{A1} is CHR^{L}; and/or

(5) c1 is 1 or 2.

Embodiment 80. The compound of Embodiment 77, wherein the compound of Formula (**I-d**) is a compound of Formula (**I-d-1**):



Formula (**I-d-1**)

or a pharmaceutically acceptable salt thereof.

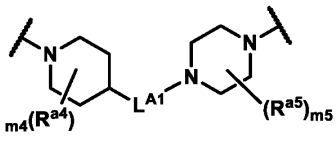
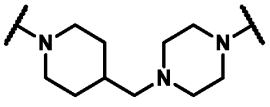
Embodiment 81. The compound of any one of Embodiments 77-80, wherein:

R^{Ya} is C_{1-3} alkyl optionally substituted with 1-3 -F, and

each R^{Yb} is independently selected from the group consisting of: -F and C_{1-3} alkyl optionally substituted with 1-3 -F.

Embodiment 82. The compound of any one of Embodiments 77-81, wherein L^{A1} is CH_2.

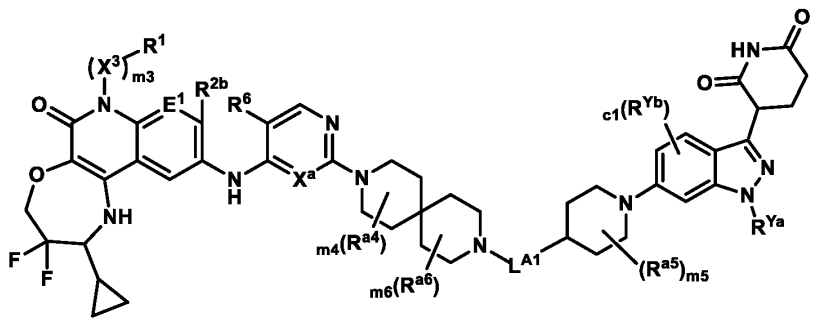
Embodiment 83. The compound of any one of Embodiments 77-82, wherein **m4** is 0; and **m5** is 0.

Embodiment 84. The compound of any one of Embodiments 77-83, wherein the  moiety is .

Embodiment 85. The compound of any one of Embodiments 77-82, wherein **m4** is 1 or 2; and **m5** is 0, wherein each $\mathbf{R^{a4}}$ is independently selected from the group consisting of: -F, Me, and CF_3.

Embodiment 86. The compound of any one of Embodiments 77-82, wherein **m4** is 0; and **m5** is 1 or 2, wherein each $\mathbf{R^{a5}}$ is independently selected from the group consisting of: Me and CF_3.

Embodiment 87. The compound of Embodiment 1 or 42, wherein the compound is a compound of Formula (**I-e**):



Formula (**I-e**)

or a pharmaceutically acceptable salt thereof, wherein:

$\mathbf{E^1}$ is $C\mathbf{R^{2a}}$ or N;

$\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are each independently selected from the group consisting of: H and F;

m4, **m5**, and **m6** are independently 0, 1, or 2, provided that **m4** + **m6** is 0, 1, 2, or 3;

each $\mathbf{R^{a4}}$, $\mathbf{R^{a5}}$, and $\mathbf{R^{a6}}$ is independently selected from the group consisting of: -F, CN, $C_{1\text{-}3}$ alkoxy, OH, and $C_{1\text{-}3}$ alkyl optionally substituted with 1-3 F;

$\mathbf{L^{A1}}$ is CH_2 or $CH\mathbf{R^L}$, and

$\mathbf{R^L}$ is $C_{1\text{-}3}$ alkyl optionally substituted with 1-3 $\mathbf{R^c}$;

c1 is 0, 1, or 2;

$\mathbf{R^{Ya}}$ is selected from the group consisting of:

(a) $C_{1\text{-}6}$ alkyl optionally substituted with 1-3 $\mathbf{R^c}$, and

(b) –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^{g}}$; and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^{c}}$.

Embodiment 88. The compound of Embodiment 87, wherein one or more of **(1)-(7)** applies:

(1) $\mathbf{R^{2b}}$ is -F;

(2) $\mathbf{E^{1}}$ is N;

(3) one or more of **m4**, **m5**, and **m6** is independently 1 or 2;

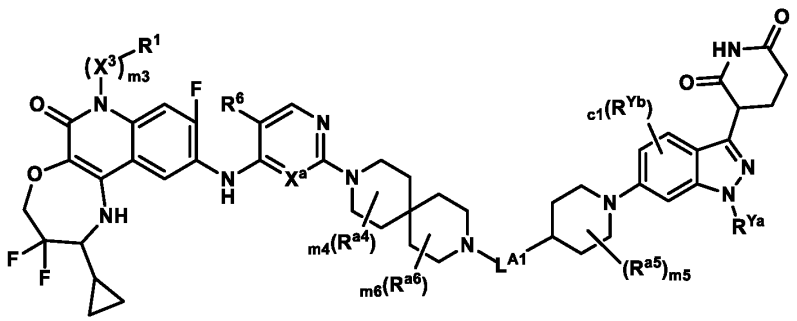
(4) $\mathbf{L^{A1}}$ is $CH\mathbf{R^{L}}$;

(5) c1 is 1, and $\mathbf{R^{Yb}}$ is C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^{c}}$;

(6) c1 is 2; and/or

(7) $\mathbf{R^{Ya}}$ is selected from the group consisting of: C_{2-6} alkyl optionally substituted with 1-3 $\mathbf{R^{c}}$, and –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^{g}}$.

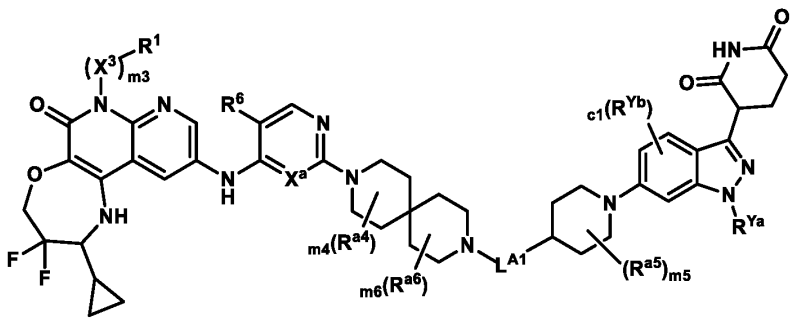
Embodiment 89. The compound of Embodiment 87, wherein the compound of Formula (**I-e**) is a compound of Formula (**I-e-1**):



Formula (**I-e-1**)

or a pharmaceutically acceptable salt thereof.

Embodiment 90. The compound of Embodiment 87, wherein the compound of Formula (**I-e**) is a compound of Formula (**I-e-2**):



Formula (**I-e-2**)

or a pharmaceutically acceptable salt thereof.

Embodiment 91. The compound of any one of Embodiments 87-90, wherein:

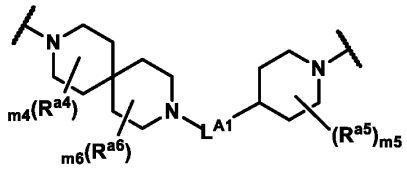
$\mathbf{R^{Ya}}$ is C_{1-3} alkyl optionally substituted with 1-3 -F, and

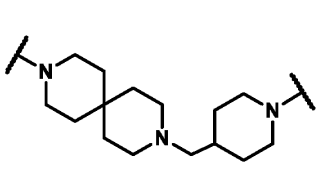
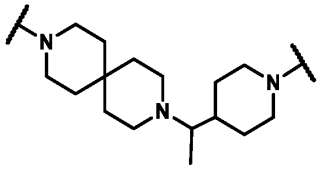
each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: -F and C_{1-3} alkyl optionally substituted with 1-3 -F.

Embodiment 92. The compound of any one of Embodiments 87-91, wherein $\mathbf{L^{A1}}$ is CH_2.

Embodiment 93. The compound of any one of Embodiments 87-91, wherein $\mathbf{L^{A1}}$ is CHMe.

Embodiment 94. The compound of any one of Embodiments 87-93, wherein **m4** is 0; **m5** is 0; and **m6** is 0.

Embodiment 95. The compound of any one of Embodiments 87-91 or 94, wherein the  moiety is:

 or .

Embodiment 96. The compound of any one of Embodiments 87-93, wherein **m4** is 0; **m6** is 0; and **m5** is 1 or 2, wherein each $\mathbf{R}^{a5}$ is independently selected from the group consisting of: -F, Me, and CF_3.

Embodiment 97. The compound of any one of Embodiments 42-96, wherein $\mathbf{R}^6$ is -F or -Cl; and $\mathbf{X}^a$ is N.

Embodiment 98. The compound of any one of Embodiments 42-97, wherein $\mathbf{R}^6$ is -Cl; and $\mathbf{X}^a$ is N.

Embodiment 99. The compound of any one of Embodiments 42-98, wherein $-(\mathbf{X}^3)_{m3}\text{-}\mathbf{R}^1$ is $C_{1\text{-}3}$ alkyl.

Embodiment 100. The compound of any one of Embodiments 42-99, wherein $-(\mathbf{X}^3)_{m3}\text{-}\mathbf{R}^1$ is methyl.

Embodiment 101. The compound of Embodiment 1, wherein the compound of Formula (**I**) is selected from the group consisting of **Compound Nos. 101**, **101a**, **101b**, **101c**, **101d**, **102**, **102a**, **102b**, **103**, **103a**, **103b**, **104**, **104a**, **104b**, **105**, **105a**, **106**, **106a**, **107**, **107a**, **107b**, **107c**, **107d**, **108**, **108a**, **109**, **109a**, **109b**, **110**, **110a**, **110b**, **110c**, **110d**, **110e**, **110f**, **111**, **111a**, **111b**, **112**, **112a**, **112b**, **113**, **113a**, **113b**, **114**, **114a**, **114b**, **115**, **115a**, **116**, **116a**, **116b**, **116c**, **116d**, **117**, **117a**, **117b**, **118**, **118a**, **118b**, **119**, **119a**, **119b**, **119c**, **119d**, **120**, **120a**, **120b**, **121**, **121a**, **121b**, **121c**, **121d**, **121e**, **122**, **122a**, **123**, **123a**, **123b**, **124**, **124a**, **124b**, **125**, **125a**, **126**, **126a**, **127**, **127a**, **127b**, **127c**, **127d**, **128**, **128a**, **129**, **129a**, **129b**, **130**, **130a**, **130b**, **130c**, **130d**, **130e**, **131**, **131a**, **131b**, **132**, **132a**, **133**, **133a**, **133b**, **134**, **134a**, **135**, **135a**, **135b**, **136**, **136a**, **137**, **137a**, **138**, **138a**, **139**, **139a**, **139b**, **140**, **140a**, **140b**, **141**, **141a**, **142**, **142a**, **142b**, **143a**, **144**, **144a**, **145**, **145a**, **146**, **146a**, **146b**, **147**, **147a**, **148**, **148a**, **148b**, **149**, **149a**, **150**, **150a**, **151**, **151a**, **151b**, **152**, **152a**, **153a**, **154**, **154a**, **155**, **155a**, **156**, **156a**, **157**, **157a**, **158**, **158a**, **159**, **159a**, **160**, **160a**, **160b**, **161**, **161a**, **162**, **162a**, **163**, **163a**, **164**, **164a**, **165**, **165a**, **166**, **166a**, **166b**, **167**, **167a**, **168**, **168a**, **169**, **169a**, **169b**, **170**, **170a**, **171**, **171a**, **172**, **172a**, **173**, **173a**, **174**, **174a**, **175**, **175a**, **176**, **176a**, **177**, **177a**, **178**, **178a**, **181**, **181a**, **182**, **182a**, **185a**, **185b**, **186**, and **186a**, as depicted in **Table C1**, or a pharmaceutically acceptable salt thereof.

Embodiment 102. A pharmaceutical composition comprising a compound of any one of Embodiments 1-101, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

Embodiment 103. A method for treating a cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of Embodiments 1-101, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to Embodiment 102.

Embodiment 104. The method of Embodiment 103, wherein the cancer is a hematological cancer, breast cancer, gastrointestinal cancer, brain cancer, lung cancer, or a combination thereof.

Embodiment 105. The method of Embodiment 104, wherein the hematological cancer is diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), nodular lymphocyte predominant Hodgkin lymphoma (NLPHL), diffuse histiocytic lymphoma (DHL), intravascular large B-cell lymphoma (IVLBCL), small lymphocytic lymphoma (SLL), Burkitt lymphoma (BL), mantle cell lymphoma (MCL), peripheral T-cell lymphoma (PTCL), chronic lymphocytic leukemia (CLL), acute lymphocytic leukemia (ALL), or chronic myeloid leukemia (CML).

Embodiment 106. The method of Embodiment 105, wherein the hematological cancer is selected from the group consisting of DLBCL, FL, MCL, BL, PTCL, and ALL (e.g., B-ALL).

Embodiment 107. The method of Embodiment 105, wherein the hematological cancer is FL or DLBCL.

Embodiment 108. The method of Embodiment 105, wherein the hematological cancer is DLBCL.

Embodiment 109. The method of Embodiment 105, wherein the hematological cancer is FL.

Embodiment 110. The method of Embodiment 105, wherein the hematological cancer is BL.

Embodiment 111. The method of Embodiment 105, wherein the hematological cancer is a PTCL.

Embodiment 112. The method of Embodiment 105, wherein, the hematological cancer is ALL (e.g., B-ALL).

Embodiment 113. The method of any one of Embodiments 103-112, wherein the therapeutically effective amount of a compound of any one of Embodiments 1-101, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to Embodiment 102, is administered to the subject as a monotherapy.

Embodiment 114. The method of any one of Embodiments 103-112, comprising administering an additional therapy or therapeutic agent to the subject.

Embodiment 115. The method of Embodiment 114, wherein the additional therapy or therapeutic agent is a PI3K inhibitor, an Abl inhibitor (e.g., a BCR-Abl inhibitor), a BTK inhibitor, a JAK inhibitor, a BRaf inhibitor, a MEK inhibitor, a BCL-2 inhibitor, a Bcl-X_L inhibitor, an XPO1 inhibitor, an inhibitor of the polycomb repressive complex 2 (PRC2), an immunomodulatory imide drug, anti-CD19 therapy, anti-CD20 therapy, anti-CD3 therapy, chemotherapy, or a combination thereof.

Embodiment 116. The method of Embodiment 115, wherein the additional therapy or therapeutic agent is an Abl inhibitor.

Embodiment 117. The method of Embodiment 116, wherein the cancer is a B-ALL (e.g., a Philadelphia chromosome positive B-ALL or Philadelphia chromosome-like B-ALL).

Embodiment 118. The method of Embodiment 115, wherein the additional therapy or therapeutic agent is a BTK inhibitor.

Embodiment 119. The method of Embodiment 118, wherein the cancer is a B-ALL (e.g., a pre-BCR+ B-ALL or a B-ALL dependent on Ras signaling).

Embodiment 120. The method of Embodiment 115, wherein the additional therapy or therapeutic agent is a JAK inhibitor.

Embodiment 121. The method of Embodiment 120, wherein the cancer is a B-ALL (e.g., a JAK2 (e.g., $JAK2^{R683G}$ or $JAK2^{I682F}$) mutant B-ALL, with or without high CRLF2 expression).

Embodiment 122. The method of Embodiment 115, wherein the additional therapy or therapeutic agent is a BCL-2 inhibitor.

Embodiment 123. The method of Embodiment 122, wherein the cancer is selected from the group consisting of DLBCL, FL, MCL, and ALL (e.g., B-ALL).

Embodiment 124. The method of Embodiment 122, wherein the cancer is a DLBCL.

Embodiment 125. The method of Embodiment 122, wherein the cancer is a FL.

Embodiment 126. The method of Embodiment 122, wherein the cancer is an MCL.

Embodiment 127. The method of Embodiment 122, wherein the cancer is a B-ALL (e.g., an *MLL*-rearranged (e.g., an MLL-Af4 fusion, an MLL-Af6 fusion, an MLL-Af9 fusion, an MLL-ENL fusion, or an MLL-PTD fusion) B-ALL, or a *BCL2* amplified B-ALL).

Embodiment 128. The method of Embodiment 115, wherein the additional therapy or therapeutic agent is an inhibitor of the PRC2.

Embodiment 129. The method of Embodiment 128, wherein the cancer is selected from the group consisting of DLBCL, FL, MCL, and ALL (e.g., B-ALL).

Embodiment 130. The method of Embodiment 129, wherein the cancer is a DLBCL.

Embodiment 131. The method of Embodiment 129, wherein the cancer is a FL.

Embodiment 132. The method of Embodiment 129, wherein the cancer is an MCL.

Embodiment 133. The method of Embodiment 129, wherein the cancer is a B-ALL (e.g., an *MLL*-rearranged (e.g., an MLL-Af4 fusion, an MLL-Af6 fusion, an MLL-Af9 fusion, an MLL-ENL fusion, or an MLL-PTD fusion) B-ALL, or a *BCL2* amplified B-ALL).

Embodiment 134. The method of Embodiment 115, wherein the additional therapy or therapeutic agent is anti-CD20 therapy.

Embodiment 135. The method of Embodiment 134, wherein the cancer is a DLBCL or a FL.

Embodiment 136. The method of Embodiment 134, wherein the cancer is a DLBCL.

Embodiment 137. The method of Embodiment 134, wherein the cancer is a FL.

Embodiment 138. The method of Embodiment 115, wherein the additional therapy or therapeutic agent is chemotherapy.

Embodiment 139. The method of Embodiment 138, wherein the cancer is B-ALL (e.g., an *MLL*-rearranged (e.g., an MLL-Af4 fusion, an MLL-Af6 fusion, an MLL-Af9 fusion, an MLL-ENL fusion, or an MLL-PTD fusion) B-ALL, a Philadelphia chromosome positive B-ALL, a Philadelphia chromosome-like B-ALL, a pre-BCR+ B-ALL, a B-ALL dependent on Ras signaling).

Embodiment 140. A method for treating or preventing an autoimmune condition in a subject in need thereof, the method comprising administering to the subject a therapeutically

effective amount of a compound of any one of Embodiments 1-101, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to Embodiment 102.

Embodiment 141. A method for treating a lymphoproliferative disorder in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of Embodiments 1-101, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to Embodiment 102.

Embodiment 142. A method for inducing degradation of a BCL6 protein in a mammalian cell, the method comprising contacting the mammalian cell with an effective amount of a compound of any one of Embodiments 1-101, or a pharmaceutically acceptable salt thereof.

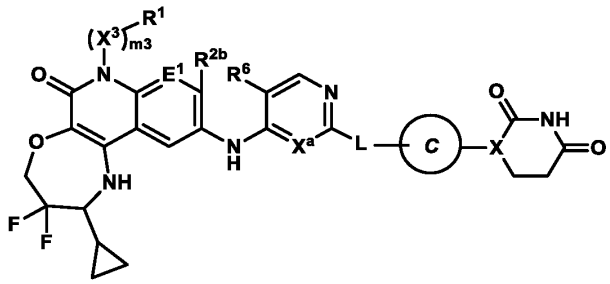
Embodiment 143. The method of Embodiment 142, wherein the contacting occurs in vivo.

Embodiment 144. The method of Embodiment 142, wherein the contacting occurs in vitro.

Embodiment 145. The method of any one of Embodiments 142-144, wherein the mammalian cell is a mammalian cancer cell.

P02 Embodiments

Embodiment 1. A compound of Formula (**I**):



Formula (**I**)

or a pharmaceutically acceptable salt thereof, wherein:

$\mathbf{E^1}$ is $\mathbf{CR^{2a}}$ or N;

$\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are independently selected from the group consisting of: H, halo, cyano, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, and C_{1-3} haloalkoxy;

m3 is 0 or 1;

$\mathbf{X^3}$ is C_{1-3} alkylene optionally substituted with 1-3 $\mathbf{R^c}$;

$\mathbf{R^1}$ is selected from the group consisting of: H, halo, and $\mathbf{R^{b1}}$;

$\mathbf{X^a}$ is selected from the group consisting of: N and $C\mathbf{R^{Xa}}$;

$\mathbf{R^6}$ and $\mathbf{R^{Xa}}$ are independently selected from the group consisting of: H, halo, C_{1-2} alkyl, C_{1-2} haloalkyl, C_{1-2} alkoxy, CN, and -C≡CH;

L is $-(\mathbf{L^A})_{n1}-$, wherein:

n1 is an integer from 1 to 5; and

each $\mathbf{L^A}$ is independently selected from the group consisting of: $\mathbf{L^{A1}}$, $\mathbf{L^{A3}}$, and $\mathbf{L^{A4}}$, wherein:

0-2 of $\mathbf{L^A}$ is $\mathbf{L^{A1}}$;

0-2 of $\mathbf{L^A}$ is $\mathbf{L^{A3}}$; and

1-3 of $\mathbf{L^A}$ is $\mathbf{L^{A4}}$,

each $\mathbf{L^{A1}}$ is independently selected from the group consisting of: $-CH_2-$, $-CH\mathbf{R^L}-$, and $-C(\mathbf{R^L})_2-$, wherein:

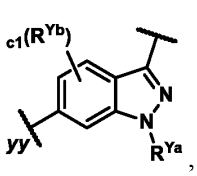
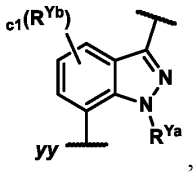
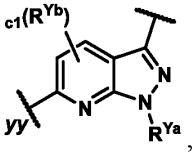
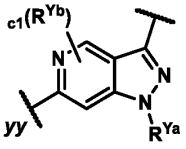
each $\mathbf{R^L}$ is independently selected from the group consisting of: halo, cyano, -OH, $-C_{1-6}$ alkoxy, $-C_{1-6}$ haloalkoxy, $-(C_{0-3}$ alkylene$)-(C_{3-5}$ cycloalkyl), $-(C_{0-3}$ alkylene$)-$(4-6 membered heterocyclyl), and C_{1-6} alkyl optionally substituted with 1-6 $\mathbf{R^c}$;

each $\mathbf{L^{A3}}$ is independently selected from the group consisting of: $-N(\mathbf{R^d})-$, $-N(\mathbf{R^b})-$, -O-, $-S(O)_{0-2}-$, and C(=O);

each $\mathbf{L^{A4}}$ is independently selected from the group consisting of:

(a) C_{3-15} cycloalkylene or 4-15 membered heterocyclylene, each of which is optionally substituted with 1-6 substituents independently selected from the group consisting of: $\mathbf{R^a}$ and $\mathbf{R^b}$; and

(b) phenylene or 5-6 membered heteroarylene, each of which is optionally substituted with 1-3 substituents independently selected from the group consisting of: $\mathbf{R^a}$ and $\mathbf{R^b}$;

Ring C is selected from the group consisting of: , , , and , wherein:

c1 is 0, 1, or 2;

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of $\mathbf{R^a}$ and $\mathbf{R^b}$;

$\mathbf{R^{Ya}}$ is selected from the group consisting of: H, $\mathbf{R^a}$, and $\mathbf{R^b}$; and

yy represents the point of attachment to **L**;

X is CH or N;

each $\mathbf{R^a}$ is independently selected from the group consisting of:

(a) halo;

(b) cyano;

(c) -OH;

(d) oxo;

(e) C_{1-6} alkoxy optionally substituted with 1-6 $\mathbf{R^c}$;

(f) $-N\mathbf{R^d}\mathbf{R^e}$;

(g) $C(=O)C_{1-6}$ alkyl;

(h) $C(=O)OC_{1-6}$ alkyl;

(i) $C(=O)N(\mathbf{R^f})_2$;

(j) $S(O)_{0-2}(C_{1-6}$ alkyl);

(k) $S(O)_{0-2}(C_{1-6}$ haloalkyl); and

(l) C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, each optionally substituted with 1-6 $\mathbf{R^c}$;

each $\mathbf{R^b}$ is independently selected from the group consisting of: $\mathbf{-(L^b)_b-R^{b1}}$ and $\mathbf{-R^{b1}}$, wherein:

each **b** is independently 1, 2, or 3;

each $\mathbf{L^b}$ is independently selected from the group consisting of: -O-, -N(H)-, -N(C_{1-3} alkyl)-, -S(O)$_{0-2}$-, C(=O), and C_{1-3} alkylene; and

each $\mathbf{R^{b1}}$ is independently selected from the group consisting of: C_{3-6} cycloalkyl and 4-8 membered heterocyclyl, each of which is optionally substituted with 1-3 $\mathbf{R^g}$;

each $\mathbf{R^c}$ is independently selected from the group consisting of: halo, cyano, -OH, -C_{1-6} alkoxy, -C_{1-6} haloalkoxy, -N$\mathbf{R^dR^e}$, C(=O)C_{1-6} alkyl, C(=O)OC_{1-6} alkyl, C(=O)N($\mathbf{R^f}$)$_2$, S(O)$_{0-2}$(C_{1-6} alkyl), and S(O)$_{0-2}$(C_{1-6} haloalkyl);

each $\mathbf{R^d}$ and $\mathbf{R^e}$ is independently selected from the group consisting of: H, C(=O)C_{1-6} alkyl, C(=O)C_{1-6} haloalkyl, C(=O)OC_{1-6} alkyl, C(=O)OC_{1-6} haloalkyl, C(=O)N($\mathbf{R^f}$)$_2$, S(O)$_{1-2}$(C_{1-6} alkyl), S(O)$_{1-2}$(C_{1-6} haloalkyl), S(O)$_{1-2}$N($\mathbf{R^f}$)$_2$, and C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^h}$;

each $\mathbf{R^f}$ is independently selected from the group consisting of: H and C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^h}$;

each $\mathbf{R^g}$ is independently selected from the group consisting of: $\mathbf{R^h}$, oxo, C_{1-3} alkyl, and C_{1-3} haloalkyl; and

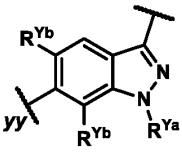
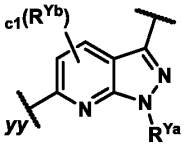
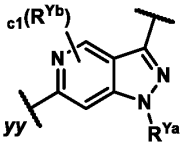
each $\mathbf{R^h}$ is independently selected from the group consisting of: halo, cyano, -OH, -(C_{0-3} alkylene)-C_{1-6} alkoxy, -(C_{0-3} alkylene)-C_{1-6} haloalkoxy, -(C_{0-3} alkylene)-NH_2, -(C_{0-3} alkylene)-N(H)(C_{1-3} alkyl), and –(C_{0-3} alkylene)-N(C_{1-3} alkyl)$_2$,

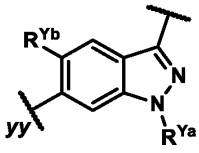
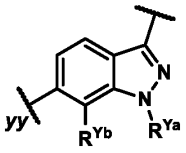
provided that the compound of Formula (**I**) does not contain any O-O, N-O, N-N, N-S(O)$_0$, O-S(O)$_{0-2}$, N-halo, O-halo, or S(O)$_{0-2}$-halo bonds.

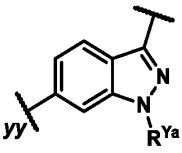
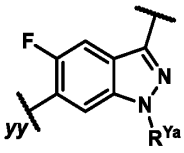
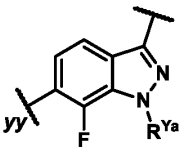
Embodiment 2. The compound of Embodiment 1, wherein one or more of **(1)-(5)** applies:

(1) $\mathbf{R^{2b}}$ is selected from the group consisting of: halo, cyano, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, and C_{1-3} haloalkoxy;

(2) $\mathbf{E^1}$ is N;

(3) Ring C is selected from the group consisting of: , , , and ;

(4) Ring C is selected from the group consisting of:  and , wherein $\mathbf{R^{Yb}}$ is $C_{1\text{-}3}$ alkyl optionally substituted with 1-3 F; and/or

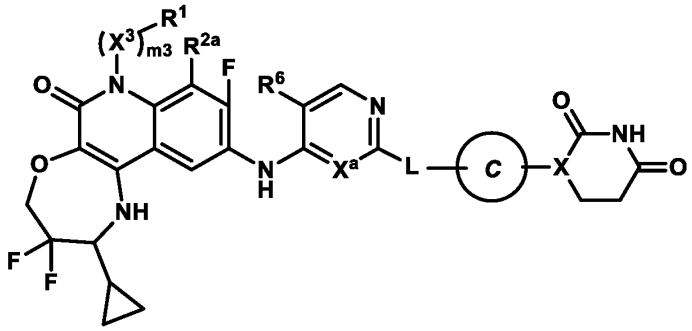
(5) Ring C is selected from the group consisting of: , , , and , wherein $\mathbf{R^{Ya}}$ is $-(C_{0\text{-}3}$ alkylene$)$-$\mathbf{R^{b1}}$ or $C_{2\text{-}4}$ alkyl optionally substituted with 1-3 $\mathbf{R^{c}}$.

Embodiment 3. The compound of Embodiment 1 or 2, wherein $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are each independently H or F.

Embodiment 4. The compound of any one of Embodiments 1-3, wherein $\mathbf{E^1}$ is $C\mathbf{R^{2a}}$; and each of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ is H.

Embodiment 5. The compound of any one of Embodiments 1-3, wherein $\mathbf{E^1}$ is $C\mathbf{R^{2a}}$; one of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ is F; and the other of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ is H.

Embodiment 6. The compound of Embodiment 1, wherein the compound of Formula (**I**) is a compound of Formula (**I-1**):

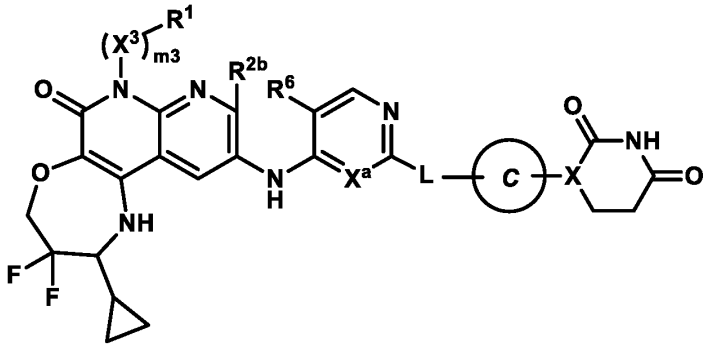


Formula (**I-1**)

or a pharmaceutically acceptable salt thereof.

Embodiment 7. The compound of Embodiment 6, wherein $\mathbf{R^{2a}}$ is H.

Embodiment 8. The compound of Embodiment 1, wherein the compound of Formula (**I**) is a compound of Formula (**I-2**):



Formula (**I-2**)

or a pharmaceutically acceptable salt thereof.

Embodiment 9. The compound of Embodiment 8, wherein $\mathbf{R^{2b}}$ is H.

Embodiment 10. The compound of any one of Embodiments 1-9, wherein $\mathbf{R^1}$ is selected from the group consisting of: H and halo.

Embodiment 11. The compound of any one of Embodiments 1-10, wherein **m3** is 1; and $\mathbf{R^1}$ is H.

Embodiment 12. The compound of any one of Embodiments 1-11, wherein –$(X^3)_{m3}$-R^1 is C_{1-3} alkyl.

Embodiment 13. The compound of any one of Embodiments 1-12, wherein –$(X^3)_{m3}$-R^1 is methyl.

Embodiment 14. The compound of any one of Embodiments 1-10, wherein **m3** is 0; and R^1 is H.

Embodiment 15. The compound of any one of Embodiments 1-9, wherein R^1 is R^{b1}.

Embodiment 16. The compound of any one of Embodiments 1-9 or 15, wherein **m3** is 1; and R^1 is R^{b1}.

Embodiment 17. The compound of any one of Embodiments 1-9 or 15-16, wherein –$(X^3)_{m3}$-R^1 is -CH_2-R^{b1}.

