

3-[3-AMINO-6-(2-HYDROXYPHENYL)PYRIDAZIN-4-YL]-3,8-DIAZABICYCLO[3.2.1]OCTANE
DERIVATIVES AS SMARCA2 DEGRADING PROTACS FOR THE TREATMENT OF CANCER

BACKGROUND

Field

[0001] The present disclosure provides Proteolysis Targeting Chimera (PROTAC) compounds and the use of such PROTAC compounds for the treatment of diseases or disorders dependent on SMARCA2 in mammals. Degradation of SMARCA2 may provide, for example, an anti-tumor effect. The present disclosure thus provides the use of SMARCA2 degraders and pharmaceutical compositions comprising SMARCA2 degraders for the treatment of cancer. It also provides intermediate compounds that may be useful in the preparation of such PROTACs.

Background

[0002] Traditional "small molecule" drugs reversibly (or sometimes irreversibly) bind to a target protein as a means of modulating a given biological activity. In contrast, PROTACs bind to their target proteins reversibly, but then bring about the target protein's degradation. Having achieved this effect, the PROTAC is in theory able to repeat this process with another target protein. Accordingly, unlike traditional small molecule inhibitors, the PROTAC-driven degradation mechanism can in theory operate in a sub-stoichiometric manner - meaning that more modest exposures of a PROTAC compound could still achieve a desired level of efficacy *in vivo*. In practice, this means that the degradation power (DC_{50} and D_{max}) of a PROTAC may have an improved effect over that reflected by its binding affinity.

[0003] PROTAC molecules are described as having three parts - (1) a part that is capable of binding to the protein to be degraded, (2) a second part that is capable of binding to an E3 ubiquitin ligase, and (3) a linker that connects parts (1) and (2) together. In use, the PROTAC binds to both the target protein and E3 ubiquitin ligase simultaneously to form a ternary complex. The E3 ligase then recruits an E2 conjugating enzyme to the ternary complex, which ubiquitinates the target protein. This has the effect of labelling the target protein for degradation by the cell's proteasome machinery. A PROTAC can then dissociate from the target protein and initiate another cycle of this process in a catalytic manner. Meanwhile, the ubiquitinated target proteins are recognized by the cell's proteasome machinery and are then degraded by it. This PROTAC-mediated approach may be valuable as a method of treating certain diseases, including cancer.

[0004] SMARCA4 is a frequently mutated in several tumor types - including lung, liver, colon, skin, bladder, esophageal, gastric, brain, endometrial, cervical and ovarian cancers. Furthermore, it has been established that SMARCA2 is essential for growth of tumors harboring such SMARCA4 mutations. Accordingly, selective suppression of SMARCA2 has been proposed as a therapeutic strategy against cancers that may include SMARCA4 mutations. Accordingly, selective suppression of SMARCA2 may be useful against a number of cancer types, including lung, liver, colon, skin, bladder, esophageal, gastric, brain, endometrial, cervical and ovarian cancers.

[0005] WO2019/207538 discloses certain PROTAC compounds described as "SMARCA 2/4 degraders" and WO2020251969 discloses PROTAC compounds which target one or more of SMARCA2, SMARCA4 and PB1. WO2019/195201 also discloses 'bifunctional' compounds described as modulators of SMARCA2. WO2019/213005 relates to compounds that are said to degrade PBRM1. WO2018/144649 and WO2021/053495 also disclose certain PROTAC molecules. WO2021/053555 discloses glue degrader compounds which bind to the E3 ubiquitin ligase, cereblon.

[0006] As part of developing a PROTAC against cancer, there is a need to develop further PROTAC compounds with a combination of beneficial/improved properties that make them more suitable for use as a therapeutic drug for human use. Properties of interest during pharmaceutical discovery and development may relate to selectivity profile, absorption/bioavailability, distribution, metabolism, elimination, toxicity and side-effect profile, stability, manufacturability, and so on.

BRIEF SUMMARY

[0007] In one aspect, the present disclosure provides PROTAC compounds represented by any one of Formulae (A) and (I)-(V), below, and the pharmaceutically acceptable salts thereof. In another aspect, the present disclosure provides any one or more of the PROTAC compounds of Compound List 1, below, and the pharmaceutically acceptable salts thereof. In another aspect, the present disclosure provides any one or more of the PROTAC compounds of Compound List 2, below, and the pharmaceutically acceptable salts thereof. In another aspect, the present disclosure provides any one or more of the PROTAC compounds of Compound List 3, below, and the pharmaceutically acceptable salts thereof. In another aspect, the present disclosure provides any one or more of the PROTAC compounds of Compound List 4, below, and the pharmaceutically acceptable salts thereof. Compounds having any one of Formulae (A) and (I)-(V), and the pharmaceutically acceptable salts thereof, and the compounds of Compound List 1, Compound List 2, Compound List 3, and/or Compound List 4, and the pharmaceutically acceptable salts thereof, are collectively referred to as "Compounds of the Disclosure" or individually as a "Compound of the Disclosure." Compounds of the Disclosure exhibit protein degradation activity against SMARCA2. Compounds of the Disclosure also may have a beneficial degree of selectivity to minimize certain undesirable off-target degradation activities. As such, Compounds of the Disclosure may be useful in the treatment of cancer.

[0008] Compounds of the Disclosure also may have a surprisingly beneficial combination of properties of relevance in the context of pharmaceutical discovery and development. Structural features found in all three regions of a PROTAC have the potential to operate (collectively or in some cases separately) towards delivering a beneficial combination and/or balance of such additional beneficial properties. Avoidance of off-target activity in pharmaceutical development is often important to avoid or reduce unwanted toxicities, side-effects or other problems with tolerability when used in patients.

[0009] As well as being degraders of SMARCA2, Compounds of the Disclosure have a surprising and beneficial combination of properties relating, for example, to chemical and metabolic stability, e.g. in human microsomes and to hydrolysis at pH 7.4, and selectivity against SALL4 and/or Ikaros (IKZF1) – which is expected to provide an improved safety profile for use *in vivo*. Without wishing to be bound by any particular theory, it is believed that degradation of SALL4 and Ikaros (IKZF1) amongst others may risk serious unwanted effects in humans, for example, developmental toxicities or bone marrow toxicities.

[0010] Also, in this regard, it has been found that molecules that degrade SMARCA2 can often also degrade SMARCA4, which is regarded as an undesirable off-target activity. Compounds of the Disclosure may show a beneficial selectivity profile by achieving a potent degree of degradation against SMARCA2 while having a margin of selectivity, i.e., relatively lower degradation, against SMARCA4. In a similar manner in the development of a SMARCA2 PROTAC for use in cancer, it is also regarded as beneficial to have a potent degree of degradation against SMARCA2 while having a good margin of selectivity, i.e., relatively lower degradation, against PBRM1. Compounds of the Disclosure may show a beneficial selectivity profile between SMARCA2 and PBRM1. Thus, in combination, Compounds of the Disclosure may show high potency against SMARCA2 while simultaneously achieving a beneficial selectivity profile with respect to SALL4 and/or Ikaros (IKZF1), and in some cases a surprisingly beneficial margin of selectivity against SMARCA4 and/or PBRM1.

[0011] In another aspect, the present disclosure provides pharmaceutical compositions comprising a Compound of the Disclosure and one or more pharmaceutically acceptable excipients.

[0012] In another aspect, the present disclosure provides methods of degrading SMARCA2 protein in a human, comprising administering to a human in need thereof an effective amount of a Compound of the Disclosure.

[0013] In another aspect, the present disclosure provides methods of reducing SMARCA2 protein in a human, comprising administering to a human in need thereof an effective amount of a Compound of the Disclosure.

[0014] In another aspect, the present disclosure provides methods of treating cancer in a human, comprising administering to a human in need thereof an effective amount of a Compound of the Disclosure.

[0015] In another aspect, the present disclosure provides a Compound of the Disclosure, or pharmaceutical composition thereof, for use in degrading SMARCA2 protein in a human.

[0016] In another aspect, the present disclosure provides a Compound of the Disclosure, or pharmaceutical composition thereof, for use in reducing SMARCA2 protein in a human.

[0017] In another aspect, the present disclosure provides a Compound of the Disclosure, or pharmaceutical composition thereof, for use in treating cancer in a human.

[0018] In another aspect, the present disclosure provides use of a Compound of the Disclosure, or pharmaceutical composition thereof in the manufacture of a medicament for degrading SMARCA2 protein in a human.

[0019] In another aspect, the present disclosure provides use of a Compound of the Disclosure, or pharmaceutical composition thereof in the manufacture of a medicament for reducing SMARCA2 protein in a human.

[0020] In another aspect, the present disclosure provides use of a Compound of the Disclosure, or pharmaceutical composition thereof in the manufacture of a medicament for treating cancer in a human.

[0021] In another aspect, the present disclosure provides methods of preparing Compounds of the Disclosure.

[0022] In another aspect, the present disclosure provides intermediates used to prepare Compounds of the Disclosure.

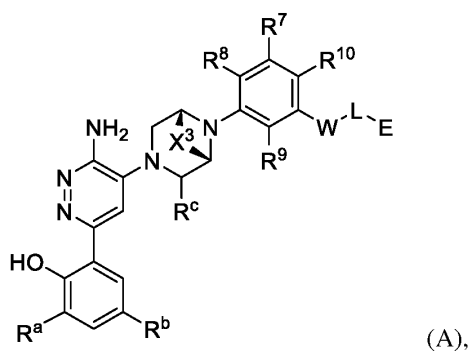
[0023] Additional embodiments and advantages of the disclosure will be set forth, in part, in the description that follows, and will flow from the description, or can be learned by practice of the disclosure. The embodiments and advantages of the disclosure will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing summary and the following detailed description are exemplary and explanatory only and are not restrictive of the invention as claimed.

DETAILED DESCRIPTION

I. Compounds of the Disclosure

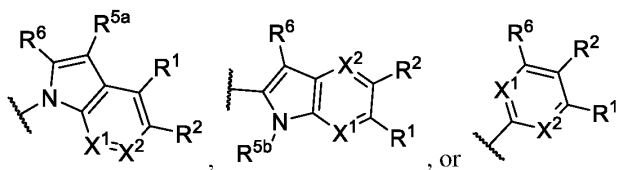
[0024] Many embodiments of this disclosure are detailed throughout the specification.

[0025] In one embodiment, Compounds of the Disclosure are compounds of Formula (A), or pharmaceutically acceptable salt thereof:

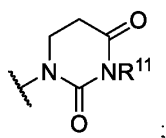


wherein:

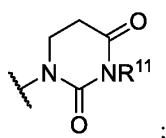
[0026] E is:



[0027] R^1 is hydrogen, halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or

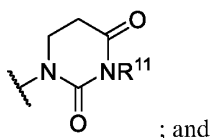


[0028] R^2 is hydrogen, halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or

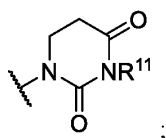


[0029] with the provisos:

[0030] (i) when R^1 is hydrogen, halogen, (C₁-C₆)alkyl, or (C₁-C₆)alkoxy, then R^2 is:



[0031] (ii) when R^2 is hydrogen, halogen, (C₁-C₆)alkyl, or (C₁-C₆)alkoxy, then R^1 is



[0032] R^{11} is hydrogen or -(C₁-C₆)alkyl-O-P(=O)-(OH)₂;

[0033] X^1 is CR³ or N;

[0034] R^3 is hydrogen, halogen, or (C₁-C₆)alkyl;

[0035] X^2 is CR⁴ or N;

[0036] R^4 is hydrogen, halogen, or (C₁-C₆)alkyl;

[0037] R^{5a} is hydrogen, halogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, 4- to 6-membered heterocycloalkyl, cyano, aryl, or 5- or 6-membered heteroaryl,

[0038] wherein (C₁-C₆)alkyl is optionally substituted with one, two, or three substituents independently selected from halogen or cyano; and 4- to 6-membered heterocycloalkyl, aryl, or 5- or 6-membered heteroaryl is optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or (C₁-C₆)alkyl;

[0039] R^{5b} is hydrogen, (C₁-C₆)alkyl, or (C₃-C₆)cycloalkyl;

[0040] R^6 is hydrogen, (C₁-C₆)alkyl, or cyano;

[0041] X^3 is -CH₂CH₂- or -CH₂-O-CH₂-;

[0042] or X^3 is absent;

[0043] L is G¹-G²-G³-G⁴-, wherein G¹ is attached to W;

[0044] G^1 is (C₁-C₆)alkylenyl; (C₃-C₆)cycloalkylenyl; -O-CH₂-CH₂-; 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, cyano, or hydroxyl; or 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or cyano;

[0045] G^2 is (C₁-C₆)alkylenyl, -C(=O)-, 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three fluoro, or a direct bond;

[0046] G^3 is -C(=O)-; -C(=O)-CH₂CH₂-; (C₁-C₆)alkylenyl; tetrahydronaphthalenyl; 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or cyano; 7- to 11-membered heterocycloalkyl-C(=O)-, or 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or cyano;

[0047] G^4 is (C₁-C₆)alkylenyl, (C₃-C₆)cycloalkylenyl; 4- to 6-membered heterocycloalkylenyl; or a direct bond;

[0048] W is -C≡C- or a direct bond;

[0049] R^7 is hydrogen; halogen; (C₁-C₆)alkyl optionally substituted with one, two, or three halogen; cyano; or (C₃-C₆)cycloalkyl;

[0050] R^8 is hydrogen; halogen; (C₁-C₆)alkyl optionally substituted with one, two, or three halogen; cyano; or (C₃-C₆)cycloalkyl;

[0051] R^9 is hydrogen; halogen; (C₁-C₆)alkyl optionally substituted with one, two, or three halogen; cyano; or (C₃-C₆)cycloalkyl;

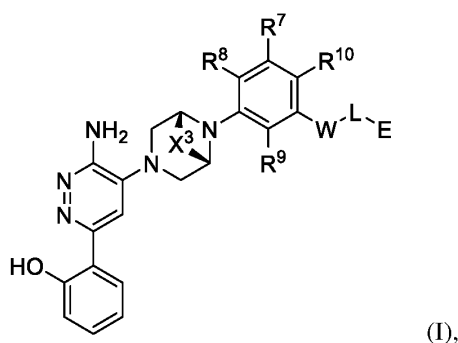
[0052] R^{10} is hydrogen; halogen; (C₁-C₆)alkyl optionally substituted with one, two, or three halogen; cyano; or (C₃-C₆)cycloalkyl;

[0053] R^a is hydrogen or halogen;

[0054] R^b is hydrogen or halogen; and

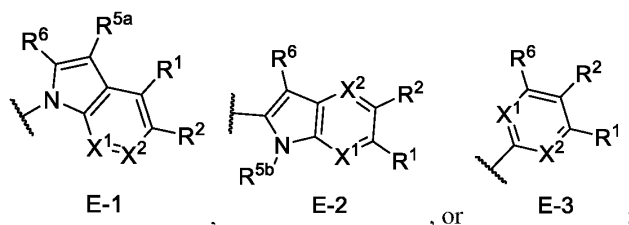
[0055] R^c is hydrogen or methyl.

[0056] In another embodiment, Compounds of the Disclosure are compounds having Formula (I), or a pharmaceutically acceptable salt thereof:

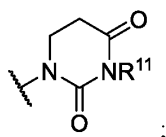


wherein:

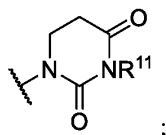
[0057] E is:



[0058] R¹ is hydrogen, halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or

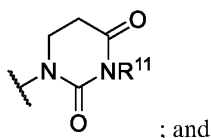


[0059] R² is hydrogen, halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or

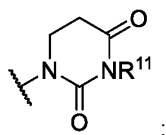


with the provisos:

[0060] (i) when R¹ is hydrogen, halogen, (C₁-C₆)alkyl, or (C₁-C₆)alkoxy, then R² is:



[0061] (ii) when R² is hydrogen, halogen, (C₁-C₆)alkyl, or (C₁-C₆)alkoxy, then R¹ is



[0062] R¹¹ is hydrogen or -(C₁-C₆)alkyl-O-P(=O)-(OH)₂;

[0063] X¹ is CR³ or N;

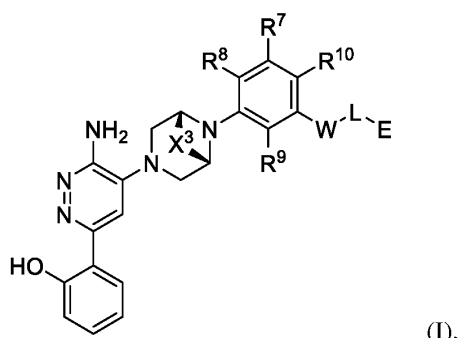
[0064] R³ is hydrogen, halogen, or (C₁-C₆)alkyl;

[0065] X² is CR⁴ or N;

[0066] R⁴ is hydrogen, halogen, or (C₁-C₆)alkyl;

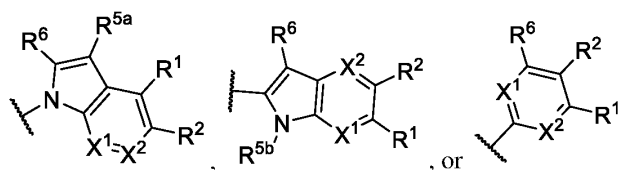
[0067] R^{5a} is hydrogen, halogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, 4- to 6-membered heterocycloalkyl, cyano, aryl, or 5- or 6-membered heteroaryl, wherein (C₁-C₆)alkyl is optionally substituted with one, two, or three substituents independently selected from halogen or cyano; and 4- to 6-membered heterocycloalkyl, aryl, or 5- or 6-membered heteroaryl is optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or (C₁-C₆)alkyl;

- [0068] R^{5b} is hydrogen, (C₁-C₆)alkyl, or (C₃-C₆)cycloalkyl;
- [0069] R^6 is hydrogen, (C₁-C₆)alkyl, or cyano;
- [0070] X^3 is -CH₂CH₂- or -CH₂-O-CH₂-; or
- [0071] X^3 is absent;
- [0072] L is -G¹-G²-G³-G⁴-, wherein G¹ is attached to W;
- [0073] G¹ is (C₁-C₆)alkylenyl; 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or cyano; or 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or cyano;
- [0074] G² is (C₁-C₆)alkylenyl or a direct bond;
- [0075] G³ is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C₁-C₆)alkyl, or (C₁-C₆)alkoxy; cyano; or 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or cyano;
- [0076] G⁴ is (C₁-C₆)alkylenyl or a direct bond;
- [0077] W is -C≡C- or a direct bond;
- [0078] R^7 is hydrogen, halogen, (C₁-C₆)alkyl optionally substituted with one, two, or three halogen, cyano, or (C₃-C₆)cycloalkyl;
- [0079] R^8 is hydrogen, halogen, (C₁-C₆)alkyl optionally substituted with one, two, or three halogen, cyano, or (C₃-C₆)cycloalkyl;
- [0080] R^9 is hydrogen, halogen, (C₁-C₆)alkyl optionally substituted with one, two, or three halogen, cyano, or (C₃-C₆)cycloalkyl; and
- [0081] R^{10} is hydrogen, halogen, (C₁-C₆)alkyl optionally substituted with one, two, or three halogen, cyano, or (C₃-C₆)cycloalkyl.
- [0082] In another embodiment, Compounds of the Disclosure are compounds having Formula (I), or pharmaceutically acceptable salt thereof:

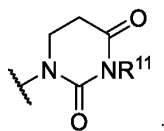


wherein:

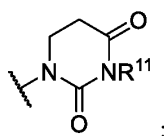
- [0083] E is:



[0084] R^1 is hydrogen, halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or

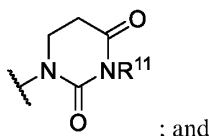


[0085] R^2 is hydrogen, halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or



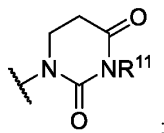
with the provisos:

[0086] (i) when R^1 is hydrogen, halogen, (C_1-C_6) alkyl, or (C_1-C_6) alkoxy, then R^2 is:



; and

[0087] (ii) when R^2 is hydrogen, halogen, (C_1-C_6) alkyl, or (C_1-C_6) alkoxy, then R^1 is:



[0088] R^{11} is hydrogen or $-(C_1-C_6)alkyl-O-P(=O)-(OH)_2$;

[0089] X^1 is CR^3 or N;

[0090] R^3 is hydrogen, halogen, or (C_1-C_6) alkyl;

[0091] X^2 is CR^4 or N;

[0092] R^4 is hydrogen, halogen, or (C_1-C_6) alkyl;

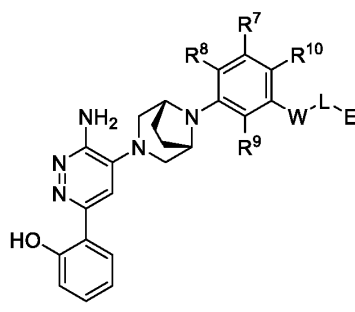
[0093] R^{5a} is hydrogen, halogen, (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, 4- to 6-membered heterocycloalkyl, cyano, aryl, or 5- or 6-membered heteroaryl, wherein (C_1-C_6) alkyl is optionally substituted with one, two, or three substituents independently selected from halogen or cyano; and 4- to 6-membered heterocycloalkyl, aryl, or 5- or 6-membered heteroaryl is optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or (C_1-C_6) alkyl;

[0094] R^{5b} is hydrogen, (C_1-C_6) alkyl, or (C_3-C_6) cycloalkyl;

[0095] R^6 is hydrogen, (C_1-C_6) alkyl, or cyano;

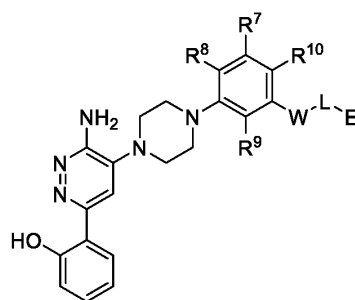
[0096] X^3 is $-CH_2CH_2-$ or $-CH_2-O-CH_2-$; or

- [0097] X^3 is absent;
- [0098] L is $-G^1-G^2-G^3-G^4-$, wherein G^1 is attached to W;
- [0099] G^1 is (C_1-C_6) alkylenyl; 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano; or 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano;
- [0100] G^2 is (C_1-C_6) alkylenyl or a direct bond;
- [0101] G^3 is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6) alkyl, or (C_1-C_6) alkoxy; cyano; 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano; or 5- to 10-membered heteroarylenyl;
- [0102] G^4 is (C_1-C_6) alkylenyl, (C_3-C_6) cycloalkylenyl, or a direct bond;
- [0103] W is $-C\equiv C-$ or a direct bond;
- [0104] R^7 is hydrogen, halogen, (C_1-C_6) alkyl optionally substituted with one, two, or three halogen, cyano, or (C_3-C_6) cycloalkyl;
- [0105] R^8 is hydrogen, halogen, (C_1-C_6) alkyl optionally substituted with one, two, or three halogen, cyano, or (C_3-C_6) cycloalkyl;
- [0106] R^9 is hydrogen, halogen, (C_1-C_6) alkyl optionally substituted with one, two, or three halogen, cyano, or (C_3-C_6) cycloalkyl; and
- [0107] R^{10} is hydrogen, halogen, (C_1-C_6) alkyl optionally substituted with one, two, or three halogen, cyano, or (C_3-C_6) cycloalkyl.
- [0108] In another embodiment, Compounds of the Disclosure are compounds having Formula (II), or a pharmaceutically acceptable salt thereof:



wherein R^7 , R^8 , R^9 , R^{10} , W, L, and E are as defined in connection with Formula (I).

- [0109] In another embodiment, Compounds of the Disclosure are compounds having Formula (III), or a pharmaceutically acceptable salt thereof:



(III),

wherein R^7 , R^8 , R^9 , R^{10} , W, L, and E are as defined in connection with Formula (I).

[0110] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein E is E-1.

[0111] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein R^{5a} is hydrogen.

[0112] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein R^{5a} is (C₁-C₆)alkyl optionally substituted with one, two, or three substituents independently selected from halogen or cyano.

[0113] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein R^{5a} is methyl.

[0114] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein R^{5a} is (C₃-C₆)cycloalkyl.

[0115] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein R^{5a} is cyclopropyl.

[0116] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein R^{5a} is 4- to 6-membered heterocycloalkyl optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or (C₁-C₆)alkyl.

[0117] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein R^{5a} is cyano.

[0118] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein R^{5a} is aryl optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or (C₁-C₆)alkyl.

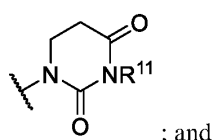
[0119] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein R^{5a} is 5- or 6-membered heteroaryl optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or (C₁-C₆)alkyl.

[0120] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein E is E-2.

[0121] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein E is E-3.

[0122] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein:

[0123] R^1 is:



[0124] R^2 is hydrogen, halogen, (C₁-C₆)alkyl, or (C₁-C₆)alkoxy.

[0125] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein R^2 is hydrogen, halogen, or (C₁-C₆)alkyl.

[0126] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein R^2 is hydrogen, fluoro, or methyl.

[0127] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein R^{11} is hydrogen.

[0128] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein X^1 is CR³.

[0129] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein R^3 is hydrogen.

[0130] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein R^3 is halogen.

[0131] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein R^3 is (C₁-C₆)alkyl.

[0132] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein X^1 is N.

[0133] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein X^2 is CR⁴.

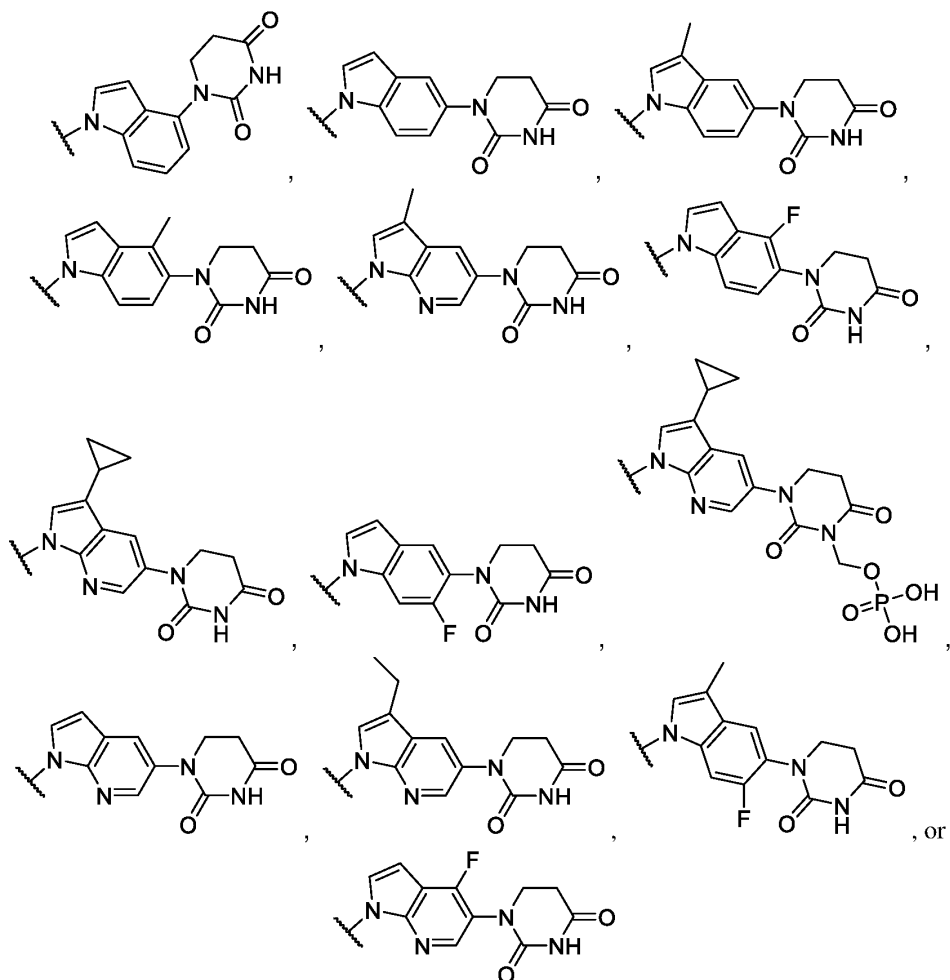
[0134] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein R^4 is hydrogen.