Embodiment 18. The compound of any one of Embodiments 1-9 or 15, wherein **m3** is 0; and R^1 is R^{b1}.

Embodiment 19. The compound of any one of Embodiments 15-18, wherein R^{b1} is C_{3-6} cycloalkyl optionally substituted with 1-3 R^g (e.g., C_{3-6} cycloalkyl optionally substituted with 1-3 F).

Embodiment 20. The compound of any one of Embodiments 1-9, wherein –$(X^3)_{m3}$-R^1 is selected from the group consisting of:

a) H;

b) C_{1-3} alkyl;

c) -R^{b1}; and

d) -CH_2R^{b1}, wherein:

R^{b1} is a C_{3-6} cycloalkyl optionally substituted with 1-3 R^g (e.g., C_{3-6} cycloalkyl optionally substituted with 1-3 F).

Embodiment 21. The compound of any one of Embodiments 1-9 or 20, wherein –$(\mathbf{X^3})_{m3}$-$\mathbf{R^1}$ is selected from the group consisting of: H and methyl.

Embodiment 22. The compound of any one of Embodiments 1-21, wherein $\mathbf{R^6}$ is -Cl or -F.

Embodiment 23. The compound of any one of Embodiments 1-22, wherein $\mathbf{R^6}$ is -Cl.

Embodiment 24. The compound of any one of Embodiments 1-23, wherein $\mathbf{X^a}$ is N.

Embodiment 25. The compound of any one of Embodiments 1-24, wherein **L** is –$(\mathbf{L^A})_{n1}$–, wherein:

n1 is an integer from 2 to 4; and

each $\mathbf{L^A}$ is independently selected from the group consisting of: $\mathbf{L^{A1}}$, $\mathbf{L^{A3}}$, and $\mathbf{L^{A4}}$, wherein:

0-2 of $\mathbf{L^A}$ is $\mathbf{L^{A1}}$;

0-2 of $\mathbf{L^A}$ is $\mathbf{L^{A3}}$; and

2-3 of $\mathbf{L^A}$ are $\mathbf{L^{A4}}$, wherein:

each $\mathbf{L^{A4}}$ is independently a C_{3-10} cycloalkylene or a 4-12 membered heterocyclylene, each of which is optionally substituted with 1-3 $\mathbf{R^a}$, wherein:

each $\mathbf{R^a}$ present on $\mathbf{L^{A4}}$ is independently selected from the group consisting of: -F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F; and

each $\mathbf{R^L}$ is independently selected from the group consisting of: -F, -OH, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$ (e.g., C_{1-3} alkyl optionally substituted with 1-3 -F).

Embodiment 26. The compound of any one of Embodiments 1-24, wherein **L** is selected from the group consisting of:

-$\mathbf{L^{A4a}}$-$\mathbf{L^{A1}}$-$\mathbf{L^{A4b}}$-*bb*;

-$\mathbf{L^{A4a}}$-$\mathbf{L^{A3}}$-$\mathbf{L^{A4b}}$-*bb*;

-$\mathbf{L^{A4a}}$-$\mathbf{L^{A4b}}$-*bb*;

-$\mathbf{L^{A4a}}$-$\mathbf{L^{A3}}$-$\mathbf{L^{A4c}}$- $\mathbf{L^{A4b}}$-*bb*; and

-$\mathbf{L}^{A4a}$-$\mathbf{L}^{A4c}$-$\mathbf{L}^{A3}$-$\mathbf{L}^{A4b}$-*bb*, wherein:

$\mathbf{L}^{A4a}$, $\mathbf{L}^{A4b}$, and $\mathbf{L}^{A4c}$ are each an independently selected $\mathbf{L}^{A4}$,

$\mathbf{L}^{A3}$ is selected from the group consisting of: -O- and -N($\mathbf{R}^{d}$)-, and

bb represents the point of attachment to **Ring C**.

Embodiment 27. The compound of any one of Embodiments 1-24, wherein **L** is selected from the group consisting of:

-$\mathbf{L}^{A4a}$-$\mathbf{L}^{A1}$-$\mathbf{L}^{A4b}$-*bb*;

-$\mathbf{L}^{A4a}$-$\mathbf{L}^{A3}$-$\mathbf{L}^{A4b}$-*bb*; and

-$\mathbf{L}^{A4a}$-$\mathbf{L}^{A4b}$-*bb*; wherein:

$\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ are each an independently selected $\mathbf{L}^{A4}$,

$\mathbf{L}^{A3}$ is selected from the group consisting of: -O- and -N($\mathbf{R}^{d}$)-, and

bb represents the point of attachment to **Ring C**.

Embodiment 28. The compound of Embodiment 26 or 27, wherein:

$\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ are independently 4-12 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R}^{a}$;

$\mathbf{L}^{A4c}$ when present is a C_{3-10} cycloalkylene optionally substituted with 1-3 $\mathbf{R}^{a}$; and

each $\mathbf{R}^{L}$ is independently selected from the group consisting of: -F, -OH, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R}^{c}$ (e.g., C_{1-3} alkyl optionally substituted with 1-3 -F).

Embodiment 29. The compound of any one of Embodiments 1-24 or 26-28, wherein **L** is:

-$\mathbf{L}^{A4a}$-$\mathbf{L}^{A1}$-$\mathbf{L}^{A4b}$-*bb*, wherein:

$\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ are independently 4-12 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R}^{a}$; and

each $\mathbf{R}^{L}$ is independently selected from the group consisting of: -F, -OH, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R}^{c}$ (e.g., C_{1-3} alkyl optionally substituted with 1-3 -F).

Embodiment 30. The compound of any one of Embodiments 26-29, wherein $\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ are independently monocyclic 4-6 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R}^{a}$.

Embodiment 31. The compound of any one of Embodiments 26-30, wherein one of $\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ is a 1,4-piperidinylene; and

the other of $\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ is independently selected from the group consisting of: 1,4-piperidinylene and 1,4-piperazinylene,

wherein each of the 1,4-piperidinylene or 1,4-piperazinylene is optionally substituted with 1-2 $\mathbf{R}^{a}$.

Embodiment 32. The compound of any one of Embodiments 26-29, wherein one of $\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ is a monocyclic 4-6 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R}^{a}$; and

the other of $\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ is a bicyclic spirocyclic 6-12 (e.g., 10-12) membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R}^{a}$.

Embodiment 33. The compound of any one of Embodiments 26-29 or 32, wherein $\mathbf{L}^{A4b}$ is a monocyclic 4-6 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R}^{a}$; and

$\mathbf{L}^{A4a}$ is a bicyclic spirocyclic 6-12 (e.g., 10-12) membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R}^{a}$.

Embodiment 34. The compound of any one of Embodiments 26-29 or 32-33, wherein $\mathbf{L}^{A4b}$ is 1,4-piperidinylene optionally substituted with 1-2 $\mathbf{R}^{a}$; and

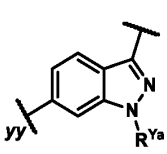
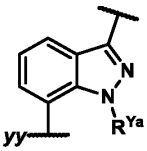
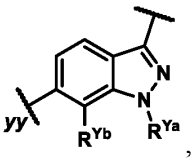
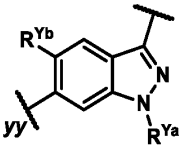
$\mathbf{L}^{A4a}$ is a bicyclic spirocyclic 10-12 membered nitrogen-containing heterocyclylene optionally substituted with 1-2 $\mathbf{R}^{a}$.

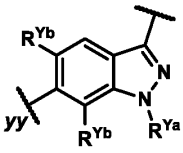
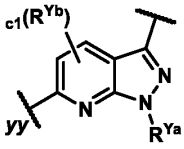
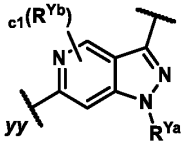
Embodiment 35. The compound of any one of Embodiments 26-34, wherein $\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ each contain 1-2 ring nitrogen atoms and no additional ring heteroatoms.

Embodiment 36. The compound of any one of Embodiments 26-35, wherein each $\mathbf{R}^{a}$ present on $\mathbf{L}^{A4a}$, $\mathbf{L}^{A4b}$, and/or $\mathbf{L}^{A4c}$ is independently selected from the group consisting of: -F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F.

Embodiment 37. The compound of any one of Embodiments 26-36, wherein $\mathbf{L}^{A1}$ is $-CH_2-$.

Embodiment 38. The compound of any one of Embodiments 26-36, wherein $\mathbf{L}^{A1}$ is -CH$\mathbf{R}^{L}$-, wherein $\mathbf{R}^{L}$ is C_{1-3} alkyl optionally substituted with 1-3 F (e.g., $\mathbf{R}^{L}$ is methyl or CF_3).

Embodiment 39. The compound of any one of Embodiments 1-38, wherein **Ring C** is selected from the group consisting of: , , ,  and .

Embodiment 40. The compound of any one of Embodiments 1-38, wherein **Ring C** is selected from the group consisting of: , , and .

Embodiment 41. The compound of any one of Embodiments 1-40, wherein $\mathbf{R}^{Ya}$ is selected from the group consisting of $\mathbf{R}^{a}$ and $\mathbf{R}^{b}$.

Embodiment 42. The compound of Embodiment 39 or 40, wherein:

$\mathbf{R}^{Ya}$ is selected from the group consisting of:

(a) H

(b) C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R}^{c}$, and

(c) –(C_{0-3} alkylene)-$\mathbf{R}^{b1}$, wherein $\mathbf{R}^{b1}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R}^{g}$ (e.g., C_{3-6} cycloalkyl optionally substituted with 1-3 F); and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$ (e.g., C_{1-3} alkyl optionally substituted with 1-3 -F).

Embodiment 43. The compound of any one of Embodiments 39-40 or 42, wherein:

$\mathbf{R^{Ya}}$ is H or C_{1-3} alkyl optionally substituted with 1-3 -F (e.g., C_{1-3} alkyl (e.g., methyl)); and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: -F and C_{1-3} alkyl optionally substituted with 1-3 -F.

Embodiment 44. The compound of any one of Embodiments 39-41, wherein:

$\mathbf{R^{Ya}}$ is selected from the group consisting of:

(a) C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$, and

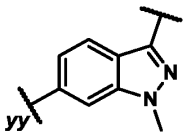
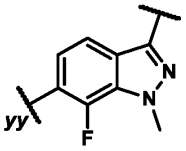
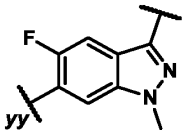
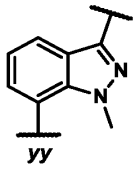
(b) –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$ (e.g., C_{3-6} cycloalkyl optionally substituted with 1-3 F); and

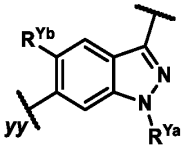
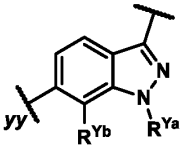
each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$ (e.g., C_{1-3} alkyl optionally substituted with 1-3 -F).

Embodiment 45. The compound of any one of Embodiments 39-41 or 44, wherein:

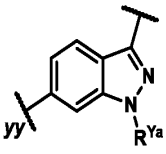
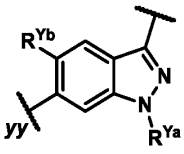
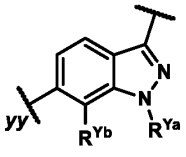
$\mathbf{R^{Ya}}$ is C_{1-3} alkyl optionally substituted with 1-3 -F (e.g., C_{1-3} alkyl (e.g., methyl)); and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: -F and C_{1-3} alkyl optionally substituted with 1-3 -F.

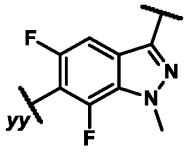
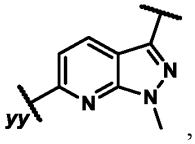
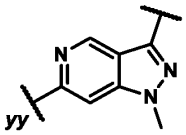
Embodiment 46. The compound of any one of Embodiments 1-39, wherein **Ring C** is selected from the group consisting of: , , , and .

Embodiment 47. The compound of any one of Embodiments 1-39, wherein **Ring C** is selected from the group consisting of:  and , wherein $\mathbf{R^{Yb}}$ is C_{1-3} alkyl optionally substituted with 1-3 F.

Embodiment 48. The compound of Embodiment 47, wherein $\mathbf{R^{Ya}}$ is methyl.

Embodiment 49. The compound of any one of Embodiments 1-39, wherein **Ring C** is selected from the group consisting of: ,  and , wherein $\mathbf{R^{Ya}}$ is $-(C_{0-3}$ alkylene$)$-$\mathbf{R^{b1}}$ or C_{2-4} alkyl optionally substituted with 1-3 $\mathbf{R^{c}}$.

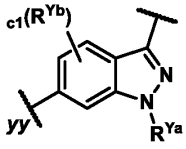
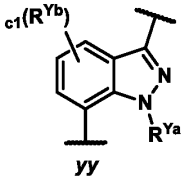
Embodiment 50. The compound of Embodiment 49, wherein $\mathbf{R^{Yb}}$ is independently -F or C_{1-3} alkyl optionally substituted with 1-3 -F.

Embodiment 51. The compound of any one of Embodiments 1-38 or 40, wherein **Ring C** is selected from the group consisting of: , , and .

Embodiment 52. The compound of any one of Embodiments 1-51, wherein **X** is CH.

Embodiment 53. The compound of any one of Embodiments 1-38, wherein:

X is CH; and

Ring C is selected from the group consisting of:  and , wherein:

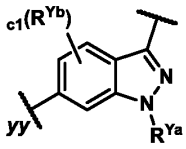
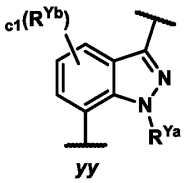
$\mathbf{R^{Ya}}$ is H, -$\mathbf{R^{b1}}$, -CH_2-$\mathbf{R^{b1}}$, or C_{1-3} alkyl optionally substituted with 1-3 -F,

wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl optionally substituted with 1-3 F, and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: -F and C_{1-3} alkyl optionally substituted with 1-3 -F.

Embodiment 54. The compound of any one of Embodiments 1-38, wherein:

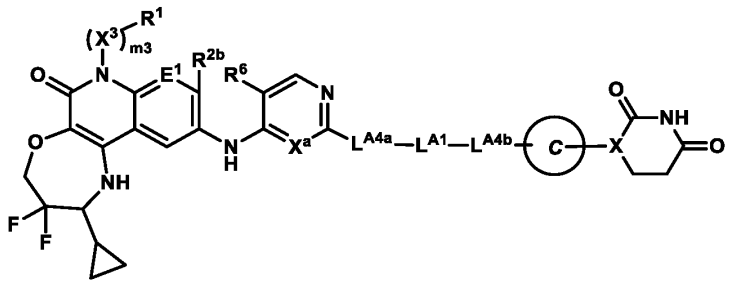
X is CH; and

Ring C is selected from the group consisting of:  and , wherein:

$\mathbf{R^{Ya}}$ is C_{1-3} alkyl optionally substituted with 1-3 -F (e.g., C_{1-3} alkyl (e.g., methyl)), and

each R^{Yb} is independently selected from the group consisting of: -F and C_{1-3} alkyl optionally substituted with 1-3 -F.

Embodiment 55. The compound of Embodiment 1, wherein the compound of Formula (**I**) is a compound of Formula (**I-a**):



Formula (**I-a**)

or a pharmaceutically acceptable salt thereof, wherein:

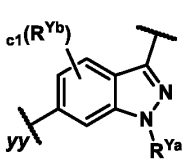
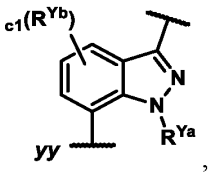
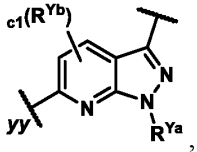
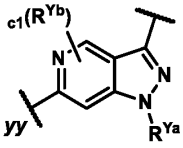
E^1 is CR^{2a} or N;

R^{2a} and R^{2b} are each independently selected from the group consisting of: H and F;

L^{A4a} and L^{A4b} are independently 4-12 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 R^a;

L^{A1} is CH_2 or CHR^L, and

R^L is selected from the group consisting of: -F, -OH, and C_{1-3} alkyl optionally substituted with 1-3 R^c; and

Ring C is selected from the group consisting of: , , , and , wherein:

c1 is 0, 1, or 2;

R^{Ya} is selected from the group consisting of:

(a) H;

(b) C_{1-6} alkyl optionally substituted with 1-3 R^c, and

(c) –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^{g}}$;

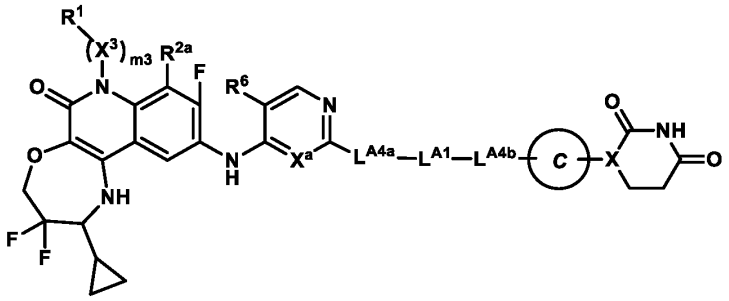
each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^{c}}$ (e.g., C_{1-3} alkyl optionally substituted with 1-3 -F); and

yy represents the point of attachment to $\mathbf{L^{A4b}}$.

Embodiment 56. The compound of Embodiment 55, wherein $\mathbf{E^1}$ is $C\mathbf{R^{2a}}$; and each of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ is H.

Embodiment 57. The compound of Embodiment 55, wherein $\mathbf{E^1}$ is $C\mathbf{R^{2a}}$; one of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ is F; and the other of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ is H.

Embodiment 58. The compound of Embodiment 55, wherein the compound of Formula (**I-a**) is a compound of Formula (**I-a-1**):

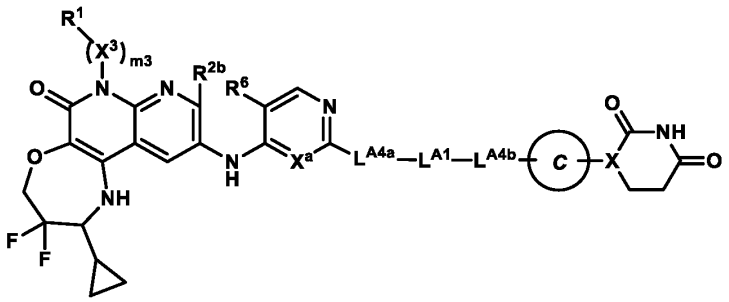


Formula (**I-a-1**)

or a pharmaceutically acceptable salt thereof.

Embodiment 59. The compound of Embodiment 58, wherein $\mathbf{R^{2a}}$ is H.

Embodiment 60. The compound of Embodiment 55, wherein the compound of Formula (**I-a**) is a compound of Formula (**I-a-2**):



Formula (**I-a-2**)

or a pharmaceutically acceptable salt thereof.

Embodiment 61. The compound of Embodiment 60, wherein $\mathbf{R^{2b}}$ is H.

Embodiment 62. The compound of any one of Embodiments 55-61, wherein $\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ are independently monocyclic 4-6 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R^a}$.

Embodiment 63. The compound of any one of Embodiments 55-61, wherein $\mathbf{L^{A4b}}$ is a monocyclic 4-6 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R^a}$; and

$\mathbf{L^{A4a}}$ is a bicyclic spirocyclic 10-12 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R^a}$.

Embodiment 64. The compound of any one of Embodiments 55-63, wherein:

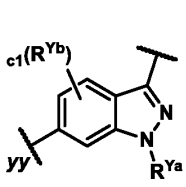
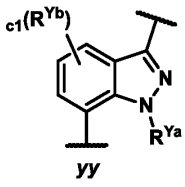
$\mathbf{R^L}$ is $C_{1\text{-}3}$ methyl optionally substituted with 1-3 F;

each $\mathbf{R^a}$ present on $\mathbf{L^{A4a}}$ and/or $\mathbf{L^{A4b}}$ is independently selected from the group consisting of: -F, CN, $C_{1\text{-}3}$ alkoxy, OH, and $C_{1\text{-}3}$ alkyl optionally substituted with 1-3 F; and

$\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ each contain 1-2 ring nitrogen atoms and no additional ring heteroatoms.

Embodiment 65. The compound of any one of Embodiments 55-64, wherein:

X is CH; and

Ring C is selected from the group consisting of:  and , wherein:

c1 is 0, 1, or 2;

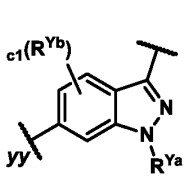
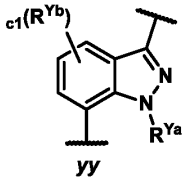
$\mathbf{R^{Ya}}$ is H, $-\mathbf{R^{b1}}$, $-CH_2-\mathbf{R^{b1}}$, or C_{1-3} alkyl optionally substituted with 1-3 -F,

wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl optionally substituted with 1-3 F, and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: -F and C_{1-3} alkyl optionally substituted with 1-3 -F.

Embodiment 66. The compound of any one of Embodiments 55-65, wherein:

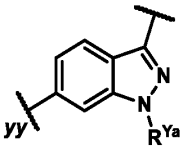
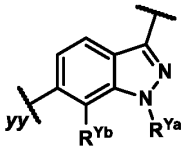
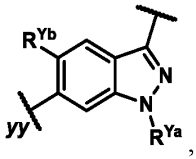
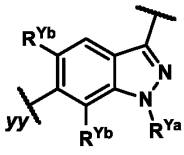
X is CH; and

Ring C is selected from the group consisting of:  and , wherein:

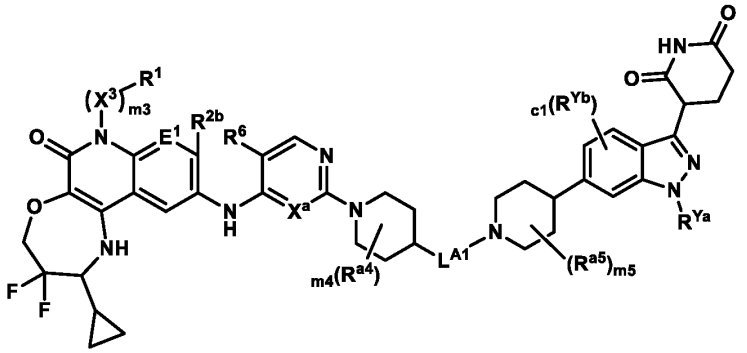
c1 is 0, 1, or 2;

$\mathbf{R^{Ya}}$ is C_{1-3} alkyl optionally substituted with 1-3 -F (e.g., C_{1-3} alkyl (e.g., methyl)); and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: -F and C_{1-3} alkyl optionally substituted with 1-3 -F.

Embodiment 67. The compound of Embodiment 65 or 66, wherein **Ring C** is selected from the group consisting of: , , , and .

Embodiment 68. The compound of Embodiment 1 or 55, wherein the compound is a compound of Formula (**I-b**):



Formula (**I-b**)

or a pharmaceutically acceptable salt thereof, wherein:

$\mathbf{E^1}$ is $C\mathbf{R^{2a}}$ or N;

$\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are each independently selected from the group consisting of: H and F;

m4 and **m5** are independently 0, 1, or 2;

each $\mathbf{R^{a4}}$ and $\mathbf{R^{a5}}$ is independently selected from the group consisting of: -F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F;

$\mathbf{L^{A1}}$ is CH_2 or $CH\mathbf{R^L}$, and

$\mathbf{R^L}$ is C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$;

c1 is 0, 1, or 2;

$\mathbf{R^{Ya}}$ is selected from the group consisting of:

(a) H;

(b) C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$, and

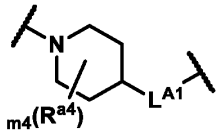
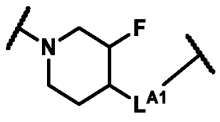
(c) –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$; and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$.

Embodiment 69. The compound of Embodiment 68, wherein one or more of **(1)-(6)** applies:

(1) $\mathbf{R^{2b}}$ is -F;

(2) E^1 is N;

(3) the  moiety is: ;

(4) R^{Ya} is selected from the group consisting of: C_{2-6} alkyl optionally substituted with 1-3 R^c, and –(C_{0-3} alkylene)-R^{b1}, wherein R^{b1} is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 R^g;

(5) c1 is 2; and/or

(6) c1 is 1, and R^{Yb} is C_{1-3} alkyl optionally substituted with 1-3 R^c (e.g., C_{1-3} alkyl optionally substituted with 1-3 F).

Embodiment 70. The compound of Embodiment 68, wherein two or more of **(1)-(4)** apply:

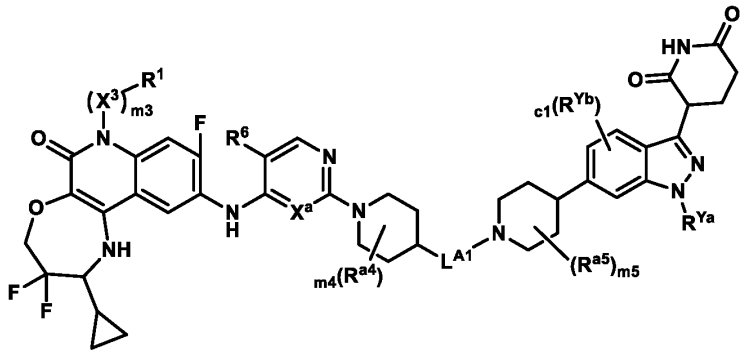
(1) m4 is 1 or 2;

(2) m5 is 1 or 2;

(3) L^{A1} is CHR^L; and/or

(4) c1 is 1 or 2.

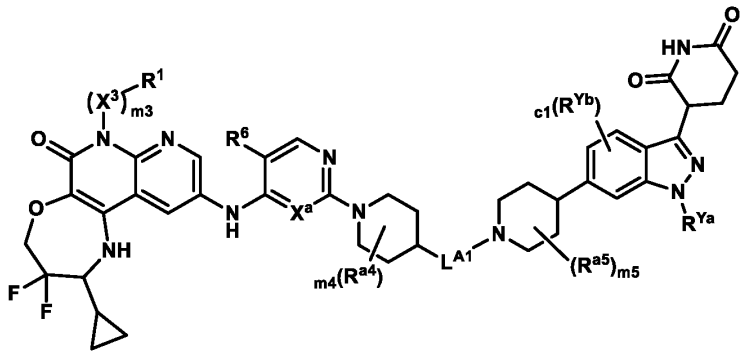
Embodiment 71. The compound of Embodiment 68, wherein the compound of Formula (**I-b**) is a compound of Formula (**I-b-1**):



Formula (**I-b-1**)

or a pharmaceutically acceptable salt thereof.

Embodiment 72. The compound of Embodiment 68, wherein the compound of Formula (**I-b**) is a compound of Formula (**I-b-2**):



Formula (**I-b-2**)

or a pharmaceutically acceptable salt thereof.

Embodiment 73. The compound of any one of Embodiments 68-72, wherein:

$\mathbf{R^{Ya}}$ is selected from the group consisting of:

(a) C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$, and

(b) –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$ (e.g.,C_{3-6} cycloalkyl optionally substituted with 1-3 F); and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$.

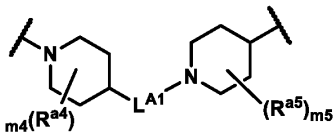
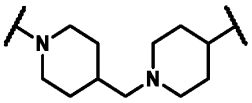
Embodiment 74. The compound of any one of Embodiments 68-73, wherein:

$\mathbf{R^{Ya}}$ is C_{1-3} alkyl optionally substituted with 1-3 -F (e.g., C_{1-3} alkyl (e.g., methyl)), and

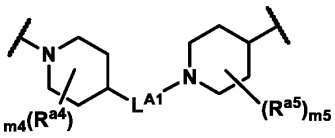
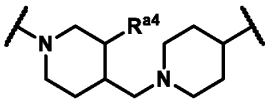
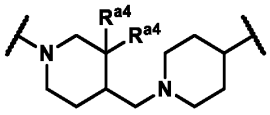
each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: -F and C_{1-3} alkyl optionally substituted with 1-3 -F.

Embodiment 75. The compound of any one of Embodiments 68-74, wherein $\mathbf{L^{A1}}$ is CH_2.

Embodiment 76. The compound of any one of Embodiments 68-75, wherein **m4** is 0; and **m5** is 0.

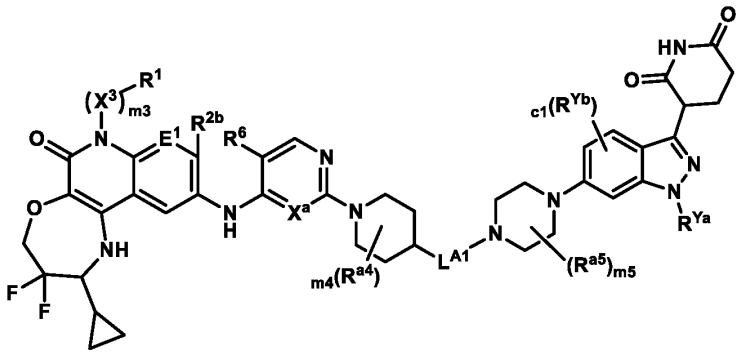
Embodiment 77. The compound of any one of Embodiments 68-76, wherein the  moiety is .

Embodiment 78. The compound of any one of Embodiments 68-75, wherein **m4** is 1 or 2; and **m5** is 0, wherein each R^{a4} is independently selected from the group consisting of: -F, Me, and CF_3.

Embodiment 79. The compound of any one of Embodiments 68-75 or 78, wherein the  moiety is  or .

Embodiment 80. The compound of any one of Embodiments 68-75, wherein **m4** is 0; and **m5** is 1 or 2, wherein each R^{a5} is independently selected from the group consisting of: -F, Me, and CF_3.

Embodiment 81. The compound of Embodiment 1 or 55, wherein the compound is a compound of Formula (**I-c**):



Formula (**I-c**)

or a pharmaceutically acceptable salt thereof, wherein:

$\mathbf{E^1}$ is $C\mathbf{R^{2a}}$ or N;

$\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are each independently selected from the group consisting of: H and F;

m4 and **m5** are independently 0, 1, or 2;

each $\mathbf{R^{a4}}$ is independently selected from the group consisting of: -F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F;

each $\mathbf{R^{a5}}$ is independently C_{1-3} alkyl optionally substituted with 1-3 F;

$\mathbf{L^{A1}}$ is CH_2 or $CH\mathbf{R^L}$, and

$\mathbf{R^L}$ is C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$;

c1 is 0, 1, or 2;

$\mathbf{R^{Ya}}$ is selected from the group consisting of:

(a) H;

(b) C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$; and

(c) –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$; and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$.

Embodiment 82. The compound of Embodiment 81, wherein one or more of **(1)-(4)** applies:

(1) $\mathbf{R^{2b}}$ is -F;

(2) $\mathbf{E^1}$ is N;

(3) $\mathbf{R^{Ya}}$ is selected from the group consisting of: C_{2-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$, and –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$; and/or

(4) c1 is 2.

Embodiment 83. The compound of Embodiment 81, wherein two or more of **(1)-(4)** apply:

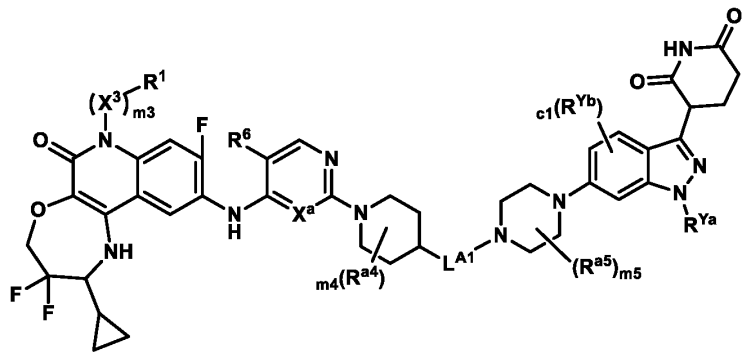
(1) m4 is 2;

(2) m5 is 1 or 2;

(3) $\mathbf{L^{A1}}$ is $CH\mathbf{R^L}$; and/or

(4) c1 is 1 or 2.