[0135] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein R^4 is halogen.

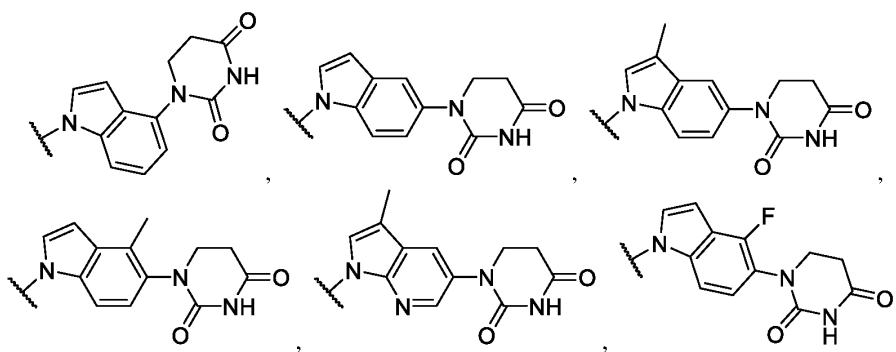
[0136] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein R^4 is (C₁-C₆)alkyl.

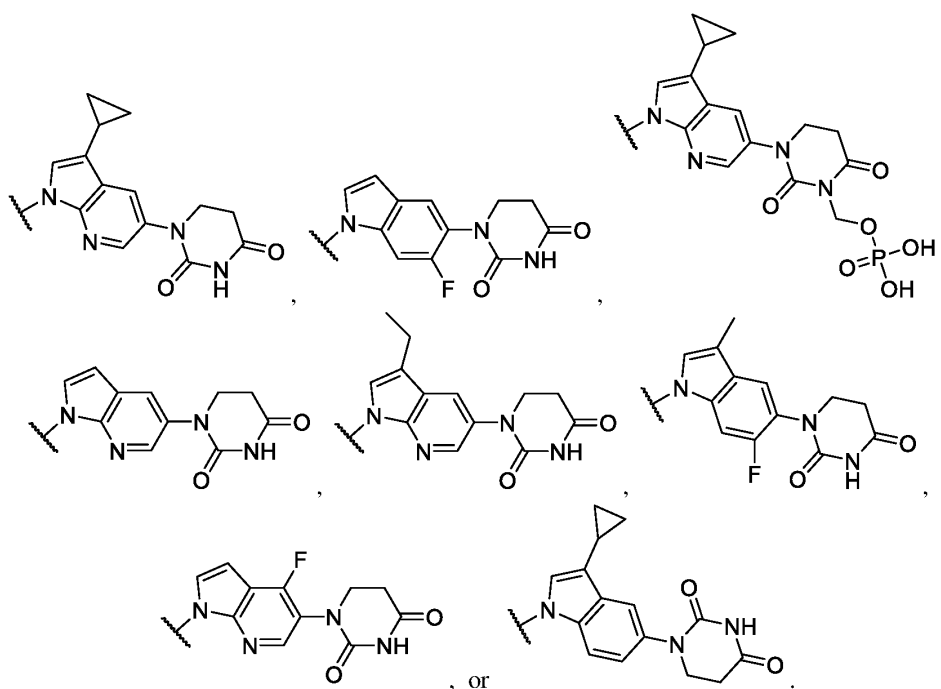
[0137] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein X^2 is N.

[0138] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein E-1 is:

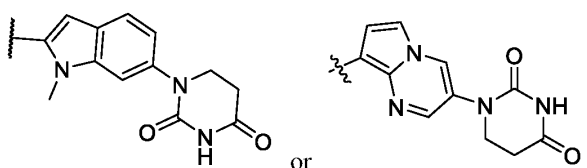


[0139] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), wherein E-1 is:

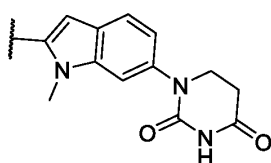




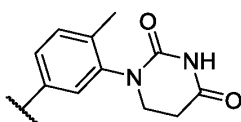
[0140] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein E is:



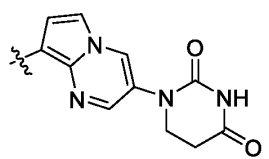
[0141] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein E-2 is:



[0142] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein E-3 is:



[0143] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein E is:

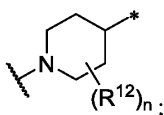


[0144] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein G^1 is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano.

[0145] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein G^1 is (C_3-C_6) cycloalkylenyl; or 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, cyano, or hydroxyl.

[0146] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein:

[0147] G^1 is:



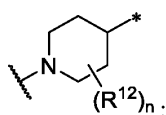
[0148] each R^{12} is independently halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano;

[0149] n is 0, 1, 2, or 3; and

[0150] the bond marked with an "*" is attached to G^2 .

[0151] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein:

[0152] G^1 is:



[0153] each R^{12} is independently halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, cyano, or hydroxyl;

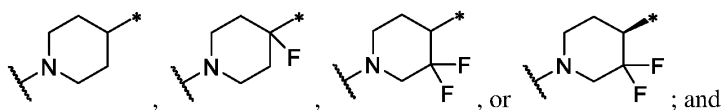
[0154] n is 0, 1, 2, or 3; and

[0155] the bond marked with an "*" is attached to G^2 .

[0156] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein each R^{12} is independently fluoro, methyl, methoxy, cyano, or $-CHF_2$; and n is 0, 1, or 2.

[0157] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein:

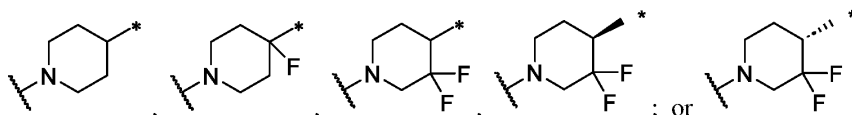
[0158] G^1 is:



[0159] the bond marked with an "*" is attached to G².

[0160] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein:

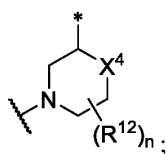
[00100] G¹ is:



[0161] and bond marked with an "*" is attached to G².

[0162] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein:

[0163] G¹ is:



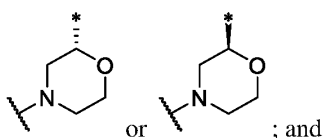
[0164] X⁴ is -O-;

[0165] each R¹² is independently halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or cyano; and

[0166] the bond marked with an "*" is attached to G².

[0167] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein:

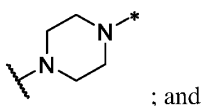
[0168] G¹ is:



[0169] the bond marked with an "*" is attached to G².

[0170] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein:

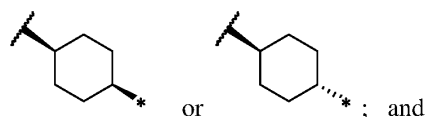
[0171] G¹ is:



[0172] the bond marked with an "*" is attached to G²

[0173] In another embodiment, Compounds of the Disclosure are compounds having Formula (A), or a pharmaceutically acceptable salt thereof, wherein G^1 is cyclohexylenyl.

[0174] In another embodiment, Compounds of the Disclosure are compounds having Formula (A), or a pharmaceutically acceptable salt thereof, wherein:

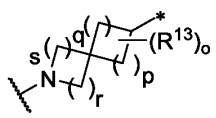


[0175] the bond marked with an "*" is attached to G^2 .

[0176] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein G^1 is 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano.

[0177] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein:

[0178] G^1 is:



[0179] each R^{13} is independently selected from halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano;

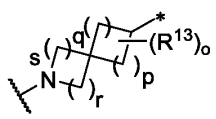
[0180] o is 0, 1, 2, or 3;

[0181] p, q, r, and s are independently 1, 2, or 3; and

[0182] the bond marked with an "*" is attached to G^2 .

[0183] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein:

[0184] G^1 is:



[0185] each R^{13} is independently selected from halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano;

[0186] o is 0, 1, 2, or 3;

[0187] p, q, r, and s are independently 1 or 2;

[0188] the bond marked with an "*" is attached to G^2 .

[0189] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein:

[0190] p and q are 1;

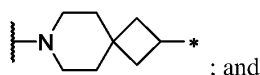
[0191] r is 1 or 2;

[0192] s is 1 or 2; and

[0193] R¹³ is halogen.

[0194] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein R¹³ is fluoro and o is 0, 1, or 2.

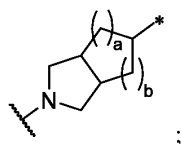
[0195] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein G¹ is:



[0196] the bond marked with an "*" is attached to G².

[0197] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein:

[0198] G¹ is:

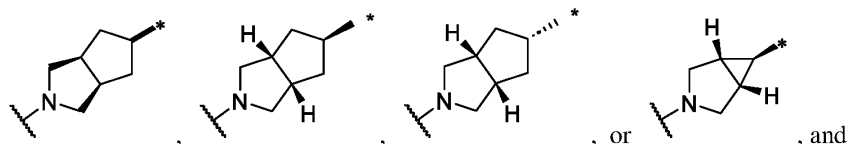


[0199] a is 0 or 1;

[0200] b is 0 or 1; and

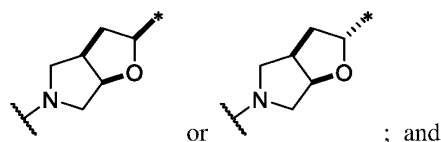
[0201] the bond marked with an "*" is attached to G².

[0202] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein G¹ is:



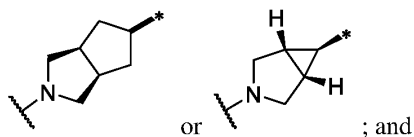
[0203] the bond marked with an "*" is attached to G².

[0204] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein G¹ is:



[0205] the bond marked with an "*" is attached to G².

[0206] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein G¹ is:



[0207] the bond marked with an "*" is attached to G^2

[0208] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein G^2 is a direct bond.

[0209] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A), or a pharmaceutically acceptable salt thereof, wherein G^2 is a $-C(=O)-$.

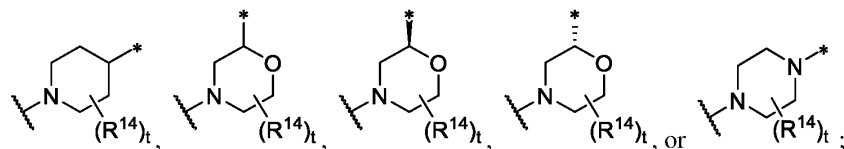
[0210] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein G^2 is (C_1-C_6) alkylenyl.

[0211] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein G^2 is $-CH_2-$.

[0212] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein G^3 is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano.

[0213] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein:

[0214] G^3 is:



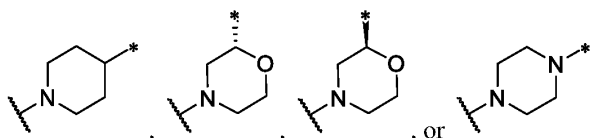
[0215] each R^{14} is independently halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano;

[0216] t is 0, 1, 2, or 3; and

[0217] the bond marked with an "*" is attached to G^4 .

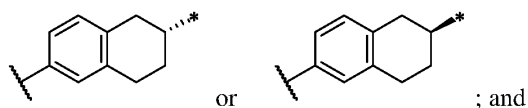
[0218] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein R^{14} is fluoro or methyl and t is 0 or 1.

[0219] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein G^3 is:



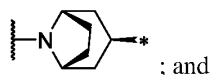
[0220] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein G^3 is 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano.

[0221] In another embodiment, Compounds of the Disclosure are compounds having Formulae (A), or a pharmaceutically acceptable salt thereof, wherein G^3 is:



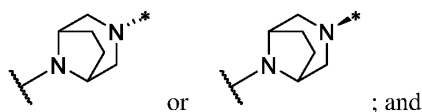
[0222] the bond marked with an "*" is attached to G^4 .

[0223] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein G^3 is:



[0224] the bond marked with an "*" is attached to G^4 .

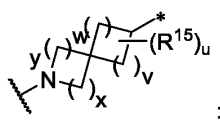
[0225] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein G^3 is:



[0226] the bond marked with an "*" is attached to G^4 .

[0227] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein:

[0228] G^3 is:



[0229] each R^{15} is independently selected from halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano;

[0230] u is 0, 1, 2, or 3;

[0231] v , w , x , and y are independently 1, 2, or 3; and

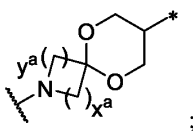
[0232] the bond marked with an "*" is attached to G^4 .

[0233] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein v , w , x , and y are independently 1 or 2.

[0234] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein R^{15} is fluoro.

[0235] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein:

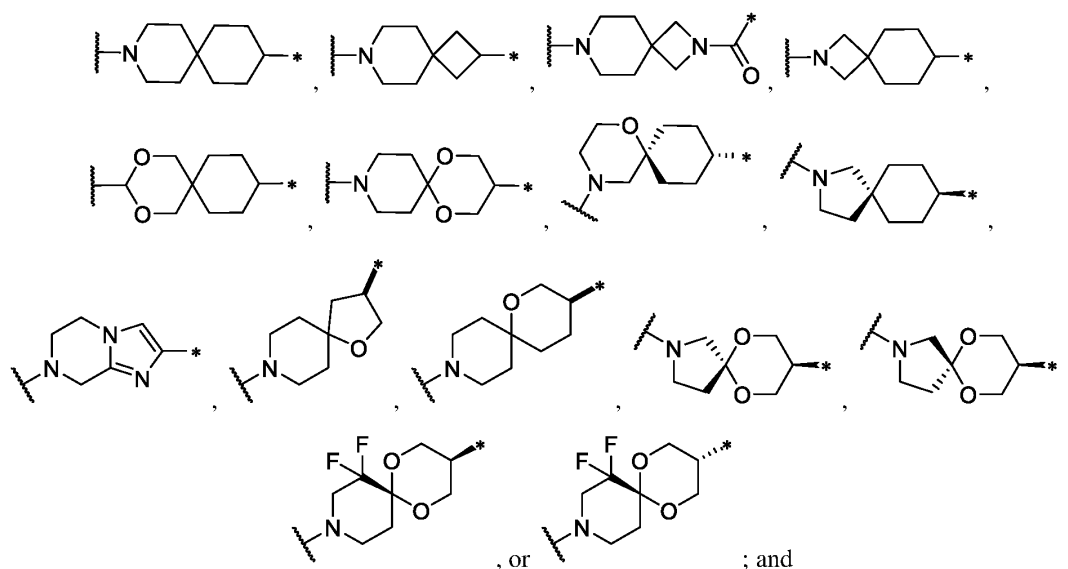
[0236] G^3 is:



[0237] x^a and y^a are independently is 1, 2, or 3; and

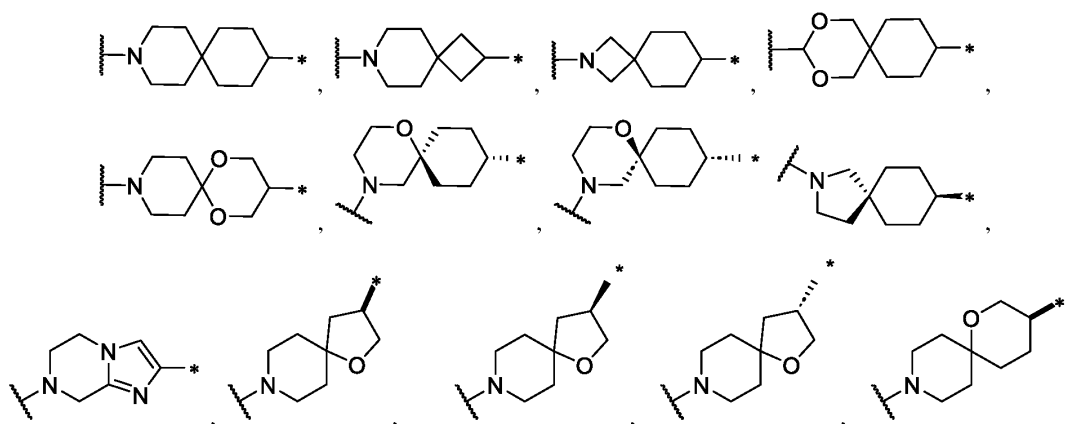
[0238] the bond marked with an "*" is attached to G⁴.

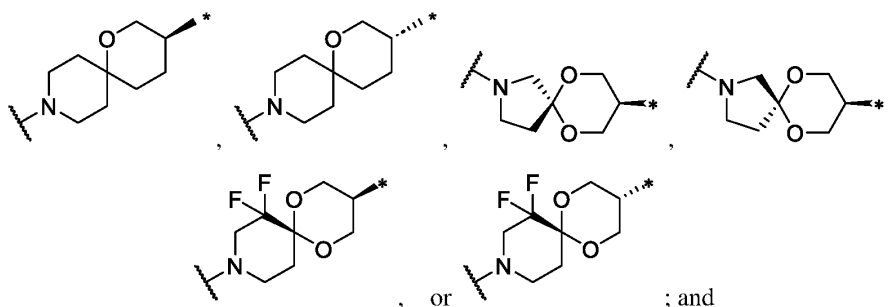
[0239] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein G³ is:



[0240] the bond marked with an “*” is attached to G⁴.

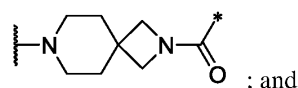
[0241] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein G³ is:





[0242] the bond marked with an “*” is attached to G⁴.

[0243] In another embodiment, Compounds of the Disclosure are compounds having Formulae (A), or a pharmaceutically acceptable salt thereof, wherein G³ is:



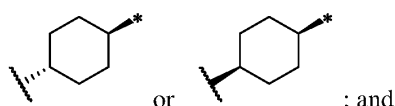
the bond marked with an “*” is attached to G⁴.

[0244] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein G⁴ is (C₁-C₆)alkylenyl.

[0245] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein G⁴ is -CH₂- or -CH₂CH₂-.

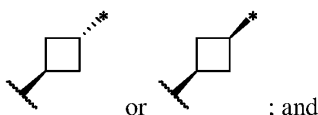
[0246] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein G⁴ is (C₃-C₆)cycloalkylenyl.

[0247] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein G⁴ is :



[0248] the bond marked with an “*” is attached to E.

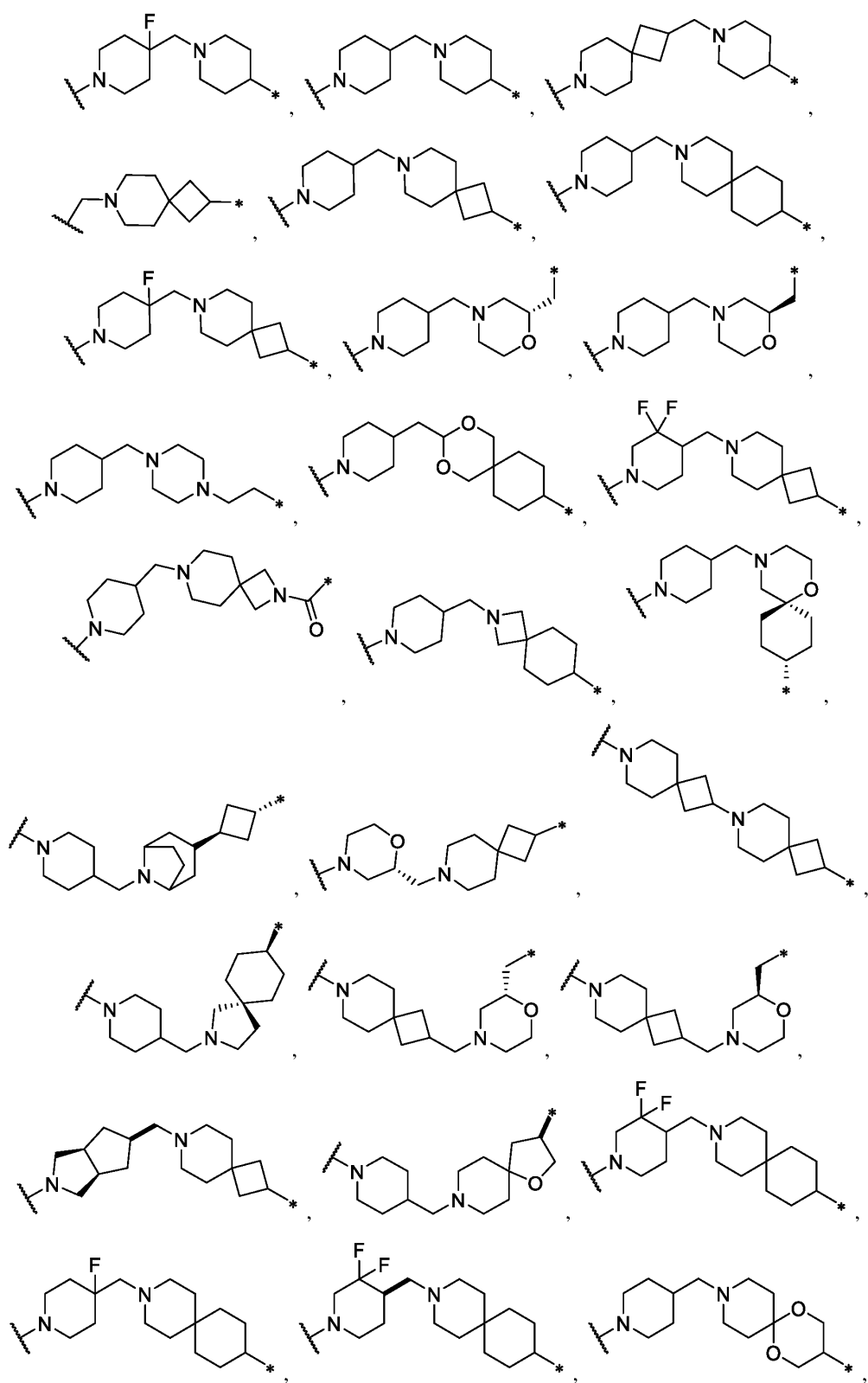
[0249] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein G⁴ is:

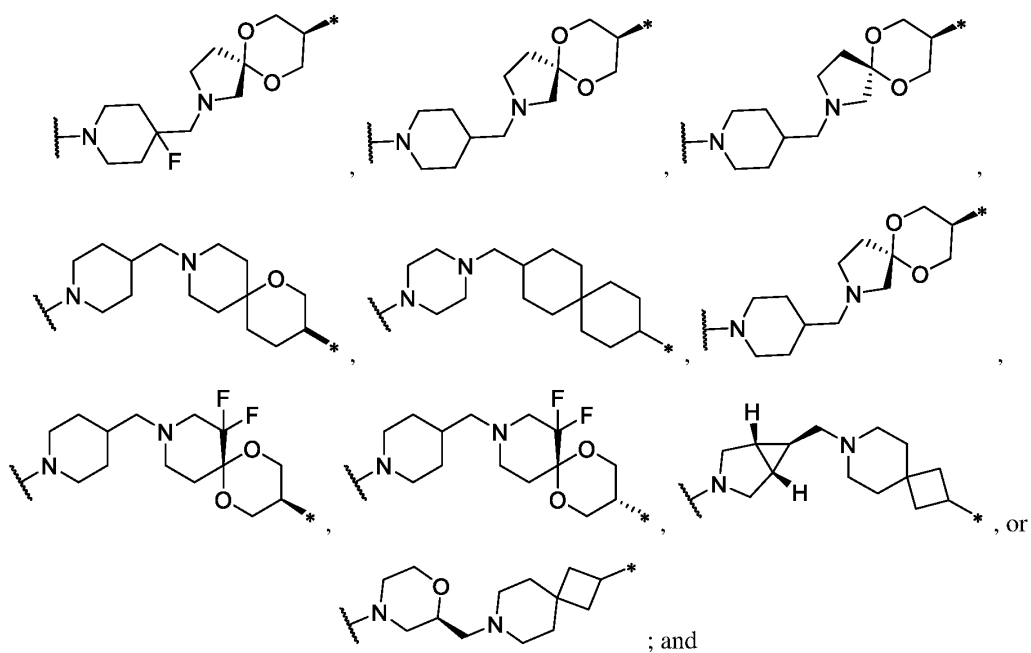


[0250] the bond marked with an “*” is attached to E.

[0251] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein G⁴ is a direct bond.

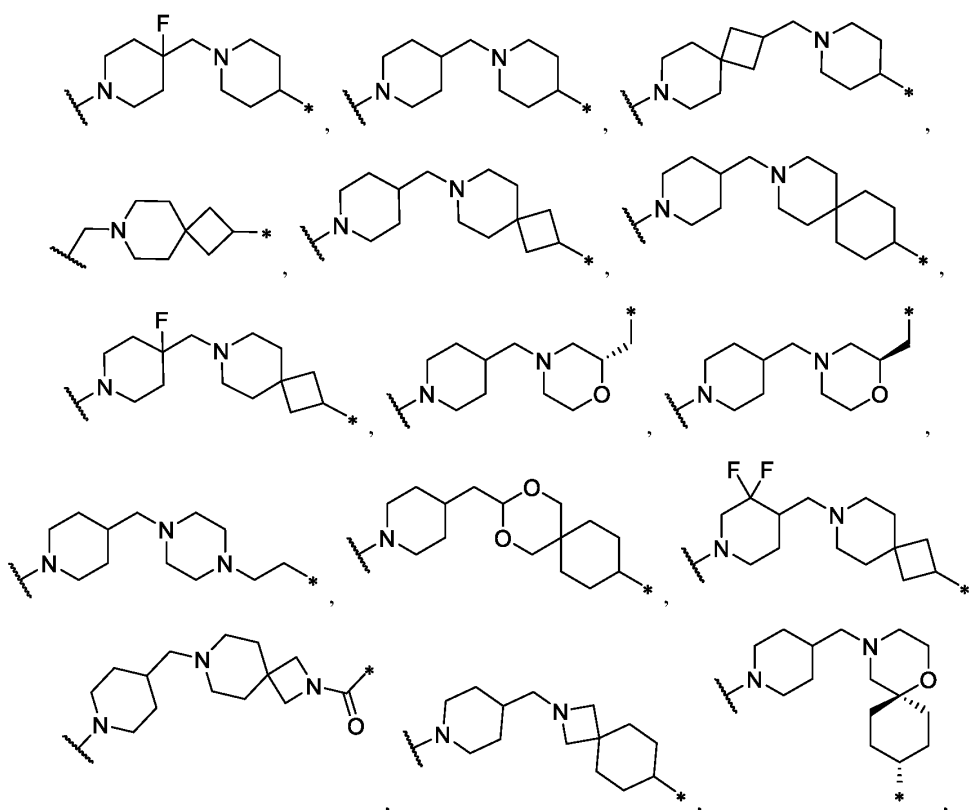
[0252] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein L is:

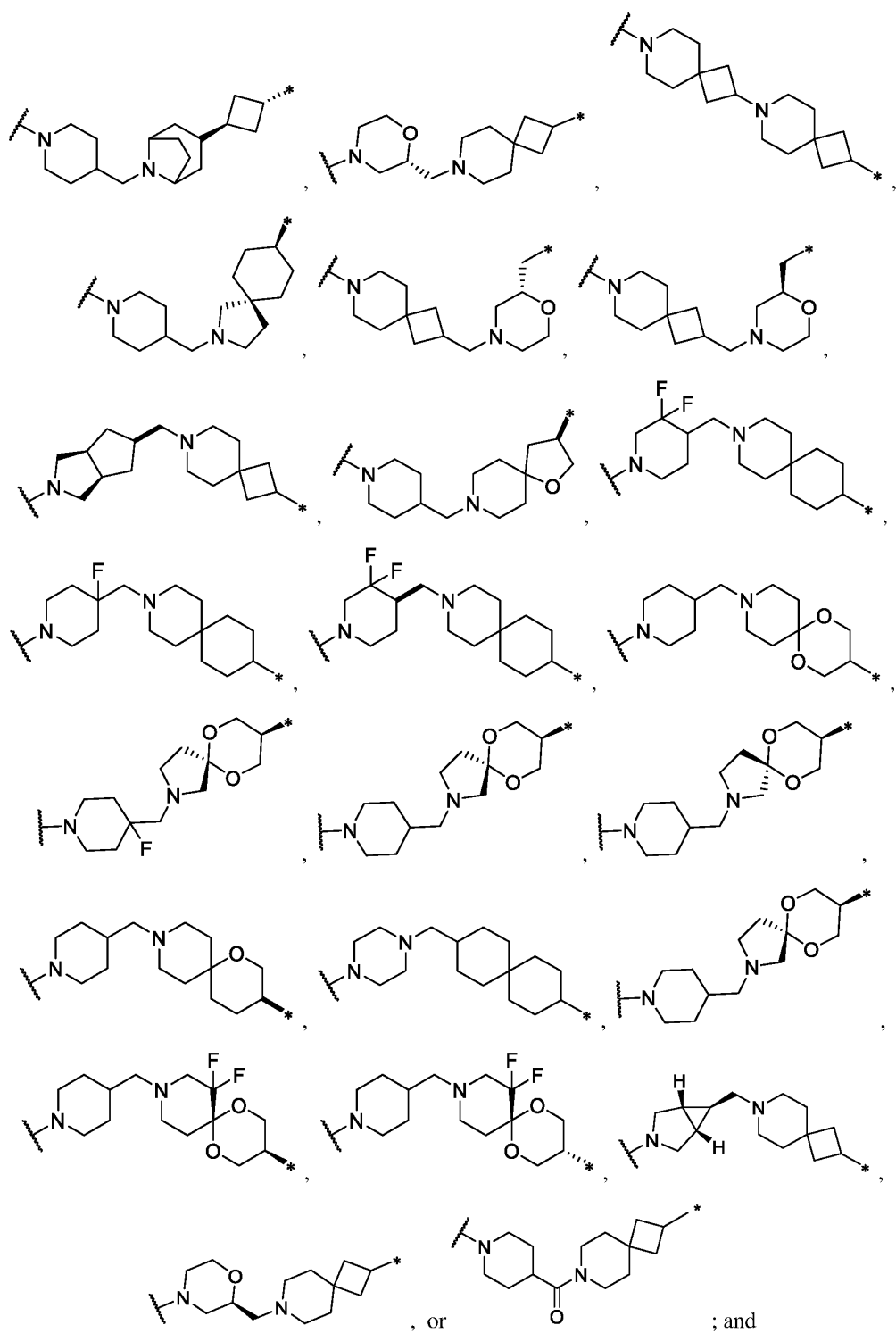




[0253] the bond marked with an "*" is attached to E.