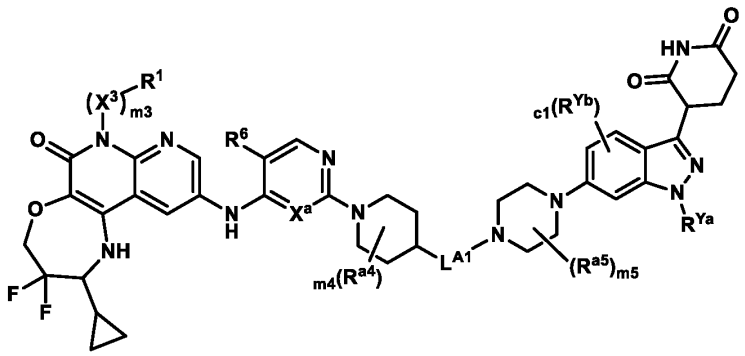
Embodiment 84. The compound of Embodiment 81, wherein the compound of Formula (**I-c**) is a compound of Formula (**I-c-1**):



Formula (**I-c-1**)

or a pharmaceutically acceptable salt thereof.

Embodiment 85. The compound of Embodiment 81, wherein the compound of Formula (**I-c**) is a compound of Formula (**I-c-2**):



Formula (**I-c-2**)

or a pharmaceutically acceptable salt thereof.

Embodiment 86. The compound of any one of Embodiments 81-85, wherein:

$\mathbf{R^{Ya}}$ is selected from the group consisting of:

(a) C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$, and

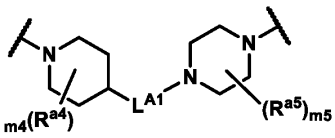
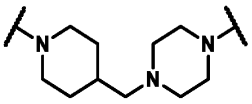
(b) –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$ (e.g., C_{3-6} cycloalkyl optionally substituted with 1-3 F); and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$.

Embodiment 87. The compound of any one of Embodiments 81-86, wherein: $\mathbf{R^{Ya}}$ is C_{1-3} alkyl optionally substituted with 1-3 -F (e.g., C_{1-3} alkyl (e.g., methyl)), and each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: -F and C_{1-3} alkyl optionally substituted with 1-3 -F.

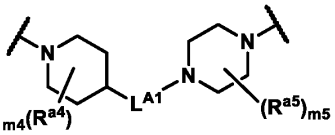
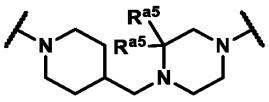
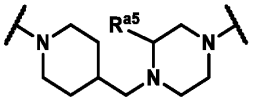
Embodiment 88. The compound of any one of Embodiments 81-87, wherein $\mathbf{L^{A1}}$ is CH_2.

Embodiment 89. The compound of any one of Embodiments 81-88, wherein **m4** is 0; and **m5** is 0.

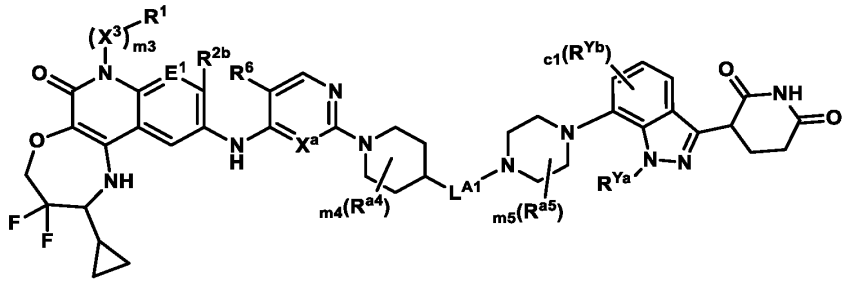
Embodiment 90. The compound of Embodiment 89, wherein the  moiety is .

Embodiment 91. The compound of any one of Embodiments 81-88, wherein **m4** is 1 or 2; and **m5** is 0, wherein each $\mathbf{R^{a4}}$ is independently selected from the group consisting of: -F, Me, and CF_3.

Embodiment 92. The compound of any one of Embodiments 81-88, wherein **m4** is 0; and **m5** is 1 or 2, wherein each $\mathbf{R^{a5}}$ is independently selected from the group consisting of Me and CF_3.

Embodiment 93. The compound of any one of Embodiments 81-88 or 92, wherein the  moiety is  or .

Embodiment 94. The compound of Embodiment 1 or 55, wherein the compound is a compound of Formula (**I-d**):



Formula (**I-d**)

or a pharmaceutically acceptable salt thereof, wherein:

$\mathbf{E^1}$ is $C\mathbf{R^{2a}}$ or N;

$\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are each independently selected from the group consisting of: H and F;

m4 and **m5** are independently 0, 1, or 2;

each $\mathbf{R^{a4}}$ is independently selected from the group consisting of: -F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F;

each $\mathbf{R^{a5}}$ is independently C_{1-3} alkyl optionally substituted with 1-3 F;

$\mathbf{L^{A1}}$ is CH_2 or $CH\mathbf{R^L}$, and

$\mathbf{R^L}$ is C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$;

c1 is 0, 1, or 2;

$\mathbf{R^{Ya}}$ is selected from the group consisting of:

(a) H;

(b) C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$; and

(c) –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$; and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$.

Embodiment 95. The compound of Embodiment 94, wherein one or more of **(1)-(4)** applies:

(1) $\mathbf{R^{2b}}$ is -F;

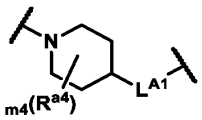
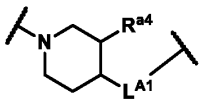
(2) E^1 is N;

(3) R^{Ya} is selected from the group consisting of: C_{2-6} alkyl optionally substituted with 1-3 R^c, and –(C_{0-3} alkylene)-R^{b1}, wherein R^{b1} is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 R^g; and/or

(4) c1 is 2.

Embodiment 96. The compound of Embodiment 94, wherein two or more of **(1)-(5)** apply:

(1) m4 is 2;

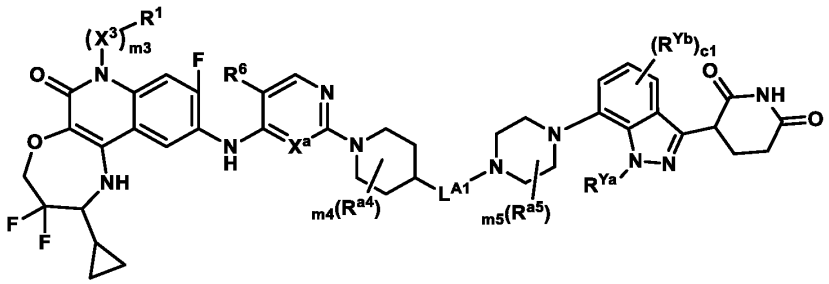
(2) m4 is 1, and the  moiety is: ;

(3) m5 is 1 or 2;

(4) L^{A1} is CHR^L; and/or

(5) c1 is 1 or 2.

Embodiment 97. The compound of Embodiment 94, wherein the compound of Formula (**I-d**) is a compound of Formula (**I-d-1**):



Formula (**I-d-1**)

or a pharmaceutically acceptable salt thereof.

Embodiment 98. The compound of any one of Embodiments 94-97, wherein:

R^{Ya} is selected from the group consisting of:

(a) C_{1-6} alkyl optionally substituted with 1-3 R^c; and

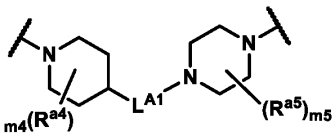
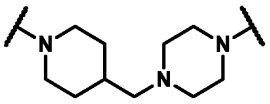
(b) –(C_{0-3} alkylene)-R^{b1}, wherein R^{b1} is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 R^g (e.g., C_{3-6} cycloalkyl optionally substituted with 1-3 F); and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$.

Embodiment 99. The compound of any one of Embodiments 94-98, wherein: $\mathbf{R^{Ya}}$ is C_{1-3} alkyl optionally substituted with 1-3 -F (e.g., C_{1-3} alkyl (e.g., methyl)), and each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: -F and C_{1-3} alkyl optionally substituted with 1-3 -F.

Embodiment 100. The compound of any one of Embodiments 94-99, wherein $\mathbf{L^{A1}}$ is CH_2.

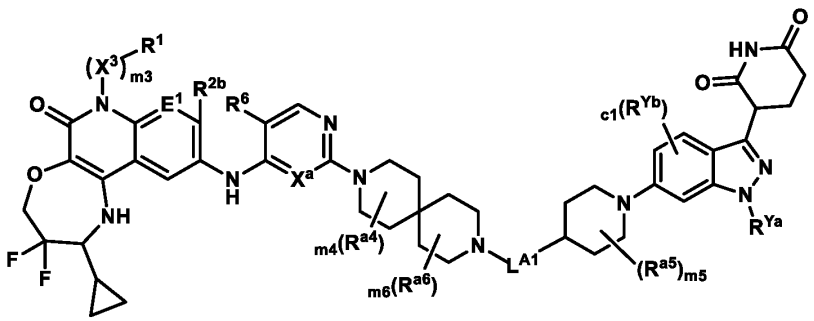
Embodiment 101. The compound of any one of Embodiments 94-100, wherein **m4** is 0; and **m5** is 0.

Embodiment 102. The compound of any one of Embodiments 94-101, wherein the  moiety is .

Embodiment 103. The compound of any one of Embodiments 94-100, wherein **m4** is 1 or 2; and **m5** is 0, wherein each $\mathbf{R^{a4}}$ is independently selected from the group consisting of: -F, Me, and CF_3.

Embodiment 104. The compound of any one of Embodiments 94-100, wherein **m4** is 0; and **m5** is 1 or 2, wherein each $\mathbf{R^{a5}}$ is independently selected from the group consisting of: Me and CF_3.

Embodiment 105. The compound of Embodiment 1 or 55, wherein the compound is a compound of Formula (**I-e**):



Formula (**I-e**)

or a pharmaceutically acceptable salt thereof, wherein:

$\mathbf{E^1}$ is $C\mathbf{R^{2a}}$ or N;

$\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are each independently selected from the group consisting of: H and F;

m4, **m5**, and **m6** are independently 0, 1, or 2, provided that **m4** + **m6** is 0, 1, 2, or 3;

each $\mathbf{R^{a4}}$, $\mathbf{R^{a5}}$, and $\mathbf{R^{a6}}$ is independently selected from the group consisting of: -F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F;

$\mathbf{L^{A1}}$ is CH_2 or $CH\mathbf{R^L}$, and

$\mathbf{R^L}$ is C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$;

c1 is 0, 1, or 2;

$\mathbf{R^{Ya}}$ is selected from the group consisting of:

(a) H,

(b) C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$, and

(c) –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$; and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$.

Embodiment 106. The compound of Embodiment 105, wherein one or more of **(1)-(7)** applies:

(1) $\mathbf{R^{2b}}$ is -F;

(2) $\mathbf{E^1}$ is N;

(3) one or more of **m4**, **m5**, and **m6** is independently 1 or 2;

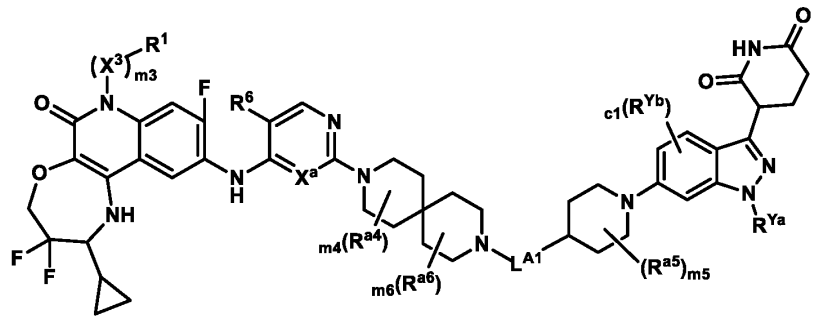
(4) $\mathbf{L^{A1}}$ is $CH\mathbf{R^L}$;

(5) c1 is 1, and $\mathbf{R^{Yb}}$ is C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$;

(6) c1 is 2; and/or

(7) $\mathbf{R^{Ya}}$ is selected from the group consisting of: C_{2-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$, and –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$.

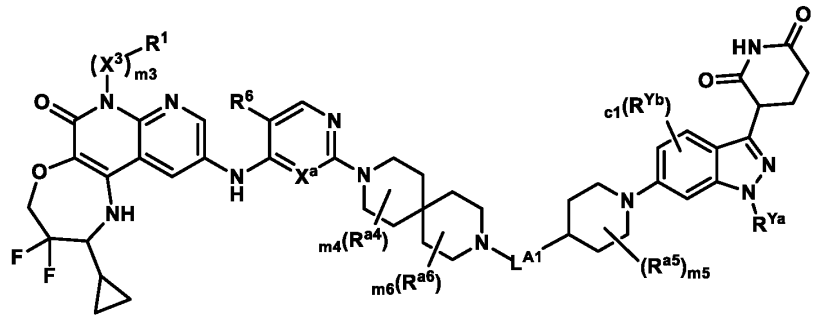
Embodiment 107. The compound of Embodiment 105, wherein the compound of Formula (**I-e**) is a compound of Formula (**I-e-1**):



Formula (**I-e-1**)

or a pharmaceutically acceptable salt thereof.

Embodiment 108. The compound of Embodiment 105, wherein the compound of Formula (**I-e**) is a compound of Formula (**I-e-2**):



Formula (**I-e-2**)

or a pharmaceutically acceptable salt thereof.

Embodiment 109. The compound of any one of Embodiments 105-108, wherein:

$\mathbf{R^{Ya}}$ is selected from the group consisting of:

(a) C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$, and

(b) –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^{g}}$ (e.g., C_{3-6} cycloalkyl optionally substituted with 1-3 F); and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^{c}}$.

Embodiment 110. The compound of any one of Embodiments 105-109, wherein:

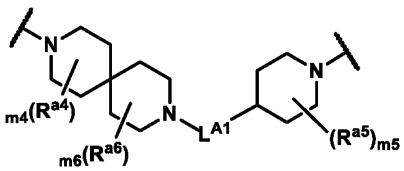
$\mathbf{R^{Ya}}$ is C_{1-3} alkyl optionally substituted with 1-3 -F (e.g., C_{1-3} alkyl (e.g., methyl)), and

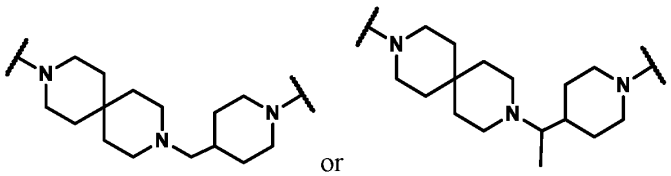
each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: -F and C_{1-3} alkyl optionally substituted with 1-3 -F.

Embodiment 111. The compound of any one of Embodiments 105-110, wherein $\mathbf{L^{A1}}$ is CH_2.

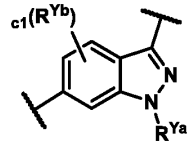
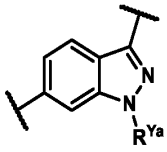
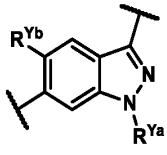
Embodiment 112. The compound of any one of Embodiments 105-110, wherein $\mathbf{L^{A1}}$ is CHMe.

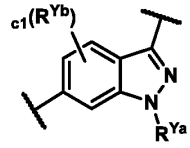
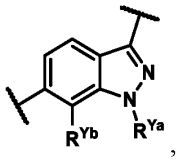
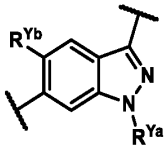
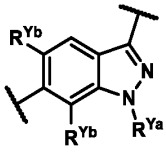
Embodiment 113. The compound of any one of Embodiments 105-112, wherein **m4** is 0; **m5** is 0; and **m6** is 0.

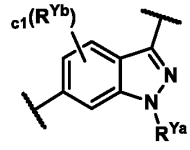
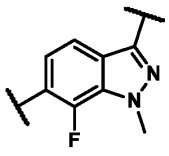
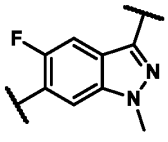
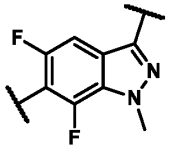
Embodiment 114. The compound of any one of Embodiments 105-110 or 113, wherein the  moiety is:



Embodiment 115. The compound of any one of Embodiments 105-110, wherein **m4** is 0; **m6** is 0; and **m5** is 1 or 2, wherein each $\mathbf{R^{a5}}$ is independently selected from the group consisting of: -F, Me, and CF_3.

Embodiment 116. The compound of any one of Embodiments 68-93 or 105-115, wherein the  moiety is selected from the group consisting of: , , , and .

Embodiment 117. The compound of any one of Embodiments 68-93 or 105-116, wherein the  moiety is selected from the group consisting of: , , and , wherein each $\mathbf{R^{Yb}}$ is independently F or C_{1-3} alkyl optionally substituted with 1-3 F; and $\mathbf{R^{Ya}}$ is C_{1-3} alkyl optionally substituted with 1-3 F (e.g., C_{1-3} alkyl (e.g., methyl)).

Embodiment 118. The compound of any one of Embodiments 68-93 or 105-117, wherein the  moiety is selected from the group consisting of: , , and .

Embodiment 119. The compound of any one of Embodiments 55-118, wherein $\mathbf{R^6}$ is -F or -Cl; and $\mathbf{X^a}$ is N.

Embodiment 120. The compound of any one of Embodiments 55-119, wherein $\mathbf{R^6}$ is -Cl; and $\mathbf{X^a}$ is N.

Embodiment 121. The compound of any one of Embodiments 55-120, wherein $-(\mathbf{X^3})_{m3}\text{-}\mathbf{R^1}$ is $C_{1\text{-}3}$ alkyl.

Embodiment 122. The compound of any one of Embodiments 55-121, wherein $-(\mathbf{X^3})_{m3}\text{-}\mathbf{R^1}$ is methyl.

Embodiment 123. The compound of any one of Embodiments 55-120, wherein $-(\mathbf{X^3})_{m3}\text{-}\mathbf{R^1}$ is H.

Embodiment 124. The compound of any one of Embodiments 55-120, wherein $-(\mathbf{X^3})_{m3}\text{-}\mathbf{R^1}$ is $\text{-}\mathbf{R^{b1}}$ or $\text{-}CH_2\text{-}\mathbf{R^{b1}}$.

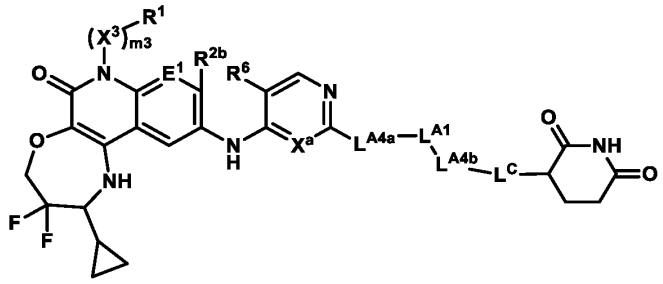
Embodiment 125. The compound of Embodiment 124, wherein the $\mathbf{R^{b1}}$ is $C_{3\text{-}6}$ cycloalkyl optionally substituted with 1-3 F.

Embodiment 126. The compound of Embodiment 1, wherein the compound of Formula (**I**) is other than a compound selected from the group consisting of the compounds depicted in **Table R1**, or a pharmaceutically acceptable salt thereof.

Embodiment 127. The compound of Embodiment 1, wherein the compound of Formula (**I**) is selected from the group consisting of Compound No. **101**, **101a**, **101b**, **101c**, **101d**, **102**, **102a**, **102b**, **103**, **103a**, **103b**, **104**, **104a**, **104b**, **105**, **105a**, **106**, **106a**, **107**, **107a**, **107b**, **107c**, **107d**, **108**, **108a**, **109**, **109a**, **109b**, **110**, **110a**, **110b**, **110c**, **110d**, **110e**, **110f**, **111**, **111a**, **111b**, **112**, **112a**, **112b**, **113**, **113a**, **113b**, **114**, **114a**, **114b**, **115**, **115a**, **116**, **116a**, **116b**, **116c**, **116d**, **117**, **117a**, **117b**, **118**, **118a**, **118b**, **119**, **119a**, **119b**, **119c**, **119d**, **120**, **120a**, **120b**, **121**, **121a**, **121b**, **121c**, **121d**, **121e**, **122**, **122a**, **123**, **123a**, **123b**, **124**, **124a**, **124b**, **125**, **125a**, **126**, **126a**, **127**, **127a**, **127b**, **127c**, **127d**, **128**, **128a**, **129**, **129a**, **129b**, **130**, **130a**, **130b**, **130c**, **130d**, **130e**, **131**, **131a**, **131b**, **132**, **132a**, **133**, **133a**, **133b**, **134**, **134a**, **135**, **135a**, **135b**, **136**, **136a**, **137**, **137a**, **138**, **138a**, **139**, **139a**, **139b**, **140**, **140a**, **140b**, **141**, **141a**, **142**, **142a**, **142b**, **143a**, **144**, **144a**, **145**, **145a**, **146**, **146a**, **146b**, **147**, **147a**, **148**, **148a**, **148b**, **149**, **149a**, **150**, **150a**, **151**, **151a**, **151b**, **152**, **152a**, **153a**, **154**, **154a**, **155**, **155a**, **156**, **156a**, **157**, **157a**, **158**,

158a, **159**, **159a**, **160**, **160a**, **160b**, **161**, **161a**, **162**, **162a**, **163**, **163a**, **164**, **164a**, **165**, **165a**, **166**, **166a**, **166b**, **167**, **167a**, **168**, **168a**, **169**, **169a**, **169b**, **170**, **170a**, **171**, **171a**, **172**, **172a**, **173**, **173a**, **174**, **174a**, **175**, **175a**, **176**, **176a**, **177**, **177a**, **178**, **178a**, **181**, **181a**, **182**, **182a**, **185a**, **185b**, **186**, **186a**, **187**, **187a**, **187b**, **188**, **188a**, **188b**, **189**, **189a**, **189b**, **190**, **190a**, **191**, **191a**, **192**, **192a**, **193**, **193a**, **194**, **194a**, **195**, **195a**, **196**, **196a**, **197**, **197a**, **198**, **198a**, **199**, **199a**, **199b**, **200**, **200a**, **201**, **201a**, **202**, **202a**, **202b**, **203**, **203a**, **203b**, **204**, **204a**, **205**, **205a**, **206**, **206a**, **207**, **207a**, **208**, **208a**, **209**, **209a**, **209b**, **210**, **210a**, **210b**, **211**, **211a**, **212**, and **212a** as depicted in **Table C1**, or a pharmaceutically acceptable salt thereof.

Embodiment 128. A compound of Formula (**II-a**):



Formula (**II-a**)

or a pharmaceutically acceptable salt thereof, wherein:

$\mathbf{E^1}$ is $C\mathbf{R^{2a}}$ or N;

$\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are independently selected from the group consisting of: H, halo, cyano, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, and C_{1-3} haloalkoxy;

m3 is 0 or 1;

$\mathbf{X^3}$ is C_{1-3} alkylene optionally substituted with 1-3 $\mathbf{R^c}$;

$\mathbf{R^1}$ is selected from the group consisting of: H, halo, and $\mathbf{R^{b1}}$;

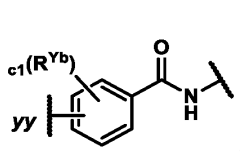
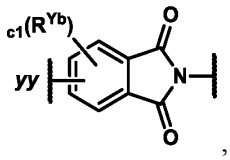
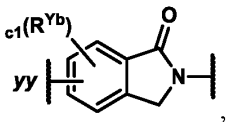
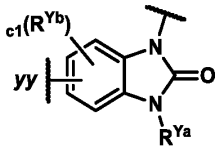
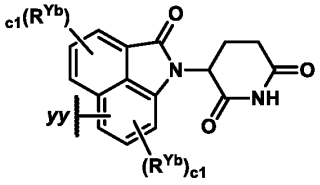
$\mathbf{X^a}$ is selected from the group consisting of: N and $C\mathbf{R^{Xa}}$;

$\mathbf{R^6}$ and $\mathbf{R^{Xa}}$ are independently selected from the group consisting of: H, halo, C_{1-2} alkyl, C_{1-2} haloalkyl, C_{1-2} alkoxy, CN, and -C≡CH;

$\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ are independently 4-12 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R^a}$;

$\mathbf{L^{A1}}$ is CH_2, $CH\mathbf{R^L}$, or $C(\mathbf{R^L})_2$, and

each $\mathbf{R^L}$ is independently selected from the group consisting of: -F, -OH, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$;

$\mathbf{L^C}$ is selected from the group consisting of: , , , , and ;

each **c1** is independently 0, 1, or 2;

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of $\mathbf{R^a}$ and $\mathbf{R^b}$;

$\mathbf{R^{Ya}}$ is selected from the group consisting of: H, $\mathbf{R^a}$, and $\mathbf{R^b}$; and

yy represents the point of attachment to $\mathbf{L^{A4b}}$;

each $\mathbf{R^a}$ is independently selected from the group consisting of:

(a) halo;

(b) cyano;

(c) -OH;

(d) oxo;

(e) C_{1-6} alkoxy optionally substituted with 1-6 $\mathbf{R^c}$;

(f) $-N\mathbf{R^d}\mathbf{R^e}$;

(g) $C(=O)C_{1-6}$ alkyl;

(h) $C(=O)OC_{1-6}$ alkyl;

(i) $C(=O)N(\mathbf{R^f})_2$;

(j) $S(O)_{0-2}(C_{1-6}$ alkyl);

(k) $S(O)_{0-2}(C_{1-6}$ haloalkyl); and

(l) C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, each optionally substituted with 1-6 $\mathbf{R^c}$;

each $\mathbf{R^b}$ is independently selected from the group consisting of: $-(\mathbf{L^b})_b-\mathbf{R^{b1}}$ and $-\mathbf{R^{b1}}$, wherein:

each **b** is independently 1, 2, or 3;

each $\mathbf{L^b}$ is independently selected from the group consisting of: -O-, -N(H)-, -N(C_{1-3} alkyl)-, -S(O)$_{0-2}$-, C(=O), and C_{1-3} alkylene; and

each $\mathbf{R^{b1}}$ is independently selected from the group consisting of: C_{3-6} cycloalkyl and 4-8 membered heterocyclyl, each of which is optionally substituted with 1-3 $\mathbf{R^g}$;

each $\mathbf{R^c}$ is independently selected from the group consisting of: halo, cyano, -OH, -C_{1-6} alkoxy, -C_{1-6} haloalkoxy, -N$\mathbf{R^d}\mathbf{R^e}$, C(=O)C_{1-6} alkyl, C(=O)OC_{1-6} alkyl, C(=O)N($\mathbf{R^f}$)$_2$, S(O)$_{0-2}$(C_{1-6} alkyl), and S(O)$_{0-2}$(C_{1-6} haloalkyl);

each $\mathbf{R^d}$ and $\mathbf{R^e}$ is independently selected from the group consisting of: H, C(=O)C_{1-6} alkyl, C(=O)C_{1-6} haloalkyl, C(=O)OC_{1-6} alkyl, C(=O)OC_{1-6} haloalkyl, C(=O)N($\mathbf{R^f}$)$_2$, S(O)$_{1-2}$(C_{1-6} alkyl), S(O)$_{1-2}$(C_{1-6} haloalkyl), S(O)$_{1-2}$N($\mathbf{R^f}$)$_2$, and C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^h}$;

each $\mathbf{R^f}$ is independently selected from the group consisting of: H and C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^h}$;

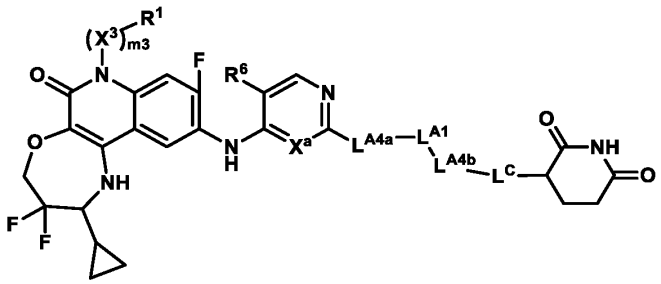
each $\mathbf{R^g}$ is independently selected from the group consisting of: $\mathbf{R^h}$, oxo, C_{1-3} alkyl, and C_{1-3} haloalkyl; and

each $\mathbf{R^h}$ is independently selected from the group consisting of: halo, cyano, -OH, -(C_{0-3} alkylene)-C_{1-6} alkoxy, -(C_{0-3} alkylene)-C_{1-6} haloalkoxy, -(C_{0-3} alkylene)-NH_2, -(C_{0-3} alkylene)-N(H)(C_{1-3} alkyl), and –(C_{0-3} alkylene)-N(C_{1-3} alkyl)$_2$,

provided that the compound of Formula (**II-a**) does not contain any O-O, N-O, N-N, N-S(O)$_0$, O-S(O)$_{0-2}$, N-halo, O-halo, or S(O)$_{0-2}$-halo bonds.

Embodiment 129. The compound of Embodiment 128, wherein **E** is C$\mathbf{R^{2a}}$ (e.g., CH).

Embodiment 130. The compound of Embodiment 128 or 129, wherein the compound of Formula (**II-a**) is a compound of Formula (**II-a-1**):



Formula (**II-a-1**)

or a pharmaceutically acceptable salt thereof.

Embodiment 131. The compound of any one of Embodiments 128-130, wherein **m3** is 1; and $\mathbf{R^1}$ is H.

Embodiment 132. The compound of any one of Embodiments 128-131, wherein $-(\mathbf{X^3})_{m3}\text{-}\mathbf{R^1}$ is $C_{1\text{-}3}$ alkyl (e.g., methyl).

Embodiment 133. The compound of any one of Embodiments 128-132, wherein $\mathbf{R^6}$ is -F or -Cl (e.g., -Cl).

Embodiment 134. The compound of any one of Embodiments 128-133, wherein $\mathbf{X^a}$ is N.

Embodiment 135. The compound of any one of Embodiments 128-134, wherein $\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ are independently a monocyclic 4-6 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R^a}$.

Embodiment 136. The compound of any one of Embodiments 128-135, wherein $\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ are independently a monocyclic 4-6 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R^a}$; and

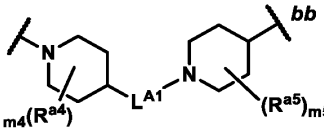
each $\mathbf{R^a}$ present on $\mathbf{L^{A4a}}$ and/or $\mathbf{L^{A4b}}$ is independently selected from the group consisting of: -F, CN, $C_{1\text{-}3}$ alkoxy, OH, and $C_{1\text{-}3}$ alkyl optionally substituted with 1-3 F.

Embodiment 137. The compound of any one of Embodiments 128-136, wherein one of $\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ is a 1,4-piperidinylene; and

the other of L^{A4a} and L^{A4b} is independently selected from the group consisting of: 1,4-piperidinylene and 1,4-piperazinylene, wherein each of the 1,4-piperidinylene or 1,4-piperazinylene is optionally substituted with 1-2 R^a, wherein:

each R^a present on L^{A4a} and/or L^{A4b} is independently selected from the group consisting of: -F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F.

Embodiment 138. The compound of any one of Embodiments 128-137, wherein each R^a present on L^{A4a} and/or L^{A4b} is independently selected from the group consisting of: -F and C_{1-3} alkyl optionally substituted with 1-3 F (e.g., F, CH_3, CF_3, CF_2H, or CH_2F).

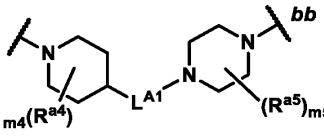
Embodiment 139. The compound of any one of Embodiments 128-134, wherein -L^{A4a}-L^{A1}-L^{A4b}- is 

, wherein:

m4 and **m5** are independently 0, 1, or 2;

each R^{a4} and R^{a5} is independently selected from the group consisting of: -F and C_{1-3} alkyl optionally substituted with 1-3 F; and

bb represents the point of attachment to L^C.

Embodiment 140. The compound of any one of Embodiments 128-134, wherein -L^{A4a}-L^{A1}-L^{A4b}- is 

, wherein:

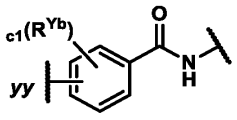
m4 and **m5** are independently 0, 1, or 2;

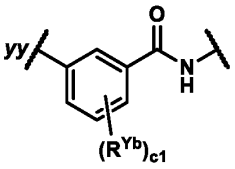
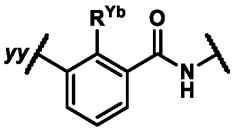
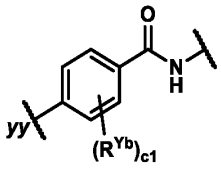
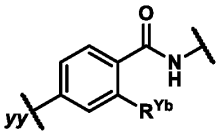
each R^{a4} is independently selected from the group consisting of: -F and C_{1-3} alkyl optionally substituted with 1-3 F;

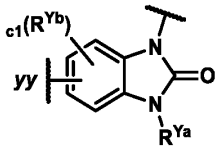
each R^{a5} is independently C_{1-3} alkyl optionally substituted with 1-3 F; and

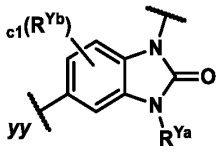
bb represents the point of attachment to L^C.

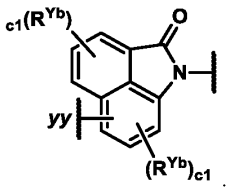
Embodiment 141. The compound of Embodiment 139 or 140, wherein **m4** is 0; and **m5** is 0.

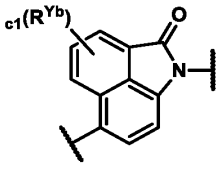
Embodiment 142. The compound of any one of Embodiments 128-141, wherein $\mathbf{L^C}$ is .

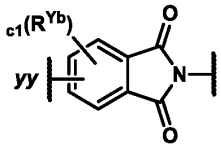
Embodiment 143. The compound of any one of Embodiments 128-142, wherein $\mathbf{L^C}$ is  (e.g., ) or  (e.g., ), wherein **c1** is 0 or 1; and each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 -F.

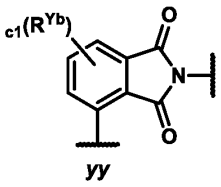
Embodiment 144. The compound of any one of Embodiments 128-141, wherein $\mathbf{L^C}$ is .

Embodiment 145. The compound of any one of Embodiments 128-141 or 144, wherein $\mathbf{L^C}$ is , wherein $\mathbf{R^{Ya}}$ is C_{1-3} alkyl optionally substituted with 1-3 F (e.g., C_{1-3} alkyl (e.g., methyl)).

Embodiment 146. The compound of any one of Embodiments 128-141, wherein $\mathbf{L^C}$ is .

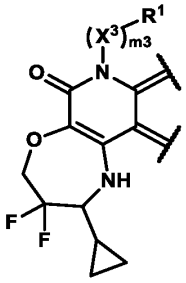
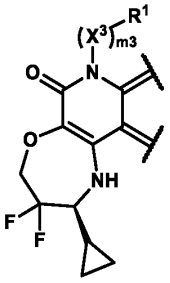
Embodiment 147. The compound of any one of Embodiments 128-141 or 146, wherein $\mathbf{L}^{C}$ is .

Embodiment 148. The compound of any one of Embodiments 128-141, wherein $\mathbf{L}^{C}$ is .

Embodiment 149. The compound of any one of Embodiments 128-141 or 148, wherein $\mathbf{L}^{C}$ is .

Embodiment 150. The compound of any one of Embodiments 144-149, wherein each $\mathbf{R}^{Yb}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 -F.

Embodiment 151. The compound of any one of Embodiments 144-149, wherein **c1** is 0.

Embodiment 152. The compound of any one of Embodiments 1-125 or 128-151, wherein the  moiety is .

Embodiment 153. The compound of Embodiment 128, wherein the compound of Formula (**II-a**) is other than a compound selected from the group consisting of the compounds depicted in **Table R2**, or a pharmaceutically acceptable salt thereof.

Embodiment 154. The compound of Embodiment 128, the compound of Formula (**II-a**) is selected from the group consisting of the compounds depicted in **Table C2**, or a pharmaceutically acceptable salt thereof.

Embodiment 155. A pharmaceutical composition comprising a compound of any one of Embodiments 1-154, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

Embodiment 156. A method for treating a cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of Embodiments 1-154, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to Embodiment 155.

Embodiment 157. The method of Embodiment 156, wherein the cancer is a hematological cancer, breast cancer, gastrointestinal cancer, brain cancer, lung cancer, or a combination thereof.

Embodiment 158. The method of Embodiment 157, wherein the hematological cancer is diffuse large B-cell lymphoma (DLBCL) (e.g., DLBCL, not otherwise specified (DLBCL-NOS), high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2) or HGBCL-NOS), primary large B cell lymphoma of privileged sites (primary LBCL of privileged sites), or primary mediastinal large B cell lymphoma (primary mediastinal LBCL)), transformed indolent B cell lymphoma, follicular lymphoma (FL), nodular lymphocyte predominant Hodgkin lymphoma (NLPHL), diffuse histiocytic lymphoma (DHL), intravascular large B-cell lymphoma (IVLBCL), small lymphocytic lymphoma (SLL), Burkitt lymphoma (BL), mantle cell lymphoma (MCL), peripheral T-cell lymphoma (PTCL) (e.g., a nodal PTCL (e.g., PTCL with a T follicular helper phenotype (PTCL-TFH), angioimmunoblastic T-cell lymphoma (AITL), anaplastic large cell lymphoma (ALCL) (e.g., ALK+ ALCL), or PTCL not otherwise specified (PTCL-NOS)), or a cutaneous T-cell lymphoma (e.g., mycosis fungoides, primary cutaneous CD4 positive small

or medium T-cell lymphoproliferative disorder, primary cutaneous gamma-delta T-cell lymphoma)), chronic lymphocytic leukemia (CLL), acute lymphocytic leukemia (ALL), chronic myeloid leukemia (CML), or early T-precursor lymphoblastic leukemia.

Embodiment 159. The method of Embodiment 158, wherein the hematological cancer is selected from the group consisting of DLBCL (e.g., DLBCL, not otherwise specified (DLBCL-NOS), high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2) or HGBCL-NOS), primary large B cell lymphoma of privileged sites (primary LBCL of privileged sites), or primary mediastinal large B cell lymphoma (primary mediastinal LBCL)), transformed indolent B cell lymphoma, FL, MCL, BL, PTCL (e.g., a nodal PTCL (e.g., PTCL with a T follicular helper phenotype (PTCL-TFH), angioimmunoblastic T-cell lymphoma (AITL), anaplastic large cell lymphoma (ALCL) (e.g., ALK+ ALCL), or PTCL not otherwise specified (PTCL-NOS)), or a cutaneous T-cell lymphoma (e.g., mycosis fungoides, primary cutaneous CD4 positive small or medium T-cell lymphoproliferative disorder, primary cutaneous gamma-delta T-cell lymphoma)), and ALL (e.g., B-ALL).

Embodiment 160. The method of Embodiment 158, wherein the hematological cancer is FL or DLBCL(e.g., DLBCL, not otherwise specified (DLBCL-NOS), high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2) or HGBCL-NOS), primary large B cell lymphoma of privileged sites (primary LBCL of privileged sites), or primary mediastinal large B cell lymphoma (primary mediastinal LBCL)).

Embodiment 161. The method of Embodiment 158, wherein the hematological cancer is DLBCL (e.g., DLBCL, not otherwise specified (DLBCL-NOS), high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2) or HGBCL-NOS), primary large B cell lymphoma of privileged sites (primary LBCL of privileged sites), or primary mediastinal large B cell lymphoma (primary mediastinal LBCL)).

Embodiment 162. The method of Embodiment 158, wherein the hematological cancer is FL.

Embodiment 163. The method of Embodiment 158, wherein the hematological cancer is BL.

Embodiment 164. The method of Embodiment 158, wherein the hematological cancer is a PTCL (e.g., a nodal PTCL (e.g., PTCL with a T follicular helper phenotype (PTCL-TFH), angioimmunoblastic T-cell lymphoma (AITL), anaplastic large cell lymphoma (ALCL) (e.g., ALK+ ALCL), or PTCL not otherwise specified (PTCL-NOS)), or a cutaneous T-cell lymphoma (e.g., mycosis fungoides, primary cutaneous CD4 positive small or medium T-cell lymphoproliferative disorder, primary cutaneous gamma-delta T-cell lymphoma)).

Embodiment 165. The method of Embodiment 158, wherein, the hematological cancer is ALL (e.g., B-ALL).

Embodiment 166. The method of any one of Embodiments 156-165, wherein the cancer is positive for BCL6 expression (e.g., as determined by an IHC test).

Embodiment 167. The method of any one of Embodiments 156-166, wherein the therapeutically effective amount of a compound of any one of Embodiments 1-154, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to Embodiment 155, is administered to the subject as a monotherapy.

Embodiment 168. The method of any one of Embodiments 156-166, comprising administering an additional therapy or therapeutic agent to the subject.

Embodiment 169. The method of Embodiment 168, wherein the additional therapy or therapeutic agent is a PI3K inhibitor, an Abl inhibitor (e.g., a BCR-Abl inhibitor), a BTK inhibitor, a JAK inhibitor, a BRaf inhibitor, a MEK inhibitor, a BCL-2 inhibitor, a Bcl-X_L inhibitor, an XPO1 inhibitor, an inhibitor of the polycomb repressive complex 2 (PRC2), an immunomodulatory imide drug, anti-CD19 therapy, anti-CD20 therapy, anti-CD3 therapy, chemotherapy, or a combination thereof.

Embodiment 170. The method of Embodiment 169, wherein the additional therapy or therapeutic agent is an Abl inhibitor.

Embodiment 171. The method of Embodiment 170, wherein the cancer is a B-ALL (e.g., a Philadelphia chromosome positive B-ALL or Philadelphia chromosome-like B-ALL).

Embodiment 172. The method of Embodiment 169, wherein the additional therapy or therapeutic agent is a BTK inhibitor.

Embodiment 173. The method of Embodiment 172, wherein the cancer is a B-ALL (e.g., a pre-BCR+ B-ALL or a B-ALL dependent on Ras signaling).

Embodiment 174. The method of Embodiment 169, wherein the additional therapy or therapeutic agent is a JAK inhibitor.

Embodiment 175. The method of Embodiment 174, wherein the cancer is a B-ALL (e.g., a JAK2 (e.g., $JAK2^{R683G}$ or $JAK2^{I682F}$) mutant B-ALL, with or without high CRLF2 expression).

Embodiment 176. The method of Embodiment 169, wherein the additional therapy or therapeutic agent is a BCL-2 inhibitor.

Embodiment 177. The method of Embodiment 176, wherein the cancer is selected from the group consisting of DLBCL (e.g., DLBCL, not otherwise specified (DLBCL-NOS), high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2) or HGBCL-NOS), primary large B cell lymphoma of privileged sites (primary LBCL of privileged sites), or primary mediastinal large B cell lymphoma (primary mediastinal LBCL)), transformed indolent B cell lymphoma, FL, MCL, and ALL (e.g., B-ALL).

Embodiment 178. The method of Embodiment 176, wherein the cancer is a DLBCL (e.g., DLBCL, not otherwise specified (DLBCL-NOS), high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2) or HGBCL-NOS), primary large B cell lymphoma of privileged sites (primary LBCL of privileged sites), or primary mediastinal large B cell lymphoma (primary mediastinal LBCL)).

Embodiment 179. The method of Embodiment 176, wherein the cancer is a FL.

Embodiment 180. The method of Embodiment 176, wherein the cancer is an MCL.

Embodiment 181. The method of Embodiment 176, wherein the cancer is a B-ALL (e.g., an *MLL*-rearranged (e.g., an MLL-Af4 fusion, an MLL-Af6 fusion, an MLL-Af9 fusion, an MLL-ENL fusion, or an MLL-PTD fusion) B-ALL, or a *BCL2* amplified B-ALL).

Embodiment 182. The method of Embodiment 169, wherein the additional therapy or therapeutic agent is an inhibitor of the PRC2 (e.g., an EZH1/2 or EZH2 inhibitor).

Embodiment 183. The method of Embodiment 182, wherein the cancer is selected from the group consisting of DLBCL (e.g., DLBCL, not otherwise specified (DLBCL-NOS), high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2) or HGBCL-NOS), primary large B cell lymphoma of privileged sites (primary LBCL of privileged sites), or primary mediastinal large B cell lymphoma (primary mediastinal LBCL)), FL, MCL, and ALL (e.g., B-ALL).

Embodiment 184. The method of Embodiment 183, wherein the cancer is a DLBCL (e.g., DLBCL, not otherwise specified (DLBCL-NOS), high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2) or HGBCL-NOS), primary large B cell lymphoma of privileged sites (primary LBCL of privileged sites), or primary mediastinal large B cell lymphoma (primary mediastinal LBCL)).

Embodiment 185. The method of Embodiment 183, wherein the cancer is a FL.

Embodiment 186. The method of Embodiment 183, wherein the cancer is an MCL.

Embodiment 187. The method of Embodiment 183, wherein the cancer is a B-ALL (e.g., an *MLL*-rearranged (e.g., an MLL-Af4 fusion, an MLL-Af6 fusion, an MLL-Af9 fusion, an MLL-ENL fusion, or an MLL-PTD fusion) B-ALL, or a *BCL2* amplified B-ALL).

Embodiment 188. The method of Embodiment 182, wherein the cancer is a peripheral T-cell lymphoma (PTCL) (e.g., a nodal PTCL (e.g., PTCL with a T follicular helper phenotype (PTCL-TFH), angioimmunoblastic T-cell lymphoma (AITL), anaplastic large cell

lymphoma (ALCL) (e.g., ALK+ ALCL), or PTCL not otherwise specified (PTCL-NOS)), or a cutaneous T-cell lymphoma (e.g., mycosis fungoides, primary cutaneous CD4 positive small or medium T-cell lymphoproliferative disorder, primary cutaneous gamma-delta T-cell lymphoma)).

Embodiment 189. The method of Embodiment 169, wherein the additional therapy or therapeutic agent is anti-CD20 therapy.

Embodiment 190. The method of Embodiment 189, wherein the cancer is a DLBCL (e.g., DLBCL, not otherwise specified (DLBCL-NOS), high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2) or HGBCL-NOS), primary large B cell lymphoma of privileged sites (primary LBCL of privileged sites), or primary mediastinal large B cell lymphoma (primary mediastinal LBCL)) or a FL.

Embodiment 191. The method of Embodiment 189, wherein the cancer is a DLBCL (e.g., DLBCL, not otherwise specified (DLBCL-NOS), high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2) or HGBCL-NOS), primary large B cell lymphoma of privileged sites (primary LBCL of privileged sites), or primary mediastinal large B cell lymphoma (primary mediastinal LBCL)).

Embodiment 192. The method of Embodiment 189, wherein the cancer is a FL.

Embodiment 193. The method of Embodiment 169, wherein the additional therapy or therapeutic agent is chemotherapy.

Embodiment 194. The method of Embodiment 193, wherein the cancer is B-ALL (e.g., an *MLL*-rearranged (e.g., an MLL-Af4 fusion, an MLL-Af6 fusion, an MLL-Af9 fusion, an MLL-ENL fusion, or an MLL-PTD fusion) B-ALL, a Philadelphia chromosome positive B-ALL, a Philadelphia chromosome-like B-ALL, a pre-BCR+ B-ALL, a B-ALL dependent on Ras signaling).

Embodiment 195. A method for treating or preventing an autoimmune condition in a subject in need thereof, the method comprising administering to the subject a therapeutically

effective amount of a compound of any one of Embodiments 1-154, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to Embodiment 155.

Embodiment 196. A method for treating a lymphoproliferative disorder in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of Embodiments 1-154, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to Embodiment 155.

Embodiment 197. A method for inducing degradation of a BCL6 protein in a mammalian cell, the method comprising contacting the mammalian cell with an effective amount of a compound of any one of Embodiments 1-154, or a pharmaceutically acceptable salt thereof.

Embodiment 198. The method of Embodiment 197, wherein the contacting occurs in vivo.

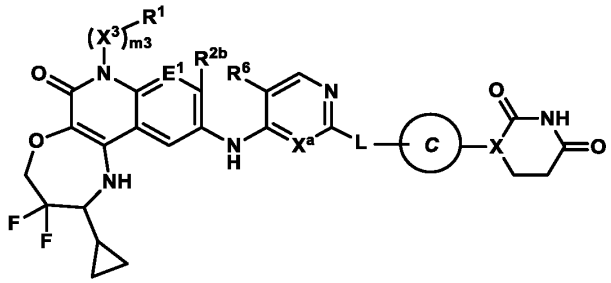
Embodiment 199. The method of Embodiment 197, wherein the contacting occurs in vitro.

Embodiment 200. The method of Embodiment 197, wherein the contacting occurs ex vivo.

Embodiment 201. The method of any one of Embodiments 197-200, wherein the mammalian cell is a mammalian cancer cell.

P04 Embodiments

Embodiment 1. A compound of Formula (**I**):



Formula (**I**)

or a pharmaceutically acceptable salt thereof, wherein:

$\mathbf{E^1}$ is $C\mathbf{R^{2a}}$ or N;

$\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are independently selected from the group consisting of: H, halo, cyano, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, and C_{1-3} haloalkoxy;

m3 is 0 or 1;

$\mathbf{X^3}$ is C_{1-3} alkylene optionally substituted with 1-3 $\mathbf{R^c}$;

$\mathbf{R^1}$ is selected from the group consisting of: H, halo, and $\mathbf{R^{b1}}$;

$\mathbf{X^a}$ is selected from the group consisting of: N and $C\mathbf{R^{Xa}}$;

$\mathbf{R^6}$ and $\mathbf{R^{Xa}}$ are independently selected from the group consisting of: H, halo, C_{1-2} alkyl, C_{1-2} haloalkyl, C_{1-2} alkoxy, CN, and -C≡CH;

L is $-(\mathbf{L^A})_{\mathbf{n1}}-$, wherein:

n1 is an integer from 1 to 5; and

each $\mathbf{L^A}$ is independently selected from the group consisting of: $\mathbf{L^{A1}}$, $\mathbf{L^{A3}}$, and $\mathbf{L^{A4}}$, wherein:

0-2 of $\mathbf{L^A}$ is $\mathbf{L^{A1}}$;

0-2 of $\mathbf{L^A}$ is $\mathbf{L^{A3}}$; and

1-3 of $\mathbf{L^A}$ is $\mathbf{L^{A4}}$,

each $\mathbf{L^{A1}}$ is independently selected from the group consisting of: $-CH_2-$, $-CH\mathbf{R^L}-$, and $-C(\mathbf{R^L})_2-$, wherein:

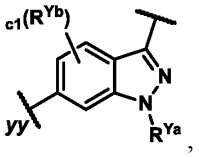
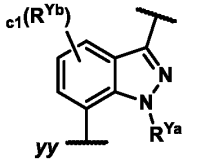
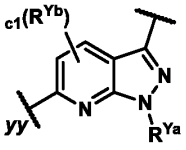
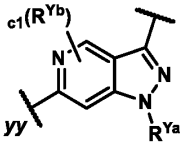
each $\mathbf{R^L}$ is independently selected from the group consisting of: halo, cyano, -OH, $-C_{1-6}$ alkoxy, $-C_{1-6}$ haloalkoxy, $-(C_{0-3}$ alkylene$)-(C_{3-5}$ cycloalkyl), $-(C_{0-3}$ alkylene$)-$(4-6 membered heterocyclyl), and C_{1-6} alkyl optionally substituted with 1-6 $\mathbf{R^c}$;

each $\mathbf{L^{A3}}$ is independently selected from the group consisting of: $-N(\mathbf{R^d})-$, $-N(\mathbf{R^b})-$, -O-, $-S(O)_{0-2}-$, and C(=O);

each $\mathbf{L^{A4}}$ is independently selected from the group consisting of:

(a) C_{3-15} cycloalkylene or 4-15 membered heterocyclylene, each of which is optionally substituted with 1-6 substituents independently selected from the group consisting of: $\mathbf{R^a}$ and $\mathbf{R^b}$; and

(b) phenylene or 5-6 membered heteroarylene, each of which is optionally substituted with 1-3 substituents independently selected from the group consisting of: $\mathbf{R^a}$ and $\mathbf{R^b}$;

Ring C is selected from the group consisting of: , , , and , wherein:

c1 is 0, 1, or 2;

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of $\mathbf{R^a}$ and $\mathbf{R^b}$;

$\mathbf{R^{Ya}}$ is selected from the group consisting of: H, $\mathbf{R^a}$, and $\mathbf{R^b}$; and

yy represents the point of attachment to **L**;

X is CH or N;

each $\mathbf{R^a}$ is independently selected from the group consisting of:

(a) halo;

(b) cyano;

(c) -OH;

(d) oxo;

(e) C_{1-6} alkoxy optionally substituted with 1-6 $\mathbf{R^c}$;

(f) $-N\mathbf{R^d}\mathbf{R^e}$;

(g) $C(=O)C_{1-6}$ alkyl;

(h) $C(=O)OC_{1-6}$ alkyl;

(i) $C(=O)N(\mathbf{R^f})_2$;

(j) $S(O)_{0-2}(C_{1-6}$ alkyl);

(k) $S(O)_{0-2}(C_{1-6}$ haloalkyl); and

(l) C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, each optionally substituted with 1-6 $\mathbf{R^c}$;

each $\mathbf{R^b}$ is independently selected from the group consisting of: $\mathbf{-(L^b)_b-R^{b1}}$ and $\mathbf{-R^{b1}}$, wherein:

each **b** is independently 1, 2, or 3;

each $\mathbf{L^b}$ is independently selected from the group consisting of: -O-, -N(H)-, -N(C_{1-3} alkyl)-, -S(O)$_{0-2}$-, C(=O), and C_{1-3} alkylene; and

each $\mathbf{R^{b1}}$ is independently selected from the group consisting of: C_{3-6} cycloalkyl and 4-8 membered heterocyclyl, each of which is optionally substituted with 1-3 $\mathbf{R^g}$;

each $\mathbf{R^c}$ is independently selected from the group consisting of: halo, cyano, -OH, -C_{1-6} alkoxy, -C_{1-6} haloalkoxy, -N$\mathbf{R^d R^e}$, C(=O)C_{1-6} alkyl, C(=O)OC_{1-6} alkyl, C(=O)N($\mathbf{R^f}$)$_2$, S(O)$_{0-2}$(C_{1-6} alkyl), and S(O)$_{0-2}$(C_{1-6} haloalkyl);

each $\mathbf{R^d}$ and $\mathbf{R^e}$ is independently selected from the group consisting of: H, C(=O)C_{1-6} alkyl, C(=O)C_{1-6} haloalkyl, C(=O)OC_{1-6} alkyl, C(=O)OC_{1-6} haloalkyl, C(=O)N($\mathbf{R^f}$)$_2$, S(O)$_{1-2}$(C_{1-6} alkyl), S(O)$_{1-2}$(C_{1-6} haloalkyl), S(O)$_{1-2}$N($\mathbf{R^f}$)$_2$, and C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^h}$;

each $\mathbf{R^f}$ is independently selected from the group consisting of: H and C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^h}$;

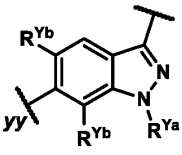
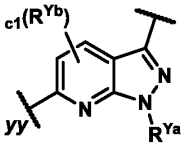
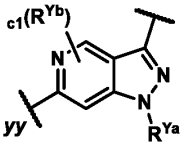
each $\mathbf{R^g}$ is independently selected from the group consisting of: $\mathbf{R^h}$, oxo, C_{1-3} alkyl, and C_{1-3} haloalkyl; and

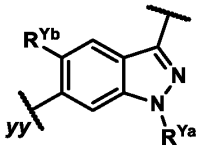
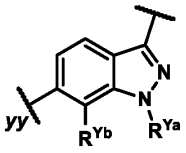
each $\mathbf{R^h}$ is independently selected from the group consisting of: halo, cyano, -OH, -(C_{0-3} alkylene)-C_{1-6} alkoxy, -(C_{0-3} alkylene)-C_{1-6} haloalkoxy, -(C_{0-3} alkylene)-NH_2, -(C_{0-3} alkylene)-N(H)(C_{1-3} alkyl), and –(C_{0-3} alkylene)-N(C_{1-3} alkyl)$_2$.

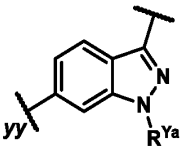
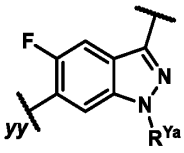
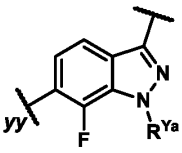
Embodiment 2. The compound of Embodiment 1, wherein one or more of **(1)-(5)** applies:

(1) $\mathbf{R^{2b}}$ is selected from the group consisting of: halo, cyano, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, and C_{1-3} haloalkoxy;

(2) $\mathbf{E^1}$ is N;

(3) Ring C is selected from the group consisting of: , , , and ;

(4) Ring C is selected from the group consisting of:  and , wherein $\mathbf{R^{Yb}}$ is $C_{1\text{-}3}$ alkyl optionally substituted with 1-3 F; and/or

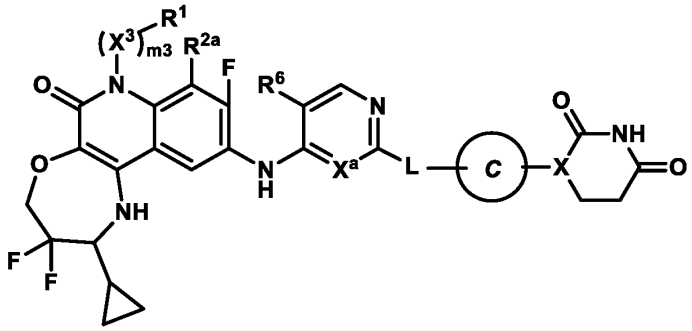
(5) Ring C is selected from the group consisting of: , , , and , wherein $\mathbf{R^{Ya}}$ is $-(C_{0\text{-}3}$ alkylene$)$-$\mathbf{R^{b1}}$ or $C_{2\text{-}4}$ alkyl optionally substituted with 1-3 $\mathbf{R^{c}}$.

Embodiment 3. The compound of Embodiment 1 or 2, wherein $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are each independently H or F.

Embodiment 4. The compound of any one of Embodiments 1-3, wherein $\mathbf{E^1}$ is $C\mathbf{R^{2a}}$; and each of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ is H.

Embodiment 5. The compound of any one of Embodiments 1-3, wherein $\mathbf{E^1}$ is $C\mathbf{R^{2a}}$; one of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ is F; and the other of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ is H.

Embodiment 6. The compound of Embodiment 1, wherein the compound of Formula (**I**) is a compound of Formula (**I-1**):

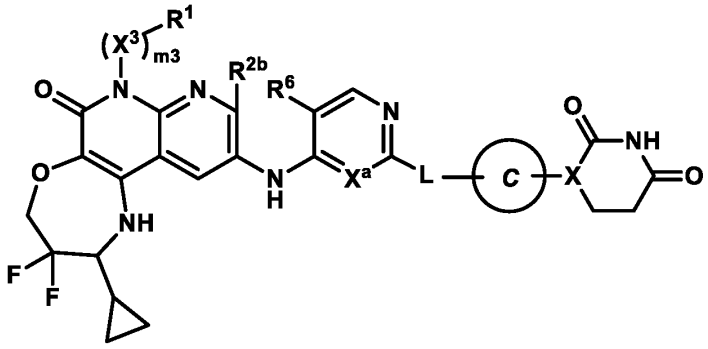


Formula (**I-1**)

or a pharmaceutically acceptable salt thereof.

Embodiment 7. The compound of Embodiment 6, wherein $\mathbf{R^{2a}}$ is H.

Embodiment 8. The compound of Embodiment 1, wherein the compound of Formula (**I**) is a compound of Formula (**I-2**):



Formula (**I-2**)

or a pharmaceutically acceptable salt thereof.

Embodiment 9. The compound of Embodiment 8, wherein $\mathbf{R^{2b}}$ is H.

Embodiment 10. The compound of any one of Embodiments 1-9, wherein $\mathbf{R^1}$ is selected from the group consisting of: H and halo.

Embodiment 11. The compound of any one of Embodiments 1-10, wherein **m3** is 1; and $\mathbf{R^1}$ is H.

Embodiment 12. The compound of any one of Embodiments 1-11, wherein –$(X^3)_{m3}$-R^1 is C_{1-3} alkyl.

Embodiment 13. The compound of any one of Embodiments 1-12, wherein –$(X^3)_{m3}$-R^1 is methyl.

Embodiment 14. The compound of any one of Embodiments 1-10, wherein **m3** is 0; and R^1 is H.

Embodiment 15. The compound of any one of Embodiments 1-9, wherein R^1 is R^{b1}.

Embodiment 16. The compound of any one of Embodiments 1-9 or 15, wherein **m3** is 1; and R^1 is R^{b1}.

Embodiment 17. The compound of any one of Embodiments 1-9 or 15-16, wherein –$(X^3)_{m3}$-R^1 is -CH_2-R^{b1}.

Embodiment 18. The compound of any one of Embodiments 1-9 or 15, wherein **m3** is 0; and R^1 is R^{b1}.

Embodiment 19. The compound of any one of Embodiments 15-18, wherein R^{b1} is C_{3-6} cycloalkyl optionally substituted with 1-3 R^g (e.g., C_{3-6} cycloalkyl optionally substituted with 1-3 F).

Embodiment 20. The compound of any one of Embodiments 1-9, wherein –$(X^3)_{m3}$-R^1 is selected from the group consisting of:

e) H;

f) C_{1-3} alkyl;

g) -R^{b1}; and

h) -CH_2R^{b1}, wherein:

R^{b1} is a C_{3-6} cycloalkyl optionally substituted with 1-3 R^g (e.g., C_{3-6} cycloalkyl optionally substituted with 1-3 F).

Embodiment 21. The compound of any one of Embodiments 1-9 or 20, wherein –$(\mathbf{X^3})_{m3}$-$\mathbf{R^1}$ is selected from the group consisting of: H and methyl.

Embodiment 22. The compound of any one of Embodiments 1-21, wherein $\mathbf{R^6}$ is -Cl or -F.

Embodiment 23. The compound of any one of Embodiments 1-22, wherein $\mathbf{R^6}$ is -Cl.

Embodiment 24. The compound of any one of Embodiments 1-23, wherein $\mathbf{X^a}$ is N.