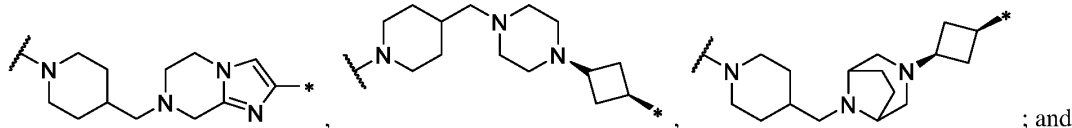
[0254] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein L is:





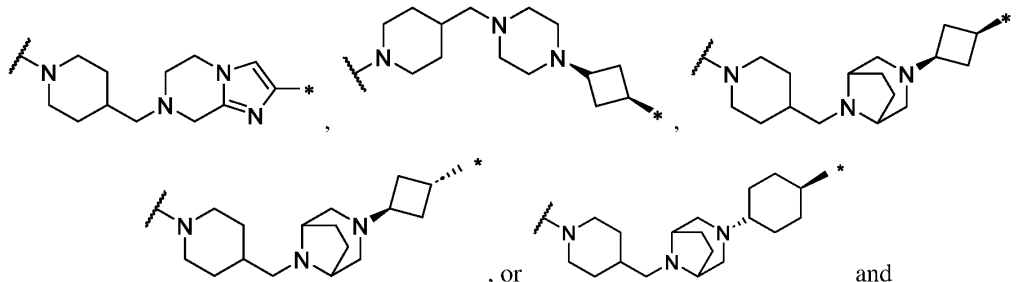
[0255] the bond marked with an "*" is attached to E.

[0256] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein L is:



[0257] the bond marked with an "*" is attached to E.

[0258] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein L is:



[0259] the bond marked with an "*" is attached to E.

[0260] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein W is $\text{-C}\equiv\text{C-}$.

[0261] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein W is a direct bond.

[0262] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein R^7 is halogen, $(\text{C}_1\text{-C}_6)\text{alkyl}$, cyano, or $(\text{C}_3\text{-C}_6)\text{cycloalkyl}$, wherein $(\text{C}_1\text{-C}_6)\text{alkyl}$ is optionally substituted with one, two, or three halogen.

[0263] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein R^7 is halogen or $(\text{C}_1\text{-C}_6)\text{alkyl}$.

[0264] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein R^7 is fluoro or methyl.

[0265] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein R^8 , R^9 , and R^{10} are H.

[0266] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein R^8 is halogen, $(\text{C}_1\text{-C}_6)\text{alkyl}$, cyano, or $(\text{C}_3\text{-C}_6)\text{cycloalkyl}$, wherein $(\text{C}_1\text{-C}_6)\text{alkyl}$ is optionally substituted with one, two, or three halogen.

[0267] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein R^8 is halogen or $(\text{C}_1\text{-C}_6)\text{alkyl}$.

[0268] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein R^8 is fluoro or methyl.

[0269] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein R^7 , R^9 , and R^{10} are hydrogen.

[0270] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein R^9 is halogen, (C_1-C_6) alkyl, cyano, or (C_3-C_6) cycloalkyl, wherein (C_1-C_6) alkyl is optionally substituted with one, two, or three halogen.

[0271] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein R^9 is halogen.

[0272] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein R^9 is fluoro.

[0273] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein R^7 , R^8 , and R^{10} are hydrogen.

[0274] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein R^{10} is halogen, (C_1-C_6) alkyl, cyano, or (C_3-C_6) cycloalkyl, wherein (C_1-C_6) alkyl is optionally substituted with one, two, or three halogen.

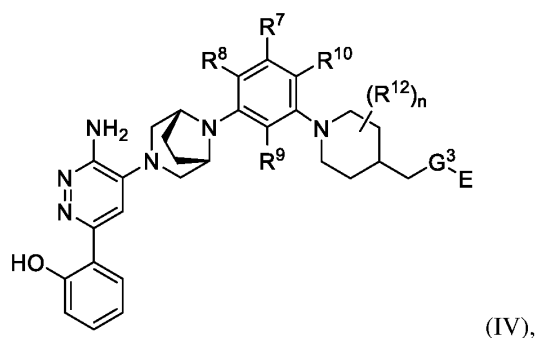
[0275] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein R^{10} is halogen.

[0276] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein R^{10} is fluoro.

[0277] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein R^7 , R^8 , and R^9 are hydrogen.

[0278] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein R^7 , R^8 , R^9 , and R^{10} are hydrogen.

[0279] In another embodiment, Compounds of the Disclosure are compounds having having Formula (IV), or a pharmaceutically acceptable salt thereof:



wherein:

[0280] each R^{12} is independently fluoro;

[0281] n is 0, 1, or 2; and

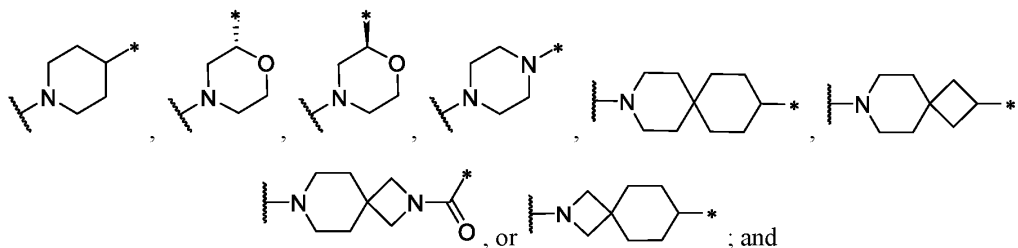
[0282] R^7 , R^8 , R^9 , and R^{10} are independently hydrogen, fluoro, or methyl

[0283] E is E-1; and

[0284] G^3 is as defined in connection with Formula (I).

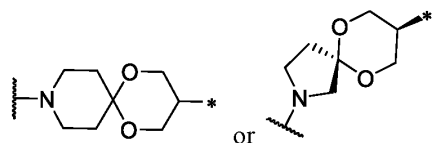
[0285] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein:

[0286] G^3 is:

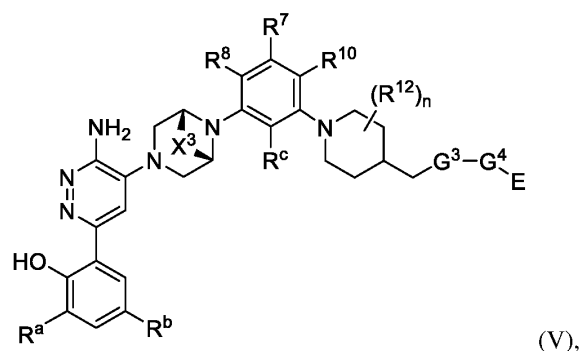


[0287] G^4 is a direct bond, $-CH_2-$ or $-CH_2CH_2-$.

[0288] In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae (A) or (I)-(III), or a pharmaceutically acceptable salt thereof, wherein G^3 is:



[0289] In another embodiment, Compounds of the Disclosure are compounds having Formula (V), or pharmaceutically acceptable salt thereof,

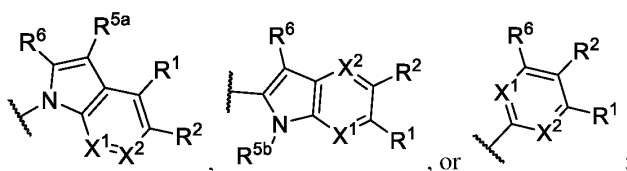


wherein:

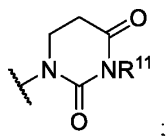
[0290] each R^{12} is fluoro or hydroxyl;

[0291] n is 0, 1, 2, or 3;

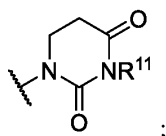
[0292] E is:



[0293] R^1 is hydrogen, halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or

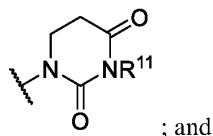


[0294] R^2 is hydrogen, halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or

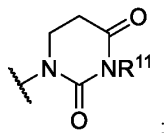


[0295] with the provisos:

[0296] (i) when R^1 is hydrogen, halogen, (C_1-C_6) alkyl, or (C_1-C_6) alkoxy, then R^2 is:

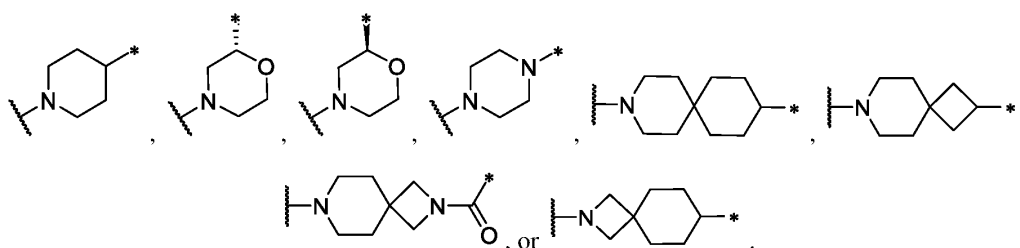


[0297] (ii) when R^2 is hydrogen, halogen, (C_1-C_6) alkyl, or (C_1-C_6) alkoxy, then R^1 is:

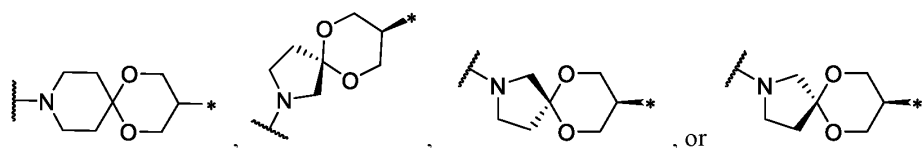


[0298] R^{11} is hydrogen or $-(C_1-C_6)alkyl-O-P(=O)-(OH)_2$;

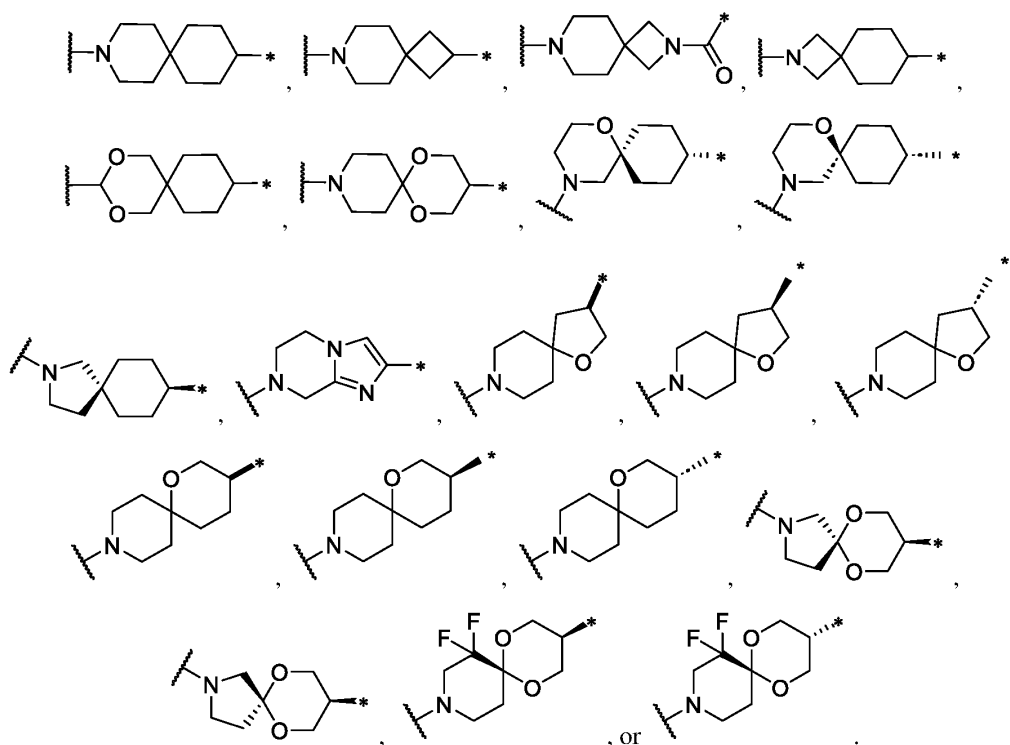
- [0299] X^1 is CR^3 or N;
- [0300] R^3 is hydrogen, halogen, or (C_1-C_6) alkyl;
- [0301] X^2 is CR^4 or N;
- [0302] R^4 is hydrogen, halogen, or (C_1-C_6) alkyl;
- [0303] R^{5a} is hydrogen, halogen, (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, 4- to 6-membered heterocycloalkyl, cyano, aryl, or 5- or 6-membered heteroaryl, wherein (C_1-C_6) alkyl is optionally substituted with one, two, or three substituents independently selected from halogen or cyano; and 4- to 6-membered heterocycloalkyl, aryl, or 5- or 6-membered heteroaryl is optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or (C_1-C_6) alkyl;
- [0304] R^{5b} is hydrogen, (C_1-C_6) alkyl, or (C_3-C_6) cycloalkyl;
- [0305] R^6 is hydrogen, (C_1-C_6) alkyl, or cyano;
- [0306] X^3 is $-CH_2CH_2-$ or absent;
- [0307] G^3 is tetrahydronaphthalene; 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano; 7- to 11-membered heterocycloalkyl- $C(=O)-$, or 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano;
- [0308] G^4 is absent or cyclobutylenyl;
- [0309] R^7 , R^8 , R^9 , and R^{10} are independently hydrogen, fluoro, methyl, or cyano;
- [0310] R^a is hydrogen, chloro, methyl, or fluoro;
- [0311] R^b is hydrogen, chloro, methyl, or fluoro; and
- [0312] R^c is hydrogen or methyl.
- [0313] In another embodiment, Compounds of the Disclosure are compounds having Formula (V), or pharmaceutically acceptable salt thereof, wherein:
- [0314] G^3 is:



- [0315] In another embodiment, Compounds of the Disclosure are compounds having Formula (V), or pharmaceutically acceptable salt thereof, wherein G^3 is:



[0316] In another embodiment, Compounds of the Disclosure are compounds having Formula (V), or pharmaceutically acceptable salt thereof, wherein G^3 is:



[0317] In another embodiment, Compounds of the Disclosure are any one or more of the compounds of Compound List 1, or a pharmaceutically acceptable salt thereof.

Compound List 1

[0318] 1-[1-[1-[[7-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-7-azaspiro[3.5]nonan-2-yl]methyl]-4-piperidyl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

[0319] 1-[1-[7-[3-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]prop-2-ynyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

[0320] 1-[1-[7-[1-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

- [0321] 1-[1-[7-[[1-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0322] 1-[1-[1-[[1-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl]methyl]-4-piperidyl]indol-4-yl]hexahydropyrimidine-2,4-dione;
- [0323] 1-[1-[3-[[1-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0324] 1-[1-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0325] 1-[1-[7-[[1-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-5-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0326] 1-[1-[7-[[1-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-5-methyl-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0327] 1-[1-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-methyl-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0328] 1-[1-[3-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0329] 1-[1-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0330] 1-[1-[3-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0331] 1-[1-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-6-fluoro-indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0332] 1-[1-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

- [0333] 1-[1-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0334] 1-[1-[7-[[1-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2,6-difluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0335] 1-[1-[3-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0336] 1-[2-[1-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indol-6-yl]hexahydropyrimidine-2,4-dione;
- [0337] 1-[1-[7-[[1-[5-[4-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]piperazin-1-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0338] 1-[1-[7-[[1-[5-[4-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]piperazin-1-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0339] 1-[1-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-4-fluoro-indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0340] 1-[1-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-4-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0341] 1-[1-[3-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]methyl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0342] 1-[1-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-fluoro-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0343] 1-[1-[1-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-fluoro-4-piperidyl]methyl]-4-piperidyl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0344] 1-[1-[7-[[1-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

- [0345]** 1-[1-[7-[[1-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0346]** 1-[1-[7-[[1-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0347]** 1-[1-[[1-(2S)-4-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]morpholin-2-yl]methyl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0348]** 1-[1-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0349]** 1-[1-[2-[4-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]piperazin-1-yl]ethyl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0350]** 1-[1-[9-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0351]** 1-(1-(3-((1-(3-(3-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-4-fluorophenyl)piperidin-4-yl)methyl)-3-azaspiro[5.5]undecan-9-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;
- [0352]** 1-[1-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3-difluoro-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0353]** 1-[1-[3-[[1-[5-[4-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]piperazin-1-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0354]** 1-(5-(7-((1-(5-(3-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-2-fluorophenyl)piperidin-4-yl)methyl)-2,7-diazaspiro[3.5]nonane-2-carbonyl)-2-methylphenyl)dihydropyrimidine-2,4(1H,3H)-dione;
- [0355]** (3-(1-(7-((1-(5-(3-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-2-fluorophenyl)piperidin-4-yl)methyl)-7-azaspiro[3.5]nonan-2-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2,6-dioxotetrahydropyrimidin-1(2H)-yl)methyl dihydrogen phosphate; or

[0356] 1-(1-(2-((1-(5-(3-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-2-fluorophenyl)piperidin-4-yl)methyl)-2-azaspiro[3.5]nonan-7-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione.

[0357] In another embodiment, Compounds of the Disclosure are any one or more of the compounds of Compound List 2, or a pharmaceutically acceptable salt thereof.

Compound List 2

[0358] 1-[1-[1-[[7-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-7-azaspiro[3.5]nonan-2-yl]methyl]-4-piperidyl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

[0359] 1-[1-[7-[[1-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

[0360] 1-[1-[7-[[1-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

[0361] 1-[1-[3-[[1-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

[0362] 1-[1-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

[0363] 1-[1-[7-[[1-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-5-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

[0364] 1-[1-[7-[[1-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-5-methyl-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

[0365] 1-[1-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-methyl-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

[0366] 1-[1-[3-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

- [0367] 1-[1-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0368] 1-[1-[3-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0369] 1-[1-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-6-fluoro-indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0370] 1-[1-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0371] 1-[1-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0372] 1-[1-[7-[[1-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2,6-difluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0373] 1-[1-[3-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0374] 1-[1-[7-[[1-[5-[4-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]piperazin-1-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0375] 1-[1-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-4-fluoro-indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0376] 1-[1-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-4-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0377] 1-[1-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-fluoro-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0378] 1-[1-[1-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-fluoro-4-piperidyl]methyl]-4-piperidyl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

- [0379] 1-[1-[7-[[1-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0380] 1-[1-[7-[[1-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0381] 1-[1-[7-[[1-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0382] 1-[1-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0383] 1-[1-[9-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0384] 1-(1-(3-((1-(3-(3-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-4-fluorophenyl)piperidin-4-yl)methyl)-3-azaspiro[5.5]undecan-9-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;
- [0385] 1-[1-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3-difluoro-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0386] 1-[1-[3-[[1-[5-[4-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]piperazin-1-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0387] (3-(1-(7-((1-(5-(3-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-2-fluorophenyl)piperidin-4-yl)methyl)-7-azaspiro[3.5]nonan-2-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2,6-dioxotetrahydropyrimidin-1(2H)-yl)methyl dihydrogen phosphate; or
- [0388] 1-(1-(2-((1-(5-(3-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-2-fluorophenyl)piperidin-4-yl)methyl)-2-azaspiro[3.5]nonan-7-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione.
- [0389] In another embodiment, Compounds of the Disclosure are any one or more of the compounds of Compound List 3, or a pharmaceutically acceptable salt thereof.

Compound List 3

- [0390]** 1-[2-[1-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indol-6-yl]hexahydropyrimidine-2,4-dione;
- [0391]** 1-[1-[7-[[1-[5-[4-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]piperazin-1-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0392]** 1-[1-[3-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]methyl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0393]** 1-[1-[(2S)-4-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]morpholin-2-yl]methyl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione; or
- [0394]** 1-(5-(7-((1-(5-(3-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-2-fluorophenyl)piperidin-4-yl)methyl)-2,7-diazaspiro[3.5]nonane-2-carbonyl)-2-methylphenyl)dihydropyrimidine-2,4(1H,3H)-dione.
- [0395]** In another embodiment, Compounds of the Disclosure are any one or more of the compounds of Compound List 4, or a pharmaceutically acceptable salt thereof.

Compound List 4

- [00101]** 1-[1-[(6r,9r)-4-[[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl]methyl]-1-oxa-4-azaspiro[5.5]undecan-9-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0396]** 1-[1-[(1r,3r)-3-[8-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]cyclobutyl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0397]** 1-[1-[7-[(2S)-4-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]morpholin-2-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0398]** 1-[1-[7-[7-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-7-azaspiro[3.5]nonan-2-yl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0399]** 1-[1-[(5r,8r)-2-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-2-azaspiro[4.5]decan-8-yl]-3-ethyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

- [0400]** 1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-ethyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0401]** 1-[1-[(2R)-4-[[7-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-7-azaspiro[3.5]nonan-2-yl]methyl]morpholin-2-yl]methyl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0402]** 1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazin-2-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0403]** 1-[1-[(2S)-4-[[7-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-7-azaspiro[3.5]nonan-2-yl]methyl]morpholin-2-yl]methyl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0404]** 1-[3-Methyl-1-[7-[[rel-(3aR,5r*,6aS)-2-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrol-5-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0405]** 1-[3-Methyl-1-[7-[[rel-(3aR,5r*,6aS)-2-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrol-5-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0406]** 1-[6-Fluoro-1-[rel-(3R*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0407]** 1-[6-Fluoro-1-[rel-(3R*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0408]** 1-[3-Cyclopropyl-1-[rel-(3R*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0409]** 1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3-difluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0410]** 1-[3-Cyclopropyl-1-[rel-(3R*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0411]** 4-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-[4-[[9-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-ethyl-pyrrolo[2,3-b]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl]methyl]-4-fluoro-1-piperidyl]benzonitrile;

- [0412]** 4-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-[4-[[9-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-ethyl-pyrrolo[2,3-b]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl]methyl]-4-fluoro-1-piperidyl]benzonitrile;
- [0413]** 1-[3-Methyl-1-[3-[[rel-(4R*)-1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3-difluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0414]** 4-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-[4-[[9-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-b]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl]methyl]-4-fluoro-1-piperidyl]benzonitrile;
- [0415]** 1-[3-Methyl-1-[3-[[rel-(4R*)-1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3-difluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0416]** 1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-4-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0417]** 1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-4-fluoro-indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0418]** 1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-6-fluoro-indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0419]** 1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxa-9-azaspiro[5.5]undecan-3-yl]-3-ethyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0420]** 1-[1-[(5s,8s)-2-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-fluoro-4-piperidyl]methyl]-6,10-dioxa-2-azaspiro[4.5]decan-8-yl]-3-ethyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0421]** 1-[1-[(5s,8s)-2-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxa-2-azaspiro[4.5]decan-8-yl]-3-ethyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0422]** 1-[3-Methyl-1-[rel-(3S*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0423]** 1-[3-Methyl-1-[rel-(3R*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione (ISOMER 1)

- [0424]** 1-[1-[(5s,8s)-2-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0425]** 1-[1-[(5r,8r)-2-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0426]** 1-[3-Methyl-1-[rel-(3S*)-9-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-9-azaspiro[5.5]undecan-3-yl]pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0427]** 1-[3-Methyl-1-[rel-(3R*)-9-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-9-azaspiro[5.5]undecan-3-yl]pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0428]** 1-[1-[(5r,8r)-2-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0429]** 1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0430]** 1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0431]** 1-[1-[9-[[4-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]piperazin-1-yl]methyl]spiro[5.5]undecan-3-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0432]** 1-[1-[(5s,8s)-2-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0433]** 1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-fluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0434]** 1-[1-[(3s,6s)-9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-11,11-difluoro-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0435]** 1-[1-[(3r,6r)-9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-11,11-difluoro-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

- [0436] 1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-fluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0437] 1-[1-[(1s,3s)-3-[4-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]piperazin-1-yl]cyclobutyl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0438] 4-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-[4-[[9-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-ethyl-pyrrolo[2,3-b]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl]methyl]-1-piperidyl]benzonitrile;
- [0439] 4-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-[4-[[2-[3-cyclopropyl-5-(2,4-dioxohexahydropyrimidin-1-yl)pyrrolo[2,3-b]pyridin-1-yl]-7-azaspiro[3.5]nonan-7-yl]methyl]-1-piperidyl]benzonitrile;
- [0440] 1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-ethyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0441] 1-[1-[3-[(1R,5S,6s)-3-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3-azabicyclo[3.1.0]hexan-6-yl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0442] 1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0443] 1-[1-[7-[(1R,5S,6s)-3-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3-azabicyclo[3.1.0]hexan-6-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0444] 1-[1-[(1s,3s)-3-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]cyclobutyl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0445] 1-[1-[7-[(2R)-4-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]morpholin-2-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0446] 1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-6-fluoro-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0447] 1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3-azabicyclo[3.2.1]octan-8-yl]-2-chloro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione; or

[0448] 1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-6-fluoro-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione.

[0449] In another embodiment, Compounds of the Disclosure are any one or more of the compounds of Compound List 5, or a pharmaceutically acceptable salt thereof.