Embodiment 25. The compound of any one of Embodiments 1-24, wherein **L** is –$(\mathbf{L^A})_{n1}$–, wherein:

n1 is an integer from 2 to 4; and

each $\mathbf{L^A}$ is independently selected from the group consisting of: $\mathbf{L^{A1}}$, $\mathbf{L^{A3}}$, and $\mathbf{L^{A4}}$, wherein:

0-2 of $\mathbf{L^A}$ is $\mathbf{L^{A1}}$;

0-2 of $\mathbf{L^A}$ is $\mathbf{L^{A3}}$; and

2-3 of $\mathbf{L^A}$ are $\mathbf{L^{A4}}$, wherein:

each $\mathbf{L^{A4}}$ is independently a C_{3-10} cycloalkylene or a 4-12 membered heterocyclylene, each of which is optionally substituted with 1-3 $\mathbf{R^a}$, wherein:

each $\mathbf{R^a}$ present on $\mathbf{L^{A4}}$ is independently selected from the group consisting of: -F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F; and

each $\mathbf{R^L}$ is independently selected from the group consisting of: -F, -OH, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$ (e.g., C_{1-3} alkyl optionally substituted with 1-3 -F).

Embodiment 26. The compound of any one of Embodiments 1-24, wherein **L** is selected from the group consisting of:

-$\mathbf{L^{A4a}}$-$\mathbf{L^{A1}}$-$\mathbf{L^{A4b}}$-*bb*;

-$\mathbf{L^{A4a}}$-$\mathbf{L^{A3}}$-$\mathbf{L^{A4b}}$-*bb*;

-$\mathbf{L^{A4a}}$-$\mathbf{L^{A4b}}$-*bb*;

-$\mathbf{L^{A4a}}$-$\mathbf{L^{A3}}$-$\mathbf{L^{A4c}}$- $\mathbf{L^{A4b}}$-*bb*; and

-L^{A4a}-L^{A4c}-L^{A3}-L^{A4b}-*bb*, wherein:

L^{A4a}, L^{A4b}, and L^{A4c} are each an independently selected L^{A4},

L^{A3} is selected from the group consisting of: -O- and -N(R^d)-, and

bb represents the point of attachment to **Ring C**.

Embodiment 27. The compound of any one of Embodiments 1-24, wherein **L** is selected from the group consisting of:

-L^{A4a}-L^{A1}-L^{A4b}-*bb*;

-L^{A4a}-L^{A3}-L^{A4b}-*bb*; and

-L^{A4a}-L^{A4b}-*bb*; wherein:

L^{A4a} and L^{A4b} are each an independently selected L^{A4},

L^{A3} is selected from the group consisting of: -O- and -N(R^d)-, and

bb represents the point of attachment to **Ring C**.

Embodiment 28. The compound of Embodiment 26 or 27, wherein:

L^{A4a} and L^{A4b} are independently 4-12 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 R^a;

L^{A4c} when present is a C_{3-10} cycloalkylene optionally substituted with 1-3 R^a; and

each R^L is independently selected from the group consisting of: -F, -OH, and C_{1-3} alkyl optionally substituted with 1-3 R^c (e.g., C_{1-3} alkyl optionally substituted with 1-3 -F).

Embodiment 29. The compound of any one of Embodiments 1-24 or 26-28, wherein **L** is:

-L^{A4a}-L^{A1}-L^{A4b}-*bb*, wherein:

L^{A4a} and L^{A4b} are independently 4-12 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 R^a; and

each R^L is independently selected from the group consisting of: -F, -OH, and C_{1-3} alkyl optionally substituted with 1-3 R^c (e.g., C_{1-3} alkyl optionally substituted with 1-3 -F).

Embodiment 30. The compound of any one of Embodiments 26-29, wherein L^{A4a} and L^{A4b} are independently monocyclic 4-6 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 R^a.

Embodiment 31. The compound of any one of Embodiments 26-30, wherein one of $\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ is a 1,4-piperidinylene; and

the other of $\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ is independently selected from the group consisting of: 1,4-piperidinylene and 1,4-piperazinylene,

wherein each of the 1,4-piperidinylene or 1,4-piperazinylene is optionally substituted with 1-2 $\mathbf{R}^{a}$.

Embodiment 32. The compound of any one of Embodiments 26-29, wherein one of $\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ is a monocyclic 4-6 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R}^{a}$; and

the other of $\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ is a bicyclic spirocyclic 6-12 (e.g., 10-12) membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R}^{a}$.

Embodiment 33. The compound of any one of Embodiments 26-29 or 32, wherein $\mathbf{L}^{A4b}$ is a monocyclic 4-6 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R}^{a}$; and

$\mathbf{L}^{A4a}$ is a bicyclic spirocyclic 6-12 (e.g., 10-12) membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R}^{a}$.

Embodiment 34. The compound of any one of Embodiments 26-29 or 32-33, wherein $\mathbf{L}^{A4b}$ is 1,4-piperidinylene optionally substituted with 1-2 $\mathbf{R}^{a}$; and

$\mathbf{L}^{A4a}$ is a bicyclic spirocyclic 10-12 membered nitrogen-containing heterocyclylene optionally substituted with 1-2 $\mathbf{R}^{a}$.

Embodiment 35. The compound of any one of Embodiments 26-34, wherein $\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ each contain 1-2 ring nitrogen atoms and no additional ring heteroatoms.

Embodiment 36. The compound of any one of Embodiments 26-35, wherein each $\mathbf{R}^{a}$ present on $\mathbf{L}^{A4a}$, $\mathbf{L}^{A4b}$, and/or $\mathbf{L}^{A4c}$ is independently selected from the group consisting of: -F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F.

Embodiment 37. The compound of any one of Embodiments 26-36, wherein $\mathbf{L}^{A1}$ is $-CH_2-$.

Embodiment 38. The compound of any one of Embodiments 26-36, wherein $\mathbf{L^{A1}}$ is -CH$\mathbf{R^L}$-, wherein $\mathbf{R^L}$ is C_{1-3} alkyl optionally substituted with 1-3 F (e.g., $\mathbf{R^L}$ is methyl or CF_3).

Embodiment 39. The compound of any one of Embodiments 1-24, wherein **L** is –$(\mathbf{L^A})_{\mathbf{n1}}$–, wherein:

n1 is 1, 2, or 3; and

each $\mathbf{L^A}$ is independently selected from the group consisting of: $\mathbf{L^{A1}}$, $\mathbf{L^{A3}}$, and $\mathbf{L^{A4}}$, wherein:

0-1 of $\mathbf{L^A}$ is $\mathbf{L^{A1}}$;

0-1 of $\mathbf{L^A}$ is $\mathbf{L^{A3}}$; and

one $\mathbf{L^A}$ is $\mathbf{L^{A4}}$, wherein:

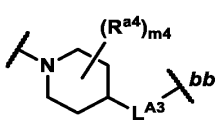
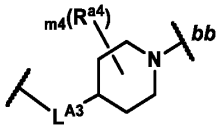
$\mathbf{L^{A4}}$ is a 4-12 membered heterocyclylene optionally substituted with 1-3 $\mathbf{R^a}$, wherein:

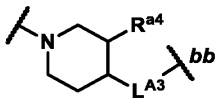
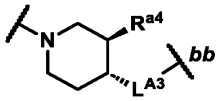
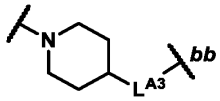
each $\mathbf{R^a}$ present on $\mathbf{L^{A4}}$ is independently selected from the group consisting of: -F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F; and

each $\mathbf{R^L}$ is independently selected from the group consisting of: -F, -OH, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$ (e.g., C_{1-3} alkyl optionally substituted with 1-3 -F).

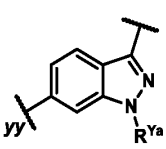
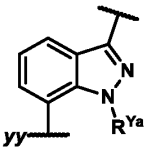
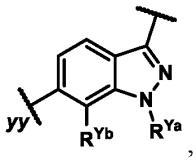
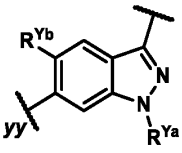
Embodiment 40. The compound of any one of Embodiments 1-24 or 39, wherein **L** is selected from the group consisting of: -$\mathbf{L^{A4}}$-$\mathbf{L^{A3}}$-*bb* and -$\mathbf{L^{A3}}$-$\mathbf{L^{A4}}$-*bb*, wherein ***bb*** represents the point of attachment to **Ring C**.

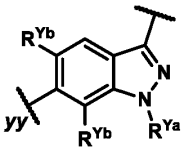
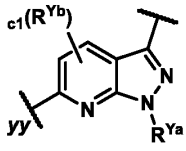
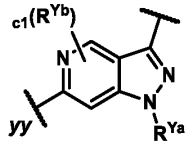
Embodiment 41. The compound of Embodiment 40, wherein $\mathbf{L^{A4}}$ is a monocyclic 4-6 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R^a}$.

Embodiment 42. The compound any one of Embodiments 1-24 or 39-41, wherein **L** is selected from the group consisting of:  and , wherein **m4** is 0, 1, or 2; each $\mathbf{R^{a4}}$ is independently selected from the group consisting of: -F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F; and ***bb*** represents the point of attachment to **Ring C**.

Embodiment 43. The compound of any one of Embodiments 1-24 or 39-42, wherein **L** is selected from the group consisting of:  (e.g., ) and , wherein $\mathbf{R}^{a4}$ is selected from the group consisting of: -F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F (e.g., $\mathbf{R}^{a4}$ is C_{1-3} alkyl optionally substituted with 1-3 F); and ***bb*** represents the point of attachment to **Ring C**.

Embodiment 44. The compound of any one of Embodiments 40-43, wherein $\mathbf{L}^{A3}$ is -N(H)-; and each $\mathbf{R}^{a4}$ is independently C_{1-3} alkyl optionally substituted with 1-3 F (e.g., methyl).

Embodiment 45. The compound of any one of Embodiments 1-44, wherein **Ring C** is selected from the group consisting of: , , ,  and .

Embodiment 46. The compound of any one of Embodiments 1-44, wherein **Ring C** is selected from the group consisting of: , , and .

Embodiment 47. The compound of any one of Embodiments 1-46, wherein $\mathbf{R}^{Ya}$ is selected from the group consisting of $\mathbf{R}^{a}$ and $\mathbf{R}^{b}$.

Embodiment 48. The compound of Embodiment 45 or 46, wherein:

$\mathbf{R^{Ya}}$ is selected from the group consisting of:

(a) H;

(b) C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$; and

(c) –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$ (e.g., C_{3-6} cycloalkyl optionally substituted with 1-3 F); and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$ (e.g., C_{1-3} alkyl optionally substituted with 1-3 -F).

Embodiment 49. The compound of any one of Embodiments 45-46 or 48, wherein:

$\mathbf{R^{Ya}}$ is H or C_{1-3} alkyl optionally substituted with 1-3 -F (e.g., C_{1-3} alkyl (e.g., methyl)); and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: -F and C_{1-3} alkyl optionally substituted with 1-3 -F.

Embodiment 50. The compound of any one of Embodiments 45-47, wherein:

$\mathbf{R^{Ya}}$ is selected from the group consisting of:

(a) C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$; and

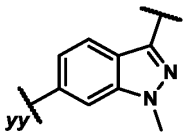
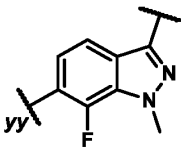
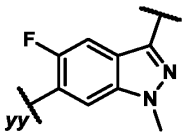
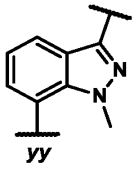
(b) –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$ (e.g., C_{3-6} cycloalkyl optionally substituted with 1-3 F); and

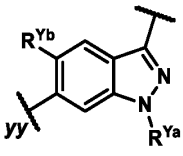
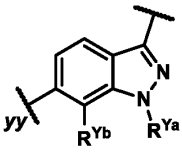
each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$ (e.g., C_{1-3} alkyl optionally substituted with 1-3 -F).

Embodiment 51. The compound of any one of Embodiments 45-47 or 50, wherein:

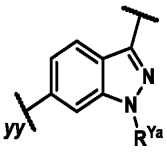
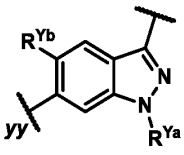
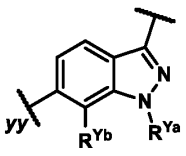
$\mathbf{R^{Ya}}$ is C_{1-3} alkyl optionally substituted with 1-3 -F (e.g., C_{1-3} alkyl (e.g., methyl)); and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: -F and C_{1-3} alkyl optionally substituted with 1-3 -F.

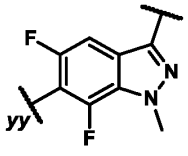
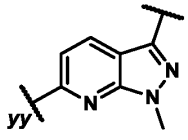
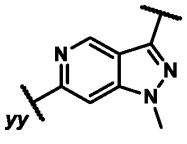
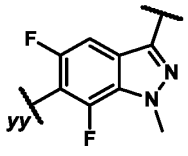
Embodiment 52. The compound of any one of Embodiments 1-45, wherein **Ring C** is selected from the group consisting of: , , , and .

Embodiment 53. The compound of any one of Embodiments 1-45, wherein **Ring C** is selected from the group consisting of:  and , wherein $\mathbf{R^{Yb}}$ is C_{1-3} alkyl optionally substituted with 1-3 F.

Embodiment 54. The compound of Embodiment 53, wherein $\mathbf{R^{Ya}}$ is methyl.

Embodiment 55. The compound of any one of Embodiments 1-45, wherein **Ring C** is selected from the group consisting of: ,  and , wherein $\mathbf{R^{Ya}}$ is $-(C_{0-3}$ alkylene$)$-$\mathbf{R^{b1}}$ or C_{2-4} alkyl optionally substituted with 1-3 $\mathbf{R^{c}}$.

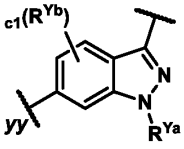
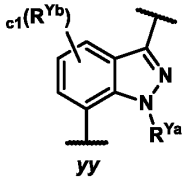
Embodiment 56. The compound of Embodiment 55, wherein $\mathbf{R^{Yb}}$ is independently -F or C_{1-3} alkyl optionally substituted with 1-3 -F.

Embodiment 57. The compound of any one of Embodiments 1-44 or 46, wherein **Ring C** is selected from the group consisting of: , , and  (e.g., **Ring C** is ).

Embodiment 58. The compound of any one of Embodiments 1-57, wherein **X** is CH.

Embodiment 59. The compound of any one of Embodiments 1-44, wherein:

X is CH; and

Ring C is selected from the group consisting of:  and , wherein:

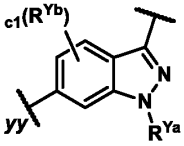
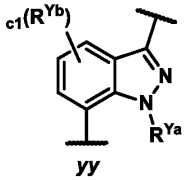
$\mathbf{R^{Ya}}$ is H, -$\mathbf{R^{b1}}$, -CH_2-$\mathbf{R^{b1}}$, or C_{1-3} alkyl optionally substituted with 1-3 -F,

wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl optionally substituted with 1-3 F, and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: -F and C_{1-3} alkyl optionally substituted with 1-3 -F.

Embodiment 60. The compound of any one of Embodiments 1-44, wherein:

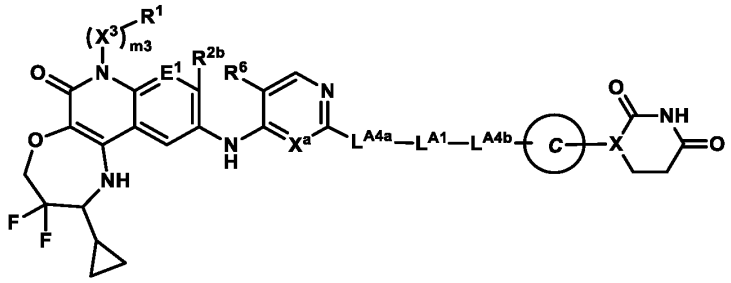
X is CH; and

Ring C is selected from the group consisting of:  and , wherein:

$\mathbf{R^{Ya}}$ is C_{1-3} alkyl optionally substituted with 1-3 -F (e.g., C_{1-3} alkyl (e.g., methyl)), and

each R^{Yb} is independently selected from the group consisting of: -F and C_{1-3} alkyl optionally substituted with 1-3 -F.

Embodiment 61. The compound of Embodiment 1, wherein the compound of Formula (**I**) is a compound of Formula (**I-a**):



Formula (**I-a**)

or a pharmaceutically acceptable salt thereof, wherein:

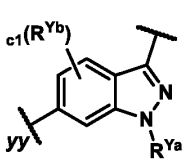
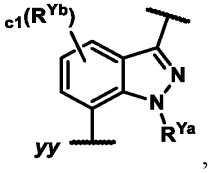
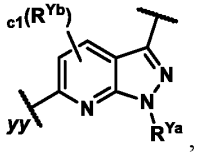
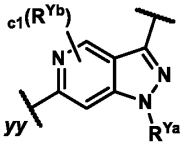
E^1 is CR^{2a} or N;

R^{2a} and R^{2b} are each independently selected from the group consisting of: H and F;

L^{A4a} and L^{A4b} are independently 4-12 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 R^a;

L^{A1} is CH_2 or CHR^L, and

R^L is selected from the group consisting of: -F, -OH, and C_{1-3} alkyl optionally substituted with 1-3 R^c; and

Ring C is selected from the group consisting of: , , , and , wherein:

c1 is 0, 1, or 2;

R^{Ya} is selected from the group consisting of:

(a) H;

(b) C_{1-6} alkyl optionally substituted with 1-3 R^c; and

(c) –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^{g}}$;

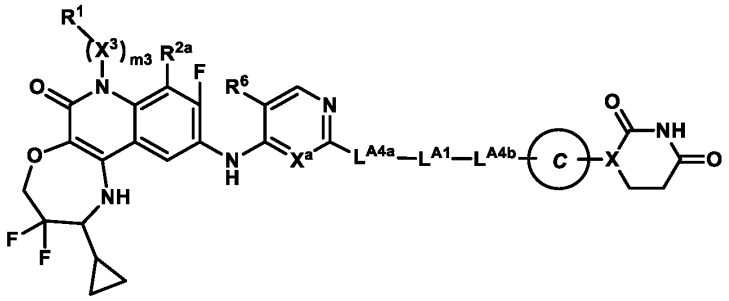
each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^{c}}$ (e.g., C_{1-3} alkyl optionally substituted with 1-3 -F); and

yy represents the point of attachment to $\mathbf{L^{A4b}}$.

Embodiment 62. The compound of Embodiment 61, wherein $\mathbf{E^1}$ is $C\mathbf{R^{2a}}$; and each of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ is H.

Embodiment 63. The compound of Embodiment 61, wherein $\mathbf{E^1}$ is $C\mathbf{R^{2a}}$; one of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ is F; and the other of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ is H.

Embodiment 64. The compound of Embodiment 61, wherein the compound of Formula (**I-a**) is a compound of Formula (**I-a-1**):

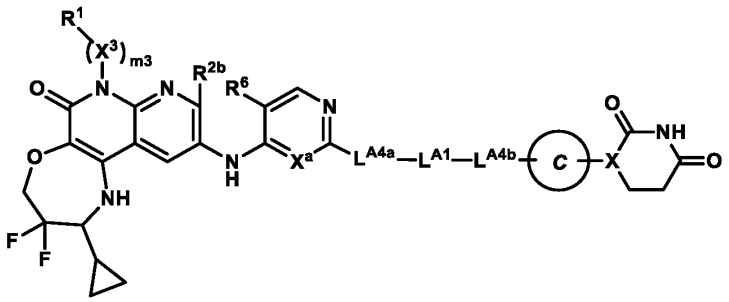


Formula (**I-a-1**)

or a pharmaceutically acceptable salt thereof.

Embodiment 65. The compound of Embodiment 64, wherein $\mathbf{R^{2a}}$ is H.

Embodiment 66. The compound of Embodiment 61, wherein the compound of Formula (**I-a**) is a compound of Formula (**I-a-2**):



Formula (**I-a-2**)

or a pharmaceutically acceptable salt thereof.

Embodiment 67. The compound of Embodiment 66, wherein $\mathbf{R^{2b}}$ is H.

Embodiment 68. The compound of any one of Embodiments 61-67, wherein $\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ are independently monocyclic 4-6 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R^a}$.

Embodiment 69. The compound of any one of Embodiments 61-67, wherein $\mathbf{L^{A4b}}$ is a monocyclic 4-6 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R^a}$; and

$\mathbf{L^{A4a}}$ is a bicyclic spirocyclic 10-12 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R^a}$.

Embodiment 70. The compound of any one of Embodiments 61-69, wherein:

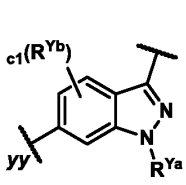
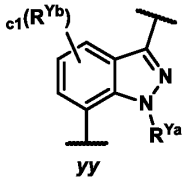
$\mathbf{R^L}$ is $C_{1\text{-}3}$ methyl optionally substituted with 1-3 F;

each $\mathbf{R^a}$ present on $\mathbf{L^{A4a}}$ and/or $\mathbf{L^{A4b}}$ is independently selected from the group consisting of: -F, CN, $C_{1\text{-}3}$ alkoxy, OH, and $C_{1\text{-}3}$ alkyl optionally substituted with 1-3 F; and

$\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ each contain 1-2 ring nitrogen atoms and no additional ring heteroatoms.

Embodiment 71. The compound of any one of Embodiments 61-70, wherein:

X is CH; and

Ring C is selected from the group consisting of:  and , wherein:

c1 is 0, 1, or 2;

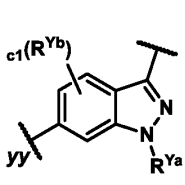
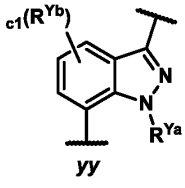
$\mathbf{R^{Ya}}$ is H, $-\mathbf{R^{b1}}$, $-CH_2-\mathbf{R^{b1}}$, or C_{1-3} alkyl optionally substituted with 1-3 -F,

wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl optionally substituted with 1-3 F, and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: -F and C_{1-3} alkyl optionally substituted with 1-3 -F.

Embodiment 72. The compound of any one of Embodiments 61-71, wherein:

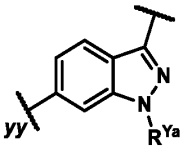
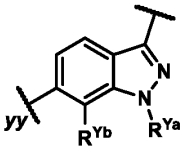
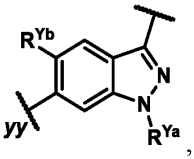
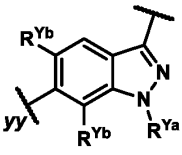
X is CH; and

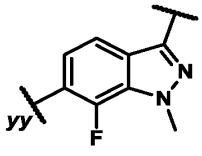
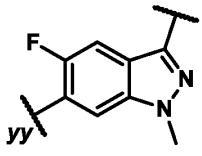
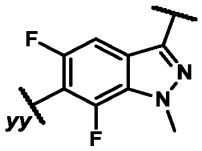
Ring C is selected from the group consisting of:  and , wherein:

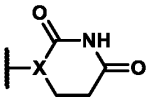
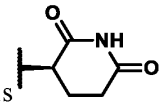
c1 is 0, 1, or 2;

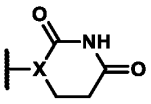
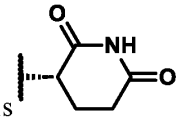
$\mathbf{R^{Ya}}$ is C_{1-3} alkyl optionally substituted with 1-3 -F (e.g., C_{1-3} alkyl (e.g., methyl)); and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: -F and C_{1-3} alkyl optionally substituted with 1-3 -F.

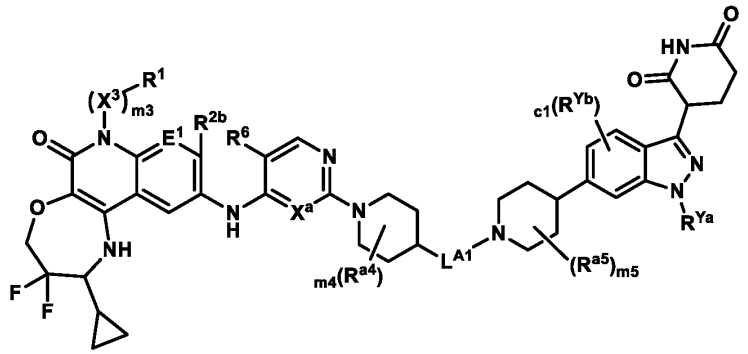
Embodiment 73. The compound of Embodiment 71 or 72, wherein **Ring C** is selected from the group consisting of: , , , and .

Embodiment 74. The compound of any one of Embodiments 71-73, wherein **Ring C** is selected from the group consisting of:, , , and .

Embodiment 75. The compound of any one of Embodiments 1-74, wherein the  moiety is .

Embodiment 76. The compound of any one of Embodiments 1-74, wherein the  moiety is .

Embodiment 77. The compound of Embodiment 1 or 61, wherein the compound is a compound of Formula (**I-b**):



Formula (**I-b**)

or a pharmaceutically acceptable salt thereof, wherein:

$\mathbf{E^1}$ is $\mathbf{CR^{2a}}$ or N;

$\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are each independently selected from the group consisting of: H and F;

m4 and **m5** are independently 0, 1, or 2;

each $\mathbf{R}^{a4}$ and $\mathbf{R}^{a5}$ is independently selected from the group consisting of: -F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F;

$\mathbf{L}^{A1}$ is CH_2 or $CH\mathbf{R}^{L}$, and

$\mathbf{R}^{L}$ is C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R}^{c}$;

c1 is 0, 1, or 2;

$\mathbf{R}^{Ya}$ is selected from the group consisting of:

(a) H;

(b) C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R}^{c}$; and

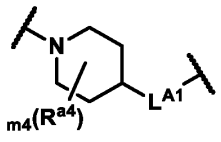
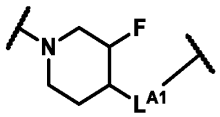
(c) –(C_{0-3} alkylene)-$\mathbf{R}^{b1}$, wherein $\mathbf{R}^{b1}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R}^{g}$; and

each $\mathbf{R}^{Yb}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R}^{c}$.

Embodiment 78. The compound of Embodiment 77, wherein one or more of **(1)-(6)** applies:

(1) $\mathbf{R}^{2b}$ is -F;

(2) $\mathbf{E}^{1}$ is N;

(3) the  moiety is: ;

(4) $\mathbf{R}^{Ya}$ is selected from the group consisting of: C_{2-6} alkyl optionally substituted with 1-3 $\mathbf{R}^{c}$, and –(C_{0-3} alkylene)-$\mathbf{R}^{b1}$, wherein $\mathbf{R}^{b1}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R}^{g}$;

(5) c1 is 2; and/or

(6) c1 is 1, and $\mathbf{R}^{Yb}$ is C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R}^{c}$ (e.g., C_{1-3} alkyl optionally substituted with 1-3 F).

Embodiment 79. The compound of Embodiment 77, wherein two or more of **(1)-(4)** apply:

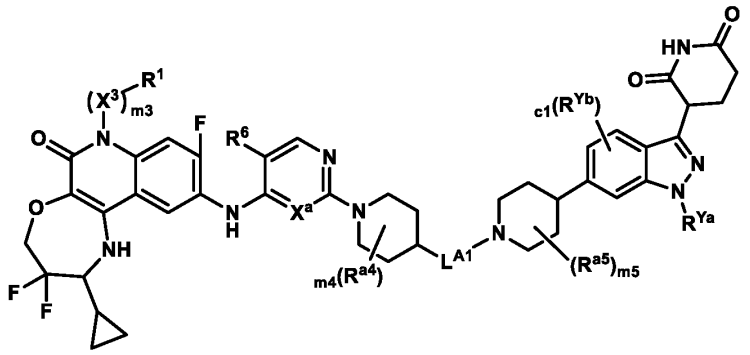
(1) m4 is 1 or 2;

(2) m5 is 1 or 2;

(3) L^{A1} is CHR^{L}; and/or

(4) c1 is 1 or 2.

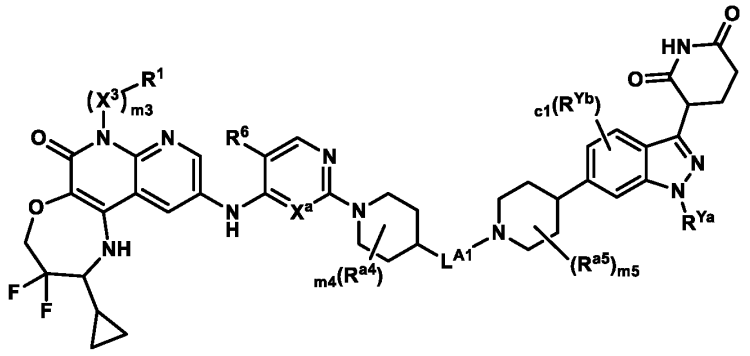
Embodiment 80. The compound of Embodiment 77, wherein the compound of Formula (**I-b**) is a compound of Formula (**I-b-1**):



Formula (**I-b-1**)

or a pharmaceutically acceptable salt thereof.

Embodiment 81. The compound of Embodiment 77, wherein the compound of Formula (**I-b**) is a compound of Formula (**I-b-2**):



Formula (**I-b-2**)

or a pharmaceutically acceptable salt thereof.

Embodiment 82. The compound of any one of Embodiments 77-81, wherein:

R^{Ya} is selected from the group consisting of:

(a) C_{1-6} alkyl optionally substituted with 1-3 R^{c}, and

(b) –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$ (e.g.,C_{3-6} cycloalkyl optionally substituted with 1-3 F); and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$.

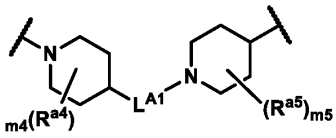
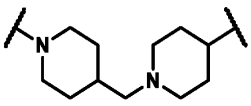
Embodiment 83. The compound of any one of Embodiments 77-82, wherein:

$\mathbf{R^{Ya}}$ is C_{1-3} alkyl optionally substituted with 1-3 -F (e.g., C_{1-3} alkyl (e.g., methyl)), and

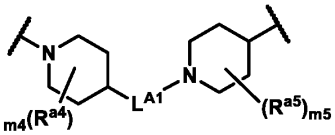
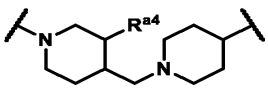
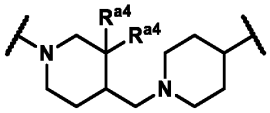
each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: -F and C_{1-3} alkyl optionally substituted with 1-3 -F.

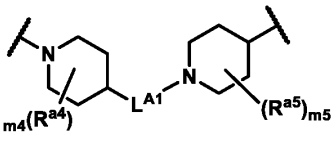
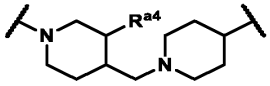
Embodiment 84. The compound of any one of Embodiments 77-83, wherein $\mathbf{L^{A1}}$ is CH_2.

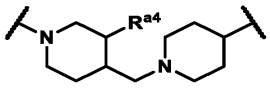
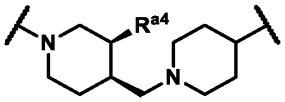
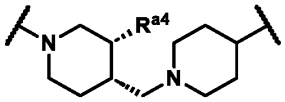
Embodiment 85. The compound of any one of Embodiments 77-84, wherein **m4** is 0; and **m5** is 0.

Embodiment 86. The compound of any one of Embodiments 77-85, wherein the  moiety is .

Embodiment 87. The compound of any one of Embodiments 77-84, wherein **m4** is 1 or 2; and **m5** is 0, wherein each $\mathbf{R^{a4}}$ is independently selected from the group consisting of: -F, Me, and CF_3.

Embodiment 88. The compound of any one of Embodiments 77-84 or 87, wherein the  moiety is  or .

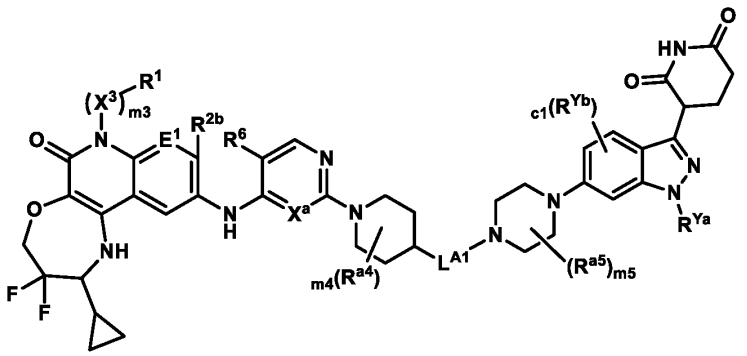
Embodiment 89. The compound of any one of Embodiments 77-84 or 87-88, wherein the  moiety is .

Embodiment 90. The compound of Embodiment 89, wherein the  moiety is  or .

Embodiment 91. The compound of Embodiment 89 or 90, wherein R^{a4} is selected from the group consisting of: -F and Me.

Embodiment 92. The compound of any one of Embodiments 77-84, wherein **m4** is 0; and **m5** is 1 or 2, wherein each R^{a5} is independently selected from the group consisting of: -F, Me, and CF_3.

Embodiment 93. The compound of Embodiment 1 or 61, wherein the compound is a compound of Formula (**I-c**):



Formula (**I-c**)

or a pharmaceutically acceptable salt thereof, wherein:

E^1 is CR^{2a} or N;

R^{2a} and R^{2b} are each independently selected from the group consisting of: H and F;

m4 and **m5** are independently 0, 1, or 2;

each $\mathbf{R^{a4}}$ is independently selected from the group consisting of: -F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F;

each $\mathbf{R^{a5}}$ is independently C_{1-3} alkyl optionally substituted with 1-3 F;

$\mathbf{L^{A1}}$ is CH_2 or $CH\mathbf{R^L}$, and

$\mathbf{R^L}$ is C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$;

c1 is 0, 1, or 2;

$\mathbf{R^{Ya}}$ is selected from the group consisting of:

(a) H;

(b) C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$, and

(c) –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$; and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$.

Embodiment 94. The compound of Embodiment 93, wherein one or more of **(1)-(4)** applies:

(1) $\mathbf{R^{2b}}$ is -F;

(2) $\mathbf{E^1}$ is N;

(3) $\mathbf{R^{Ya}}$ is selected from the group consisting of: C_{2-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$, and –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$; and/or

(4) c1 is 2.

Embodiment 95. The compound of Embodiment 93, wherein two or more of **(1)-(4)** apply:

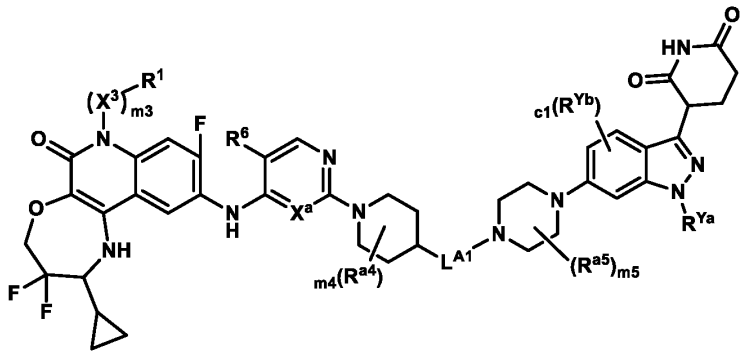
(1) m4 is 2;

(2) m5 is 1 or 2;

(3) $\mathbf{L^{A1}}$ is $CH\mathbf{R^L}$; and/or

(4) c1 is 1 or 2.

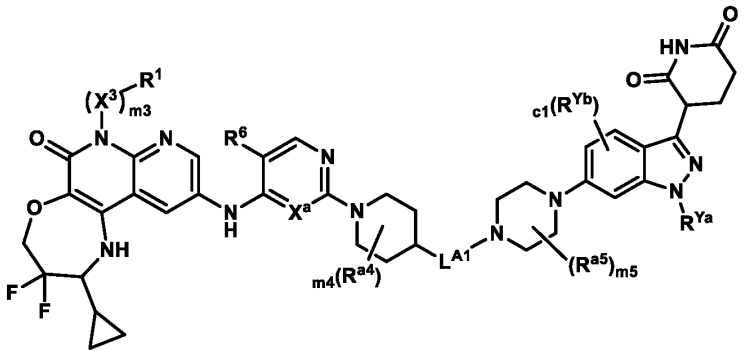
Embodiment 96. The compound of Embodiment 93, wherein the compound of Formula (**I-c**) is a compound of Formula (**I-c-1**):



Formula (**I-c-1**)

or a pharmaceutically acceptable salt thereof.

Embodiment 97. The compound of Embodiment 93, wherein the compound of Formula (**I-c**) is a compound of Formula (**I-c-2**):



Formula (**I-c-2**)

or a pharmaceutically acceptable salt thereof.

Embodiment 98. The compound of any one of Embodiments 93-97, wherein:

$\mathbf{R^{Ya}}$ is selected from the group consisting of:

(a) C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$, and

(b) –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$ (e.g., C_{3-6} cycloalkyl optionally substituted with 1-3 F); and

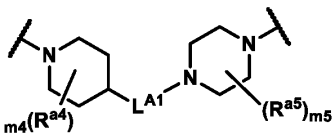
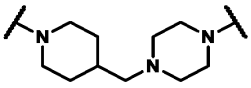
each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$.

Embodiment 99. The compound of any one of Embodiments 93-98, wherein:

$\mathbf{R^{Ya}}$ is C_{1-3} alkyl optionally substituted with 1-3 -F (e.g., C_{1-3} alkyl (e.g., methyl)), and each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: -F and C_{1-3} alkyl optionally substituted with 1-3 -F.

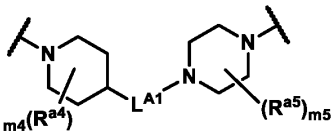
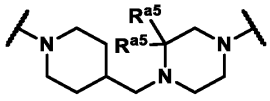
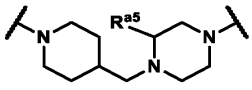
Embodiment 100. The compound of any one of Embodiments 93-99, wherein $\mathbf{L^{A1}}$ is CH_2.

Embodiment 101. The compound of any one of Embodiments 93-100, wherein **m4** is 0; and **m5** is 0.

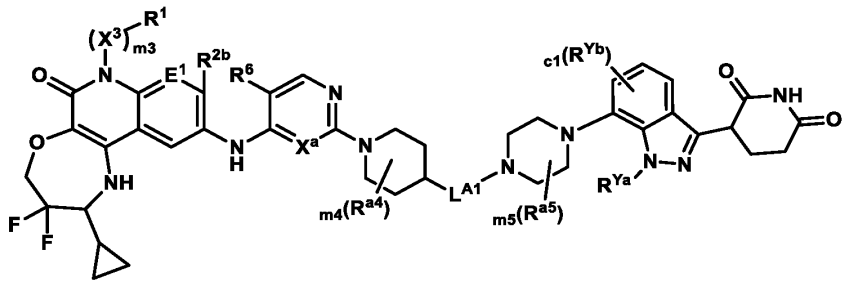
Embodiment 102. The compound of Embodiment 101, wherein the  moiety is .

Embodiment 103. The compound of any one of Embodiments 93-100, wherein **m4** is 1 or 2; and **m5** is 0, wherein each $\mathbf{R^{a4}}$ is independently selected from the group consisting of: -F, Me, and CF_3.

Embodiment 104. The compound of any one of Embodiments 93-100, wherein **m4** is 0; and **m5** is 1 or 2, wherein each $\mathbf{R^{a5}}$ is independently selected from the group consisting of Me and CF_3.

Embodiment 105. The compound of any one of Embodiments 93-100 or 104, wherein the  moiety is  or .

Embodiment 106. The compound of Embodiment 1 or 61, wherein the compound is a compound of Formula (**I-d**):



Formula (**I-d**)

or a pharmaceutically acceptable salt thereof, wherein:

$\mathbf{E^1}$ is CR^{2a} or N;

$\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are each independently selected from the group consisting of: H and F;

m4 and **m5** are independently 0, 1, or 2;

each $\mathbf{R^{a4}}$ is independently selected from the group consisting of: -F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F;

each $\mathbf{R^{a5}}$ is independently C_{1-3} alkyl optionally substituted with 1-3 F;

$\mathbf{L^{A1}}$ is CH_2 or CHR^L, and

$\mathbf{R^L}$ is C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$;

c1 is 0, 1, or 2;

$\mathbf{R^{Ya}}$ is selected from the group consisting of:

(a) H;

(b) C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$, and

(c) –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$; and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$.

Embodiment 107. The compound of Embodiment 106, wherein one or more of **(1)-(4)** applies:

(1) $\mathbf{R^{2b}}$ is -F;

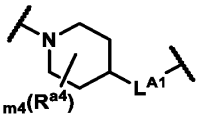
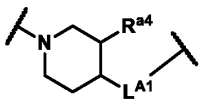
(2) $\mathbf{E^1}$ is N;

(3) $\mathbf{R^{Ya}}$ is selected from the group consisting of: C_{2-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$, and –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$; and/or

(4) c1 is 2.

Embodiment 108. The compound of Embodiment 106, wherein two or more of **(1)-(5)** apply:

(1) m4 is 2;

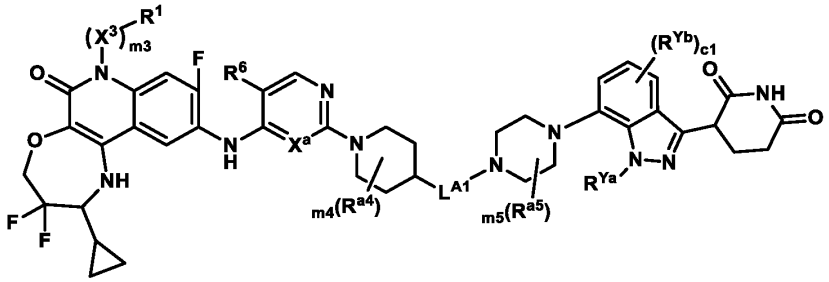
(2) m4 is 1, and the  moiety is: ;

(3) m5 is 1 or 2;

(4) $\mathbf{L^{A1}}$ is $CH\mathbf{R^L}$; and/or

(5) c1 is 1 or 2.

Embodiment 109. The compound of Embodiment 106, wherein the compound of Formula (**I-d**) is a compound of Formula (**I-d-1**):



Formula (**I-d-1**)

or a pharmaceutically acceptable salt thereof.

Embodiment 110. The compound of any one of Embodiments 106-109, wherein:

$\mathbf{R^{Ya}}$ is selected from the group consisting of:

(a) C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$, and

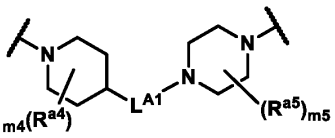
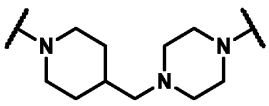
(b) –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$ (e.g., C_{3-6} cycloalkyl optionally substituted with 1-3 F); and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$.

Embodiment 111. The compound of any one of Embodiments 106-110, wherein: $\mathbf{R^{Ya}}$ is C_{1-3} alkyl optionally substituted with 1-3 -F (e.g., C_{1-3} alkyl (e.g., methyl)), and each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: -F and C_{1-3} alkyl optionally substituted with 1-3 -F.

Embodiment 112. The compound of any one of Embodiments 106-111, wherein $\mathbf{L^{A1}}$ is CH_2.

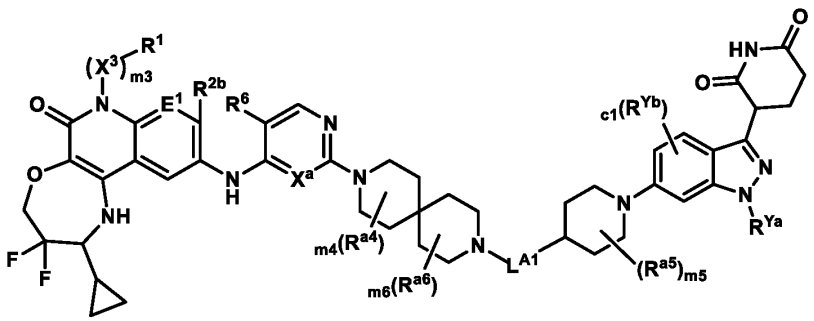
Embodiment 113. The compound of any one of Embodiments 106-112, wherein **m4** is 0; and **m5** is 0.

Embodiment 114. The compound of any one of Embodiments 106-113, wherein the  moiety is .

Embodiment 115. The compound of any one of Embodiments 106-112, wherein **m4** is 1 or 2; and **m5** is 0, wherein each $\mathbf{R^{a4}}$ is independently selected from the group consisting of: -F, Me, and CF_3.

Embodiment 116. The compound of any one of Embodiments 106-112, wherein **m4** is 0; and **m5** is 1 or 2, wherein each $\mathbf{R^{a5}}$ is independently selected from the group consisting of: Me and CF_3.

Embodiment 117. The compound of Embodiment 1 or 61, wherein the compound is a compound of Formula (**I-e**):



Formula (**I-e**)

or a pharmaceutically acceptable salt thereof, wherein:

$\mathbf{E^1}$ is $C\mathbf{R^{2a}}$ or N;

$\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are each independently selected from the group consisting of: H and F;

m4, **m5**, and **m6** are independently 0, 1, or 2, provided that **m4** + **m6** is 0, 1, 2, or 3;

each $\mathbf{R^{a4}}$, $\mathbf{R^{a5}}$, and $\mathbf{R^{a6}}$ is independently selected from the group consisting of: -F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F;

$\mathbf{L^{A1}}$ is CH_2 or $CH\mathbf{R^L}$, and

$\mathbf{R^L}$ is C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$;

c1 is 0, 1, or 2;

$\mathbf{R^{Ya}}$ is selected from the group consisting of:

(a) H,

(b) C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$, and

(c) –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$; and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$.

Embodiment 118. The compound of Embodiment 117, wherein one or more of **(1)-(7)** applies:

(1) $\mathbf{R^{2b}}$ is -F;

(2) $\mathbf{E^1}$ is N;

(3) one or more of **m4**, **m5**, and **m6** is independently 1 or 2;

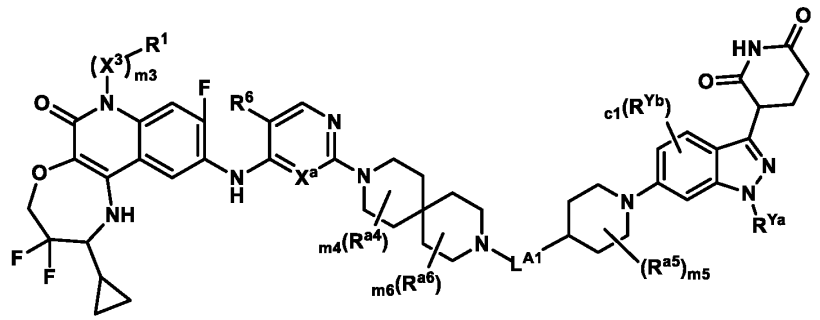
(4) $\mathbf{L^{A1}}$ is $CH\mathbf{R^L}$;

(5) c1 is 1, and $\mathbf{R^{Yb}}$ is C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$;

(6) c1 is 2; and/or

(7) $\mathbf{R^{Ya}}$ is selected from the group consisting of: C_{2-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$, and –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$.

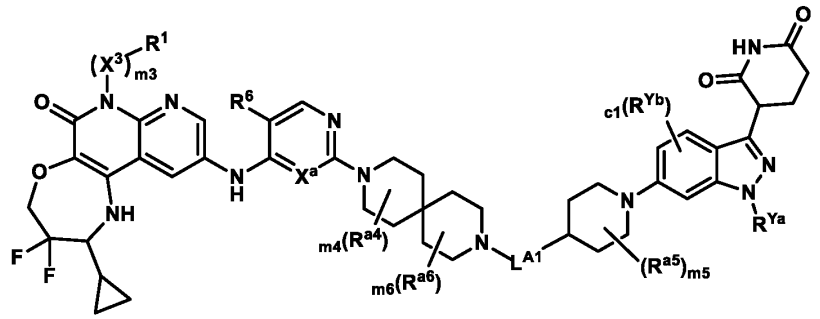
Embodiment 119. The compound of Embodiment 117, wherein the compound of Formula (**I-e**) is a compound of Formula (**I-e-1**):



Formula (**I-e-1**)

or a pharmaceutically acceptable salt thereof.

Embodiment 120. The compound of Embodiment 117, wherein the compound of Formula (**I-e**) is a compound of Formula (**I-e-2**):



Formula (**I-e-2**)

or a pharmaceutically acceptable salt thereof.

Embodiment 121. The compound of any one of Embodiments 117-120, wherein:

$\mathbf{R^{Ya}}$ is selected from the group consisting of:

(a) C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$, and

(b) –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^{g}}$ (e.g., C_{3-6} cycloalkyl optionally substituted with 1-3 F); and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^{c}}$.

Embodiment 122. The compound of any one of Embodiments 117-121, wherein:

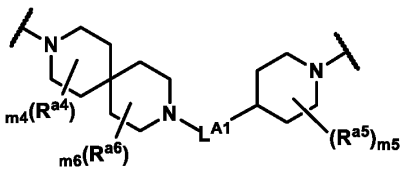
$\mathbf{R^{Ya}}$ is C_{1-3} alkyl optionally substituted with 1-3 -F (e.g., C_{1-3} alkyl (e.g., methyl)), and

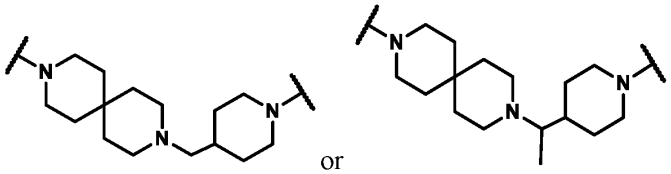
each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: -F and C_{1-3} alkyl optionally substituted with 1-3 -F.

Embodiment 123. The compound of any one of Embodiments 117-122, wherein $\mathbf{L^{A1}}$ is CH_2.

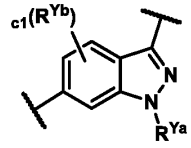
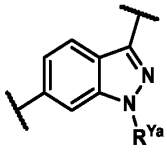
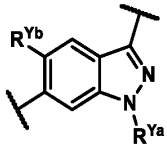
Embodiment 124. The compound of any one of Embodiments 117-122, wherein $\mathbf{L^{A1}}$ is CHMe.

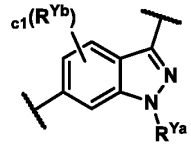
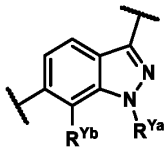
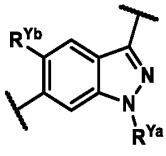
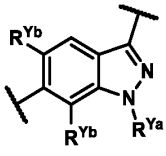
Embodiment 125. The compound of any one of Embodiments 117-124, wherein **m4** is 0; **m5** is 0; and **m6** is 0.

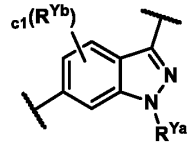
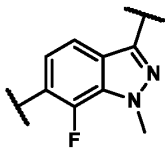
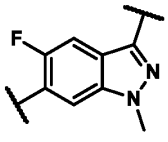
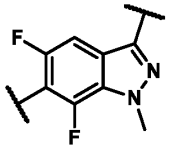
Embodiment 126. The compound of any one of Embodiments 117-122 or 125, wherein the  moiety is:



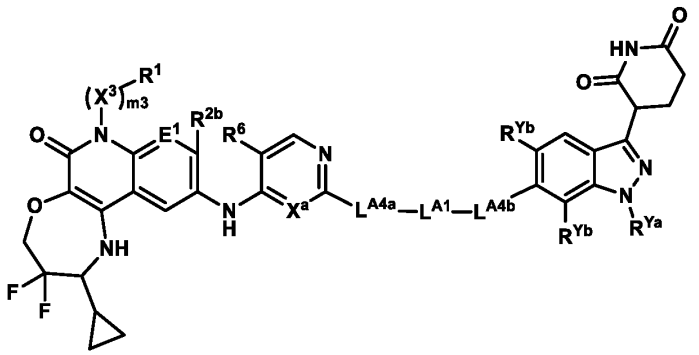
Embodiment 127. The compound of any one of Embodiments 117-122, wherein **m4** is 0; **m6** is 0; and **m5** is 1 or 2, wherein each $\mathbf{R^{a5}}$ is independently selected from the group consisting of: -F, Me, and CF_3.

Embodiment 128. The compound of any one of Embodiments 77-105 or 117-127, wherein the  moiety is selected from the group consisting of: , , , and .

Embodiment 129. The compound of any one of Embodiments 77-105 or 117-128, wherein the  moiety is selected from the group consisting of: , , and , wherein each $\mathbf{R^{Yb}}$ is independently F or C_{1-3} alkyl optionally substituted with 1-3 F; and $\mathbf{R^{Ya}}$ is C_{1-3} alkyl optionally substituted with 1-3 F (e.g., C_{1-3} alkyl (e.g., methyl)).

Embodiment 130. The compound of any one of Embodiments 77-105 or 117-128, wherein the  moiety is selected from the group consisting of: , , and .

Embodiment 131. The compound of Embodiment 1 or 61, wherein the compound is a compound of Formula (**I-a-3**):



Formula (**I-a-3**)

or a pharmaceutically acceptable salt thereof, wherein:

$\mathbf{E^1}$ is $C\mathbf{R^{2a}}$ or N;

$\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are each independently selected from the group consisting of: H and F;

$\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ are independently 4-12 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R^a}$;

$\mathbf{L^{A1}}$ is CH_2 or $CH\mathbf{R^L}$, and

$\mathbf{R^L}$ is selected from the group consisting of: -F, -OH, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$;

$\mathbf{R^{Ya}}$ is selected from the group consisting of:

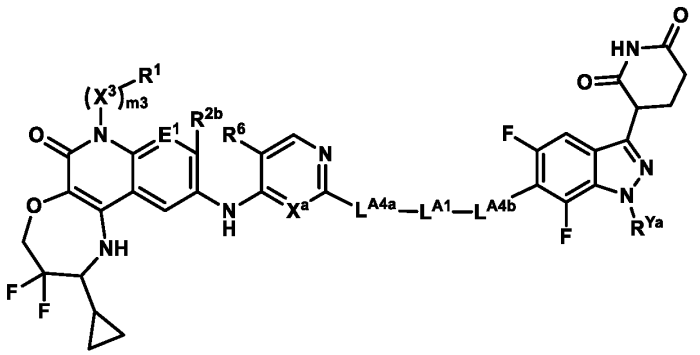
(a) H;

(b) C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$; and

(c) –(C_{0-3} alkylene)-$\mathbf{R^{b1}}$, wherein $\mathbf{R^{b1}}$ is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 $\mathbf{R^g}$ (e.g., C_{3-6} cycloalkyl optionally substituted with 1-3 F); and

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$ (e.g., C_{1-3} alkyl optionally substituted with 1-3 -F).

Embodiment 132. The compound of Embodiment 131, wherein the compound is a compound of Formula (**I-a-4**):



Formula (**I-a-4**)

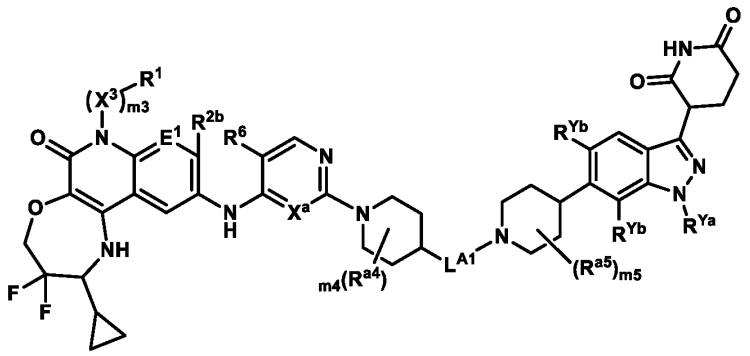
or a pharmaceutically acceptable salt thereof.

Embodiment 133. The compound of Embodiment 131 or 132, wherein $\mathbf{L}^{A4a}$ and $\mathbf{L}^{A4b}$ are independently monocyclic 4-6 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R}^{a}$;

$\mathbf{R}^{L}$ is C_{1-3} methyl optionally substituted with 1-3 F; and

each $\mathbf{R}^{a}$ present on $\mathbf{L}^{A4a}$ and/or $\mathbf{L}^{A4b}$ is independently selected from the group consisting of: -F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F.

Embodiment 134. The compound of any one of Embodiments 1, 61, or 131, wherein the compound is a compound of Formula (**I-b-3**):



Formula (**I-b-3**)

or a pharmaceutically acceptable salt thereof, wherein:

$\mathbf{E}^{1}$ is $C\mathbf{R}^{2a}$ or N;

$\mathbf{R}^{2a}$ and $\mathbf{R}^{2b}$ are each independently selected from the group consisting of: H and F;

m4 and **m5** are independently 0, 1, or 2;

each R^{a4} and R^{a5} is independently selected from the group consisting of: -F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F;

L^{A1} is CH_2 or CHR^L, and

R^L is C_{1-3} alkyl optionally substituted with 1-3 R^c;

R^{Ya} is selected from the group consisting of:

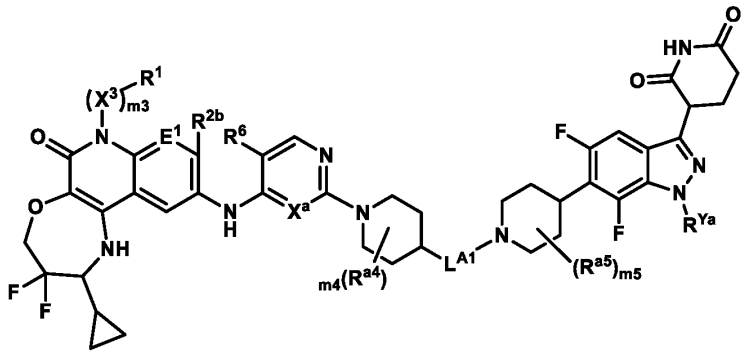
(a) H;

(b) C_{1-6} alkyl optionally substituted with 1-3 R^c; and

(c) –(C_{0-3} alkylene)-R^{b1}, wherein R^{b1} is C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, each of which is optionally substituted with 1-2 R^g (e.g., C_{3-6} cycloalkyl optionally substituted with 1-3 F); and

each R^{Yb} is independently selected from the group consisting of: halo and C_{1-3} alkyl optionally substituted with 1-3 -F.

Embodiment 135. The compound of Embodiment 134, wherein the compound is a compound of Formula (**I-b-4**):



Formula (**I-b-4**)

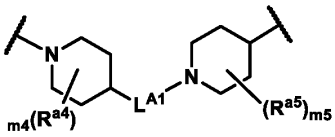
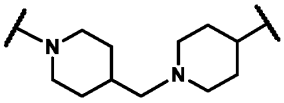
or a pharmaceutically acceptable salt thereof.

Embodiment 136. The compound of any one of Embodiments 131-135, wherein E^1 is CH; and R^{2b} is H.

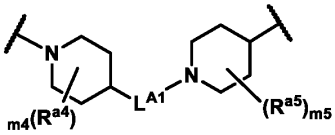
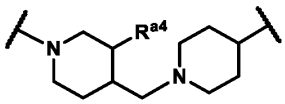
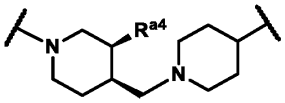
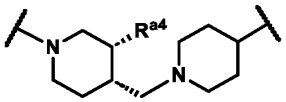
Embodiment 137. The compound of any one of Embodiments 131-135, wherein E^1 is CH; and R^{2b} is F.

Embodiment 138. The compound of any one of Embodiments 131-137, wherein L^{A1} is CH_2.

Embodiment 139. The compound of any one of Embodiments 131-138, wherein **m4** is 0; and **m5** is 0.

Embodiment 140. The compound of Embodiment 139, wherein the  moiety is .

Embodiment 141. The compound of any one of Embodiments 131-138, wherein **m4** is 1 or 2; and **m4** is 0.

Embodiment 142. The compound of Embodiment 141, wherein the  moiety is  (e.g.,  or ).

Embodiment 143. The compound of any one of Embodiments 131-138 or 141-142, wherein each R^{a4} is independently selected from the group consisting of: -F and C_{1-3} alkyl optionally substituted with 1-3 F.

Embodiment 144. The compound of Embodiment 143, wherein each R^{a4} is independently -F or methyl.

Embodiment 145. The compound of any one of Embodiments 131-144, wherein R^{Ya} is C_{1-3} alkyl optionally substituted with 1-3 F (e.g., R^{Ya} is C_{1-3} alkyl (e.g., methyl)).

Embodiment 146. The compound of any one of Embodiments 61-145, wherein $\mathbf{R^6}$ is -F or -Cl; and $\mathbf{X^a}$ is N.

Embodiment 147. The compound of any one of Embodiments 61-146, wherein $\mathbf{R^6}$ is -Cl; and $\mathbf{X^a}$ is N.

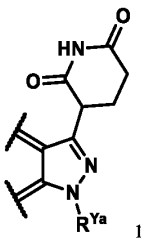
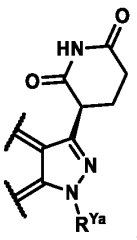
Embodiment 148. The compound of any one of Embodiments 61-147, wherein $-(\mathbf{X^3})_{m3}\text{-}\mathbf{R^1}$ is $C_{1\text{-}3}$ alkyl.

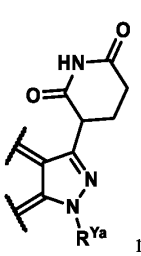
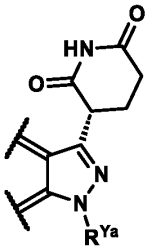
Embodiment 149. The compound of any one of Embodiments 61-148, wherein $-(\mathbf{X^3})_{m3}\text{-}\mathbf{R^1}$ is methyl.

Embodiment 150. The compound of any one of Embodiments 61-147, wherein $-(\mathbf{X^3})_{m3}\text{-}\mathbf{R^1}$ is H.

Embodiment 151. The compound of any one of Embodiments 61-147, wherein $-(\mathbf{X^3})_{m3}\text{-}\mathbf{R^1}$ is $\text{-}\mathbf{R^{b1}}$ or $\text{-}CH_2\text{-}\mathbf{R^{b1}}$.

Embodiment 152. The compound of Embodiment 151, wherein the $\mathbf{R^{b1}}$ is $C_{3\text{-}6}$ cycloalkyl optionally substituted with 1-3 F.

Embodiment 153. The compound of any one of Embodiments 77-152, wherein the  moiety is .

Embodiment 154. The compound of any one of Embodiments 77-152, wherein the  moiety is .

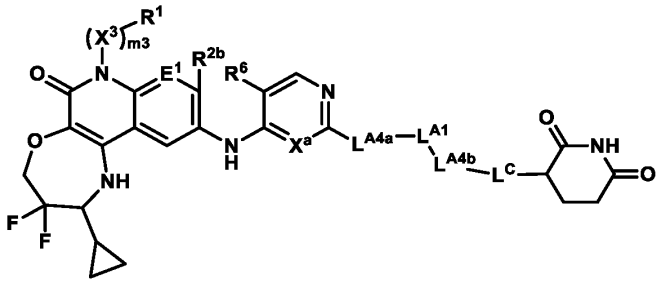
Embodiment 155. The compound of Embodiment 1, wherein the compound of Formula (**I**) is other than a compound selected from the group consisting of the compounds depicted in **Table R1**, or a pharmaceutically acceptable salt thereof.