Compound List 5

[0450] 1-[1-[1-[[7-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-7-azaspiro[3.5]nonan-2-yl]methyl]-4-piperidyl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

[0451] 1-[1-[7-[3-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]prop-2-ynyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

[0452] 1-[1-[7-[[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

[0453] 1-[1-[7-[[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

[0454] 1-[1-[1-[[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl]methyl]-4-piperidyl]indol-4-yl]hexahydropyrimidine-2,4-dione;

[0455] 1-[1-[3-[[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

[0456] 1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

[0457] 1-[1-[7-[[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-5-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

[0458] 1-[1-[7-[[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)43ridine43e-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-5-methyl-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]43ridine-5-yl]hexahydropyrimidine-2,4-dione;

- [0459] 1-[1-[7-[[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)44yridine44e-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-5-methyl-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]44yridine-5-yl]hexahydropyrimidine-2,4-dione;
- [0460] 1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-methyl-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0461] 1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0462] 1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0463] 1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0464] 1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-6-fluoro-indol-5-yl]hexahydropyrimidine-2,4-dione
- [0465] 1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0466] 1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0467] 1-[1-[7-[[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2,6-difluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0468] 1-[1-[3-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0469] 1-[2-[1-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indol-6-yl]hexahydropyrimidine-2,4-dione;
- [0470] 1-[1-[7-[[1-[5-[4-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]piperazin-1-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

- [0471] 1-[1-[7-[[1-[5-[4-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]piperazin-1-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0472] 1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-4-fluoro-indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0473] 1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-4-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0474] 1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]methyl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0475] 1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-fluoro-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0476] 1-[1-[1-[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-fluoro-4-piperidyl]methyl]-4-piperidyl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0477] 1-[1-[7-[[1-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0478] 1-[1-[7-[[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0479] 1-[1-[7-[[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0480] 1-[1-[[(2*S*)-4-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]morpholin-2-yl]methyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0481] 1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0482] 1-[1-[2-[4-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]piperazin-1-yl]ethyl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

- [0483] 1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0484] 1-[1-[3-[[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-4-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0485] 1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3-difluoro-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0486] 1-[1-[3-[[1-[5-[4-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]piperazin-1-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0487] 1-[5-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-2,7-diazaspiro[3.5]nonane-2-carbonyl]-2-methyl-phenyl]hexahydropyrimidine-2,4-dione;
- [0488] [3-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]-2,6-dioxo-hexahydropyrimidin-1-yl]methyl dihydrogen phosphate;
- [0489] 1-[1-[2-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-2-azaspiro[3.5]nonan-7-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0490] 1-[1-[(6*r*,9*r*)-4-[[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl]methyl]-1-oxa-4-azaspiro[5.5]undecan-9-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0491] 1-[1-[(1*r*,3*r*)-3-[8-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)46yridine46e-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]cyclobutyl]-3-methyl-pyrrolo[2,3-*b*]46yridine-5-yl]hexahydropyrimidine-2,4-dione;
- [0492] 1-[1-[7-[(2*S*)-4-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]morpholin-2-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0493] 1-[1-[7-[7-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-7-azaspiro[3.5]nonan-2-yl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

- [0494] 1-[1-[(5*r*,8*r*)-2-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-2-azaspiro[4.5]decan-8-yl]-3-ethyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0495] 1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-ethyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0496] 1-[1-[(2*S*)-4-[[7-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-7-azaspiro[3.5]nonan-2-yl]methyl]morpholin-2-yl]methyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0497] 1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazin-2-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0498] 1-[1-[(2*R*)-4-[[7-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-7-azaspiro[3.5]nonan-2-yl]methyl]morpholin-2-yl]methyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0499] 1-[3-Methyl-1-[7-[[*rel*-(3*aR*,5*r*^{*},6*aS*)-2-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3*a*,4,5,6,6*a*-hexahydro-1*H*-cyclopenta[*c*]pyrrol-5-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione (ISOMER 1) [*absolute configuration not yet confirmed];
- [0500] 1-[3-Methyl-1-[7-[[3*aR*,5*s*,6*aS*)-2-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3*a*,4,5,6,6*a*-hexahydro-1*H*-cyclopenta[*c*]pyrrol-5-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0501] 1-[3-Methyl-1-[7-[[3*aR*,5*r*,6*aS*)-2-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3*a*,4,5,6,6*a*-hexahydro-1*H*-cyclopenta[*c*]pyrrol-5-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0502] 1-[3-Methyl-1-[7-[[*rel*-(3*aR*,5*r*^{*},6*aS*)-2-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3*a*,4,5,6,6*a*-hexahydro-1*H*-cyclopenta[*c*]pyrrol-5-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione (ISOMER 2) [*absolute configuration not yet confirmed];
- [0504] 1-[3-Methyl-1-[7-[[3*aR*,5*s*,6*aS*)-2-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3*a*,4,5,6,6*a*-hexahydro-1*H*-cyclopenta[*c*]pyrrol-5-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0505] 1-[3-Methyl-1-[7-[[3*aR*,5*r*,6*aS*)-2-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3*a*,4,5,6,6*a*-hexahydro-1*H*-cyclopenta[*c*]pyrrol-5-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

- [0506] 1-[6-Fluoro-1-[(*rel*-(3*R**)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl)methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]indol-5-yl]hexahydropyrimidine-2,4-dione (ISOMER 1) [*absolute configuration not yet confirmed];
- [0507] 1-[6-Fluoro-1-[(3*R*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl)methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0508] 1-[6-Fluoro-1-[(3*S*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl)methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0509] 1-[6-Fluoro-1-[(*rel*-(3*R**)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl)methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]indol-5-yl]hexahydropyrimidine-2,4-dione (ISOMER 2) [*absolute configuration not yet confirmed];
- [0510] 1-[6-Fluoro-1-[(3*R*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl)methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0511] 1-[6-Fluoro-1-[(3*S*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl)methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0512] 1-[3-Cyclopropyl-1-[(*rel*-(3*R**)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl)methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione (ISOMER 2) [*absolute configuration not yet confirmed];
- [0513] 1-[3-Cyclopropyl-1-[(3*R*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl)methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- 1-[3-Cyclopropyl-1-[(3*S*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl)methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0514] 1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl)methyl]-7-azaspiro[3.5]nonan-2-yl]-6-fluoro-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0515] 1-[3-Cyclopropyl-1-[(*rel*-(3*R**)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl)methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione (ISOMER 1) [*absolute configuration not yet confirmed];

- [0516] 1-[3-Cyclopropyl-1-[(3*R*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0517] 1-[3-Cyclopropyl-1-[(3*S*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0518] 4-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-[4-[[9-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-ethyl-pyrrolo[2,3-*b*]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl]methyl]-4-fluoro-1-piperidyl]benzonitrile;
- [0519] 1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-fluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-ethyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0520] 1-[3-Methyl-1-[3-[[*rel*-(4*R**)-1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3-difluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione (ISOMER 2) [*absolute configuration not yet confirmed];
- [0521] 1-[3-Methyl-1-[3-[[4*R*)-1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3-difluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0522] 1-[3-Methyl-1-[3-[[4*S*)-1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3-difluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0523] 4-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-[4-[[9-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl]methyl]-4-fluoro-1-piperidyl]benzonitrile;
- [0524] 1-[3-Methyl-1-[3-[[*rel*-(4*R**)-1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3-difluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione (ISOMER 1) [*absolute configuration not yet confirmed];
- [0525] 1-[3-Methyl-1-[3-[[4*R*)-1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3-difluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0526] 1-[3-Methyl-1-[3-[[4*S*)-1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3-difluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

- [0527] 1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-4-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0528] 1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-4-fluoro-indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0529] 1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-6-fluoro-indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0530] 1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxa-9-azaspiro[5.5]undecan-3-yl]-3-ethyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0531] 1-[1-[(5*s*,8*s*)-2-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-fluoro-4-piperidyl]methyl]-6,10-dioxa-2-azaspiro[4.5]decan-8-yl]-3-ethyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0532] 1-[1-[(5*s*,8*s*)-2-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxa-2-azaspiro[4.5]decan-8-yl]-3-ethyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0533] 1-[3-Methyl-1-[(*rel*-(3*S**)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione (ISOMER 2) [*absolute configuration not yet confirmed];
- [0534] 1-[3-Methyl-1-[(3*S*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0535] 1-[3-Methyl-1-[(3*R*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0536] 1-[3-Methyl-1-[(*rel*-(3*R**)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione (ISOMER 1) [*absolute configuration not yet confirmed];
- [0537] 1-[3-Methyl-1-[(3*S*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

- [0538]** 1-[3-Methyl-1-[(3*R*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0539]** 1-[1-[(5*s*,8*s*)-2-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0540]** 1-[1-[(5*r*,8*r*)-2-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0541]** 1-[3-Methyl-1-*rel*-(3*S**)-9-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-9-azaspiro[5.5]undecan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione (ISOMER 1) [*absolute configuration not yet confirmed];
- [0542]** 1-[3-Methyl-1-[(3*S*)-9-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-9-azaspiro[5.5]undecan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0543]** 1-[3-Methyl-1-[(3*R*)-9-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-9-azaspiro[5.5]undecan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0544]** 1-[3-Methyl-1-*rel*-(3*R**)-9-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-9-azaspiro[5.5]undecan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione (ISOMER 2) [*absolute configuration not yet confirmed];
- [0545]** 1-[3-Methyl-1-[(3*S*)-9-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-9-azaspiro[5.5]undecan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0546]** 1-[3-Methyl-1-[(3*R*)-9-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-9-azaspiro[5.5]undecan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0547]** 1-[1-[(5*r*,8*r*)-2-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0548]** 1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]indol-5-yl]hexahydropyrimidine-2,4-dione;

- [0549] 1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0550] 1-[1-[9-[[4-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]piperazin-1-yl]methyl]spiro[5.5]undecan-3-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0551] 1-[1-[(5*s*,8*s*)-2-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0552] 1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-fluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0553] 1-[1-[(3*s*,6*s*)-9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-11,11-difluoro-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0554] 1-[1-[(3*r*,6*r*)-9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-11,11-difluoro-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0555] 1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-fluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0556] 1-[1-[3-[4-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]piperazin-1-yl]cyclobutyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0557] 4-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-[4-[[9-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-ethyl-pyrrolo[2,3-*b*]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl]methyl]-1-piperidyl]benzonitrile;
- [0558] 4-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-[4-[[2-[3-cyclopropyl-5-(2,4-dioxohexahydropyrimidin-1-yl)pyrrolo[2,3-*b*]pyridin-1-yl]-7-azaspiro[3.5]nonan-7-yl]methyl]-1-piperidyl]benzonitrile;
- [0559] 1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-ethyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0560] 1-[1-[3-[[1-(1*R*,5*S*,6*s*)-3-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3-azabicyclo[3.1.0]hexan-6-yl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

- [0561] 1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0562] 1-[1-[7-[[1-*R*,5*S*,6*S*)-3-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3-azabicyclo[3.1.0]hexan-6-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0563] 1-[1-[(1*s*,3*s*)-3-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]cyclobutyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0564] 1-[1-[7-[[1-*R*)-4-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]morpholin-2-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0565] 1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-6-fluoro-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0566] 1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3-azabicyclo[3.2.1]octan-8-yl]-2-chloro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0567] 1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0568] 1-[8-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[1,2-*a*]pyrimidin-3-yl]hexahydropyrimidine-2,4-dione;
- [0569] 1-[1-[(2*S*)-6-[[4-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]piperazin-1-yl]methyl]tetralin-2-yl]indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0570] 1-[1-[(2*R*)-6-[[4-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]piperazin-1-yl]methyl]tetralin-2-yl]indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0571] 1-[1-[(2*S*)-6-[[4-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-
- [0572] diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]piperazin-1-yl]methyl]tetralin-2-yl]indol-5-yl]hexahydropyrimidine-2,4-dione;
- 1-[1-[(2*R*)-6-[[4-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-
- [0573] diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]piperazin-1-yl]methyl]tetralin-2-yl]indol-5-yl]hexahydropyrimidine-2,4-dione;

- [0574] 1-[1-[3-[[1-(1*s*,4*s*)-4-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]cyclohexyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0575] 1-[1-[3-[[1-(1*r*,4*r*)-4-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]cyclohexyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0576] 1-[1-[(3*r*,6*r*)-9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-11,11-difluoro-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0577] 1-[1-[(1*r*,4*r*)-4-[8-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]cyclohexyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0578] 1-[1-[(1*s*,4*s*)-4-[8-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]cyclohexyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0579] 1-[1-[(1*r*,3*r*)-3-[8-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-fluoro-4-piperidyl]methyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]cyclobutyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0580] 1-[1-[3-[[1-[5-[3-[3-Amino-6-(5-fluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-ethyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0581] 1-[1-[3-[[1-[5-[3-[3-Amino-6-(3,5-difluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-ethyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0582] 1-[1-[3-[[1-[5-[3-[3-Amino-6-(3-fluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-ethyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0583] 1-[1-[(5*s*,8*s*)-2-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0584] 1-[1-[3-[[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

- [0585]** 1-[1-[7-[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]piperidine-4-carbonyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0586]** 1-[1-[3-[[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-ethyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0587]** 1-[1-[9-[[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0588]** 4-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-[4-[[3-[3-cyclopropyl-5-(2,4-dioxohexahydropyrimidin-1-yl)pyrrolo[2,3-*b*]pyridin-1-yl]-1,5-dioxo-9-azaspiro[5.5]undecan-9-yl]methyl]-1-piperidyl]benzotrile;
- [0589]** 1-[1-[3-[[1-[5-[3-[3-Amino-6-(5-fluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0590]** 1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-4-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0591]** 1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0592]** 1-[1-[9-[[1-[5-[3-[3-Amino-6-(5-fluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0593]** 1-[1-[9-[[1-[5-[3-[3-Amino-6-(5-fluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0594]** 1-[1-[9-[[1-[5-[3-[3-Amino-6-(3-fluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0595]** 1-[1-[9-[[1-[5-[3-[3-Amino-6-(3-fluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0596]** 1-[1-[9-[[1-[5-[3-[3-Amino-6-(3,5-difluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

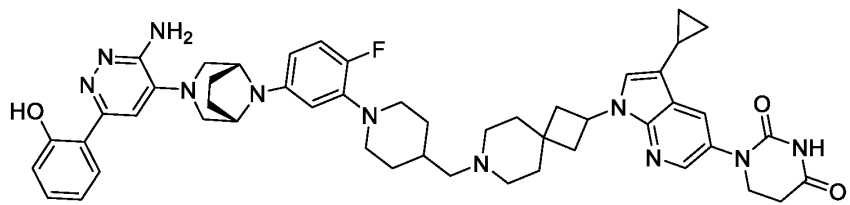
- [0597] 1-[1-[9-[[1-[5-[3-[3-Amino-6-(3,5-difluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0598] 1-[1-[3-[[1-[5-[3-[3-Amino-6-(3-fluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0599] 1-[1-[3-[[1-[5-[3-[3-Amino-6-(3,5-difluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0600] 1-[1-[3-[2-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenoxy]ethyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0601] 1-[1-[7-[2-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenoxy]ethyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0602] 1-[1-[1-[[1-[2-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenoxy]ethyl]-4-fluoro-4-piperidyl]methyl]-4-piperidyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0603] 1-[1-[(3*S*)-1-[[1-[2-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenoxy]ethyl]-4-fluoro-4-piperidyl]methyl]pyrrolidin-3-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0604] 1-[1-[(3*R*)-1-[[1-[2-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenoxy]ethyl]-4-fluoro-4-piperidyl]methyl]pyrrolidin-3-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0605] 1-[1-[3-[2-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenoxy]ethyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0606] 1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0607] 1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3-azabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-cyclopropyl-indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0608] 1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-ethyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

- [0609] 1-[3-Methyl-1-[7-[[*rac*-(2*S*,3*aR*,6*aR*)-5-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-2,3,3*a*,4,6,6*a*-hexahydrofuro[2,3-*c*]pyrrol-2-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0610] 1-[3-Methyl-1-[7-[[*rac*-(2*S*,3*aR*,6*aR*)-5-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-2,3,3*a*,4,6,6*a*-hexahydrofuro[2,3-*c*]pyrrol-2-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0611] 1-[1-[9-[[1-[5-[3-[3-Amino-6-(3-chloro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxa-9-azaspiro[5.5]undecan-3-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0612] 1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxy-3-methyl-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxa-9-azaspiro[5.5]undecan-3-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0613] 1-[1-[(5*s*,8*s*)-2-[[1-[5-[3-[3-Amino-6-(5-fluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxa-2-azaspiro[4.5]decan-8-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0614] 1-[1-[(5*s*,8*s*)-2-[[1-[5-[3-[3-Amino-6-(3-fluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxa-2-azaspiro[4.5]decan-8-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0615] 1-[1-[(5*s*,8*s*)-2-[[1-[5-[3-[3-Amino-6-(3,5-difluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxa-2-azaspiro[4.5]decan-8-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0616] 1-[1-[3-[[1-[5-[(3*S*)-4-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3-methyl-piperazin-1-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0617] 1-[1-[9-[[1-[5-[(3*S*)-4-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3-methyl-piperazin-1-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxa-9-azaspiro[5.5]undecan-3-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0618] 1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-hydroxy-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0619] 1-[1-[(5*s*,8*s*)-2-[[1-[5-[3-[3-Amino-6-(3-fluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxa-2-azaspiro[4.5]decan-8-yl]indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0620] 1-[1-[(5*s*,8*s*)-2-[[1-[5-[3-[3-Amino-6-(5-fluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxa-2-azaspiro[4.5]decan-8-yl]indol-5-yl]hexahydropyrimidine-2,4-dione;

- [0621] 1-[1-[(5*s*,8*s*)-2-[[1-[5-[3-[3-Amino-6-(3,5-difluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl)methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0622] 1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl)methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-6-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0623] 1-[1-[1-[2-[4-[2-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenoxy]ethyl]piperazin-1-yl]ethyl]-4-piperidyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0624] 1-[1-[1-[2-[4-[2-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenoxy]ethyl]piperazin-1-yl]ethyl]-4-piperidyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0625] 1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl)methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-4-fluoro-indol-5-yl]hexahydropyrimidine-2,4-dione;
- [0626] 1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl)methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]indol-4-yl]hexahydropyrimidine-2,4-dione;
- [0627] 1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-hydroxy-4-piperidyl)methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0628] 1-[1-[1-[4-[[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]methyl]piperazine-1-carbonyl]-4-piperidyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0629] 1-[1-[1-[4-[[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]methyl]piperazine-1-carbonyl]-4-piperidyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0630] 1-[1-[1-[3-[4-[[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]methyl]piperazin-1-yl]-3-oxo-propyl]-4-piperidyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- [0631] 1-[1-[1-[3-[4-[[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]methyl]piperazin-1-yl]-3-oxo-propyl]-4-piperidyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;
- or pharmaceutically acceptable salts thereof.

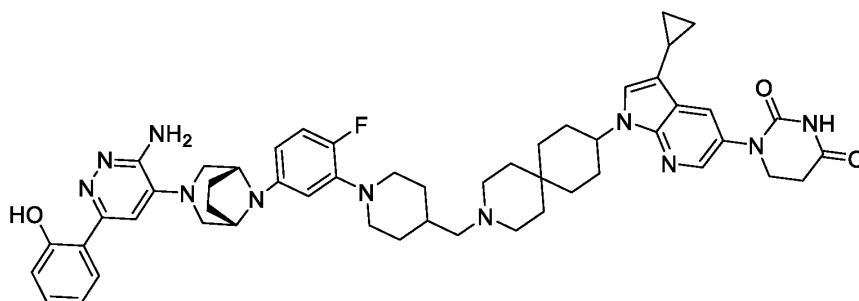
[0632] In another embodiment, Compounds of the Disclosure are any one or more of the compounds of Compound List 1, Compound List 2, Compound List 3, Compound List 4, and/or Compound List 5, or a pharmaceutically acceptable salt thereof

[0633] In another embodiment, a Compound of the Disclosure is:



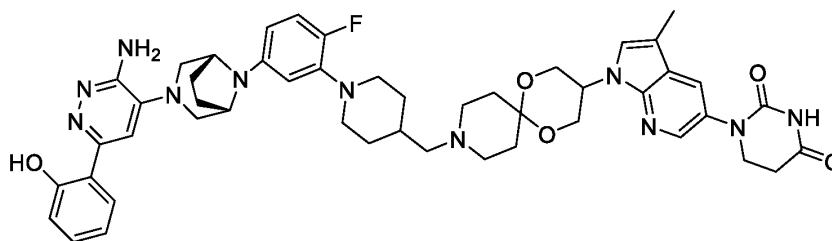
or a pharmaceutically acceptable salt thereof.

[0634] In another embodiment, a Compound of the Disclosure is:



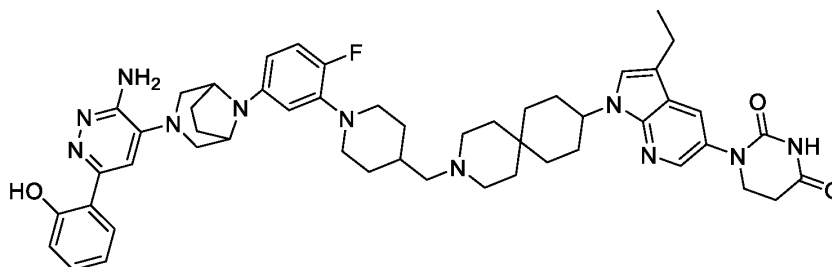
or a pharmaceutically acceptable salt thereof.

[0635] In another embodiment, a Compound of the Disclosure is:



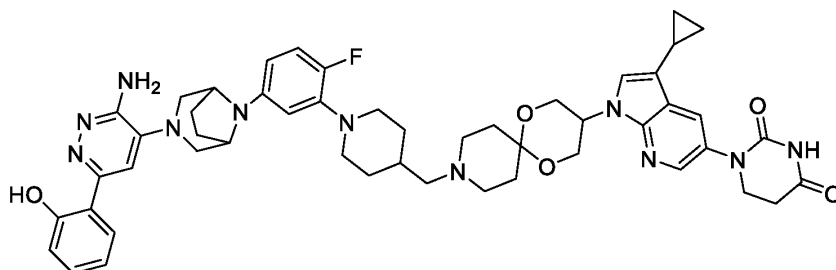
or a pharmaceutically acceptable salt thereof.

[0636] In another embodiment, a Compound of the Disclosure is:



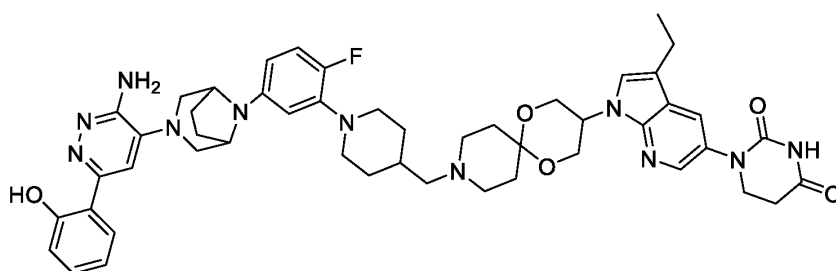
or a pharmaceutically acceptable salt thereof.

[0637] In another embodiment, a Compound of the Disclosure is:



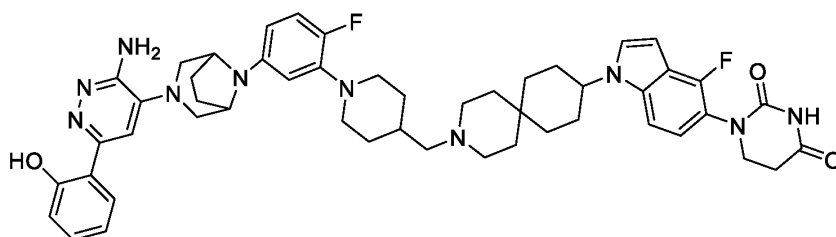
or a pharmaceutically acceptable salt thereof.

[0638] In another embodiment, a Compound of the Disclosure is:



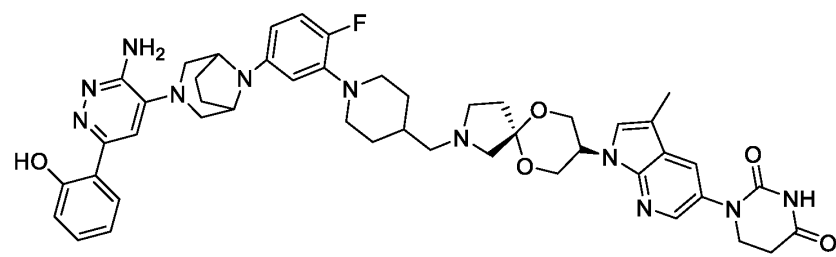
or a pharmaceutically acceptable salt thereof.

[0639] In another embodiment, a Compound of the Disclosure is:



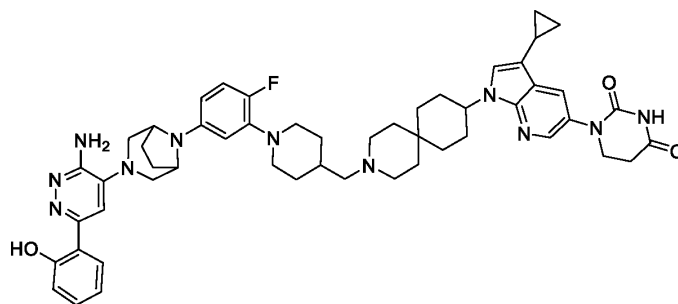
or a pharmaceutically acceptable salt thereof.

[0640] In another embodiment, a Compound of the Disclosure is:



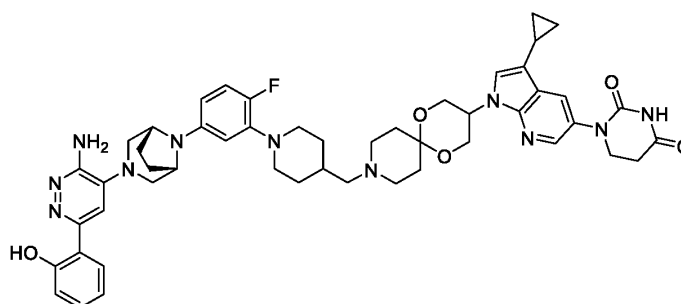
or a pharmaceutically acceptable salt thereof.

[0641] In another embodiment, a Compound of the Disclosure is:



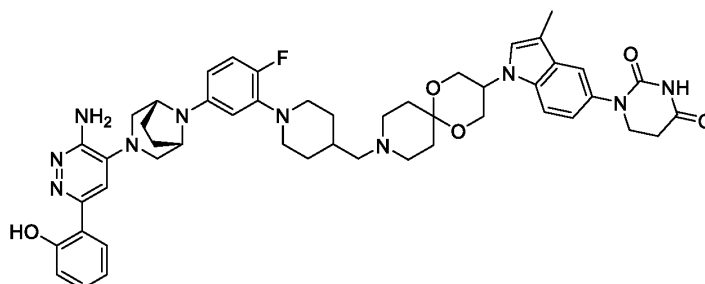
or a pharmaceutically acceptable salt thereof.

[0642] In another embodiment, a Compound of the Disclosure is:



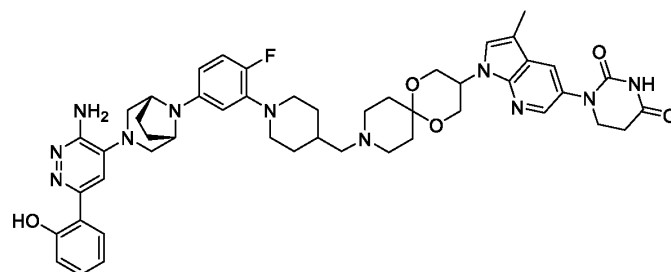
or a pharmaceutically acceptable salt thereof.

[0643] In another embodiment, a Compound of the Disclosure is:



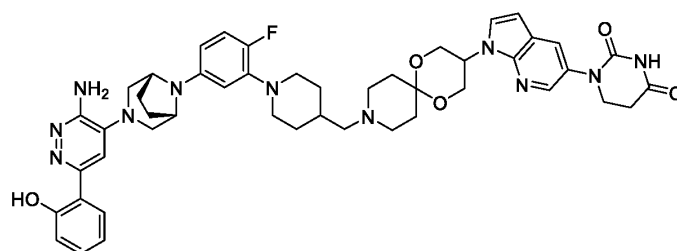
or a pharmaceutically acceptable salt thereof.

[0644] In another embodiment, a Compound of the Disclosure is:



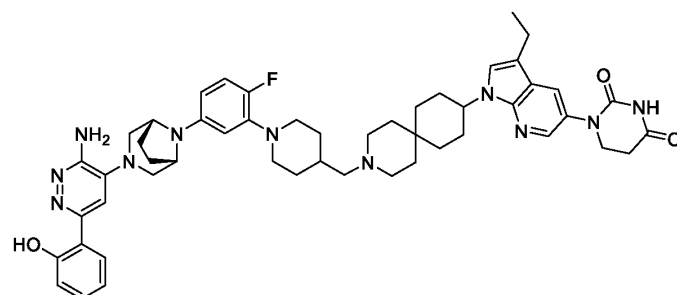
or a pharmaceutically acceptable salt thereof.

[0645] In another embodiment, a Compound of the Disclosure is:



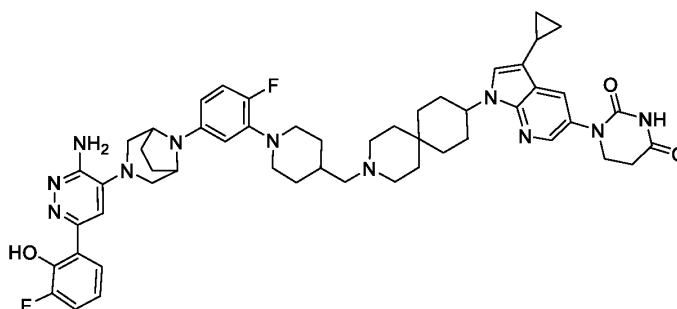
or a pharmaceutically acceptable salt thereof.

[0646] In another embodiment, a Compound of the Disclosure is:



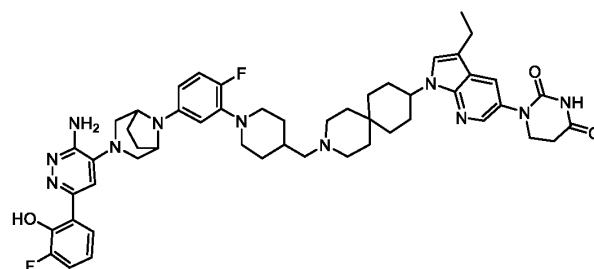
or a pharmaceutically acceptable salt thereof.

[0647] In another embodiment, a Compound of the Disclosure is:



or a pharmaceutically acceptable salt thereof.

[0648] In another embodiment, a Compound of the Disclosure is:



or a pharmaceutically acceptable salt thereof.

[0649] In another embodiment, the present disclosure provides pharmaceutical compositions comprising a Compound of the Disclosure and one or more pharmaceutically acceptable excipients.

[0650] Compounds of the Disclosure may have one or more chiral centres and it will be recognised that such compounds may be prepared, isolated and/or supplied with or without the presence of one or more of the other possible enantiomeric and/or diastereomeric isomers of the compounds, or that such isomers may be provided in any relative proportions. The preparation of enantioenriched or enantiopure and/or diastereoenriched or diastereopure compounds may be carried out by standard techniques of organic chemistry that are well known in the art, for example by synthesis from enantioenriched or enantiopure starting materials, and/or by use of an appropriately enantioenriched or enantiopure catalyst during synthesis, and/or by resolution of a racemic or partially enriched mixture of stereoisomers, for example via chiral chromatography. The scope of the present disclosure includes mixtures of stereoisomers as well as purified enantiomers or enantiomerically/diastereomerically enriched mixtures. It is to be understood that the present disclosure includes all combinations and subsets of the particular groups defined hereinabove.

[0651] In one embodiment, the present disclosure provides a composition comprising a Compound of the Disclosure optionally together with one or more of the other stereoisomeric forms of the compound, if any, wherein the Compound of the Disclosure is present within the composition with a diastereomeric excess (%de) of $\geq 55\%$.

[0652] In another embodiment, the %de in the above-mentioned composition is $\geq 90\%$.

[0653] In another embodiment, the %de in the above-mentioned composition is $\geq 95\%$.

[0654] In another embodiment, the %de in the above-mentioned composition is $\geq 98\%$.

[0655] In another embodiment, the %de in the above-mentioned composition is $\geq 99\%$.

[0656] In another embodiment, the present disclosure provides a composition comprising a Compound of the Disclosure optionally together with one or more of the other stereoisomeric forms of the compound, if any, wherein the Compound of the Disclosure is present within the composition with an enantiomeric excess (%ee) of $\geq 55\%$.

[0657] In another embodiment, the %ee in the above-mentioned composition is $\geq 90\%$.

[0658] In another embodiment, the %ee in the above-mentioned composition is $\geq 95\%$.

[0659] In another embodiment, the %ee in the above-mentioned composition is $\geq 98\%$.

[0660] In another embodiment, the %ee in the above-mentioned composition is $\geq 99\%$.

[0661] In another embodiment, the present disclosure provides a composition comprising a Compound of the Disclosure optionally together with one or more of the other stereoisomeric forms of the compound, if any, wherein the Compound of the Disclosure is present within the composition with an enantiomeric excess (%ee) of $\geq 90\%$ and a diastereomeric excess (%de) of $\geq 90\%$.

[0662] In another embodiment, the present disclosure provides a composition comprising a Compound of the Disclosure optionally together with one or more of the other stereoisomeric forms of the compound, if any, wherein the the %ee and %de of the Compound of the Disclosure take any combination of values, e.g., the %ee is $\leq 5\%$ and the %de is $\geq 80\%$; the %ee is $\leq 5\%$ and the %de is $\geq 90\%$; the %ee is $\leq 5\%$ and the

%de is $\geq 95\%$; the %ee is $\leq 5\%$ and the %de is $\geq 98\%$; the %ee is $\geq 95\%$ and the %de is $\geq 95\%$; the %ee is $\geq 98\%$ and the %de is $\geq 98\%$; or the %ee is $\geq 99\%$ and the %de is $\geq 99\%$.

[0663] Compounds of the Disclosure may be prepared, used or supplied in amorphous form, crystalline form, or semicrystalline form, and any given Compound of the Disclosure may be formed into more than one crystalline / polymorphic forms, including hydrated, e.g., hemi-hydrate, a mono-hydrate, a di-hydrate, a tri-hydrate or other stoichiometry of hydrate, and/or solvated forms. The present disclosure encompasses any and all such solid forms of Compounds of the Disclosure.

[0664] The present disclosure encompasses the preparation and use of salts of Compounds of the Disclosure. Pharmaceutically acceptable salts include, amongst others, those described in Berge, J. Pharm. Sci., 66, 1-19, (1977) or those listed in P.H. Stahl and C.G. Wermuth, editors, *Handbook of Pharmaceutical Salts; Properties, Selection and Use, Second Edition* Stahl/Wermuth: Wiley- VCH/VHCA (2011) (see <http://www.wiley.com/WileyCDA/WileyTitle/productCd-3906390519.html>).

[00102] Suitable pharmaceutically acceptable salts can include acid or base addition salts.

[0665] Such base addition salts can be formed by reaction of a Compound of the Disclosure with the appropriate base, optionally in a suitable solvent such as an organic solvent, to give the salt which can be isolated by a variety of methods, including crystallisation and filtration.

[0666] Such acid addition salts can be formed by reaction of a Compound of the Disclosure with the appropriate acid, optionally in a suitable solvent such as an organic solvent, to give the salt which can be isolated by a variety of methods, including crystallisation and filtration.

[0667] Salts may be prepared *in situ* during the final isolation and purification of a Compound of the Disclosure. If a basic compound of a Compound of the Disclosure is isolated as a salt, the corresponding free base form of that compound may be prepared by any suitable method known to the art, including treatment of the salt with an inorganic or organic base. Similarly, if a Compound of the Disclosure containing a carboxylic acid or other acidic functional group is isolated as a salt, the corresponding free acid form of that compound may be prepared by any suitable method known to the art, including treatment of the salt with an inorganic or organic acid.

[0668] It will be understood that if a Compound of the Disclosure contains two or more basic moieties, the stoichiometry of salt formation may include 1, 2 or more equivalents of acid. Such salts would contain 1, 2 or more acid counterions, for example, a dihydrochloride salt.

[0669] Stoichiometric and non-stoichiometric forms of a pharmaceutically acceptable salt of a Compound of the Disclosure are included within the scope of the specification, including sub-stoichiometric salts, for example where a counterion contains more than one acidic proton.

[0670] Representative pharmaceutically acceptable acid addition salts include, but are not limited to, 4-acetamidobenzoate, acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate (besylate), benzoate, bisulfate, bitartrate, butyrate, calcium edetate, camphorate, camphorsulfonate (camsylate), caprate (decanoate), caproate (hexanoate), caprylate (octanoate), cinnamate, citrate, cyclamate, digluconate, 2,5-

dihydroxybenzoate, disuccinate, dodecylsulfate (estolate), edetate (ethylenediaminetetraacetate), estolate (lauryl sulfate), ethane-1,2-disulfonate (edisylate), ethanesulfonate (esylate), formate, fumarate, galactarate (mucate), gentisate (2,5-dihydroxybenzoate), glucoheptonate (gluceptate), gluconate, glucuronate, glutamate, glutarate, glycerophosphate, glycolate, hexylresorcinat, hippurate, hydrabamine (*N,N'*-di(dehydroabietyl)-ethylenediamine), hydrobromide, hydrochloride, hydroiodide, hydroxynaphthoate, isobutyrate, lactate, lactobionate, laurate, malate, maleate, malonate, mandelate, methanesulfonate (mesylate), methylsulfate, mucate, naphthalene-1,5-disulfonate (napadisylate), naphthalene-2-sulfonate (napsylate), nicotinate, nitrate, oleate, palmitate, *p*-aminobenzenesulfonate, *p*-aminosalicylate, pamoate (embonate), pantothenate, pectinate, persulfate, phenylacetate, phenylethylbarbiturate, phosphate, polygalacturonate, propionate, *p*-toluenesulfonate (tosylate), pyroglutamate, pyruvate, salicylate, sebacate, stearate, subacetate, succinate, sulfamate, sulfate, tannate, tartrate, teoclate (8-chlorotheophyllinate), thiocyanate, triethiodide, undecanoate, undecylenate, and valerate.

[0671] Representative pharmaceutically acceptable base addition salts include, but are not limited to, aluminium, 2-amino-2-(hydroxymethyl)-1,3-propanediol (TRIS), arginine, benethamine (*N*-benzylphenethylamine), benzathine (*N,N'*-dibenzylethylenediamine), *bis*-(2-hydroxyethyl)amine, bismuth, calcium, chlorprocaine, choline, clemizole (1-*p* chlorobenzyl-2-pyrrolidine-1'-ylmethylbenzimidazole), cyclohexylamine, dibenzylethylenediamine, diethylamine, diethyltriamine, dimethylamine, dimethylethanolamine, dopamine, ethanolamine, ethylenediamine, L-histidine, iron, isoquinoline, lepidine, lithium, lysine, magnesium, meglumine (*N*-methylglucamine), piperazine, piperidine, potassium, procaine, quinine, quinoline, sodium, strontium, *t*-butylamine, tromethamine (*tris*(hydroxymethyl)aminomethane), and zinc.

[0672] The present disclosure also includes isotopically-labeled compounds, which are identical to a Compound of the Disclosure except that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into Compounds of the Disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, chlorine, and iodine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{17}O , ^{18}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , ^{36}Cl , ^{123}I , and ^{125}I .

[0673] Compounds of the Disclosure that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of the disclosure. Isotopically-labeled compounds of the disclosure, for example those into which radioactive isotopes such as ^3H , ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^3H , and carbon-14, i.e., ^{14}C , isotopes are particularly used for their ease of preparation and detectability. ^{11}C and ^{18}F isotopes are particularly useful in PET (positron emission tomography), and ^{125}I isotopes are particularly useful in SPECT (single photon emission computerized tomography), all useful in brain imaging. Further, substitution with heavier isotopes such as deuterium, i.e., ^2H , can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be used in some

circumstances. Isotopically labeled Compounds of the Disclosure can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples below, by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

[0674] In another embodiment, the present disclosure provides a pharmaceutical composition comprising a Compound of the Disclosure and one or more excipients (also referred to as carriers and/or diluents in the pharmaceutical arts). The excipients are acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof, i.e., the patient.

II. Methods of Use

[0675] It is known that SMARCA4 mutations may be present in certain tumor/cancer types, including lung, liver, colon skin, bladder, cervical and ovarian tumors/cancers, and that SMARCA2 is essential for growth of tumors containing such SMARCA4 mutations. Accordingly, Compounds of the Disclosure may be of value as anti-cancer agents / anti-tumor agents, in particular against cancer/tumor types known to harbor SMARCA4 mutations, for example, lung cancer, liver cancer, colon cancer, skin cancer, bladder cancer, liver cancer, cervical cancer and ovarian cancer.

[0676] Compounds of the Disclosure may also be of value against cancer types/tumors sensitive to the degradation of SMARCA2, for example, lung cancer, liver cancer, colon cancer, skin cancer, bladder cancer, liver cancer, cervical cancer and ovarian cancer.

[0677] Compounds of the Disclosure may also be of value as anti-tumor agents, in particular as selective inhibitors of the proliferation, survival, motility, dissemination and invasiveness of mammalian cancer cells leading to inhibition of tumor growth and survival and to inhibition of metastatic tumor growth. In particular, Compounds of the Disclosure may be of value as anti-proliferative and anti-invasive agents in the containment and/or treatment of solid tumor disease.

[0678] Compounds of the Disclosure may also be useful in the prevention or treatment of those tumors which are sensitive to degradation of SMARCA2 and that are involved in the signal transduction steps which lead to the proliferation and survival of tumor cells and the migratory ability and invasiveness of metastasising tumor cells. Further, Compounds of the Disclosure may be useful in the prevention or treatment of those tumors which are mediated alone or in part by degradation of SMARCA2, i.e., the compounds may be used to produce an SMARCA2 degradation effect in a subject, e.g., a warm-blooded animal, e.g., a human, in need of such treatment.

[0679] In one embodiment, the present disclosure provides a Compound of the Disclosure or pharmaceutical composition thereof for use in the treatment of cancer.

[0680] In another embodiment, the present disclosure provides a Compound of the Disclosure or pharmaceutical composition thereof for use in the treatment of a solid tumor.

[0681] In another embodiment, the present disclosure provides a Compound of the Disclosure or pharmaceutical composition thereof for use in the treatment of a SMARCA2-sensitive tumor type.

[0682] In another embodiment, the present disclosure provides a Compound of the Disclosure or pharmaceutical composition thereof for use in the treatment of tumor types that harbor SMARCA4 mutations.

[0683] In another embodiment, the present disclosure provides a Compound of the Disclosure or pharmaceutical composition thereof for use in the treatment of lung, liver, colon, skin, bladder, cervical or ovarian cancer.

[0684] In another embodiment, the present disclosure provides a Compound of the Disclosure or pharmaceutical composition thereof for use in the treatment of SMARCA4-mutated cancer.

[0685] The amount of the Compound of the Disclosure that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the subject being treated and the particular route of administration.

[0686] The size of the dose for therapeutic or prophylactic purposes of Compounds of the Disclosure will naturally vary according to the nature and severity of the disease state, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

[0687] In another embodiment, the present disclosure provides a Compound of the Disclosure or pharmaceutical composition thereof for use as a medicament.

[0688] In another embodiment, the present disclosure provides a Compound of the Disclosure or pharmaceutical composition thereof for use in therapy.

[0689] In another embodiment, the present disclosure provides a Compound of the Disclosure or pharmaceutical composition thereof for use in a method of treatment of the human or animal body by therapy.

[0690] In another embodiment, the present disclosure provides a Compound of the Disclosure or pharmaceutical composition thereof for use in the production of an anti-proliferative effect , for example, in a warm-blooded animal such as a human.

[0691] In another embodiment, the present disclosure provides the use of a Compound of the Disclosure or pharmaceutical composition thereof for the manufacture of a medicament for the production of an anti-proliferative effect , for example, in a warm-blooded animal such as a human.

[0692] In another embodiment, the present disclosure provides a method for producing an anti-proliferative effect in a warm-blooded animal, such as man, in need of such effect, which comprises administering to the animal an effective amount of a Compound of the Disclosure or pharmaceutical composition thereof.

[0693] In another embodiment, the present disclosure provides a Compound of the Disclosure or pharmaceutical composition thereof for use as an anti-invasive agent in the containment and/or treatment of solid tumor disease, for example: in a warm-blooded animal such as a human,.

[0694] In another embodiment, the present disclosure provides the use of a Compound of the Disclosure or pharmaceutical composition thereof for the manufacture of a medicament for use as an anti-invasive agent in the containment and/or treatment of solid tumor disease, for example, in a warm-blooded animal such as a human.

[0695] In another embodiment, the present disclosure provides a method for producing an anti-invasive effect by the containment and/or treatment of solid tumor disease, in a warm-blooded animal, such as man, in need of such effect, which comprises administering to the animal an effective amount of a Compound of the Disclosure or pharmaceutical composition thereof.

[0696] In another embodiment, the present disclosure provides a Compound of the Disclosure or pharmaceutical composition thereof for use in the prevention or treatment of cancer, for example, in a warm-blooded animal such as a human.

[0697] In another embodiment, the present disclosure provides the use of a Compound of the Disclosure or pharmaceutical composition thereof for the manufacture of a medicament for the prevention or treatment of cancer, for example, in a warm-blooded animal such as a human.

[0698] In another embodiment, the present disclosure provides a method for the prevention or treatment of cancer in a warm-blooded animal, such as man, in need of such treatment, which comprises administering to the animal an effective amount of a Compound of the Disclosure or pharmaceutical composition thereof.

[0699] In another embodiment, the present disclosure provides a Compound of the Disclosure or pharmaceutical composition thereof for use in the prevention or treatment of solid tumor(s), for example, in a warm-blooded animal such as a human.

[0700] In another embodiment, the present disclosure provides the use of a Compound of the Disclosure or pharmaceutical composition thereof for the manufacture of a medicament for the prevention or treatment of solid tumor(s), for example, in a warm-blooded animal such as a human.

[0701] In another embodiment, the present disclosure provides a method for the prevention or treatment of solid tumor(s) in a warm-blooded animal, such as man, in need of such treatment, which comprises administering to the animal an effective amount of a Compound of the Disclosure or pharmaceutical composition thereof.

[0702] In another embodiment, the present disclosure provides a Compound of the Disclosure or pharmaceutical composition thereof for use in the prevention or treatment of tumor types that are sensitive to degradation of SMARCA2.

[0703] In another embodiment, the present disclosure provides the use of a Compound of the Disclosure or pharmaceutical composition thereof for the manufacture of a medicament for the prevention or treatment of those tumor types that are sensitive to degradation of SMARCA2.

[0704] In another embodiment, the present disclosure provides a method for the prevention or treatment of those tumor types that are sensitive to degradation of SMARCA2, in a warm-blooded animal,

such as man, in need of such treatment, which comprises administering to the animal an effective amount of a Compound of the Disclosure or pharmaceutical composition thereof. Tumor types that are sensitive to degradation of SMARCA2 include, for example, lung tumor, liver tumor, colon tumor, skin tumor, bladder tumor, cervical tumor and ovarian tumor.

[0705] In another embodiment, the present disclosure provides a Compound of the Disclosure or pharmaceutical composition thereof for use in providing a degrading effect on SMARCA2, for example, in a warm-blooded animal such as a human.

[0706] In another embodiment, the present disclosure provides the use of a Compound of the Disclosure or pharmaceutical composition thereof for the manufacture of a medicament for providing a degrading effect on SMARCA2, for example, in a warm-blooded animal such as a human.

[0707] In another embodiment, the present disclosure provides a method for providing a degrading effect on SMARCA2 in a warm-blooded animal, such as man, in need of such effect, which comprises administering to the animal an effective amount of a Compound of the Disclosure or pharmaceutical composition thereof.

[0708] In another embodiment, the present disclosure provides a Compound of the Disclosure or pharmaceutical composition thereof for use in providing a selective degrading effect on SMARCA2 in, for example, a warm-blooded animal such as man.

[0709] In another embodiment, the present disclosure provides the use of a Compound of the Disclosure or pharmaceutical composition thereof for the manufacture of a medicament for providing a selective degrading effect on SMARCA2, for example, in a warm-blooded animal such as a human.

[0710] In another embodiment, the present disclosure provides a method for providing a selective degrading effect on SMARCA2 in a warm-blooded animal, such as man, in need of such effect, which comprises administering an effective amount of a Compound of the Disclosure or pharmaceutical composition thereof. SMARCA2 has been found to be essential for growth of tumors containing SMARCA4 mutations and certain tumor/cancer types are associated with such SMARCA4 mutations.

[0711] In another embodiment, the present disclosure provides a Compound of the Disclosure or pharmaceutical composition thereof for use in the treatment of tumor types that harbor SMARCA4 mutations.

[0712] In another embodiment, the present disclosure provides the use of a Compound of the Disclosure or pharmaceutical composition thereof for the manufacture of a medicament for the prevention or treatment of those tumor types that harbor SMARCA4 mutations.

[0713] In another embodiment, the present disclosure provides a method for the prevention or treatment of those tumor types that harbor SMARCA4 mutations in a warm-blooded animal, such as man, in need of such prevention or treatment, which comprises administering to the animal an effective amount of a Compound of the Disclosure or pharmaceutical composition thereof. Tumor types known to harbor SMARCA4 mutations include lung tumors, liver tumors, colon tumors, skin tumors, bladder tumors,

cervical tumors and ovarian tumors, e.g., lung cancer, liver cancer, colon cancer, skin cancer, bladder cancer, cervical cancer and ovarian cancer.

[0714] In another embodiment, the present disclosure provides a Compound of the Disclosure or pharmaceutical composition thereof for use in the treatment of lung, liver, colon, skin, bladder, cervical or ovarian cancer.

[0715] In another embodiment, the present disclosure provides the use of a Compound of the Disclosure or pharmaceutical composition thereof for the manufacture of a medicament for the treatment of lung, liver, colon, skin, bladder, cervical or ovarian cancer.

[0716] In another embodiment, the present disclosure provides a method for treating lung, liver, colon, skin, bladder, cervical or ovarian cancer in a warm-blooded animal, such as man, in need of such treatment, which comprises administering to the animal an effective amount of a Compound of the Disclosure or pharmaceutical composition thereof.

[0717] In another embodiment where cancer is mentioned herein, the cancer is lung cancer.

[0718] In another embodiment where cancer is mentioned herein, the cancer is liver cancer.

[0719] In another embodiment where cancer is mentioned herein, the cancer is colon cancer.

[0720] In another embodiment where cancer is mentioned herein, the cancer is skin cancer.

[0721] In another embodiment where cancer is mentioned herein, the cancer is bladder cancer.

[0722] In another embodiment where cancer is mentioned herein, the cancer is cervical cancer.

[0723] In another embodiment where cancer is mentioned herein, the cancer is ovarian cancer.

[0724] In another embodiment, the present disclosure provides a Compound of the Disclosure or pharmaceutical composition thereof for use in the treatment of a SMARCA4-mutated cancer.

[0725] In another embodiment, the present disclosure provides the use of a Compound of the Disclosure or pharmaceutical composition thereof for the manufacture of a medicament for the treatment of a SMARCA4-mutated cancer.

[0726] In another embodiment, the present disclosure provides method for treating a SMARCA4-mutated cancer in a warm-blooded animal, such as man, in need of such treatment, which comprises administering an effective amount of a Compound of the Disclosure or pharmaceutical composition thereof.

III. Definitions

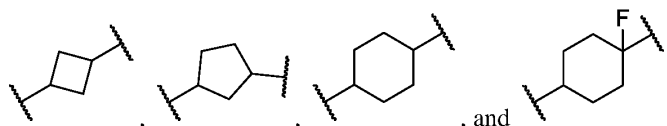
[0727] As used herein, the term "alkyl" represents a saturated, straight or branched hydrocarbon moiety having the specified number of carbon atoms. The term "(C₁-C₆)alkyl" refers to an alkyl moiety containing from 1 to 6 carbon atoms. Exemplary alkyls include, but are not limited to, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *s*-butyl, *t*-butyl, pentyl, and hexyl.

[0728] The term "alkylenyl" as used herein by itself or part of another group refers to a divalent form of an alkyl group having the specified number of carbon atoms. For example, the term "(C₁-C₆)alkylenyl" refers to an alkylenyl moiety containing from 1 to 6 carbon atoms. The alkylenyl may be optionally

substituted with one, two, or three substituents independently selected from halogen, cyano, and (C₁-C₆)alkoxy. Exemplary alkylenyl groups include, but are not limited to, -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, -CH₂(CH₂)₂CH₂-, and -CH₂(CH₂)₃CH₂-.

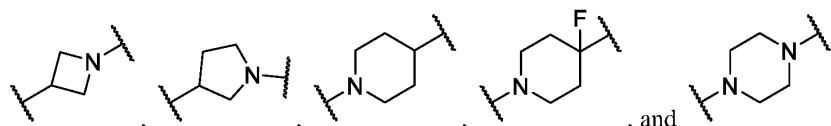
[0729] "Alkoxy" refers to a group containing an alkyl radical, defined hereinabove, attached through an oxygen linking atom. The term "(C₁-C₆)alkoxy" refers to a straight- or branched-chain hydrocarbon radical having at least 1 and up to 6 carbon atoms attached through an oxygen linking atom. Exemplary "(C₁-C₆)alkoxy" groups useful in the present specification include methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, *s*-butoxy, isobutoxy, and *t*-butoxy.

[0730] The term "cycloalkylenyl" as used herein by itself or part of another group refers to a divalent form of a cycloalkyl group having the specified number of carbon atoms in the ring. For example, the term "(C₃-C₆)cycloalkylenyl" refers to an cycloalkylenyl moiety containing from 3 to 6 carbon atoms in the ring. The cycloalkylenyl may be optionally substituted with one, two, or three substituents independently selected from halogen, (C₁-C₆)alkyl, cyano, and (C₁-C₆)alkoxy. Exemplary cycloalkylenyl groups include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl:



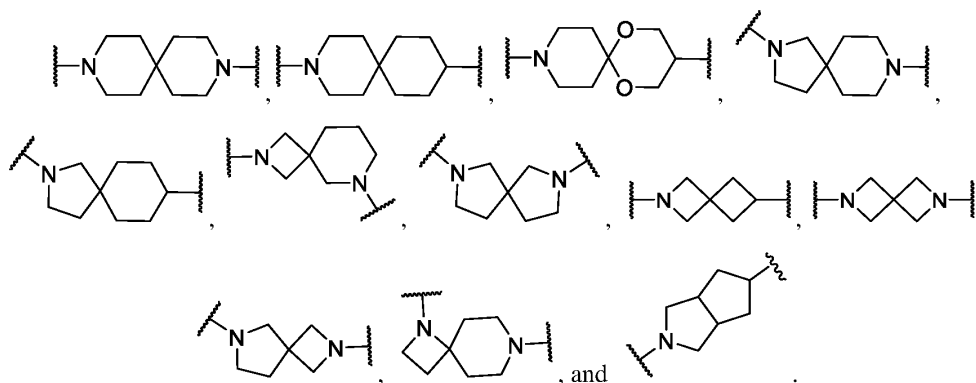
[0731] The term "heterocycloalkyl" as used herein by itself or part of another group refers to group or moiety comprising a non-aromatic, monovalent, monocyclic, bicyclic, or spirocyclic radical, which is saturated or partially unsaturated, having 4- to 11-ring atoms, which includes carbon and one or two heteroatoms selected independently from oxygen, sulfur, and/or nitrogen.