Embodiment 156. The compound of Embodiment 1, wherein the compound of Formula (**I**) is selected from the group consisting of Compound Nos. **101**, **101a**, **101b**, **101c**, **101d**, **102**, **102a**, **102b**, **103**, **103a**, **103b**, **104**, **104a**, **104b**, **105**, **105a**, **105b**, **106**, **106a**, **107**, **107a**, **107b**, **107c**, **107d**, **108**, **108a**, **109**, **109a**, **109b**, **110**, **110a**, **110b**, **110c**, **110d**, **110e**, **110f**, **111**, **111a**, **111b**, **112**, **112a**, **112b**, **113**, **113a**, **113b**, **114**, **114a**, **114b**, **115**, **115a**, **116**, **116a**, **116b**, **116c**, **116d**, **117**, **117a**, **117b**, **118**, **118a**, **118b**, **119**, **119a**, **119b**, **119c**, **119d**, **120**, **120a**, **120b**, **121**, **121a**, **121b**, **121c**, **121d**, **121e**, **122**, **122a**, **123**, **123a**, **123b**, **124**, **124a**, **124b**, **125**, **125a**, **126**, **126a**, **127**, **127a**, **127b**, **127c**, **127d**, **128**, **128a**, **129**, **129a**, **129b**, **130**, **130a**, **130b**, **130c**, **130d**, **130e**, **131**, **131a**, **131b**, **132**, **132a**, **133**, **133a**, **133b**, **134**, **134a**, **135**, **135a**, **135b**, **136**, **136a**, **137**, **137a**, **138**, **138a**, **139**, **139a**, **139b**, **140**, **140a**, **140b**, **141**, **141a**, **142**, **142a**, **142b**, **143a**, **144**, **144a**, **145**, **145a**, **146**, **146a**, **146b**, **147**, **147a**, **148**, **148a**, **148b**, **149**, **149a**, **150**, **150a**, **151**, **151a**, **151b**, **152**, **152a**, **153a**, **154**, **154a**, **155**, **155a**, **156**, **156a**, **157**, **157a**, **158**, **158a**, **159**, **159a**, **160**, **160a**, **160b**, **161**, **161a**, **162**, **162a**, **163**, **163a**, **164**, **164a**, **165**, **165a**, **166**, **166a**, **166b**, **167**, **167a**, **168**, **168a**, **169**, **169a**, **169b**, **170**, **170a**, **171**, **171a**, **172**, **172a**, **173**, **173a**, **174**, **174a**, **175**, **175a**, **175b**, **176**, **176a**, **177**, **177a**, **178**, **178a**, **181**, **181a**, **182**, **182a**, **185a**, **185b**, **186**, **186a**, **187**, **187a**, **187b**, **188**, **188a**, **188b**, **189**, **189a**, **189b**, **190**, **190a**, **191**, **191a**, **192**, **192a**, **193**, **193a**, **194**, **194a**, **195**, **195a**, **196**, **196a**, **197**, **197a**, **198**, **198a**, **199**, **199a**, **199b**, **200**, **200a**, **201**, **201a**, **202**, **202a**, **202b**, **203**, **203a**, **203b**, **204**, **204a**, **205**, **205a**, **206**, **206a**, **207**, **207a**, **208**, **208a**, **209**, **209a**, **209b**, **210**, **210a**, **210b**, **211**, **211a**, **212**, **212a**, **213**, **213a**, **214**, **214a**, **215**, **215a**, **216**, **216a**, **217**, **217a**, **218**, **218a**, **219**, **219a**, **219b**, **220**, **220a**, **220b**, **221**, **221a**, **222**, **222a**, **223**, **223a**, **224**, **224a**, **225**, **225a**, **226**, **226a**, **227**, **227a**, **228**, **228a**, **229**, **229a**, **230**, **230a**, **231**, **231a**, **231b**, **232**, **232a**, **232b**, **233**, **233a**, **233b**, **234**, **234a**, **234b**, **235**, **235a**, **236**, **236a**, **237**, and **237a** as depicted in **Table C1**, or a pharmaceutically acceptable salt thereof; or

Compound Nos. **101**, **101a**, **101b**, **101c**, **101d**, **102**, **102a**, **102b**, **103**, **103a**, **103b**, **104**, **104a**, **104b**, **105**, **105a**, **105b**, **106**, **106a**, **107**, **107a**, **107b**, **107c**, **107d**, **108**, **108a**, **109**, **109a**, **109b**, **110**, **110a**, **110b**, **110c**, **110d**, **110e**, **110f**, **111**, **111a**, **111b**, **112**, **112a**, **112b**, **113**, **113a**, **113b**, **114**, **114a**, **114b**, **115**, **115a**, **116**, **116a**, **116b**, **116c**, **116d**, **117**, **117a**, **117b**, **118**, **118a**, **118b**, **119**, **119a**, **119b**, **119c**, **119d**, **120**, **120a**, **120b**, **121**, **121a**, **121b**, **121c**, **121d**, **121e**, **122**, **122a**,

123, **123a**, **123b**, **124**, **124a**, **124b**, **125**, **125a**, **126**, **126a**, **127**, **127a**, **127b**, **127c**, **127d**, **128**, **128a**, **129**, **129a**, **129b**, **130**, **130a**, **130b**, **130c**, **130d**, **130e**, **131**, **131a**, **131b**, **132**, **132a**, **133**, **133a**, **133b**, **134**, **134a**, **135**, **135a**, **135b**, **136**, **136a**, **137**, **137a**, **138**, **138a**, **139**, **139a**, **139b**, **140**, **140a**, **140b**, **141**, **141a**, **142**, **142a**, **142b**, **143a**, **144**, **144a**, **145**, **145a**, **146**, **146a**, **146b**, **147**, **147a**, **148**, **148a**, **148b**, **149**, **149a**, **150**, **150a**, **151**, **151a**, **151b**, **152**, **152a**, **153a**, **154**, **154a**, **155**, **155a**, **156**, **156a**, **157**, **157a**, **158**, **158a**, **159**, **159a**, **160**, **160a**, **160b**, **161**, **161a**, **162**, **162a**, **163**, **163a**, **164**, **164a**, **165**, **165a**, **166**, **166a**, **166b**, **167**, **167a**, **168**, **168a**, **169**, **169a**, **169b**, **170**, **170a**, **171**, **171a**, **172**, **172a**, **173**, **173a**, **174**, **174a**, **175**, **175a**, **176**, **176a**, **177**, **177a**, **178**, **178a**, **181**, **181a**, **182**, **182a**, **185a**, **185b**, **186**, **186a**, **187**, **187a**, **187b**, **188**, **188a**, **188b**, **189**, **189a**, **189b**, **190**, **190a**, **191**, **191a**, **192**, **192a**, **193**, **193a**, **194**, **194a**, **195**, **195a**, **196**, **196a**, **197**, **197a**, **198**, **198a**, **199**, **199a**, **199b**, **200**, **200a**, **201**, **201a**, **202**, **202a**, **202b**, **203**, **203a**, **203b**, **204**, **204a**, **205**, **205a**, **206**, **206a**, **207**, **207a**, **208**, **208a**, **209**, **209a**, **209b**, **210**, **210a**, **210b**, **211**, **211a**, **212**, **212a**, **213**, **213a**, **214**, **214a**, **215**, **215a**, **216**, **216a**, **217**, **217a**, **218**, **218a**, **219**, **219a**, **219b**, **220**, **220a**, and **220b** as depicted in **Table C1**, or a pharmaceutically acceptable salt thereof.

Embodiment 157. A compound of Formula (**II-a**):



Formula (**II-a**)

or a pharmaceutically acceptable salt thereof, wherein:

$\mathbf{E^1}$ is $\mathbf{CR^{2a}}$ or N;

$\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are independently selected from the group consisting of: H, halo, cyano, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, and C_{1-3} haloalkoxy;

m3 is 0 or 1;

$\mathbf{X^3}$ is C_{1-3} alkylene optionally substituted with 1-3 $\mathbf{R^c}$;

$\mathbf{R^1}$ is selected from the group consisting of: H, halo, and $\mathbf{R^{b1}}$;

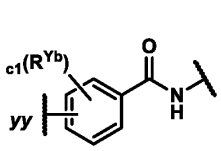
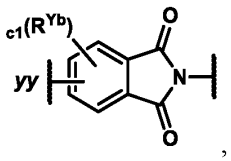
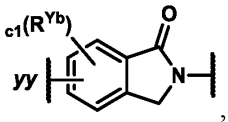
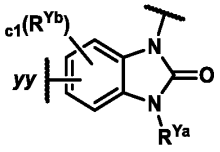
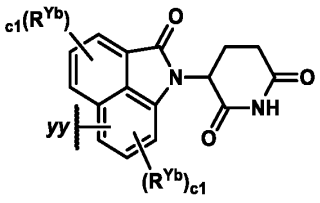
$\mathbf{X^a}$ is selected from the group consisting of: N and $C\mathbf{R^{Xa}}$;

$\mathbf{R^6}$ and $\mathbf{R^{Xa}}$ are independently selected from the group consisting of: H, halo, C_{1-2} alkyl, C_{1-2} haloalkyl, C_{1-2} alkoxy, CN, and -C≡CH;

$\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ are independently 4-12 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R^a}$;

$\mathbf{L^{A1}}$ is CH_2, $CH\mathbf{R^L}$, or $C(\mathbf{R^L})_2$, and

each $\mathbf{R^L}$ is independently selected from the group consisting of: -F, -OH, and C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$;

$\mathbf{L^C}$ is selected from the group consisting of: , , , , and ;

each **c1** is independently 0, 1, or 2;

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of $\mathbf{R^a}$ and $\mathbf{R^b}$;

$\mathbf{R^{Ya}}$ is selected from the group consisting of: H, $\mathbf{R^a}$, and $\mathbf{R^b}$; and

yy represents the point of attachment to $\mathbf{L^{A4b}}$;

each $\mathbf{R^a}$ is independently selected from the group consisting of:

(a) halo;

(b) cyano;

(c) -OH;

(d) oxo;

(e) C_{1-6} alkoxy optionally substituted with 1-6 $\mathbf{R^c}$;

(f) $-N\mathbf{R^d}\mathbf{R^e}$;

(g) $C(=O)C_{1-6}$ alkyl;

(h) $C(=O)OC_{1-6}$ alkyl;

(i) $C(=O)N(\mathbf{R^f})_2$;

(j) $S(O)_{0-2}(C_{1-6}$ alkyl);

(k) $S(O)_{0-2}(C_{1-6}$ haloalkyl); and

(l) C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, each optionally substituted with 1-6 $\mathbf{R^c}$;

each $\mathbf{R^b}$ is independently selected from the group consisting of: $\mathbf{-(L^b)_b-R^{b1}}$ and $\mathbf{-R^{b1}}$, wherein:

each **b** is independently 1, 2, or 3;

each $\mathbf{L^b}$ is independently selected from the group consisting of: -O-, -N(H)-, $-N(C_{1-3}$ alkyl)-, $-S(O)_{0-2}$-, C(=O), and C_{1-3} alkylene; and

each $\mathbf{R^{b1}}$ is independently selected from the group consisting of: C_{3-6} cycloalkyl and 4-8 membered heterocyclyl, each of which is optionally substituted with 1-3 $\mathbf{R^g}$;

each $\mathbf{R^c}$ is independently selected from the group consisting of: halo, cyano, -OH, $-C_{1-6}$ alkoxy, $-C_{1-6}$ haloalkoxy, $-N\mathbf{R^dR^e}$, $C(=O)C_{1-6}$ alkyl, $C(=O)OC_{1-6}$ alkyl, $C(=O)N(\mathbf{R^f})_2$, $S(O)_{0-2}(C_{1-6}$ alkyl), and $S(O)_{0-2}(C_{1-6}$ haloalkyl);

each $\mathbf{R^d}$ and $\mathbf{R^e}$ is independently selected from the group consisting of: H, $C(=O)C_{1-6}$ alkyl, $C(=O)C_{1-6}$ haloalkyl, $C(=O)OC_{1-6}$ alkyl, $C(=O)OC_{1-6}$ haloalkyl, $C(=O)N(\mathbf{R^f})_2$, $S(O)_{1-2}(C_{1-6}$ alkyl), $S(O)_{1-2}(C_{1-6}$ haloalkyl), $S(O)_{1-2}N(\mathbf{R^f})_2$, and C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^h}$;

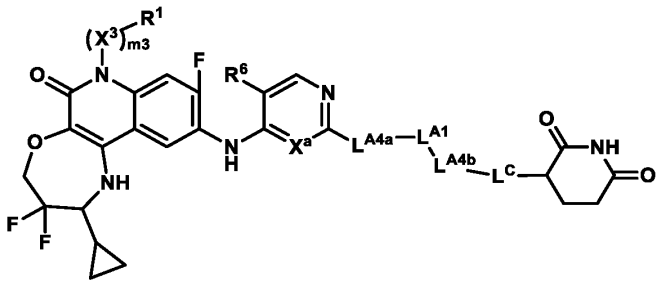
each $\mathbf{R^f}$ is independently selected from the group consisting of: H and C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^h}$;

each $\mathbf{R^g}$ is independently selected from the group consisting of: $\mathbf{R^h}$, oxo, C_{1-3} alkyl, and C_{1-3} haloalkyl; and

each $\mathbf{R^h}$ is independently selected from the group consisting of: halo, cyano, -OH, $-(C_{0-3}$ alkylene)-C_{1-6} alkoxy, $-(C_{0-3}$ alkylene)-C_{1-6} haloalkoxy, $-(C_{0-3}$ alkylene)-NH_2, $-(C_{0-3}$ alkylene)-N(H)(C_{1-3} alkyl), and $-(C_{0-3}$ alkylene)-$N(C_{1-3}$ alkyl)$_2$.

Embodiment 158. The compound of Embodiment 157, wherein **E** is $C\mathbf{R^{2a}}$ (e.g., CH).

Embodiment 159. The compound of Embodiment 157 or 158, wherein the compound of Formula (**II-a**) is a compound of Formula (**II-a-1**):



Formula (**II-a-1**)

or a pharmaceutically acceptable salt thereof.

Embodiment 160. The compound of any one of Embodiments 157-159, wherein **m3** is 1; and $\mathbf{R^1}$ is H.

Embodiment 161. The compound of any one of Embodiments 157-160, wherein $-(\mathbf{X^3})_{m3}\text{-}\mathbf{R^1}$ is $C_{1\text{-}3}$ alkyl (e.g., methyl).

Embodiment 162. The compound of any one of Embodiments 157-161, wherein $\mathbf{R^6}$ is -F or -Cl (e.g., -Cl).

Embodiment 163. The compound of any one of Embodiments 157-162, wherein $\mathbf{X^a}$ is N.

Embodiment 164. The compound of any one of Embodiments 157-163, wherein $\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ are independently a monocyclic 4-6 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R^a}$.

Embodiment 165. The compound of any one of Embodiments 157-164, wherein $\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ are independently a monocyclic 4-6 membered nitrogen-containing heterocyclylene optionally substituted with 1-3 $\mathbf{R^a}$; and

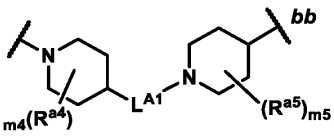
each $\mathbf{R^a}$ present on $\mathbf{L^{A4a}}$ and/or $\mathbf{L^{A4b}}$ is independently selected from the group consisting of: -F, CN, $C_{1\text{-}3}$ alkoxy, OH, and $C_{1\text{-}3}$ alkyl optionally substituted with 1-3 F.

Embodiment 166. The compound of any one of Embodiments 157-165, wherein one of $\mathbf{L^{A4a}}$ and $\mathbf{L^{A4b}}$ is a 1,4-piperidinylene; and

the other of L^{A4a} and L^{A4b} is independently selected from the group consisting of: 1,4-piperidinylene and 1,4-piperazinylene, wherein each of the 1,4-piperidinylene or 1,4-piperazinylene is optionally substituted with 1-2 R^a, wherein:

each R^a present on L^{A4a} and/or L^{A4b} is independently selected from the group consisting of: -F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F.

Embodiment 167. The compound of any one of Embodiments 157-166, wherein each R^a present on L^{A4a} and/or L^{A4b} is independently selected from the group consisting of: -F and C_{1-3} alkyl optionally substituted with 1-3 F (e.g., F, CH_3, CF_3, CF_2H, or CH_2F).

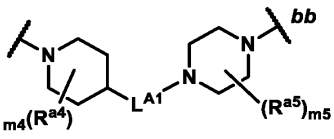
Embodiment 168. The compound of any one of Embodiments 157-163, wherein -L^{A4a}-L^{A1}-L^{A4b}- is 

, wherein:

m4 and **m5** are independently 0, 1, or 2;

each R^{a4} and R^{a5} is independently selected from the group consisting of: -F and C_{1-3} alkyl optionally substituted with 1-3 F; and

bb represents the point of attachment to L^C.

Embodiment 169. The compound of any one of Embodiments 157-163, wherein -L^{A4a}-L^{A1}-L^{A4b}- is 

, wherein:

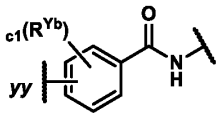
m4 and **m5** are independently 0, 1, or 2;

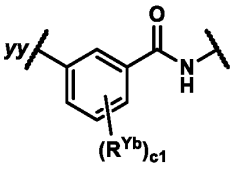
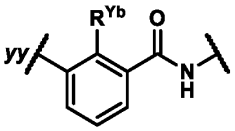
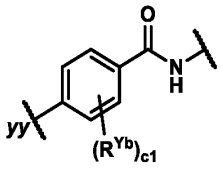
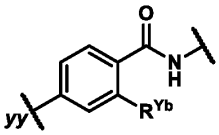
each R^{a4} is independently selected from the group consisting of: -F and C_{1-3} alkyl optionally substituted with 1-3 F;

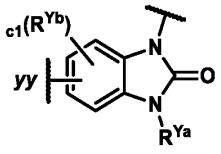
each R^{a5} is independently C_{1-3} alkyl optionally substituted with 1-3 F; and

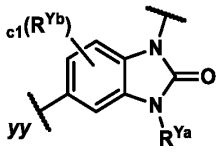
bb represents the point of attachment to L^C.

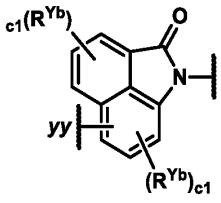
Embodiment 170. The compound of Embodiment 168 or 169, wherein **m4** is 0; and **m5** is 0.

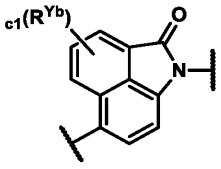
Embodiment 171. The compound of any one of Embodiments 157-170, wherein $\mathbf{L^C}$ is .

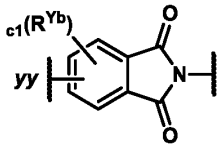
Embodiment 172. The compound of any one of Embodiments 157-171, wherein $\mathbf{L^C}$ is  (e.g., ) or  (e.g., ), wherein **c1** is 0 or 1; and each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 -F.

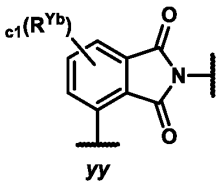
Embodiment 173. The compound of any one of Embodiments 157-170, wherein $\mathbf{L^C}$ is .

Embodiment 174. The compound of any one of Embodiments 157-170 or 173, wherein $\mathbf{L^C}$ is , wherein $\mathbf{R^{Ya}}$ is C_{1-3} alkyl optionally substituted with 1-3 F (e.g., C_{1-3} alkyl (e.g., methyl)).

Embodiment 175. The compound of any one of Embodiments 157-170, wherein $\mathbf{L^C}$ is .

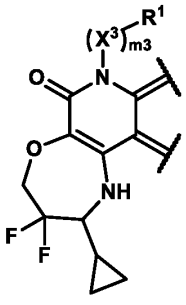
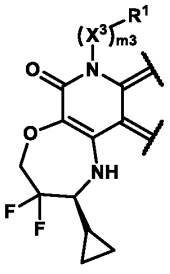
Embodiment 176. The compound of any one of Embodiments 157-170 or 175, wherein $\mathbf{L}^{C}$ is .

Embodiment 177. The compound of any one of Embodiments 157-170, wherein $\mathbf{L}^{C}$ is .

Embodiment 178. The compound of any one of Embodiments 157-170 or 177, wherein $\mathbf{L}^{C}$ is .

Embodiment 179. The compound of any one of Embodiments 157-178, wherein each $\mathbf{R}^{Yb}$ is independently selected from the group consisting of: halo, CN, C_{1-3} alkoxy, and C_{1-3} alkyl optionally substituted with 1-3 -F.

Embodiment 180. The compound of any one of Embodiments 157-178, wherein **c1** is 0.

Embodiment 181. The compound of any one of Embodiments 1-154 or 157-180, wherein the  moiety is .

Embodiment 182. The compound of Embodiment 157, wherein the compound of Formula (**II-a**) is other than a compound selected from the group consisting of the compounds depicted in **Table R2**, or a pharmaceutically acceptable salt thereof.

Embodiment 183. The compound of Embodiment 157, the compound of Formula (**II-a**) is selected from the group consisting of the compounds depicted in **Table C2**, or a pharmaceutically acceptable salt thereof.

Embodiment 184. A pharmaceutical composition comprising a compound of any one of Embodiments 1-183, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

Embodiment 185. A method for treating a cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of Embodiments 1-183, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to Embodiment 184.

Embodiment 186. The method of Embodiment 185, wherein the cancer is a hematological cancer, breast cancer, gastrointestinal cancer, brain cancer, lung cancer, or a combination thereof.

Embodiment 187. The method of Embodiment 186, wherein the cancer is a hematological cancer (e.g., lymphoma (e.g., Hodgkin lymphoma (e.g., nodular lymphocyte predominant Hodgkin lymphoma (NLPHL)), non-Hodgkin lymphoma (e.g., B cell lymphoid proliferations and lymphomas (e.g., mature B cell neoplasms (e.g., Burkitt lymphoma (BL), large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), T-cell/histiocyte-rich large B-cell lymphoma, diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary large B cell lymphoma of immune-privileged sites (primary LBCL of immune-privileged sites), primary mediastinal large B cell lymphoma (primary mediastinal LBCL), or high grade B-cell lymphoma NOS), follicular lymphoma (FL), or transformations of indolent B cell lymphomas)), T-cell and NK-cell lymphoid proliferations and lymphomas (e.g., mature T-cell and NK-cell neoplasms (e.g., mature T-cell and NK-cell leukemias (e.g., adult T-cell leukemia/lymphoma or Sezary syndrome), primary cutaneous T-cell lymphoid

proliferations and lymphomas (cutaneous T-cell lymphoma (CTCL)) (e.g., primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder, mycosis fungoides, primary cutaneous CD30-positive T-cell lymphoproliferative disorder: lymphomatoid papulosis, primary cutaneous CD30-positive T-cell lymphoproliferative disorder: primary cutaneous anaplastic large cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, primary cutaneous gamma-delta T-cell lymphoma, or primary cutaneous peripheral T-cell lymphoma NOS), peripheral T-cell lymphoma (PTCL) (e.g., anaplastic large cell lymphoma (ALCL) (e.g., ALK-positive anaplastic large cell lymphoma, or ALK-negative anaplastic large cell lymphoma), nodal T follicular helper cell lymphoma (e.g., nodal T follicular helper cell lymphoma angioimmunoblastic type (also known as angioimmunoblastic T-cell lymphoma (AITL) or follicular helper T-cell lymphoma, angioimmunoblastic type), nodal T follicular helper cell lymphoma follicular type (also known as follicular helper T-cell lymphoma, follicular type), or nodal T follicular helper cell lymphoma NOS (also known as follicular helper T-cell lymphoma, NOS)), or other peripheral T-cell lymphomas (e.g., peripheral T-cell lymphoma NOS))))))).

Embodiment 188. The method of Embodiment 187, wherein the hematological cancer is selected from the group consisting of lymphomas (e.g., non-Hodgkin lymphoma (e.g., B cell lymphoid proliferations and lymphomas (e.g., mature B cell neoplasms (e.g., large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), or primary mediastinal large B cell lymphoma (primary mediastinal LBCL)), follicular lymphoma (FL), or transformations of indolent B cell lymphomas)), T-cell and NK-cell lymphoid proliferations and lymphomas (e.g., mature T-cell and NK-cell neoplasms (e.g., primary cutaneous T-cell lymphoid proliferations and lymphomas (cutaneous T-cell lymphoma (CTCL)) (e.g., primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder, or mycosis fungoides), or peripheral T-cell lymphoma (PTCL) (e.g., nodal T follicular helper cell lymphoma (e.g., nodal T follicular helper cell lymphoma angioimmunoblastic type (also known as angioimmunoblastic T-cell lymphoma (AITL) or follicular helper T-cell lymphoma, angioimmunoblastic type), nodal T follicular helper cell lymphoma follicular type (also known as follicular helper T-cell lymphoma, follicular type), or nodal T follicular helper cell lymphoma NOS (also known as follicular helper T-cell lymphoma, NOS)), or other peripheral T-cell lymphomas (e.g., peripheral T-cell lymphoma NOS))))))).

Embodiment 189. The method of Embodiment 187, wherein the hematological cancer is FL or a large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary LBCL of immune-privileged sites, primary mediastinal LBCL, or HBGCL-NOS).

Embodiment 190. The method of Embodiment 187, wherein the hematological cancer is a large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary LBCL of immune-privileged sites, primary mediastinal LBCL, or HBGCL-NOS).

Embodiment 191. The method of Embodiment 187, wherein the hematological cancer is FL.

Embodiment 192. The method of Embodiment 187, wherein the hematological cancer is BL.

Embodiment 193. The method of Embodiment 187, wherein the hematological cancer is a peripheral T-cell lymphoma (PTCL) (e.g., anaplastic large cell lymphoma (ALCL) (e.g., ALK-positive anaplastic large cell lymphoma, or ALK-negative anaplastic large cell lymphoma), nodal T follicular helper cell lymphoma (e.g., nodal T follicular helper cell lymphoma angioimmunoblastic type (also known as angioimmunoblastic T-cell lymphoma (AITL) or follicular helper T-cell lymphoma, angioimmunoblastic type), nodal T follicular helper cell lymphoma follicular type (also known as follicular helper T-cell lymphoma, follicular type), or nodal T follicular helper cell lymphoma NOS (also known as follicular helper T-cell lymphoma, NOS))).

Embodiment 194. The method of any one of Embodiments 185-193, wherein the cancer is positive for BCL6 expression (e.g., as determined by an IHC test).

Embodiment 195. The method of any one of Embodiments 185-194, wherein the therapeutically effective amount of a compound of any one of Embodiments 1-183, or a

pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to Embodiment 184, is administered to the subject as a monotherapy.

Embodiment 196. The method of any one of Embodiments 185-194, comprising administering an additional therapy or therapeutic agent to the subject.

Embodiment 197. The method of Embodiment 196, wherein the additional therapy or therapeutic agent is a PI3K inhibitor, an Abl inhibitor (e.g., a BCR-Abl inhibitor), a BTK inhibitor, a JAK inhibitor, a BRaf inhibitor, a MEK inhibitor, a BCL-2 inhibitor, a Bcl-X_L inhibitor, an XPO1 inhibitor, an inhibitor of the polycomb repressive complex 2 (PRC2), an immunomodulatory imide drug, anti-CD19 therapy, anti-CD20 therapy, anti-CD3 therapy, chemotherapy, or a combination thereof.

Embodiment 198. The method of Embodiment 197, wherein the additional therapy or therapeutic agent is a BCL-2 inhibitor.

Embodiment 199. The method of Embodiment 198, wherein the cancer is selected from the group consisting of a large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary large B cell lymphoma of immune-privileged sites (primary LBCL of immune-privileged sites), intravascular large B-cell lymphoma (IVLBCL), primary mediastinal large B cell lymphoma (primary mediastinal LBCL), or high grade B-cell lymphoma NOS (HBGCL-NOS)), follicular lymphoma (FL), mantle cell lymphoma (MCL), and transformations of indolent B cell lymphomas.

Embodiment 200. The method of Embodiment 199, wherein the cancer is a large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary large B cell lymphoma of immune-privileged sites (primary LBCL of immune-privileged sites), intravascular large B-cell lymphoma (IVLBCL), primary mediastinal large B cell lymphoma (primary mediastinal LBCL), or high grade B-cell lymphoma NOS (HBGCL-NOS)).

Embodiment 201. The method of Embodiment 200, wherein the cancer is DLBCL-NOS.

Embodiment 202. The method of Embodiment 199, wherein the cancer is a FL.

Embodiment 203. The method of Embodiment 199, wherein the cancer is a transformation of an indolent B cell lymphoma.

Embodiment 204. The method of Embodiment 199, wherein the cancer is an MCL.

Embodiment 205. The method of Embodiment 197, wherein the additional therapy or therapeutic agent is an inhibitor of the PRC2 (e.g., an EZH1/2 or EZH2 inhibitor).

Embodiment 206. The method of Embodiment 205, wherein the cancer is selected from the group consisting of a large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary large B cell lymphoma of immune-privileged sites (primary LBCL of immune-privileged sites), intravascular large B-cell lymphoma (IVLBCL), primary mediastinal large B cell lymphoma (primary mediastinal LBCL), or high grade B-cell lymphoma NOS (HBGCL-NOS)), follicular lymphoma (FL), mantle cell lymphoma (MCL), and transformations of indolent B cell lymphomas.

Embodiment 207. The method of Embodiment 206, wherein the cancer is a large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary large B cell lymphoma of immune-privileged sites (primary LBCL of immune-privileged sites), intravascular large B-cell lymphoma (IVLBCL), primary mediastinal large B cell lymphoma (primary mediastinal LBCL), or high grade B-cell lymphoma NOS (HBGCL-NOS)).

Embodiment 208. The method of Embodiment 207, wherein the cancer is DLBCL-NOS.

Embodiment 209. The method of Embodiment 206, wherein the cancer is a FL.

Embodiment 210. The method of Embodiment 206, wherein the cancer is a transformation of an indolent B cell lymphoma.

Embodiment 211. The method of Embodiment 206, wherein the cancer is an MCL.

Embodiment 212. The method of Embodiment 206, wherein the cancer is diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)).

Embodiment 213. The method of Embodiment 206, wherein the cancer is primary large B cell lymphoma of immune-privileged sites (primary LBCL of immune-privileged sites).

Embodiment 214. The method of Embodiment 206, wherein the cancer is primary mediastinal large B cell lymphoma (primary mediastinal LBCL).

Embodiment 215. The method of Embodiment 205, wherein the cancer is a BL.

Embodiment 216. The method of Embodiment 205, wherein the cancer is a NLPHL.

Embodiment 217. The method of Embodiment 205, wherein the cancer is a peripheral T-cell lymphoma (PTCL) (e.g., anaplastic large cell lymphoma (ALCL) (e.g., ALK-positive anaplastic large cell lymphoma, or ALK-negative anaplastic large cell lymphoma), nodal T follicular helper cell lymphoma (e.g., nodal T follicular helper cell lymphoma angioimmunoblastic type (also known as angioimmunoblastic T-cell lymphoma (AITL) or follicular helper T-cell lymphoma, angioimmunoblastic type), nodal T follicular helper cell lymphoma follicular type (also known as follicular helper T-cell lymphoma, follicular type), or nodal T follicular helper cell lymphoma NOS (also known as follicular helper T-cell lymphoma, NOS))), or a primary cutaneous T-cell lymphoid proliferation or lymphoma (cutaneous T-cell lymphoma (CTCL)) (e.g., primary cutaneous CD4-positive small or medium

T-cell lymphoproliferative disorder, mycosis fungoides, or primary cutaneous gamma-delta T-cell lymphoma).