[0732] The term "4- to 6-membered heterocycloalkylenyl" as used herein by itself or part of another group refers to a divalent form of a monocyclic or bicyclic heterocycloalkyl having 4, 5, or 6 ring atoms, which includes carbon and one or two heteroatoms selected independently from oxygen, sulfur, and/or nitrogen. The 4- to 6-membered heterocycloalkylenyl may be optionally substituted with one, two, or three substituents independently selected from halogen, (C₁-C₆)alkyl, cyano, or (C₁-C₆)alkoxy. In one embodiment, the 4- to 6-membered heterocycloalkylenyl is a divalent form of an optionally substituted azetidine. In another embodiment, the the 4- to 6-membered heterocycloalkylenyl is a divalent form of an optionally substituted piperidiny. In another embodiment, the heterocycloalkylenyl is a divalent form of an optionally substituted piperaziny. Exemplary heterocycloalkylenyl groups include, but are not limited to:



[0733] The term "7- to 11-membered heterocycloalkylenyl" as used herein by itself or part of another group refers to a divalent form of a bicyclic (including bridged bicyclic), fused ring systems, or spirocyclic heterocycloalkyl having 7, 8, 9, 10, or 11 ring atoms, which includes carbon and one, two, or three

heteroatoms selected independently from oxygen, sulfur, and/or nitrogen. Exemplary 7- to 11-membered heterocycloalkylenyl groups include, but are not limited to:

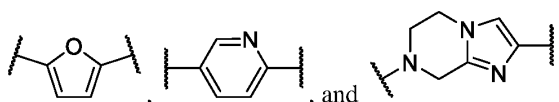


[0734] "Aryl" refers to optionally substituted monocyclic, fused bicyclic, or fused tricyclic groups having 6 to 14 carbon atoms and having at least one aromatic ring that complies with Hückel's Rule. Examples of "aryl" groups are phenyl, naphthyl, indenyl, dihydroindenyl, anthracenyl, phenanthrenyl, and the like.

[0735] "Heteroaryl" represents a group or moiety comprising an aromatic monovalent monocyclic or bicyclic radical, containing 5 to 10 ring atoms, including 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur. This term also encompasses bicyclic heterocyclic-aryl compounds containing an aryl ring moiety fused to a heterocycloalkyl ring moiety, containing 5 to 10 ring atoms, including 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur, or bicyclic heterocyclic-heteroaryl compounds containing a heteroaryl ring moiety fused to a heterocycloalkyl ring moiety, containing 5 to 10 ring atoms, including 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur. Illustrative examples of heteroaryls useful in the present specification include, but are not limited to, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, isothiazolyl, pyridinyl, pyridazinyl, pyrazinyl, pyrimidinyl, triazinyl, benzofuranyl, isobenzofuryl, 2,3-dihydrobenzofuryl, 1,3-benzodioxolyl, dihydrobenzodioxinyl, benzothienyl, indoliziny, indolyl, isoindolyl, dihydroindolyl, benzimidazolyl, dihydrobenzimidazolyl, benzoxazolyl, dihydrobenzoxazolyl, benzthiazolyl, benzoisothiazolyl, dihydrobenzoisothiazolyl, indazolyl, imidazopyridinyl, pyrazolopyridinyl, benzotriazolyl, triazolopyridinyl, purinyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, quinoxaliny, cinnolinyl, phthalazinyl, quinazolinyl, 1,5-naphthyridinyl, 1,6-naphthyridinyl, 1,7-naphthyridinyl, 1,8-naphthyridinyl, and pteridinyl. Examples of 5-membered "heteroaryl" groups include furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, and isothiazolyl. Examples of 6-membered "heteroaryl" groups include oxo-pyridyl, pyridinyl, pyridazinyl, pyrazinyl, and pyrimidinyl. Examples of 6,6-fused "heteroaryl" groups include quinolinyl, isoquinolinyl, quinoxaliny, cinnolinyl, phthalazinyl, quinazolinyl, 1,5-naphthyridinyl, 1,6-naphthyridinyl, 1,7-naphthyridinyl, 1,8-

naphthyridinyl, and pteridinyl. Examples of 6,5-fused "heteroaryl" groups include benzofuranyl, benzothieryl, benzimidazolyl, benzthiazolyl, indoliziny, indolyl, isoindolyl, and indazolyl.

[0736] The term "5- to 10-membered heteroarylenyl" as used herein by itself or part of another group refers to a divalent form of a "heteroaryl" group. Examples of "5- to 10-membered heteroarylenyl" groups include:



[0737] As used herein, "5- or 6-membered heteroaryl" represents a group or moiety comprising an aromatic monovalent monocyclic radical, containing 5 or 6 ring atoms, including at least one carbon atom and 1 to 4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. Selected 5-membered heteroaryl groups contain one nitrogen, oxygen, or sulfur ring heteroatom, and optionally contain 1, 2, or 3 additional nitrogen ring atoms. Selected 6-membered heteroaryl groups contain 1, 2, or 3 nitrogen ring heteroatoms. Illustrative examples of 5- or 6-membered heteroaryl groups useful in the present specification include, but are not limited to furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrazinyl, pyrimidinyl, and triazinyl.

[0738] The terms "halogen" and "halo" represent fluoro, chloro, bromo, or iodo substituents.

[0739] "Hydroxy" as used herein by itself or as part of a group refers to the radical -OH.

[0740] The term "cyano" as used herein by itself or as part of a group refers to the radical -CN.

[0741] As used herein, the term "optionally" means that the subsequently described event(s) may or may not occur and includes both event(s) that occur and event(s) that do not occur. As such, use of the term "optionally" includes instances where the feature is present, and also instances where the feature is not present. For example, "methyl optionally substituted by one or more F" includes -CH₃, -CH₂F, -CHF₂ and -CF₃.

[0742] In present disclosure, a group such as "A-B-C" where B is defined as "a direct bond" equates to "A-C," i.e., where A and C are directly linked to each other by a covalent bond.

[0743] The term "substituted" means that one or more hydrogens on the designated atom or group is replaced by the indicated substituent(s) provided that any atom(s) bearing such substituent(s) maintains its permitted valency where the skilled person understands that the standard valencies of carbon, nitrogen and oxygen are 4, 3 and 2 respectively.

[0744] "Pharmaceutically acceptable" refers to those compounds (including salts), materials, compositions, and dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0745] As used herein, the term "treatment" refers to alleviating the specified condition, eliminating or reducing one or more symptoms of the condition, slowing or eliminating the progression of the condition, and delaying the reoccurrence of the condition in a previously afflicted or diagnosed patient or subject.

[0746] The term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal, or human that is being sought, for instance, by a researcher or clinician

[0747] The term "therapeutically effective amount" means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function. For use in therapy, therapeutically effective amounts of a Compound of the Disclosure may be administered as the raw chemical. Additionally, the active ingredient may be presented as a pharmaceutical composition.

[0748] Compounds of the Disclosure may have asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms. The present disclosure encompasses the preparation and use of all such possible stereoisomeric forms, as well as their racemic and resolved forms, and mixtures thereof. The enantiomers and diastereomers can be separated according to methods known in the art in view of the present disclosure. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that they include both E and Z geometric isomers. All tautomers are also encompassed by the present disclosure.

[0749] As used herein, the term "stereoisomers" is a general term for all isomers of individual molecules that differ only in the orientation of their atoms in space. It includes enantiomers, atropisomers, and isomers of compounds with more than one chiral center that are not mirror images of one another (diastereomers).

[0750] The term "chiral center" or "asymmetric carbon atom" refers to a carbon atom to which four different groups are attached.

[0751] The terms "enantiomer" and "enantiomeric" refer to a molecule that cannot be superimposed on its mirror image and hence is optically active wherein the enantiomer rotates the plane of polarized light in one direction and its mirror image compound rotates the plane of polarized light in the opposite direction. Enantiomers may be separated by chiral chromatography using methods well known in the art.

[0752] The term "racemic" or "racemate" refers to a mixture of equal parts of enantiomers and which mixture is optically inactive.

[0753] The term "absolute configuration" refers to the spatial arrangement of the atoms of a chiral molecular entity (or group) and its stereochemical description, e.g., R or S.

[0754] The stereochemical terms and conventions used in the specification are meant to be consistent with those described in *Pure & Appl. Chem* 68:2193 (1996), unless otherwise indicated.

[0755] The term "enantiomeric excess" or "ee" refers to a measure for how much of one enantiomer is present compared to the other. For a mixture of *R* and *S* enantiomers, the percent enantiomeric excess is defined as $|R - S| * 100$, where *R* and *S* are the respective mole or weight fractions of enantiomers in a mixture such that $R + S = 1$. With knowledge of the optical rotation of a chiral substance, the percent enantiomeric excess is defined as $([\alpha]_{\text{obs}}/[\alpha]_{\text{max}})*100$, where $[\alpha]_{\text{obs}}$ is the optical rotation of the mixture of enantiomers and $[\alpha]_{\text{max}}$ is the optical rotation of the pure enantiomer. Determination of enantiomeric excess is possible using a variety of analytical techniques, including NMR spectroscopy, chiral column chromatography, or optical polarimetry. Compounds of the Disclosure that are racemic can be separated by chiral HPLC, e.g., using a CHIRALPAK IE column. In one embodiment, Compounds of the Disclosure have an ee of about 70% or more, e.g., about 80% or more, about 90% or more, about 91% or more, about 92% or more, about 93% or more, about 94% or more, about 95% or more, about 96% or more, about 97% or more, about 98% or more, or about 99% or more.

[0756] The terms "enantiomerically pure" or "enantiopure" refer to a sample of a chiral substance all of whose molecules (within the limits of detection) have the same chirality sense.

[0757] The terms "enantiomerically enriched" or "enantioenriched" refer to a sample of a chiral substance whose enantiomeric ratio is greater than 50:50. Enantiomerically enriched compounds may be enantiomerically pure. Certain compounds of the Disclosure are enantioenriched.

[0758] The term "diastereomeric excess" or "de" refers to a measure for how much of one diastereomer is present compared to another, and is defined by analogy to enantiomeric excess. Determination of diastereomeric excess is possible using a variety of analytical techniques, including NMR spectroscopy and column chromatography.

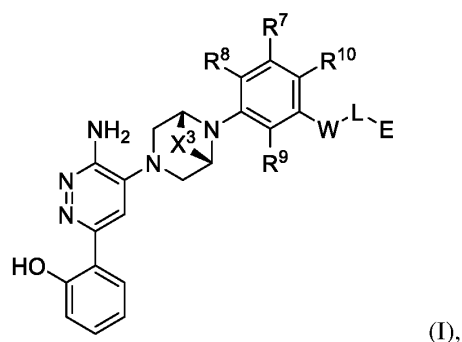
[0759] The term "diastereoenriched enriched" refer to a sample of a chiral substance whose diastereomeric ratio is greater than 50:50. Diastereoenriched enriched compounds may be diastereomerically pure. Certain compounds of the Disclosure are diastereoenriched.

[0760] The term "about," as used herein, includes the recited number $\pm 10\%$. Thus, "about 10" means 9 to 11.

IV. Particular Embodiments

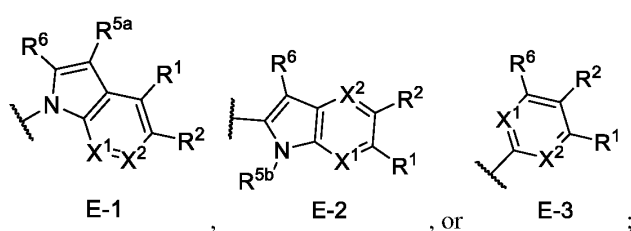
[0761] The present disclosure also provides the following particular embodiments.

[0762] Embodiment 1. A compound having Formula (I), or pharmaceutically acceptable salt thereof:

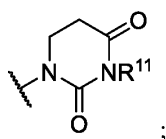


wherein:

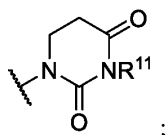
[0763] E is:



[0764] R¹ is hydrogen, halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or

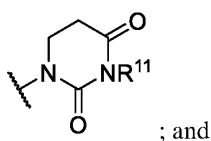


[0765] R² is hydrogen, halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or

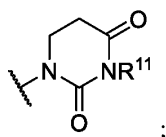


with the provisos:

[0766] (i) when R¹ is hydrogen, halogen, (C₁-C₆)alkyl, or (C₁-C₆)alkoxy, then R² is:



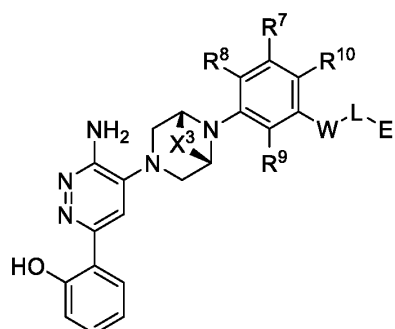
[0767] (ii) when R² is hydrogen, halogen, (C₁-C₆)alkyl, or (C₁-C₆)alkoxy, then R¹ is



[0768] R¹¹ is hydrogen or -(C₁-C₆)alkyl-O-P(=O)-(OH)₂;

[0769] X¹ is CR³ or N;

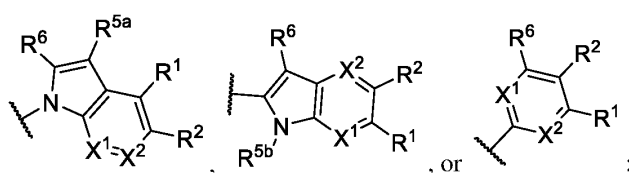
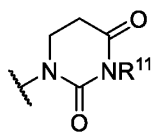
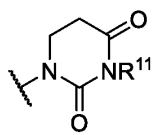
- [0770] R^3 is hydrogen, halogen, or (C₁-C₆)alkyl;
- [0771] X^2 is CR⁴ or N;
- [0772] R^4 is hydrogen, halogen, or (C₁-C₆)alkyl;
- [0773] R^{5a} is hydrogen, halogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, 4- to 6-membered heterocycloalkyl, cyano, aryl, or 5- or 6-membered heteroaryl, wherein (C₁-C₆)alkyl is optionally substituted with one, two, or three substituents independently selected from halogen or cyano; and 4- to 6-membered heterocycloalkyl, aryl, or 5- or 6-membered heteroaryl is optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or (C₁-C₆)alkyl;
- [0774] R^{5b} is hydrogen, (C₁-C₆)alkyl, or (C₃-C₆)cycloalkyl;
- [0775] R^6 is hydrogen, (C₁-C₆)alkyl, or cyano;
- [0776] X^3 is -CH₂CH₂- or -CH₂-O-CH₂-; or
- [0777] X^3 is absent;
- [0778] L is -G¹-G²-G³-G⁴-, wherein G¹ is attached to W;
- [0779] G¹ is (C₁-C₆)alkylenyl; 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or cyano; or 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or cyano;
- [0780] G² is (C₁-C₆)alkylenyl or a direct bond;
- [0781] G³ is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C₁-C₆)alkyl, or (C₁-C₆)alkoxy; cyano; or 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or cyano;
- [0782] G⁴ is (C₁-C₆)alkylenyl or a direct bond;
- [0783] W is -C≡C- a direct bond;
- [0784] R^7 is hydrogen, halogen, (C₁-C₆)alkyl optionally substituted with one, two, or three halogen, cyano, or (C₃-C₆)cycloalkyl;
- [0785] R^8 is hydrogen, halogen, (C₁-C₆)alkyl optionally substituted with one, two, or three halogen, cyano, or (C₃-C₆)cycloalkyl;
- [0786] R^9 is hydrogen, halogen, (C₁-C₆)alkyl optionally substituted with one, two, or three halogen, cyano, or (C₃-C₆)cycloalkyl; and
- [0787] R^{10} is hydrogen, halogen, (C₁-C₆)alkyl optionally substituted with one, two, or three halogen, cyano, or (C₃-C₆)cycloalkyl.
- [0788] Embodiment 2. A compound of Formula (I), or pharmaceutically acceptable salt thereof:



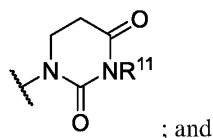
(I),

wherein:

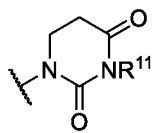
[0789] E is:

[0790] R¹ is hydrogen, halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or[0791] R² is hydrogen, halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or

with the provisos:

[0792] (i) when R¹ is hydrogen, halogen, (C₁-C₆)alkyl, or (C₁-C₆)alkoxy, then R² is:

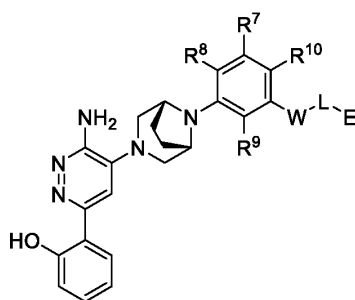
; and

[0793] (ii) when R² is hydrogen, halogen, (C₁-C₆)alkyl, or (C₁-C₆)alkoxy, then R¹ is:

;

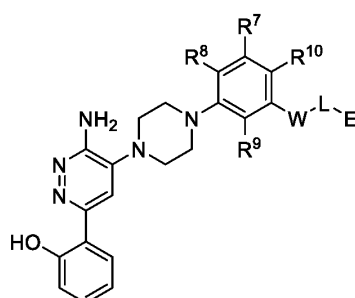
[0794] R¹¹ is hydrogen or -(C₁-C₆)alkyl-O-P(=O)-(OH)₂;[0795] X¹ is CR³ or N;[0796] R³ is hydrogen, halogen, or (C₁-C₆)alkyl;

- [0797] X^2 is CR^4 or N;
- [0798] R^4 is hydrogen, halogen, or (C_1-C_6) alkyl;
- [0799] R^{5a} is hydrogen, halogen, (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, 4- to 6-membered heterocycloalkyl, cyano, aryl, or 5- or 6-membered heteroaryl, wherein (C_1-C_6) alkyl is optionally substituted with one, two, or three substituents independently selected from halogen or cyano; and 4- to 6-membered heterocycloalkyl, aryl, or 5- or 6-membered heteroaryl is optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or (C_1-C_6) alkyl;
- [0800] R^{5b} is hydrogen, (C_1-C_6) alkyl, or (C_3-C_6) cycloalkyl;
- [0801] R^6 is hydrogen, (C_1-C_6) alkyl, or cyano;
- [0802] X^3 is $-CH_2CH_2-$ or $-CH_2-O-CH_2-$; or
- [0803] X^3 is absent;
- [0804] L is $-G^1-G^2-G^3-G^4-$, wherein G^1 is attached to W;
- [0805] G^1 is (C_1-C_6) alkylenyl; 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano; or 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano;
- [0806] G^2 is (C_1-C_6) alkylenyl or a direct bond;
- [0807] G^3 is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6) alkyl, or (C_1-C_6) alkoxy; cyano; 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano; or 5- to 10-membered heteroarylenyl;
- [0808] G^4 is (C_1-C_6) alkylenyl, (C_3-C_6) cycloalkylenyl, or a direct bond;
- [0809] W is $-C\equiv C-$ or a direct bond;
- [0810] R^7 is hydrogen, halogen, (C_1-C_6) alkyl optionally substituted with one, two, or three halogen, cyano, or (C_3-C_6) cycloalkyl;
- [0811] R^8 is hydrogen, halogen, (C_1-C_6) alkyl optionally substituted with one, two, or three halogen, cyano, or (C_3-C_6) cycloalkyl;
- [0812] R^9 is hydrogen, halogen, (C_1-C_6) alkyl optionally substituted with one, two, or three halogen, cyano, or (C_3-C_6) cycloalkyl; and
- [0813] R^{10} is hydrogen, halogen, (C_1-C_6) alkyl optionally substituted with one, two, or three halogen, cyano, or (C_3-C_6) cycloalkyl.
- [0814] Embodiment 3. The compound of Embodiment 1 or 2, or pharmaceutically acceptable salt thereof, having Formula (II):



(II).

[0815] Embodiment 4. The compound of claim 1 or 2, or pharmaceutically acceptable salt thereof, having Formula (III):



(III).

[0816] Embodiment 5. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-4, wherein E is E-1.

[0817] Embodiment 6. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 5, wherein R^{5a} is hydrogen.

[0818] Embodiment 7. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 5, wherein R^{5a} is (C₁-C₆)alkyl optionally substituted with one, two, or three substituents independently selected from halogen or cyano.

[0819] Embodiment 8. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 7, wherein R^{5a} is methyl.

[0820] Embodiment 9. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 5, wherein R^{5a} is (C₃-C₆)cycloalkyl.

[0821] Embodiment 10. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 9, wherein R^{5a} is cyclopropyl.

[0822] Embodiment 11. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 5, wherein R^{5a} is 4- to 6-membered heterocycloalkyl optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or (C₁-C₆)alkyl.

[0823] Embodiment 12. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 5, wherein R^{5a} is cyano.

[0824] Embodiment 13. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 5, wherein R^{5a} is aryl optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or (C₁-C₆)alkyl.

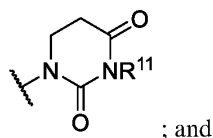
[0825] Embodiment 14. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 5, wherein R^{5a} is 5- or 6-membered heteroaryl optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or (C₁-C₆)alkyl.

[0826] Embodiment 15. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-4, wherein E is E-2.

[0827] Embodiment 16. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-4, wherein E is E-3.

[0828] Embodiment 17. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-16, wherein:

[0829] R¹ is:



[0830] R² is hydrogen, halogen, (C₁-C₆)alkyl, or (C₁-C₆)alkoxy.

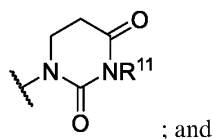
[0831] Embodiment 18. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 17, wherein R² is hydrogen, halogen, or (C₁-C₆)alkyl.

[0832] Embodiment 19. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 18, wherein R² is hydrogen, fluoro, or methyl.

[0833] Embodiment 20. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 17-19, wherein R¹¹ is hydrogen.

[0834] Embodiment 21. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-16, wherein:

[0835] R^2 is:



[0836] R¹ is hydrogen, halogen, (C₁-C₆)alkyl, or (C₁-C₆)alkoxy.

[0837] Embodiment 22. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 21, wherein R¹ is hydrogen, halogen, or (C₁-C₆)alkyl.

[0838] Embodiment 23. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 22, wherein R¹ is hydrogen, fluoro, or methyl.

[0839] Embodiment 24. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 21-23, wherein R^{11} is hydrogen.

[0840] Embodiment 25. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-24, wherein X^1 is CR^3 .

[0841] Embodiment 26. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 25, wherein R^3 is hydrogen.

[0842] Embodiment 27. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 25, wherein R^3 is halogen.

[0843] Embodiment 28. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 25, wherein R^3 is (C_1-C_6) alkyl.

[0844] Embodiment 29. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-24, wherein X^1 is N.

[0845] Embodiment 30. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-29, wherein X^2 is CR^4 .

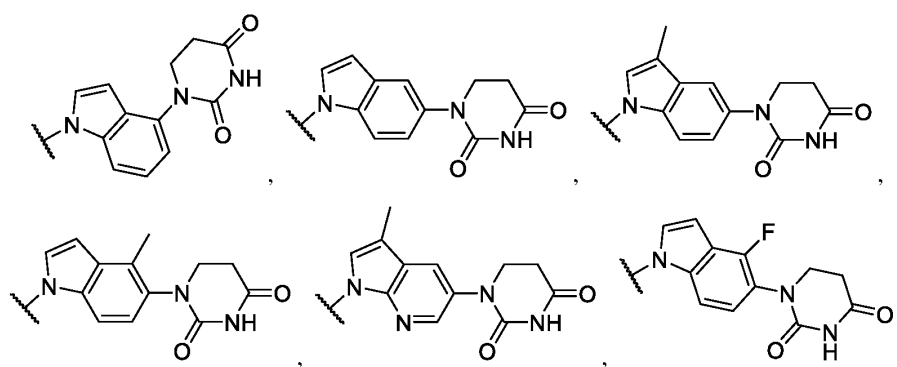
[0846] Embodiment 31. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 30, wherein R^4 is hydrogen.

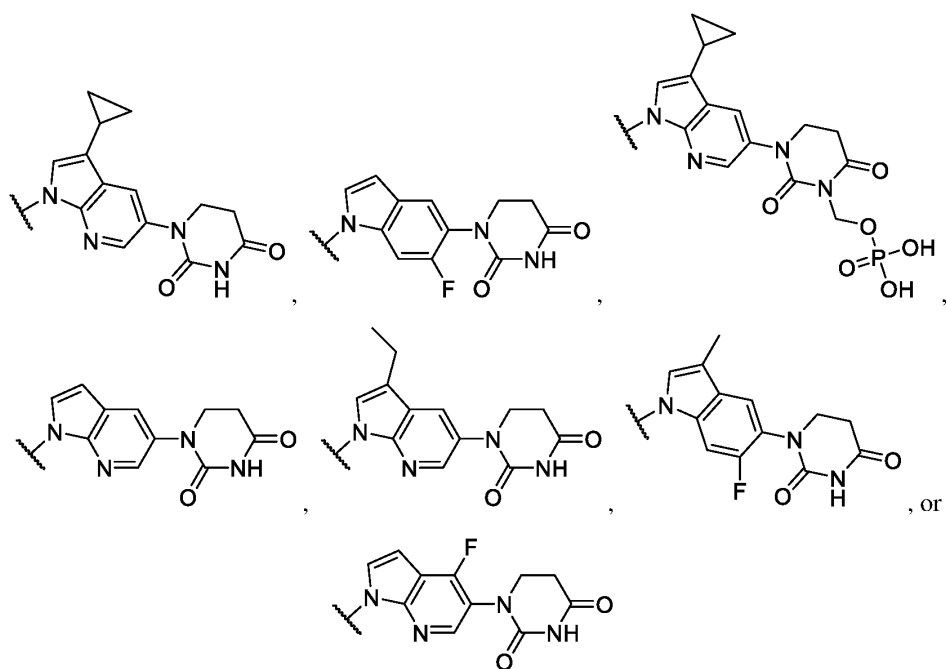
[0847] Embodiment 32. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 30, wherein R^4 is halogen.

[0848] Embodiment 33. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 30, wherein R^4 is (C_1-C_6) alkyl.

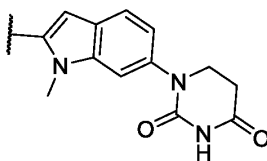
[0849] Embodiment 34. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-29, wherein X^2 is N.

[0850] Embodiment 35. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 5, wherein E-1 is:

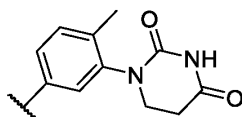




[0851] Embodiment 36. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 15, wherein E-2 is:



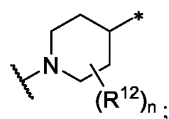
[0852] Embodiment 37. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 16, wherein E-3 is:



[0853] Embodiment 38. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-37, wherein G¹ is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or cyano.

[0854] Embodiment 39. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 38, wherein:

[0855] G¹ is:



[0856] each R^{12} is independently halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano;

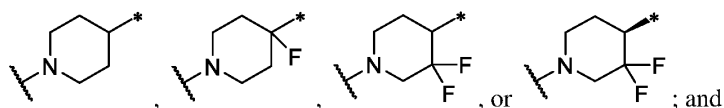
[0857] n is 0, 1, 2, or 3; and

[0858] the bond marked with an "*" is attached to G^2 .

[0859] Embodiment 40. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 39, wherein each R^{12} is independently fluoro, methyl, methoxy, cyano, or $-CHF_2$; and n is 0, 1, or 2.

[0860] Embodiment 41. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 38, wherein:

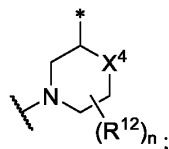
[0861] G^1 is:



[0862] the bond marked with an "*" is attached to G^2 .

[0863] Embodiment 42. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 38, wherein:

[0864] G^1 is:



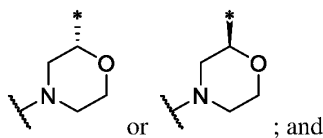
[0865] X^4 is $-O-$;

[0866] each R^{12} is independently halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano; and

[0867] the bond marked with an "*" is attached to G^2 .

[0868] Embodiment 43. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 42, wherein:

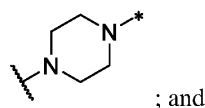
[0869] G^1 is:



[0870] the bond marked with an "*" is attached to G^2 .

[0871] Embodiment 44. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 38, wherein:

[0872] G^1 is:



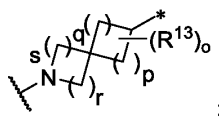
; and

[0873] the bond marked with an "*" is attached to G^2 .

[0874] Embodiment 45. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-37, wherein G^1 is 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano.

[0875] Embodiment 46. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 45, wherein:

[0876] G^1 is:



;

[0877] each R^{13} is independently selected from halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano;

[0878] o is 0, 1, 2, or 3;

[0879] p, q, r, and s are independently 1, 2, or 3; and

[0880] the bond marked with an "*" is attached to G^2 .

[0881] Embodiment 47. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 46, wherein:

[0882] p and q are 1;

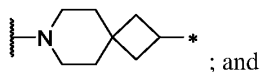
[0883] r is 1 or 2;

[0884] s is 1 or 2; and

[0885] R^{13} is halogen.

[0886] Embodiment 48. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 46, wherein R^{13} is fluoro and o is 0, 1, or 2.

[0887] Embodiment 49. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 46, wherein G^1 is:

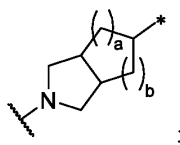


; and

[0888] the bond marked with an "*" is attached to G^2 .

[0889] Embodiment 50. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 45, wherein:

[0890] G^1 is:

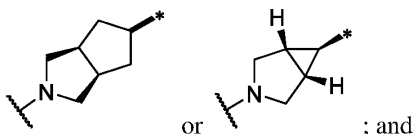


[0891] a is 0 or 1;

[0892] b is 0 or 1; and

[0893] the bond marked with an "*" is attached to G².

[0894] Embodiment 51. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 50, wherein G¹ is:



[0895] the bond marked with an "*" is attached to G².

[0896] Embodiment 52. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-49, wherein G² is a direct bond.

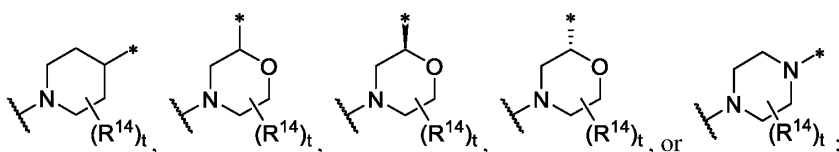
[0897] Embodiment 53. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-49, wherein G² is (C₁-C₆)alkylenyl.

[0898] Embodiment 54. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 53, wherein G² is -CH₂-.

[0899] Embodiment 55. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-54, wherein G³ is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or cyano.

[0900] Embodiment 56. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 55, wherein:

[0901] G³ is:



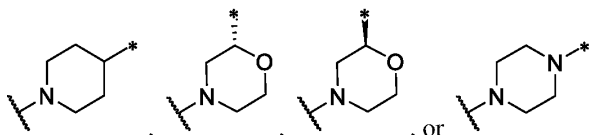
[0902] each R¹⁴ is independently halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or cyano;

[0903] t is 0, 1, 2, or 3; and

[0904] the bond marked with an "*" is attached to G⁴.

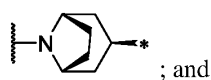
[0905] Embodiment 57. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 56, wherein R¹⁴ is fluoro or methyl and t is 0 or 1.

[0906] Embodiment 58. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 56, wherein G^3 is:



[0907] Embodiment 59. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-54, wherein G^3 is 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano.

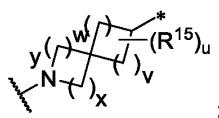
[0908] Embodiment 60. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 59, wherein G^3 is:



[0909] the bond marked with an "*" is attached to G^4

[0910] Embodiment 61. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 59, wherein:

[0911] G^3 is:



[0912] each R^{15} is independently selected from halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano;

[0913] u is 0, 1, 2, or 3;

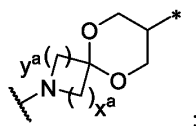
[0914] v , w , x , and y are independently 1, 2, or 3; and

[0915] the bond marked with an "*" is attached to G^4 .

[0916] Embodiment 62. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 61, wherein v , w , x , and y are independently 1 or 2.

[00103] Embodiment 63. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 59, wherein:

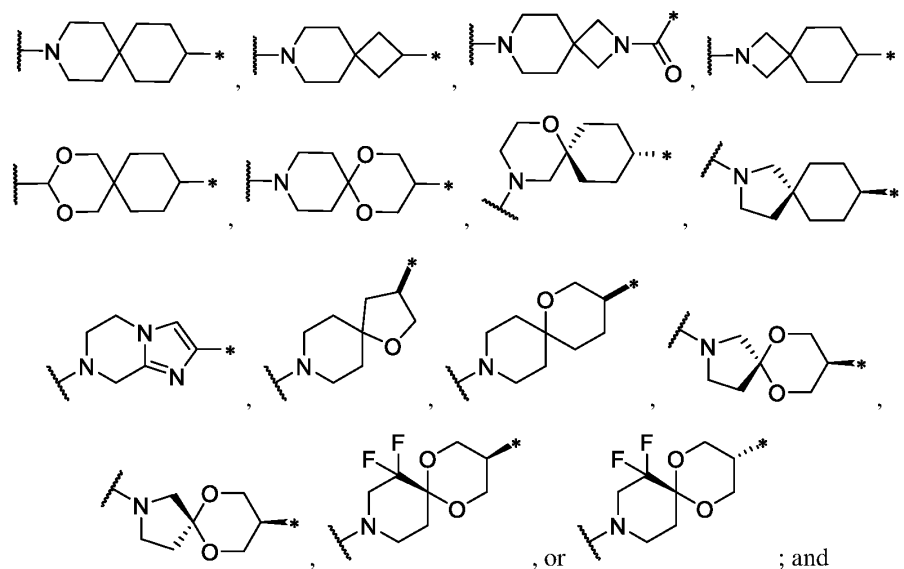
[0917] G^3 is:



[0918] x^a and y^a are independently 1, 2, or 3; and

[0919] the bond marked with an "*" is attached to G^4 .

[0920] Embodiment 64. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 59, wherein G^3 is:

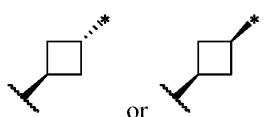


[0921] Embodiment 65. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-64, wherein G^4 is (C_1-C_6) alkylenyl.

[0922] Embodiment 66. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 65, wherein G^4 is $-CH_2-$ or $-CH_2CH_2-$.

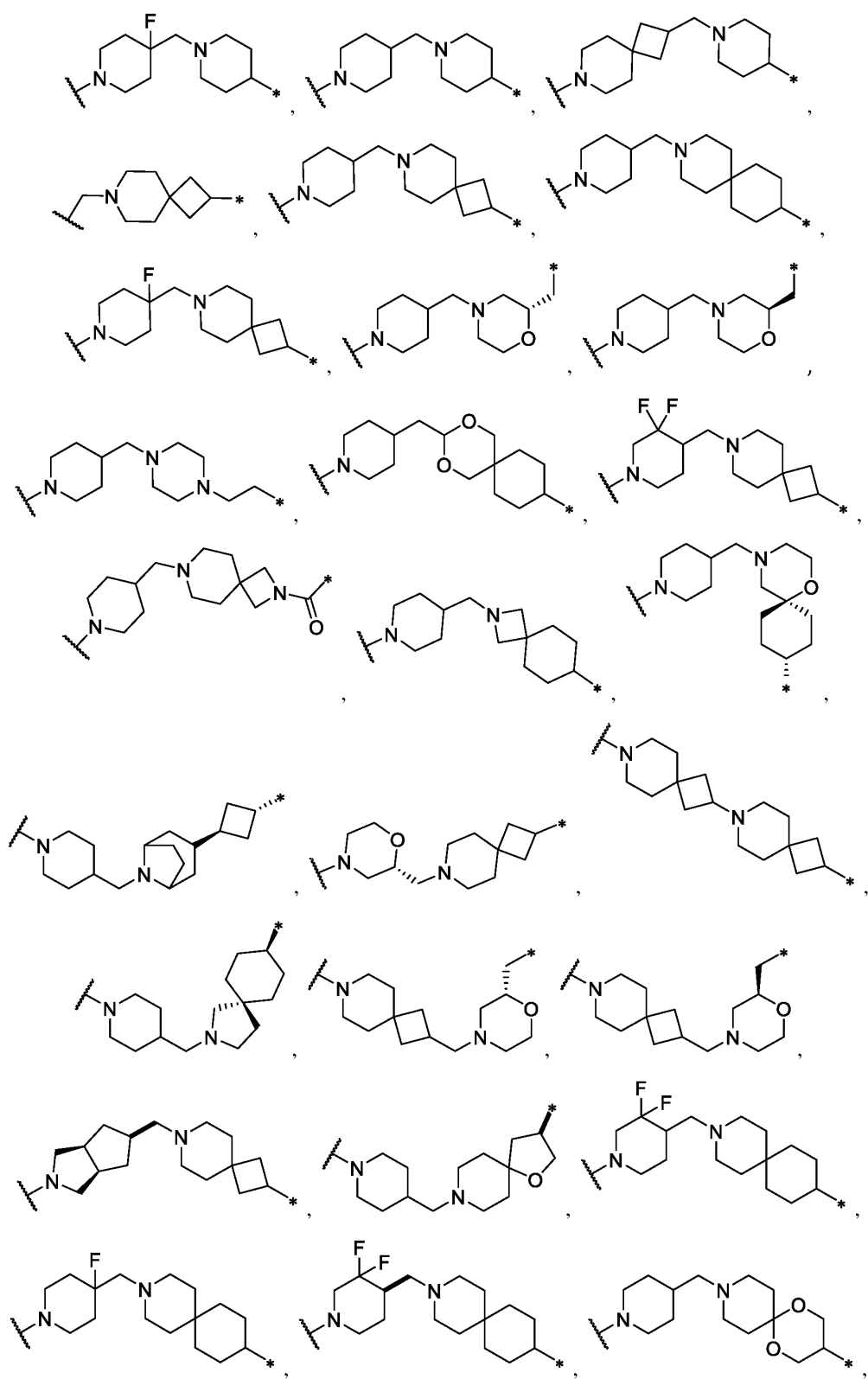
[0923] Embodiment 67. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 2-64, wherein G^4 is (C_3-C_6) cycloalkylenyl.

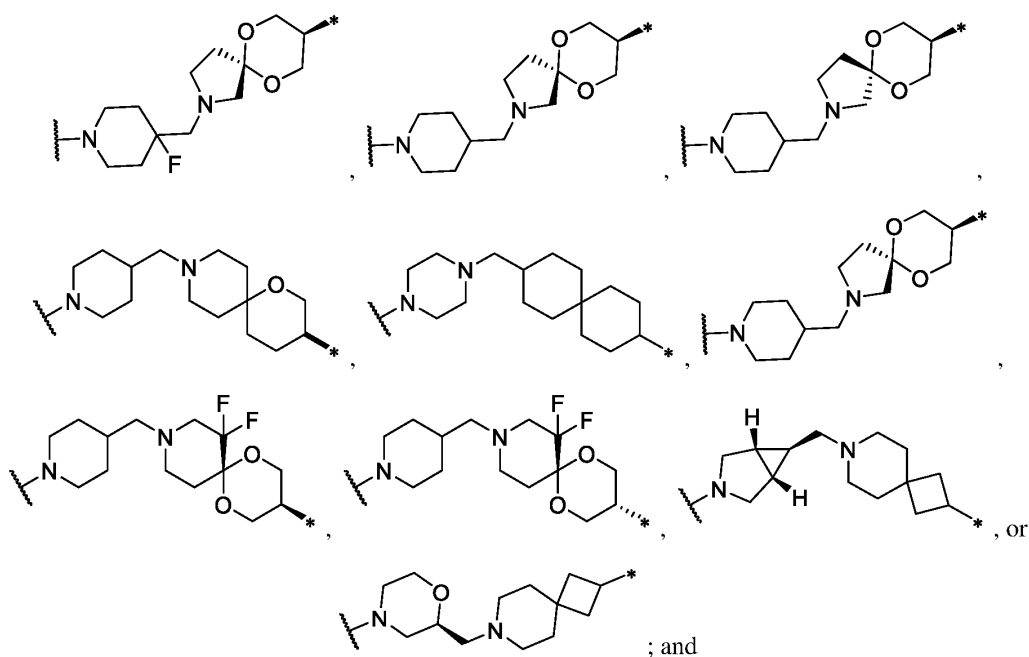
[0924] Embodiment 68. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 67, wherein G^4 is:



[0925] Embodiment 69. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-64, wherein G^4 is a direct bond.

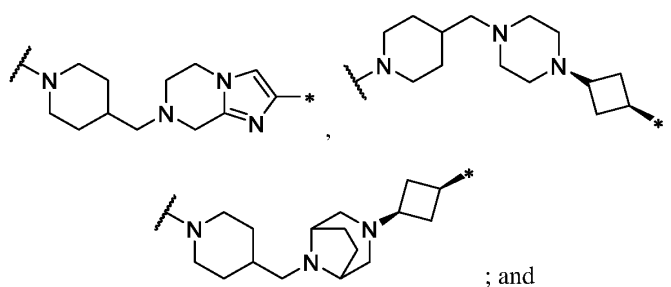
[0926] Embodiment 70. The compound, or pharmaceutically acceptable salt thereof, of any one of Embodiments 1-37, wherein L is:





the bond marked with an "*" is attached to E.

[0927] Embodiment 71. The compound, or pharmaceutically acceptable salt thereof, of any one of Embodiments 2-37, wherein L is:



[0928] the bond marked with an "*" is attached to E.

[0929] Embodiment 72. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-71, wherein W is $\text{-C}\equiv\text{C-}$.

[0930] Embodiment 73. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-71, wherein W is a direct bond.

[0931] Embodiment 74. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-73, wherein R^7 is halogen, $(\text{C}_1\text{-C}_6)\text{alkyl}$, cyano, or $(\text{C}_3\text{-C}_6)\text{cycloalkyl}$, wherein $(\text{C}_1\text{-C}_6)\text{alkyl}$ is optionally substituted with one, two, or three halogen.

[0932] Embodiment 75. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 74, wherein R^7 is halogen or $(\text{C}_1\text{-C}_6)\text{alkyl}$.

[0933] Embodiment 76. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 75, wherein R⁷ is fluoro or methyl.

[0934] Embodiment 77. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 74-76, wherein R⁸, R⁹, and R¹⁰ are H.

[0935] Embodiment 78. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-76, wherein R⁸ is halogen, (C₁-C₆)alkyl, cyano, or (C₃-C₆)cycloalkyl, wherein (C₁-C₆)alkyl is optionally substituted with one, two, or three halogen.

[0936] Embodiment 79. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 78, wherein R⁸ is halogen or (C₁-C₆)alkyl.

[0937] Embodiment 80. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 79, wherein R⁸ is fluoro or methyl.

[0938] Embodiment 81. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 78-80, wherein R⁷, R⁹, and R¹⁰ are hydrogen.

[0939] Embodiment 82. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-76 or 67-69, wherein R⁹ is halogen, (C₁-C₆)alkyl, cyano, or (C₃-C₆)cycloalkyl, wherein (C₁-C₆)alkyl is optionally substituted with one, two, or three halogen.

[0940] Embodiment 83. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 82, wherein R⁹ is halogen.

[0941] Embodiment 84. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 83, wherein R⁹ is fluoro.

[0942] Embodiment 85. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 82-84, wherein R⁷, R⁸, and R¹⁰ are hydrogen.

[0943] Embodiment 86. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-76, 78-80, or 82-84, wherein R¹⁰ is halogen, (C₁-C₆)alkyl, cyano, or (C₃-C₆)cycloalkyl, wherein (C₁-C₆)alkyl is optionally substituted with one, two, or three halogen.

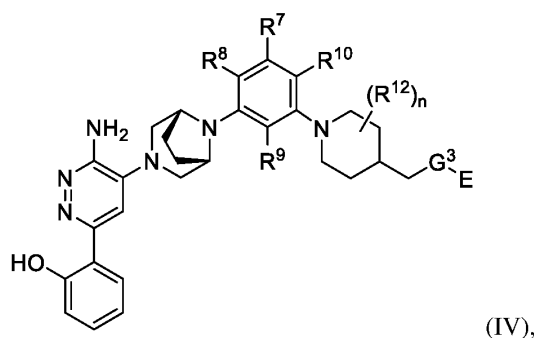
[0944] Embodiment 87. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 86, wherein R¹⁰ is halogen.

[0945] Embodiment 88. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 87, wherein R¹⁰ is fluoro.

[0946] Embodiment 89. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 86-88, wherein R⁷, R⁸, and R⁹ are hydrogen.

[0947] Embodiment 90. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-73, wherein R⁷, R⁸, R⁹, and R¹⁰ are H.

[0948] Embodiment 91. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-2, 5-9, or 35 having Formula (IV):



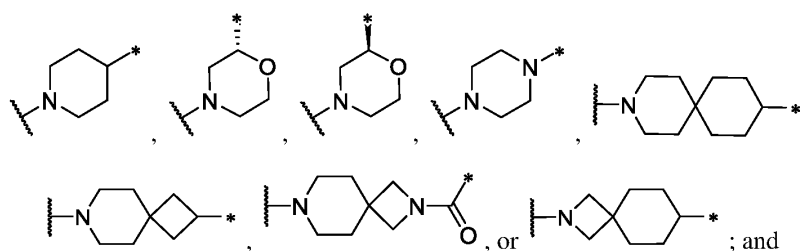
wherein:

[0949] each R^{12} is independently fluoro;

[0950] n is 0, 1, or 2; and

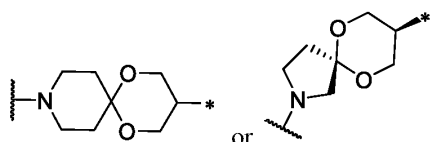
[0951] R^7 , R^8 , R^9 , and R^{10} are independently hydrogen, fluoro, or methyl.

[0952] Embodiment 92. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 91, wherein: G^3 is:



[0953] G^4 is a direct bond, $-\text{CH}_2-$ or $-\text{CH}_2\text{CH}_2-$.

[0954] Embodiment 93. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 91, wherein G^3 is:

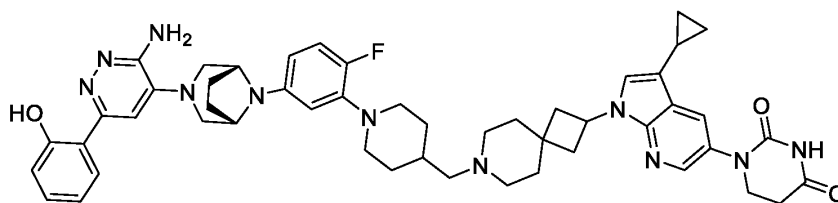


[0955] Embodiment 94. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 1 selected from any one or more of the compounds of Compound List 1.

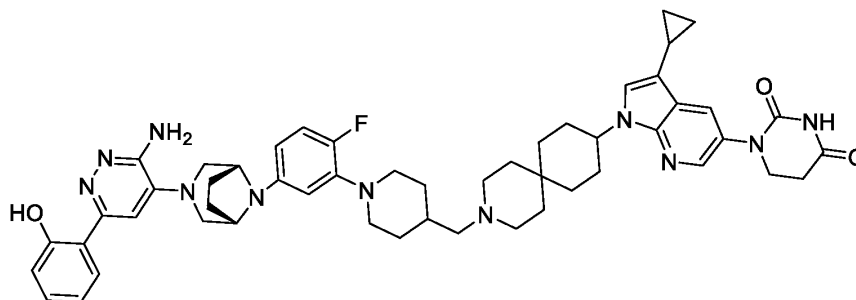
[0956] Embodiment 95. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 1 selected from any one or more of the compounds of Compound List 2 and/or Compound List 3.

[0957] Embodiment 96. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 2 selected from any one or more of the compounds of Compound List 4.

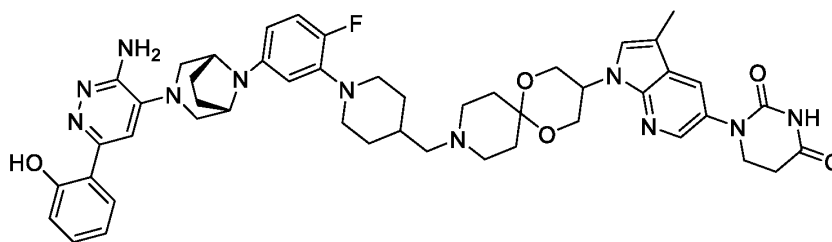
[0958] Embodiment 97. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 94, wherein the compound is:



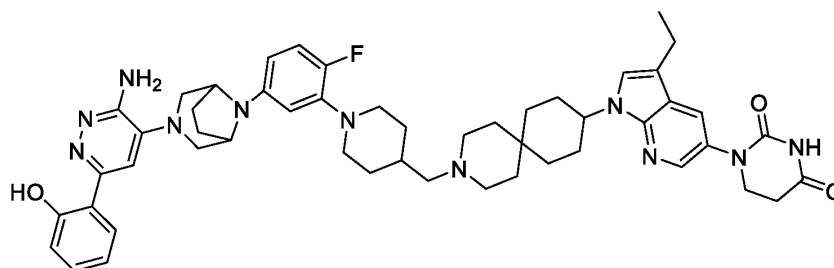
[0959] Embodiment 98. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 94, wherein the compound is:



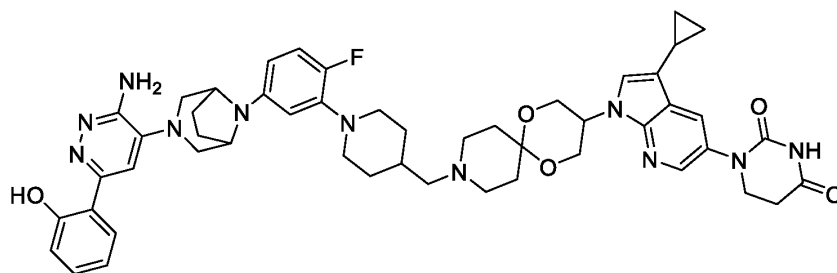
[0960] Embodiment 99. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 94, wherein the compound is:



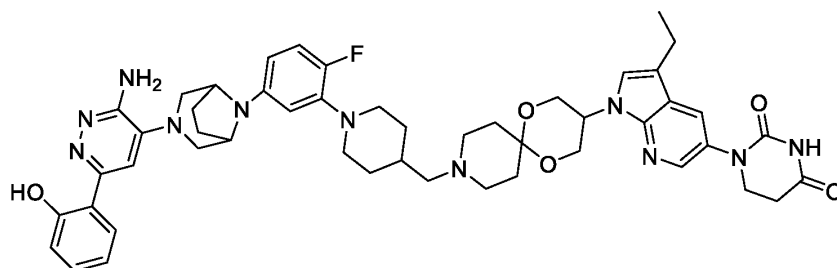
[0961] Embodiment 100. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 96, wherein the compound is:



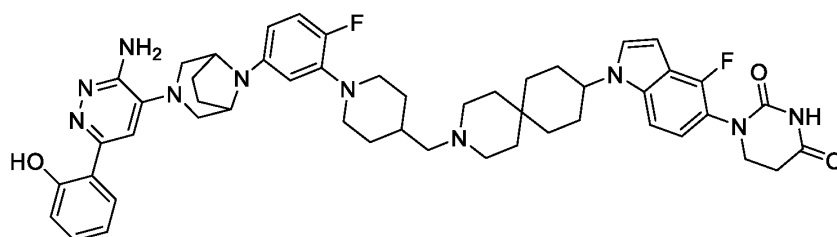
[0962] Embodiment 101. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 96, wherein the compound is:



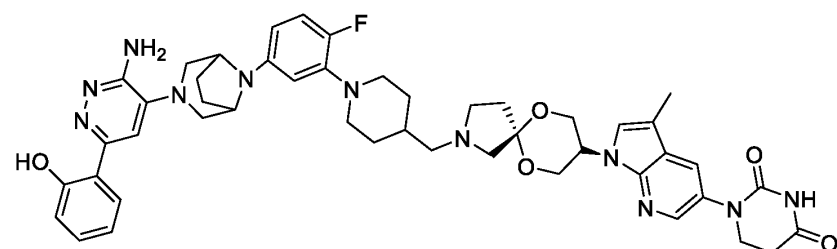
[0963] Embodiment 102. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 96, wherein the compound is:



[0964] Embodiment 103. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 96, wherein the compound is:



[0965] Embodiment 104. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment 96, wherein the compound is:



[0966] Embodiment 105. A pharmaceutical composition comprising the compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-104, and a pharmaceutically acceptable excipient.

[0967] Embodiment 106. A method of degrading SMARCA2 protein in a human, comprising administering to a human in need thereof an effective amount of the compound, or pharmaceutically

acceptable salt thereof, according to any one of Embodiments 1-104, or the composition of Embodiment 105.

[0968] Embodiment 107. A method of reducing the level of SMARCA2 activity in a human, comprising administering to a human in need thereof an effective amount of the compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-104, or the composition of Embodiment 105.

[0969] Embodiment 108. A method of treating cancer in a human, comprising administering to a human in need thereof an effective amount of the compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-104, or the composition of Embodiment 105.

[0970] Embodiment 109. The method of Embodiment 108, wherein the cancer is a SMARCA2-sensitive cancer.

[0971] Embodiment 110. The method of Embodiment 108, wherein the cancer is a SMARCA2-mutated cancer.

[0972] Embodiment 111. The method of any one of Embodiments 108-110, wherein the cancer is a solid tumor.

[0973] Embodiment 112. The method of any one of Embodiments 108-110, wherein the cancer is lung, liver, colon, skin, bladder, cervical or ovarian cancer.

[0974] Embodiment 113. A compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-104, or the composition of Embodiment 105 for use in degrading SMARCA2 protein in a human.

[0975] Embodiment 114. A compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-104, or the composition of Embodiment 105 for use in reducing the level of SMARCA2 activity in a human.

[0976] Embodiment 115. A compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-104, or the composition of Embodiment 105 for use in treating cancer in a human.

[0977] Embodiment 116. The compound for use of Embodiment 115, wherein the cancer is a SMARCA2-sensitive cancer.

[0978] Embodiment 117. The compound for use of Embodiment 115, wherein the cancer is a SMARCA2-mutated cancer.

[0979] Embodiment 118. The compound for use of any one of Embodiments 115-117, wherein the cancer is a solid tumor.

[0980] Embodiment 119. The compound for use of any one of Embodiments 115-117, wherein the cancer is lung, liver, colon, skin, bladder, cervical or ovarian cancer.

[0981] Embodiment 120. Use of a compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-104, or the composition of Embodiment 105 in the manufacture of a medicament for degrading SMARCA2 protein in a human.

[0982] Embodiment 121. Use of a compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-104, or the composition of Embodiment 105 in the manufacture of a medicament for reducing the level of SMARCA2 activity in a human.

[0983] Embodiment 122. Use of a compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments 1-104, or the composition of Embodiment 105 in the manufacture of a medicament for treating cancer in a human.

[0984] Embodiment 123. The compound, or pharmaceutically acceptable salt thereof, for use of Embodiment 122, wherein the cancer is a SMARCA2-sensitive cancer.

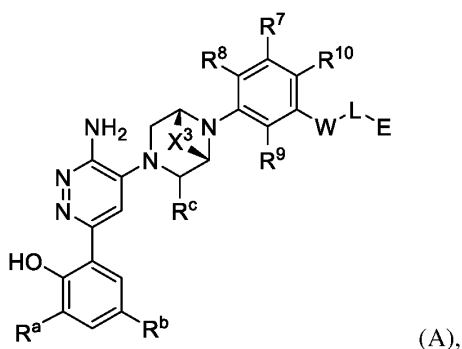
[0985] Embodiment 124. The compound, or pharmaceutically acceptable salt thereof, for use of Embodiment 122, wherein the cancer is a SMARCA2-mutated cancer.

[0986] Embodiment 125. The compound, or pharmaceutically acceptable salt thereof, for use of any one of Embodiments 122-124, wherein the cancer is a solid tumor.

[0987] Embodiment 126. The compound, or pharmaceutically acceptable salt thereof, for use of any one of Embodiments 122-124, wherein the cancer is lung, liver, colon, skin, bladder, cervical or ovarian cancer.

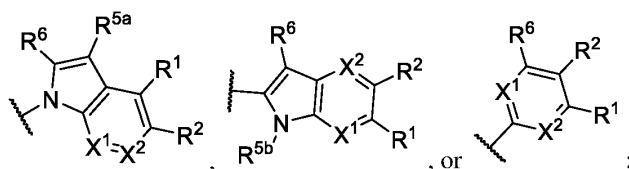
[0988] The present disclosure also provides the following particular embodiments.