Embodiment 218. The method of Embodiment 217, wherein the cancer is nodal T follicular helper cell lymphoma angioimmunoblastic type (also known as angioimmunoblastic T-cell lymphoma (AITL) or follicular helper T-cell lymphoma, angioimmunoblastic type).

Embodiment 219. The method of Embodiment 217, wherein the cancer is nodal T follicular helper cell lymphoma follicular type (also known as follicular helper T-cell lymphoma, follicular type).

Embodiment 220. The method of Embodiment 217, wherein the cancer is nodal T follicular helper cell lymphoma NOS (also known as follicular helper T-cell lymphoma, NOS).

Embodiment 221. The method of Embodiment 217, wherein the cancer is ALK-positive anaplastic large cell lymphoma.

Embodiment 222. The method of Embodiment 217, wherein the cancer is ALK-negative anaplastic large cell lymphoma.

Embodiment 223. The method of Embodiment 217, wherein the cancer is mycosis fungoides.

Embodiment 224. The method of Embodiment 205, wherein the cancer is Sezary syndrome.

Embodiment 225. The method of Embodiment 197, wherein the additional therapy or therapeutic agent is anti-CD20 therapy.

Embodiment 226. The method of Embodiment 225, wherein the cancer is a large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary large B cell lymphoma of immune-privileged sites (primary LBCL of immune-privileged sites), intravascular large B-

cell lymphoma (IVLBCL), primary mediastinal large B cell lymphoma (primary mediastinal LBCL), or high grade B-cell lymphoma NOS (HBGCL-NOS)), follicular lymphoma (FL), mantle cell lymphoma (MCL), or transformations of indolent B cell lymphomas.

Embodiment 227. The method of Embodiment 226, wherein the cancer is a large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary large B cell lymphoma of immune-privileged sites (primary LBCL of immune-privileged sites), intravascular large B-cell lymphoma (IVLBCL), primary mediastinal large B cell lymphoma (primary mediastinal LBCL), or high grade B-cell lymphoma NOS (HBGCL-NOS)).

Embodiment 228. The method of Embodiment 227, wherein the cancer is a FL.

Embodiment 229. The method of Embodiment 197, wherein the additional therapy or therapeutic agent is chemotherapy.

Embodiment 230. The method of Embodiment 229, wherein the cancer is selected from the group consisting of a large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary large B cell lymphoma of immune-privileged sites (primary LBCL of immune-privileged sites), intravascular large B-cell lymphoma (IVLBCL), primary mediastinal large B cell lymphoma (primary mediastinal LBCL), or high grade B-cell lymphoma NOS (HBGCL-NOS)), follicular lymphoma (FL), mantle cell lymphoma (MCL), and transformations of indolent B cell lymphomas.

Embodiment 231. The method of Embodiment 230, wherein the cancer is a large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary large B cell lymphoma of immune-privileged sites (primary LBCL of immune-privileged sites), intravascular large B-cell lymphoma (IVLBCL), primary mediastinal large B cell lymphoma (primary mediastinal LBCL), or high grade B-cell lymphoma NOS (HBGCL-NOS)).

Embodiment 232. The method of Embodiment 231, wherein the cancer is DLBCL-NOS.

Embodiment 233. The method of Embodiment 230, wherein the cancer is a FL.

Embodiment 234. The method of Embodiment 230, wherein the cancer is a transformation of an indolent B cell lymphoma.

Embodiment 235. The method of Embodiment 230, wherein the cancer is an MCL.

Embodiment 236. The method of Embodiment 230, wherein the cancer is diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)).

Embodiment 237. The method of Embodiment 230, wherein the cancer is primary large B cell lymphoma of immune-privileged sites (primary LBCL of immune-privileged sites).

Embodiment 238. The method of Embodiment 230, wherein the cancer is primary mediastinal large B cell lymphoma (primary mediastinal LBCL).

Embodiment 239. The method of Embodiment 229, wherein the cancer is a BL.

Embodiment 240. The method of Embodiment 229, wherein the cancer is a NLPHL.

Embodiment 241. The method of Embodiment 229, wherein the cancer is a peripheral T-cell lymphoma (PTCL) (e.g., anaplastic large cell lymphoma (ALCL) (e.g., ALK-positive anaplastic large cell lymphoma, or ALK-negative anaplastic large cell lymphoma), nodal T follicular helper cell lymphoma (e.g., nodal T follicular helper cell lymphoma angioimmunoblastic type (also known as angioimmunoblastic T-cell lymphoma (AITL) or follicular helper T-cell lymphoma, angioimmunoblastic type), nodal T follicular helper cell lymphoma follicular type (also known as follicular helper T-cell lymphoma, follicular type),

or nodal T follicular helper cell lymphoma NOS (also known as follicular helper T-cell lymphoma, NOS))), or a primary cutaneous T-cell lymphoid proliferation or lymphoma (cutaneous T-cell lymphoma (CTCL)) (e.g., primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder, mycosis fungoides, or primary cutaneous gamma-delta T-cell lymphoma).

Embodiment 242. The method of Embodiment 241, wherein the cancer is nodal T follicular helper cell lymphoma angioimmunoblastic type (also known as angioimmunoblastic T-cell lymphoma (AITL) or follicular helper T-cell lymphoma, angioimmunoblastic type).

Embodiment 243. The method of Embodiment 241, wherein the cancer is nodal T follicular helper cell lymphoma follicular type (also known as follicular helper T-cell lymphoma, follicular type).

Embodiment 244. The method of Embodiment 241, wherein the cancer is nodal T follicular helper cell lymphoma NOS (also known as follicular helper T-cell lymphoma, NOS).

Embodiment 245. The method of Embodiment 241, wherein the cancer is ALK-positive anaplastic large cell lymphoma.

Embodiment 246. The method of Embodiment 241, wherein the cancer is ALK-negative anaplastic large cell lymphoma.

Embodiment 247. The method of Embodiment 241, wherein the cancer is mycosis fungoides.

Embodiment 248. The method of Embodiment 229, wherein the cancer is Sezary syndrome.

Embodiment 249. A method for treating or preventing an autoimmune condition in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of Embodiments 1-183, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to Embodiment 184.

Embodiment 250. A method for treating a lymphoproliferative disorder in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of Embodiments 1-183, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to Embodiment 184.

Embodiment 251. A method for inducing degradation of a BCL6 protein in a mammalian cell, the method comprising contacting the mammalian cell with an effective amount of a compound of any one of Embodiments 1-183, or a pharmaceutically acceptable salt thereof.

Embodiment 252. The method of Embodiment 251, wherein the contacting occurs in vivo.

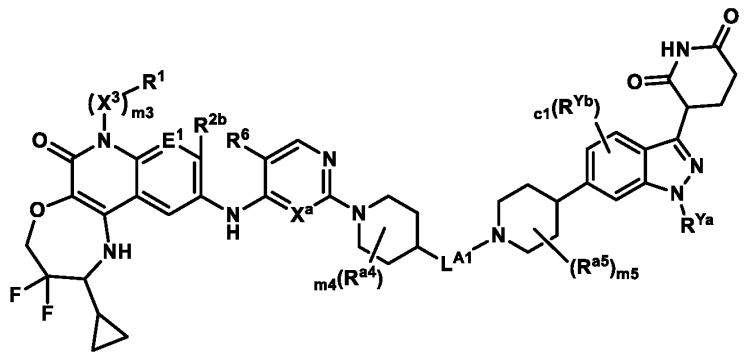
Embodiment 253. The method of Embodiment 251, wherein the contacting occurs in vitro.

Embodiment 254. The method of Embodiment 251, wherein the contacting occurs ex vivo.

Embodiment 255. The method of any one of Embodiments 251-254, wherein the mammalian cell is a mammalian cancer cell.

WHAT IS CLAIMED IS:

1. A compound of Formula (**I-b**):



Formula (**I-b**)

or a pharmaceutically acceptable salt thereof, wherein:

$\mathbf{E^1}$ is $\mathbf{CR^{2a}}$;

$\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are each independently selected from the group consisting of: H and F;

$\mathbf{-(X^3)_{m3}-R^1}$ is C_{1-3} alkyl;

$\mathbf{X^a}$ is N;

$\mathbf{R^6}$ is F or Cl;

m4 and **m5** are independently 0, 1, or 2;

each $\mathbf{R^{a4}}$ and $\mathbf{R^{a5}}$ is independently selected from the group consisting of: F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F;

$\mathbf{L^{A1}}$ is CH_2 or $\mathbf{CHR^L}$, and

$\mathbf{R^L}$ is C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R^c}$;

c1 is 0, 1, or 2;

$\mathbf{R^{Ya}}$ is selected from the group consisting of:

(a) H; and

(b) C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^c}$;

each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: F and C_{1-3} alkyl optionally substituted with 1-3 F;

each $\mathbf{R^c}$ is independently selected from the group consisting of: halo, cyano, OH, -C_{1-6} alkoxy, -C_{1-6} haloalkoxy, -N$\mathbf{R^d}\mathbf{R^e}$, C(=O)C_{1-6} alkyl, C(=O)OC_{1-6} alkyl, C(=O)N($\mathbf{R^f}$)$_2$, S(O)$_{0-2}$(C_{1-6} alkyl), and S(O)$_{0-2}$(C_{1-6} haloalkyl);

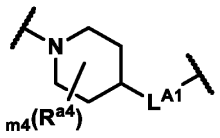
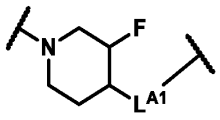
each $\mathbf{R^d}$ and $\mathbf{R^e}$ is independently selected from the group consisting of: H, C(=O)C_{1-6} alkyl, C(=O)C_{1-6} haloalkyl, C(=O)OC_{1-6} alkyl, C(=O)OC_{1-6} haloalkyl, C(=O)N($\mathbf{R^f}$)$_2$, S(O)$_{1-2}$(C_{1-6} alkyl), S(O)$_{1-2}$(C_{1-6} haloalkyl), S(O)$_{1-2}$N($\mathbf{R^f}$)$_2$, and C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^h}$;

each $\mathbf{R^f}$ is independently selected from the group consisting of: H and C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R^h}$; and

each $\mathbf{R^h}$ is independently selected from the group consisting of: halo, cyano, OH, -(C_{0-3} alkylene)-C_{1-6} alkoxy, -(C_{0-3} alkylene)-C_{1-6} haloalkoxy, -(C_{0-3} alkylene)-NH_2, -(C_{0-3} alkylene)-N(H)(C_{1-3} alkyl), and –(C_{0-3} alkylene)-N(C_{1-3} alkyl)$_2$.

2. The compound of claim 1, wherein one or more of **(1), (3) or (5)** applies:

(1) $\mathbf{R^{2b}}$ is F;

(3) the  moiety is:  ; and/or

(5) c1 is 2.

3. The compound of claim 1, wherein two or more of **(1)-(4)** apply:

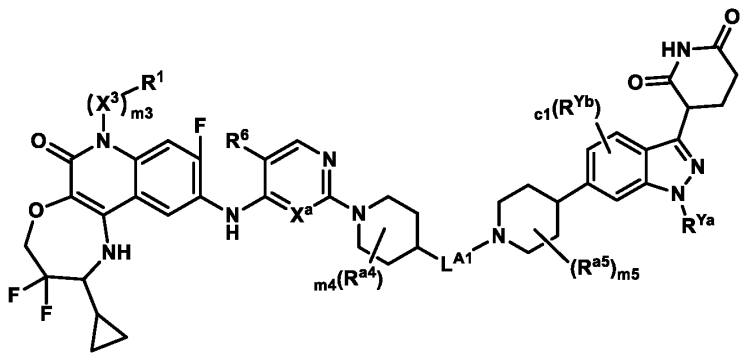
(1) m4 is 1 or 2;

(2) m5 is 1 or 2;

(3) $\mathbf{L^{A1}}$ is CH$\mathbf{R^L}$; and/or

(4) c1 is 1 or 2.

4. The compound of claim 1, wherein the compound of Formula (**I-b**) is a compound of Formula (**I-b-1**):



Formula (**I-b-1**)

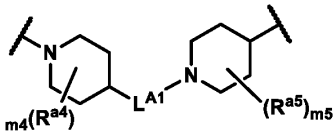
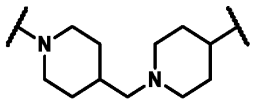
or a pharmaceutically acceptable salt thereof.

5. The compound of any one of claims 1-4, wherein:

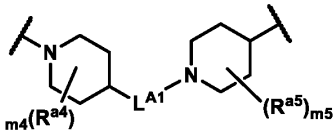
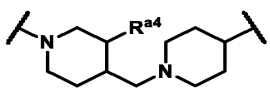
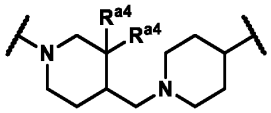
$\mathbf{R^{Ya}}$ is $C_{1\text{-}3}$ alkyl optionally substituted with 1-3 F (e.g., $C_{1\text{-}3}$ alkyl (e.g., methyl)), and each $\mathbf{R^{Yb}}$ is independently selected from the group consisting of: F and $C_{1\text{-}3}$ alkyl optionally substituted with 1-3 F.

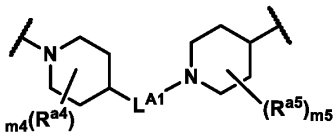
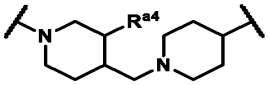
6. The compound of any one of claims 1-5, wherein $\mathbf{L^{A1}}$ is CH_2.

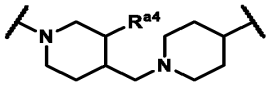
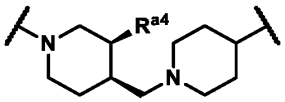
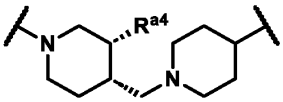
7. The compound of any one of claims 1-6, wherein **m4** is 0; and **m5** is 0.

8. The compound of any one of claims 1-7, wherein the  moiety is .

9. The compound of any one of claims 1-6, wherein **m4** is 1 or 2; and **m5** is 0, wherein each $\mathbf{R^{a4}}$ is independently selected from the group consisting of: F, Me, and CF_3.

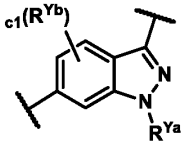
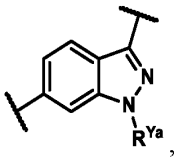
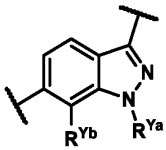
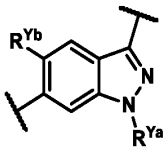
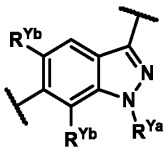
10. The compound of any one of claims 1-6 or 9, wherein the  moiety is  or .

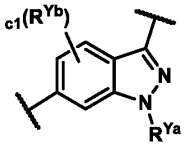
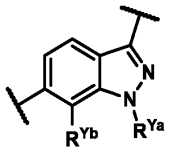
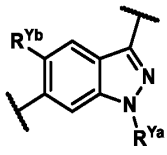
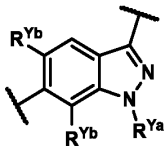
11. The compound of any one of claims 1-6 or 9-10, wherein the  moiety is .

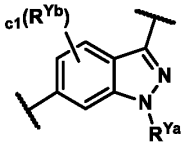
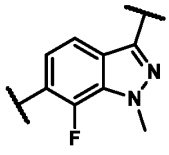
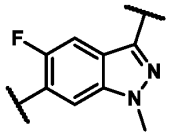
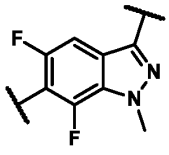
12. The compound of claim 11, wherein the  moiety is  or .

13. The compound of claim 11 or 12, wherein $\mathbf{R^{a4}}$ is selected from the group consisting of: F and Me.

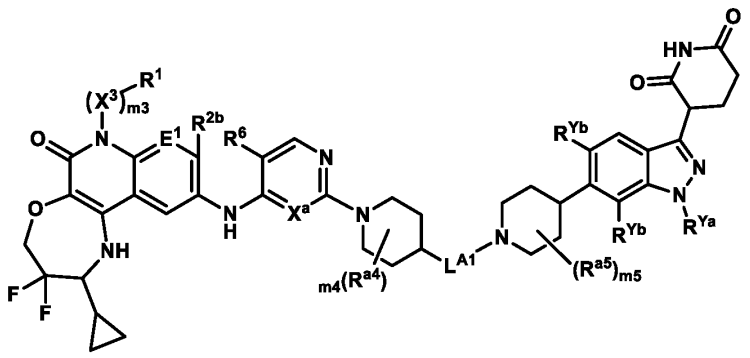
14. The compound of any one of claims 1-6, wherein **m4** is 0; and **m5** is 1 or 2, wherein each $\mathbf{R^{a5}}$ is independently selected from the group consisting of: F, Me, and CF_3.

15. The compound of any one of claims 1-14, wherein the  moiety is selected from the group consisting of: , , , and .

16. The compound of any one of claims 1-15, wherein the  moiety is selected from the group consisting of: , , and , wherein each $\mathbf{R^{Yb}}$ is independently F or C_{1-3} alkyl optionally substituted with 1-3 F; and $\mathbf{R^{Ya}}$ is C_{1-3} alkyl optionally substituted with 1-3 F (e.g., C_{1-3} alkyl (e.g., methyl)).

17. The compound of any one of claims 1-15, wherein the  moiety is selected from the group consisting of: , , and .

18. The compound of claim 1, wherein the compound is a compound of Formula (**I-b-3**):



Formula (**I-b-3**)

or a pharmaceutically acceptable salt thereof, wherein:

$\mathbf{E^1}$ is $C\mathbf{R^{2a}}$;

$\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are each independently selected from the group consisting of: H and F;

m4 and **m5** are independently 0, 1, or 2;

each $\mathbf{R}^{a4}$ and $\mathbf{R}^{a5}$ is independently selected from the group consisting of: F, CN, C_{1-3} alkoxy, OH, and C_{1-3} alkyl optionally substituted with 1-3 F;

$\mathbf{L}^{A1}$ is CH_2 or $CH\mathbf{R}^{L}$, and

$\mathbf{R}^{L}$ is C_{1-3} alkyl optionally substituted with 1-3 $\mathbf{R}^{c}$;

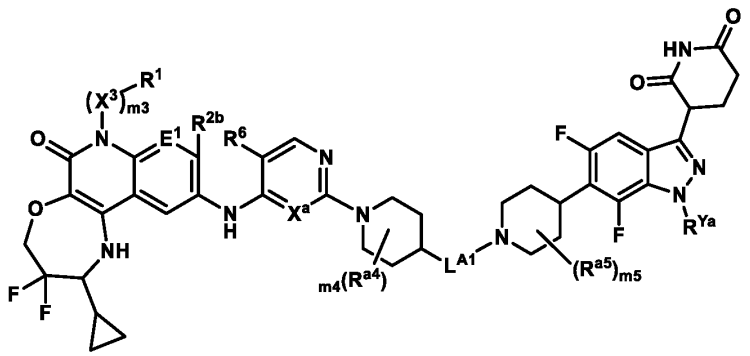
$\mathbf{R}^{Ya}$ is selected from the group consisting of:

(a) H; and

(b) C_{1-6} alkyl optionally substituted with 1-3 $\mathbf{R}^{c}$;

each $\mathbf{R}^{Yb}$ is independently selected from the group consisting of: F and C_{1-3} alkyl optionally substituted with 1-3 F.

19. The compound of claim 18, wherein the compound is a compound of Formula (**I-b-4**):



Formula (**I-b-4**)

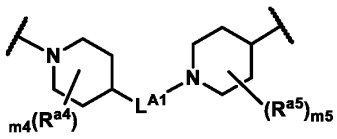
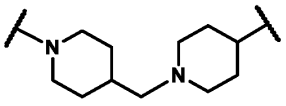
or a pharmaceutically acceptable salt thereof.

20. The compound of claim 18 or 19, wherein $\mathbf{R}^{2b}$ is H.

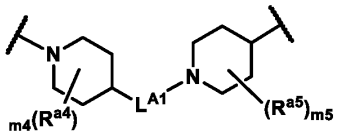
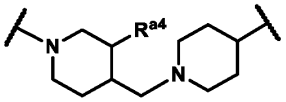
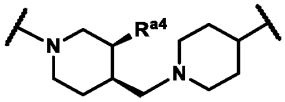
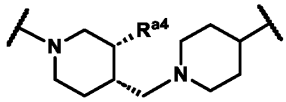
21. The compound of claim 18 or 19, wherein $\mathbf{R}^{2b}$ is F.

22. The compound of any one of claims 18-21, wherein $\mathbf{L}^{A1}$ is CH_2.

23. The compound of any one of claims 18-22, wherein **m4** is 0; and **m5** is 0.

24. The compound of claim 23, wherein the  moiety is .

25. The compound of any one of claims 18-22, wherein **m4** is 1 or 2; and **m5** is 0.

26. The compound of claim 25, wherein the  moiety is  (e.g.,  or ).

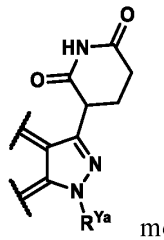
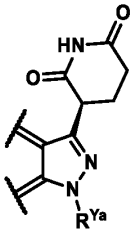
27. The compound of any one of claims 18-22 or 25-26, wherein each $\mathbf{R^{a4}}$ is independently selected from the group consisting of: F and C_{1-3} alkyl optionally substituted with 1-3 F.

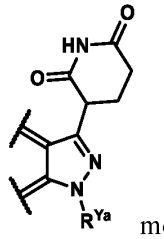
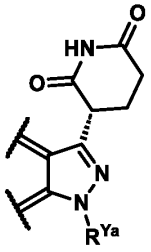
28. The compound of claim 27, wherein each $\mathbf{R^{a4}}$ is independently F or methyl.

29. The compound of any one of claims 18-28, wherein $\mathbf{R^{Ya}}$ is C_{1-3} alkyl optionally substituted with 1-3 F (e.g., $\mathbf{R^{Ya}}$ is C_{1-3} alkyl (e.g., methyl)).

30. The compound of any one of claims 1-29, wherein $\mathbf{R^6}$ is Cl.

31. The compound of any one of claims 1-30, wherein $-(\mathbf{X^3})_{m3}\text{-}\mathbf{R^1}$ is methyl.

32. The compound of any one of claims 1-31, wherein the  moiety is .

33. The compound of any one of claims 1-31, wherein the  moiety is .

34. The compound of claim 1, wherein the compound of Formula (**I-b**) is other than a compound selected from the group consisting of Compound Nos. **R412**, **R412a**, **R472**, **R472a**, **R474**, **R474a**, **R504**, **R504a**, **R507**, **R507a**, **R522**, **R522a**, **R522b**, **R525**, **R525a**, **R525b**, **R525c**, **R525d**, **R526**, **R526a**, **R531**, **R531a**, **R533**, **R533a**, **R538**, **R538a**, **R538b**, **R538c**, **R558**, and **R558a**, as depicted in **Table R1**, or a pharmaceutically acceptable salt thereof.

35. The compound of claim 1, wherein the compound of Formula (**I-b**) is selected from the group consisting of Compound Nos. **105**, **105a**, **105b**, **106**, **106a**, **109**, **109a**, **109b**, **110**, **110a**, **110b**, **110c**, **110d**, **110e**, **110f**, **111**, **111a**, **111b**, **112**, **112a**, **112b**, **113**, **113a**, **113b**, **117**, **117a**, **117b**, **118**, **118a**, **118b**, **120**, **120a**, **120b**, **121**, **121a**, **121b**, **121c**, **121d**, **121e**, **123**,

123a, **123b**, **124**, **124a**, **124b**, **125**, **125a**, **127**, **127a**, **127b**, **127c**, **127d**, **128**, **128a**, **129**, **129a**, **129b**, **130**, **130a**, **130b**, **130c**, **130d**, **130e**, **132**, **132a**, **133**, **133a**, **133b**, **135**, **135a**, **135b**, **136**, **136a**, **139**, **139a**, **139b**, **140**, **140a**, **140b**, **145**, **145a**, **151**, **151a**, **151b**, **152**, **152a**, **153a**, **154**, **154a**, **157**, **157a**, **158**, **158a**, **160**, **160a**, **160b**, **162**, **162a**, **163**, **163a**, **169**, **169a**, **169b**, **171**, **171a**, **172**, **172a**, **173**, **173a**, **175**, **175a**, **175b**, **178**, **178a**, **186**, **186a**, **191**, **191a**, **194**, **194a**, **199**, **199a**, **199b**, **199c**, **199d**, **201**, **201a**, **202**, **202a**, **202b**, **207**, **207a**, **209**, **209a**, **209b**, **210**, **210a**, **210b**, **213**, **213a**, **214**, **214a**, **216**, **216a**, **219**, **219a**, **219b**, **220**, **220a**, **220b**, **231**, **231a**, **231b**, **232**, **232a**, **232b**, **233**, **233a**, **233b**, **234**, **234a**, **234b**, **238**, **238a**, **238b**, **238c**, **238d**, **239**, **239a**, and **239b**, as depicted in **Table C1**, or a pharmaceutically acceptable salt thereof.

36. A pharmaceutical composition comprising a compound of any one of claims 1-35, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

37. A method for treating a cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-35, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 36.

38. The method of claim 37, wherein the cancer is a hematological cancer, breast cancer, gastrointestinal cancer, brain cancer, lung cancer, or a combination thereof.

39. The method of claim 38, wherein the cancer is a hematological cancer (e.g., lymphoma (e.g., Hodgkin lymphoma (e.g., nodular lymphocyte predominant Hodgkin lymphoma (NLPHL)), non-Hodgkin lymphoma (e.g., B cell lymphoid proliferations and lymphomas (e.g., mature B cell neoplasms (e.g., Burkitt lymphoma (BL), large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), T-cell/histiocyte-rich large B-cell lymphoma, diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary large B cell lymphoma of immune-privileged sites (primary LBCL of immune-privileged sites), primary mediastinal large B cell lymphoma (primary mediastinal LBCL), or high grade B-cell lymphoma NOS), follicular lymphoma (FL), or transformations of indolent B cell lymphomas)), T-cell and NK-cell lymphoid proliferations and lymphomas (e.g., mature T-cell and NK-cell neoplasms (e.g., mature T-cell and NK-cell leukemias (e.g., adult T-cell leukemia/lymphoma), primary cutaneous T-cell lymphoid proliferations and

lymphomas (cutaneous T-cell lymphoma (CTCL)) (e.g., primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder, mycosis fungoides, Sezary syndrome, primary cutaneous CD30-positive T-cell lymphoproliferative disorder: lymphomatoid papulosis, primary cutaneous CD30-positive T-cell lymphoproliferative disorder: primary cutaneous anaplastic large cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, primary cutaneous gamma-delta T-cell lymphoma, or primary cutaneous peripheral T-cell lymphoma NOS), peripheral T-cell lymphoma (PTCL) (e.g., anaplastic large cell lymphoma (ALCL) (e.g., ALK-positive anaplastic large cell lymphoma, or ALK-negative anaplastic large cell lymphoma), nodal T follicular helper cell lymphoma (e.g., nodal T follicular helper cell lymphoma angioimmunoblastic type (also known as angioimmunoblastic T-cell lymphoma (AITL) or follicular helper T-cell lymphoma, angioimmunoblastic type), nodal T follicular helper cell lymphoma follicular type (also known as follicular helper T-cell lymphoma, follicular type), or nodal T follicular helper cell lymphoma NOS (also known as follicular helper T-cell lymphoma, NOS)), or other peripheral T-cell lymphomas (e.g., peripheral T-cell lymphoma NOS))))))).

40. The method of claim 39, wherein the hematological cancer is selected from the group consisting of lymphomas (e.g., non-Hodgkin lymphoma (e.g., B cell lymphoid proliferations and lymphomas (e.g., mature B cell neoplasms (e.g., large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), or primary mediastinal large B cell lymphoma (primary mediastinal LBCL)), follicular lymphoma (FL), or transformations of indolent B cell lymphomas)), T-cell and NK-cell lymphoid proliferations and lymphomas (e.g., mature T-cell and NK-cell neoplasms (e.g., primary cutaneous T-cell lymphoid proliferations and lymphomas (cutaneous T-cell lymphoma (CTCL)) (e.g., primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder, mycosis fungoides, or Sezary syndrome), or peripheral T-cell lymphoma (PTCL) (e.g., nodal T follicular helper cell lymphoma (e.g., nodal T follicular helper cell lymphoma angioimmunoblastic type (also known as angioimmunoblastic T-cell lymphoma (AITL) or follicular helper T-cell lymphoma, angioimmunoblastic type), nodal T follicular helper cell lymphoma follicular type (also known as follicular helper T-cell lymphoma, follicular type), or nodal T follicular helper cell lymphoma NOS (also known as follicular helper T-cell lymphoma, NOS)), or other peripheral T-cell lymphomas (e.g., peripheral T-cell lymphoma NOS))))))).

41. The method of claim 39, wherein the hematological cancer is FL or a large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary LBCL of immune-privileged sites, primary mediastinal LBCL, or HBGCL-NOS).

42. The method of claim 39, wherein the hematological cancer is a large B cell lymphoma (e.g., diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), diffuse large B-cell lymphoma/high grade B cell lymphoma (HGBCL) (e.g., HGBCL with MYC and/or BCL2 rearrangements (HGBCL-MYC/BCL-2)), primary LBCL of immune-privileged sites, primary mediastinal LBCL, or HBGCL-NOS).

43. The method of claim 39, wherein the hematological cancer is FL.

44. The method of claim 39, wherein the hematological cancer is DLBCL.

45. The method of claim 39, wherein the hematological cancer is a peripheral T-cell lymphoma (PTCL) (e.g., anaplastic large cell lymphoma (ALCL) (e.g., ALK-positive anaplastic large cell lymphoma, or ALK-negative anaplastic large cell lymphoma), nodal T follicular helper cell lymphoma (e.g., nodal T follicular helper cell lymphoma angioimmunoblastic type (also known as angioimmunoblastic T-cell lymphoma (AITL) or follicular helper T-cell lymphoma, angioimmunoblastic type), nodal T follicular helper cell lymphoma follicular type (also known as follicular helper T-cell lymphoma, follicular type), or nodal T follicular helper cell lymphoma NOS (also known as follicular helper T-cell lymphoma, NOS))).

46. The method of any one of claims 37-45, wherein the cancer is positive for BCL6 expression (e.g., as determined by an IHC test).

47. The method of any one of claims 37-46, wherein the therapeutically effective amount of a compound of any one of claims 1-35, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 36, is administered to the subject as a monotherapy.

48. The method of any one of claims 37-46, comprising administering an additional therapy or therapeutic agent to the subject.

49. The method of claim 48, wherein the additional therapy or therapeutic agent is a PI3K inhibitor, an Abl inhibitor (e.g., a BCR-Abl inhibitor), a BTK inhibitor, a JAK inhibitor, a BRaf inhibitor, a MEK inhibitor, a BCL-2 inhibitor, a Bcl-X_L inhibitor, an XPO1 inhibitor, an inhibitor of the polycomb repressive complex 2 (PRC2), an immunomodulatory imide drug, anti-CD19 therapy, anti-CD20 therapy, anti-CD3 therapy, chemotherapy, or a combination thereof.

50. The method of claim 49, wherein the additional therapy or therapeutic agent is an inhibitor of the PRC2 (e.g., an EZH1/2 or EZH2 inhibitor).

51. A method for treating or preventing an autoimmune condition in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-35, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 36.

52. A method for treating a lymphoproliferative disorder in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-35, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 36.