[0989] Embodiment A 1. A compound of Formula (A), or pharmaceutically acceptable salt thereof:

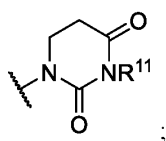


wherein:

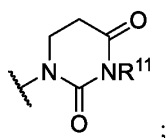
[0990] E is:



[0991] R¹ is hydrogen, halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or

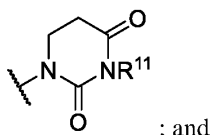


[0992] R^2 is hydrogen, halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or



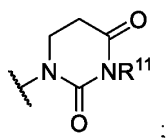
[0993] with the provisos:

[0994] (i) when R^1 is hydrogen, halogen, (C₁-C₆)alkyl, or (C₁-C₆)alkoxy, then R^2 is:



; and

[0995] (ii) when R^2 is hydrogen, halogen, (C₁-C₆)alkyl, or (C₁-C₆)alkoxy, then R^1 is



[0996] R^{11} is hydrogen or -(C₁-C₆)alkyl-O-P(=O)-(OH)₂;

[0997] X^1 is CR³ or N;

[0998] R^3 is hydrogen, halogen, or (C₁-C₆)alkyl;

[0999] X^2 is CR⁴ or N;

[1000] R^4 is hydrogen, halogen, or (C₁-C₆)alkyl;

[1001] R^{5a} is hydrogen, halogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, 4- to 6-membered heterocycloalkyl, cyano, aryl, or 5- or 6-membered heteroaryl,

[1002] wherein (C₁-C₆)alkyl is optionally substituted with one, two, or three substituents independently selected from halogen or cyano; and 4- to 6-membered heterocycloalkyl, aryl, or 5- or 6-membered heteroaryl is optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or (C₁-C₆)alkyl;

[1003] R^{5b} is hydrogen, (C₁-C₆)alkyl, or (C₃-C₆)cycloalkyl;

[1004] R^6 is hydrogen, (C₁-C₆)alkyl, or cyano;

[1005] X^3 is -CH₂CH₂- or -CH₂-O-CH₂-;

[1006] Or X^3 is absent;

[1007] L is G¹-G²-G³-G⁴-, wherein G¹ is attached to W;

[1008] G¹ is (C₁-C₆)alkylenyl; (C₃-C₆)cycloalkylenyl; -O-CH₂-CH₂-; 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, cyano, or hydroxyl; or 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or cyano;

[1009] G^2 is (C_1-C_6) alkylenyl, $-C(=O)-$, 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three fluoro, or a direct bond;

[1010] G^3 is $-C(=O)-$; $-C(=O)-CH_2CH_2-$; (C_1-C_6) alkylenyl; tetrahydronaphthalenylenyl; 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy or cyano; 7- to 11-membered heterocycloalkyl- $C(=O)-$, or 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano;

[1011] G^4 is (C_1-C_6) alkylenyl, (C_3-C_6) cycloalkylenyl; 4- to 6-membered heterocycloalkylenyl; or a direct bond;

[1012] W is $-C\equiv C-$ or a direct bond;

[1013] R^7 is hydrogen; halogen; (C_1-C_6) alkyl optionally substituted with one, two, or three halogen; cyano; or (C_3-C_6) cycloalkyl;

[1014] R^8 is hydrogen; halogen; (C_1-C_6) alkyl optionally substituted with one, two, or three halogen; cyano; or (C_3-C_6) cycloalkyl;

[1015] R^9 is hydrogen; halogen; (C_1-C_6) alkyl optionally substituted with one, two, or three halogen; cyano; or (C_3-C_6) cycloalkyl;

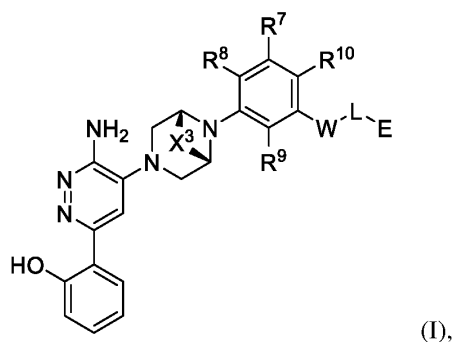
[1016] R^{10} is hydrogen; halogen; (C_1-C_6) alkyl optionally substituted with one, two, or three halogen; cyano; or (C_3-C_6) cycloalkyl;

[1017] R^a is hydrogen or halogen;

[1018] R^b is hydrogen or halogen; and

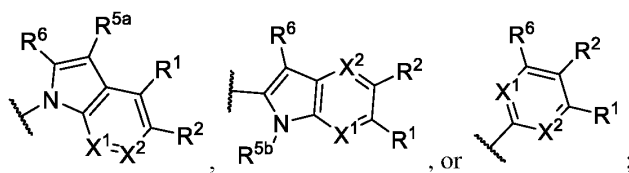
[1019] R^c is hydrogen or methyl.

[1020] Embodiment A 2. A compound of Formula (I), or pharmaceutically acceptable salt thereof:

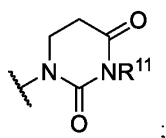


wherein:

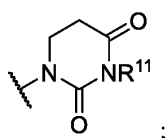
[1021] E is:



[1022] R^1 is hydrogen, halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or

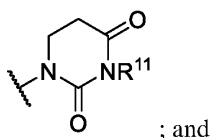


[1023] R^2 is hydrogen, halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or

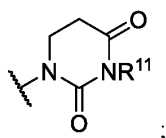


with the provisos:

[1024] (i) when R^1 is hydrogen, halogen, (C₁-C₆)alkyl, or (C₁-C₆)alkoxy, then R^2 is:



[1025] (ii) when R^2 is hydrogen, halogen, (C₁-C₆)alkyl, or (C₁-C₆)alkoxy, then R^1 is



[1026] R^{11} is hydrogen or -(C₁-C₆)alkyl-O-P(=O)-(OH)₂;

[1027] X^1 is CR³ or N;

[1028] R^3 is hydrogen, halogen, or (C₁-C₆)alkyl;

[1029] X^2 is CR⁴ or N;

[1030] R^4 is hydrogen, halogen, or (C₁-C₆)alkyl;

[1031] R^{5a} is hydrogen, halogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, 4- to 6-membered heterocycloalkyl, cyano, aryl, or 5- or 6-membered heteroaryl, wherein (C₁-C₆)alkyl is optionally substituted with one, two, or three substituents independently selected from halogen or cyano; and 4- to 6-membered heterocycloalkyl, aryl, or 5- or 6-membered heteroaryl is optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or (C₁-C₆)alkyl;

[1032] R^{5b} is hydrogen, (C₁-C₆)alkyl, or (C₃-C₆)cycloalkyl;

[1033] R^6 is hydrogen, (C₁-C₆)alkyl, or cyano;

[1034] X^3 is -CH₂CH₂- or -CH₂-O-CH₂-;

[1035] Or X^3 is absent;

[1036] L is -G¹-G²-G³-G⁴-, wherein G¹ is attached to W;

[1037] G¹ is (C₁-C₆)alkenyl; 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or cyano; or

7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or cyano;

[1038] G² is (C₁-C₆)alkylenyl or a direct bond;

[1039] G³ is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or cyano; or 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or cyano;

[1040] G⁴ is (C₁-C₆)alkylenyl or a direct bond;

[1041] W is -C≡C- or a direct bond;

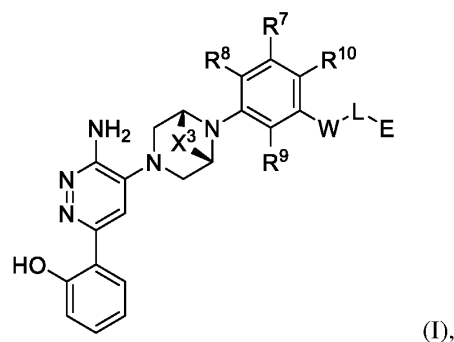
[1042] R⁷ is hydrogen, halogen, (C₁-C₆)alkyl optionally substituted with one, two, or three halogen, cyano, or (C₃-C₆)cycloalkyl;

[1043] R⁸ is hydrogen, halogen, (C₁-C₆)alkyl optionally substituted with one, two, or three halogen, cyano, or (C₃-C₆)cycloalkyl;

[1044] R⁹ is hydrogen, halogen, (C₁-C₆)alkyl optionally substituted with one, two, or three halogen, cyano, or (C₃-C₆)cycloalkyl; and

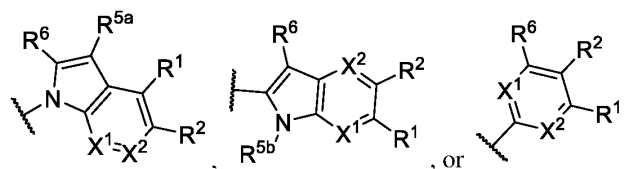
[1045] R¹⁰ is hydrogen, halogen, (C₁-C₆)alkyl optionally substituted with one, two, or three halogen, cyano, or (C₃-C₆)cycloalkyl.

[1046] Embodiment A 3. A compound of Formula (I), or pharmaceutically acceptable salt thereof:

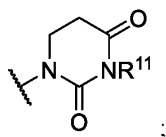


wherein:

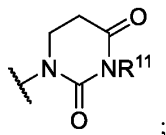
[1047] E is:



[1048] R¹ is hydrogen, halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or

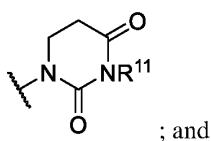


[1049] R^2 is hydrogen, halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or



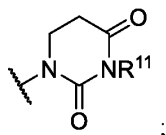
with the provisos:

[1050] (i) when R^1 is hydrogen, halogen, (C_1-C_6) alkyl, or (C_1-C_6) alkoxy, then R^2 is:



; and

[1051] (ii) when R^2 is hydrogen, halogen, (C_1-C_6) alkyl, or (C_1-C_6) alkoxy, then R^1 is:



[1052] R^{11} is hydrogen or $-(C_1-C_6)$ alkyl-O-P(=O)-(OH)₂;

[1053] X^1 is CR^3 or N;

[1054] R^3 is hydrogen, halogen, or (C_1-C_6) alkyl;

[1055] X^2 is CR^4 or N;

[1056] R^4 is hydrogen, halogen, or (C_1-C_6) alkyl;

[1057] R^{5a} is hydrogen, halogen, (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, 4- to 6-membered heterocycloalkyl, cyano, aryl, or 5- or 6-membered heteroaryl, wherein (C_1-C_6) alkyl is optionally substituted with one, two, or three substituents independently selected from halogen or cyano; and 4- to 6-membered heterocycloalkyl, aryl, or 5- or 6-membered heteroaryl is optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or (C_1-C_6) alkyl;

[1058] R^{5b} is hydrogen, (C_1-C_6) alkyl, or (C_3-C_6) cycloalkyl;

[1059] R^6 is hydrogen, (C_1-C_6) alkyl, or cyano;

[1060] X^3 is $-CH_2CH_2-$ or $-CH_2-O-CH_2-$; or

[1061] X^3 is absent;

[1062] L is $-G^1-G^2-G^3-G^4-$, wherein G^1 is attached to W;

[1000] G^1 is (C_1-C_6) alkenyl; 4- to 6-membered heterocycloalkenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano; or

7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or cyano;

[1064] G² is (C₁-C₆)alkylenyl or a direct bond;

[1065] G³ is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or cyano; 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or cyano; or 5- to 10-membered heteroarylenyl;

[1066] G⁴ is (C₁-C₆)alkylenyl, (C₃-C₆)cycloalkylenyl, or a direct bond;

[1067] W is $\text{-C}\equiv\text{C-}$ or a direct bond:

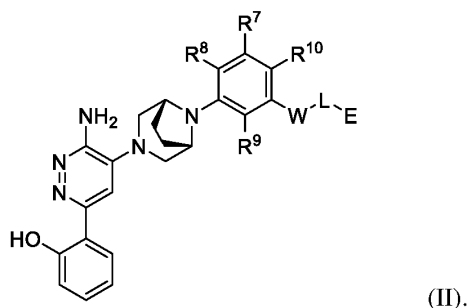
[1068] R⁷ is hydrogen, halogen, (C₁-C₆)alkyl optionally substituted with one, two, or three halogen, cyano, or (C₃-C₆)cycloalkyl;

[1069] R⁸ is hydrogen, halogen, (C₁-C₆)alkyl optionally substituted with one, two, or three halogen, cyano, or (C₃-C₆)cycloalkyl;

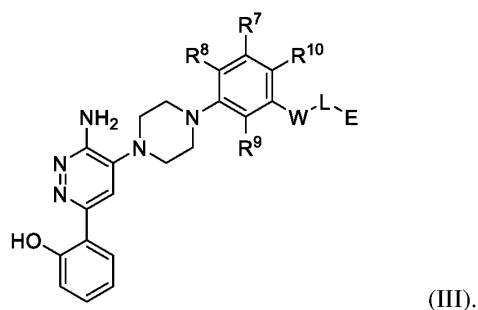
[1070] R⁹ is hydrogen, halogen, (C₁-C₆)alkyl optionally substituted with one, two, or three halogen, cyano, or (C₃-C₆)cycloalkyl; and

[1071] R¹⁰ is hydrogen, halogen, (C₁-C₆)alkyl optionally substituted with one, two, or three halogen, cyano, or (C₃-C₆)cycloalkyl.

[1072] Embodiment A 4. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 2 or 3 having Formula (II):



[1073] Embodiment A 5. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 2 or 3 having Formula (III):



[1074] Embodiment A 6. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-5, wherein R^{5a} is hydrogen.

[1075] Embodiment A 7. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-5, wherein R^{5a} is (C₁-C₆)alkyl optionally substituted with one, two, or three substituents independently selected from halogen or cyano.

[1076] Embodiment A 8. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 7, wherein R^{5a} is methyl.

[1077] Embodiment A 9. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-5, wherein R^{5a} is (C₃-C₆)cycloalkyl.

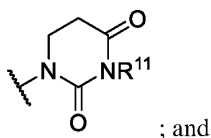
[1078] Embodiment A 10. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 9, wherein R^{5a} is cyclopropyl.

[1079] Embodiment A 11. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-5, wherein R^{5a} is 4- to 6-membered heterocycloalkyl optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or (C₁-C₆)alkyl.

[1080] Embodiment A 12. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-5, wherein R^{5a} is cyano.

[1081] Embodiment A 13. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-5, wherein:

[1082] R¹ is:



[1083] R² is hydrogen, halogen, (C₁-C₆)alkyl, or (C₁-C₆)alkoxy.

[1084] Embodiment A 14. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-5, wherein R² is hydrogen, halogen, or (C₁-C₆)alkyl.

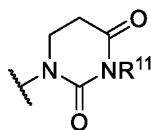
[1085] Embodiment A 15. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-5, wherein R² is hydrogen, fluoro, or methyl.

[1086] Embodiment A 16. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-5, wherein R¹¹ is hydrogen.

[1087] Embodiment A 17. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-5, wherein:

[1088] R¹ is hydrogen, halogen, (C₁-C₆)alkyl, or (C₁-C₆)alkoxy; and

[1089] R² is:



[1090] Embodiment A 18. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 17, wherein R¹ is hydrogen, halogen, or (C₁-C₆)alkyl.

[1091] Embodiment A 19. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 18, wherein R¹ is hydrogen, fluoro, or methyl.

[1092] Embodiment A 20. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 17-19, wherein R¹¹ is hydrogen.

[1093] Embodiment A 21. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-5, wherein X¹ is CR³.

[1094] Embodiment A 22. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 21, wherein R³ is hydrogen.

[1095] Embodiment A 23. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 21, wherein R³ is halogen.

[1096] Embodiment A 24. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 21, wherein R³ is (C₁-C₆)alkyl.

[1097] Embodiment A 25. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-5, wherein X¹ is N.

[1098] Embodiment A 26. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-5, wherein X² is CR⁴.

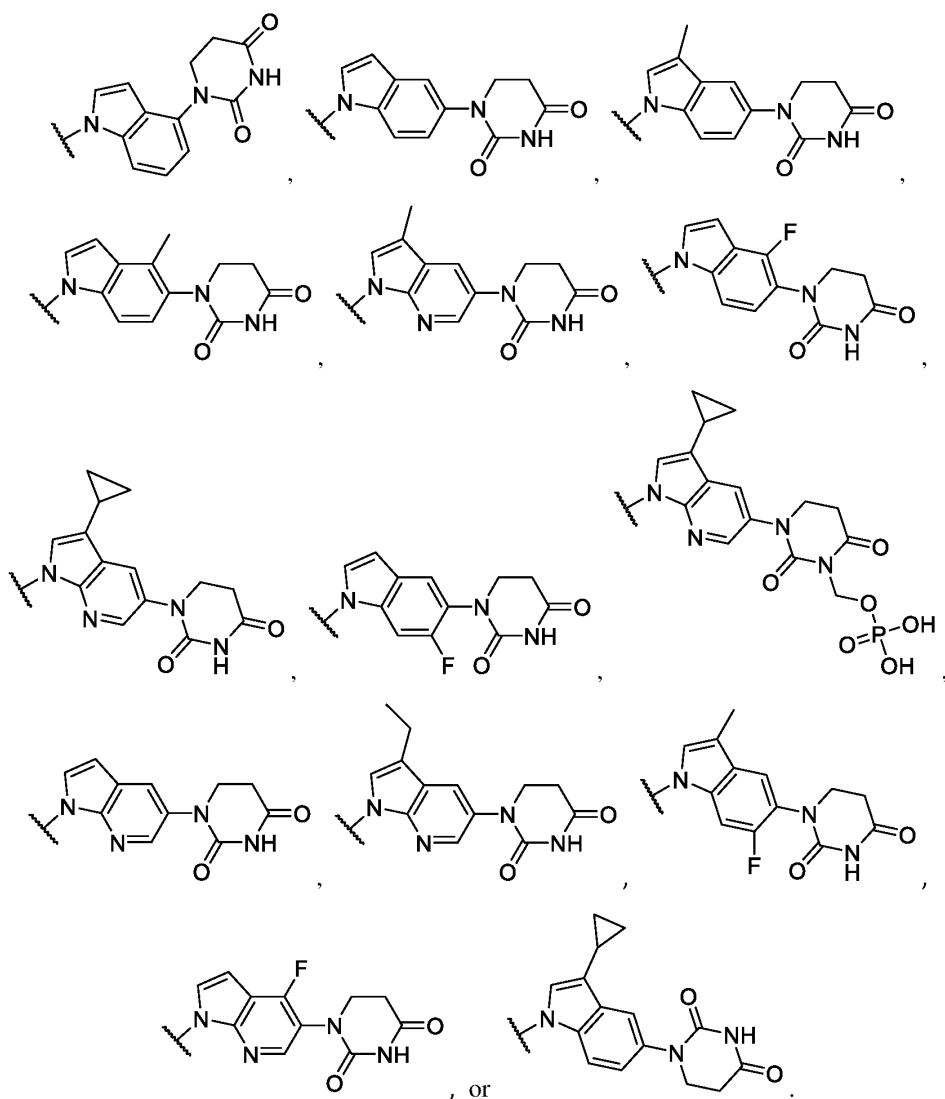
[1099] Embodiment A 27. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 26, wherein R⁴ is hydrogen.

[1100] Embodiment A 28. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 26, wherein R⁴ is halogen.

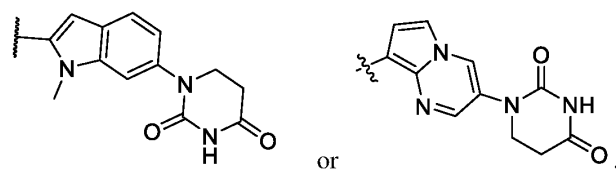
[1101] Embodiment A 29. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 26, wherein R⁴ is (C₁-C₆)alkyl.

[1102] Embodiment A 30. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-5, wherein X² is N.

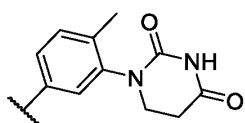
[1103] Embodiment A 31. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-5, wherein E is:



[1104] Embodiment A 32. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-5, wherein E is:



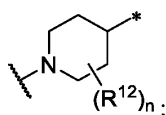
[1105] Embodiment A 33. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-5, wherein E is:



[1106] Embodiment A 34. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-33, wherein G^1 is (C_3-C_6) cycloalkylenyl; or 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, cyano, or hydroxyl.

[1107] Embodiment A 35. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 34, wherein:

[1108] G^1 is:



[1109] each R^{12} is independently halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, cyano, or hydroxyl;

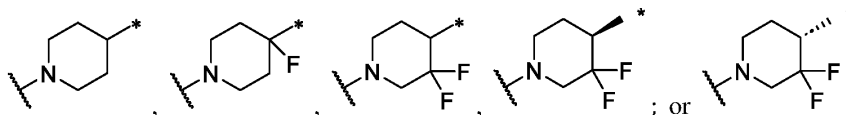
[1110] n is 0, 1, 2, or 3; and

[1111] the bond marked with an "*" is attached to G^2 .

[1112] Embodiment A 36. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 35, wherein each R^{12} is independently fluoro, methyl, methoxy, cyano, or $-CHF_2$; and n is 0, 1, or 2.

[1113] Embodiment A 37. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 35, wherein:

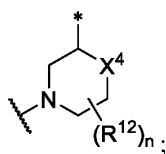
[1114] G^1 is:



[1115] and bond marked with an "*" is attached to G^2 .

[1116] Embodiment A 38. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 34, wherein:

[1117] G^1 is:



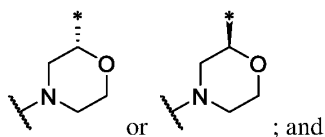
[1118] wherein X^4 is $-O-$;

[1119] each R^{12} is independently halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano; and

[1120] the bond marked with an "*" is attached to G^2 .

[1121] Embodiment A 39. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 38, wherein:

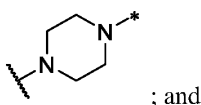
[1122] G^1 is:



[1123] the bond marked with an "*" is attached to G².

[1124] Embodiment A 44. The compound, or pharmaceutically acceptable salt thereof, according Embodiment A 34, wherein:

[1125] G¹ is:

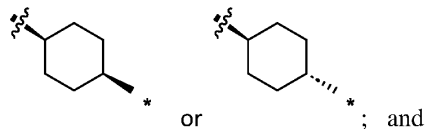


[1126] the bond marked with an "*" is attached to G².

[1127] Embodiment A 41. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 1, wherein G¹ is cyclohexylenyl.

[1128] Embodiment A 42. The compound, or pharmaceutically acceptable salt thereof, according Embodiment A 41, wherein:

[1129] G¹ is:

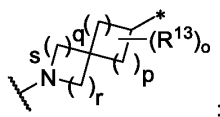


[1130] the bond marked with an "*" is attached to G².

[1131] Embodiment A 43. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-33, wherein G¹ is 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or cyano.

[1132] Embodiment A 44. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 43, wherein:

[1133] G¹ is:



[1134] each R¹³ is independently selected from halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or cyano;

[1135] o is 0, 1, 2, or 3;

[1136] p, q, r, and s are independently 1 or 2;

[1137] the bond marked with an "*" is attached to G².

[1138] Embodiment A 45. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 44, wherein:

[1139] p and q are 1;

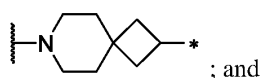
[1140] r is 1 or 2;

[1141] s is 1 or 2; and

[1142] R^{13} is halogen.

[1143] Embodiment A 46. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 45, wherein R^{13} is fluoro and o is 0, 1, or 2.

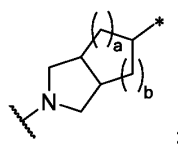
[1144] Embodiment A 47. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 44, wherein G^1 is:



[1145] the bond marked with an "*" is attached to G^2 .

[1146] Embodiment A 48. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 43, wherein:

[1147] G^1 is:

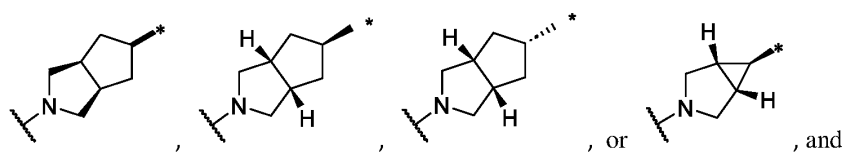


[1148] a is 0 or 1;

[1149] b is 0 or 1; and

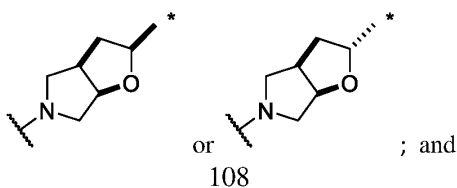
[1150] the bond marked with an "*" is attached to G^2 .

[1151] Embodiment A 49. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 48, wherein G^1 is:



[1152] the bond marked with an "*" is attached to G^2 .

[1153] Embodiment A 50. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 43, wherein G^1 is:



[1154] the bond marked with an "*" is attached to G².

[1155] Embodiment A 51. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-50, wherein G² is a direct bond.

[1156] Embodiment A 52. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1 or 6-50, wherein G² is a C(=O).

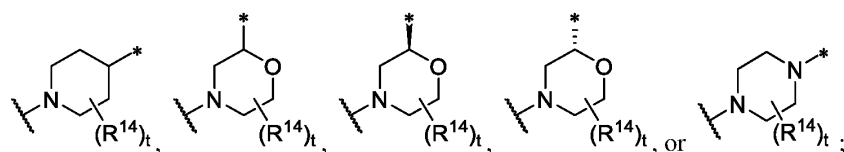
[1157] Embodiment A 53. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-50, wherein G² is (C₁-C₆)alkylenyl.

[1158] Embodiment A 54. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 53, wherein G² is -CH₂-.

[1159] Embodiment A 55. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-54, wherein G³ is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or cyano.

[1160] Embodiment A 56. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 55, wherein:

[1161] G³ is:



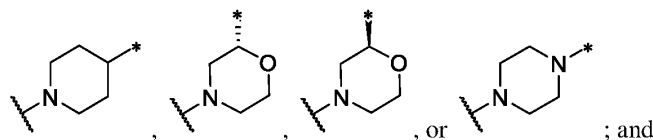
[1162] each R¹⁴ is independently halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or cyano;

[1163] t is 0, 1, 2, or 3; and

[1164] the bond marked with an "*" is attached to G⁴.

[1165] Embodiment A 57. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 56, wherein R¹⁴ is fluoro or methyl and t is 0 or 1.

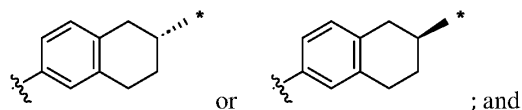
[1166] Embodiment A 58. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 56, wherein G³ is:



[1167] the bond marked with an "*" is attached to G⁴.

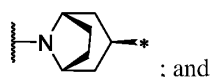
[1168] Embodiment A 59. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-54, wherein G³ is 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or cyano.

[1169] Embodiment A 60. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 1, wherein G^3 is



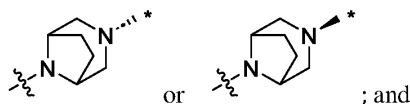
[1170] the bond marked with an "*" is attached to G^4 .

[1171] Embodiment A 61. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 59, wherein G^3 is:



[1172] the bond marked with an "*" is attached to G^4 .

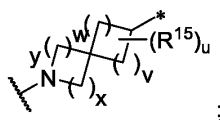
[1173] Embodiment A 62. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 59, wherein G^3 is:



[1174] the bond marked with an "*" is attached to G^4 .

[1175] Embodiment A 63. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 59, wherein:

[1176] G^3 is:



[1177] each R^{15} is independently selected from halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano;

[1178] u is 0, 1, 2, or 3;

[1179] v , w , x , and y are independently 1, 2, or 3; and

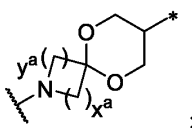
[1180] the bond marked with an "*" is attached to G^4 .

[1181] Embodiment A 64. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 63, wherein v , w , x , and y are independently 1 or 2.

[1182] Embodiment A 65. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 63, wherein R^{15} is fluoro.

[1183] Embodiment A 66. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 59, wherein:

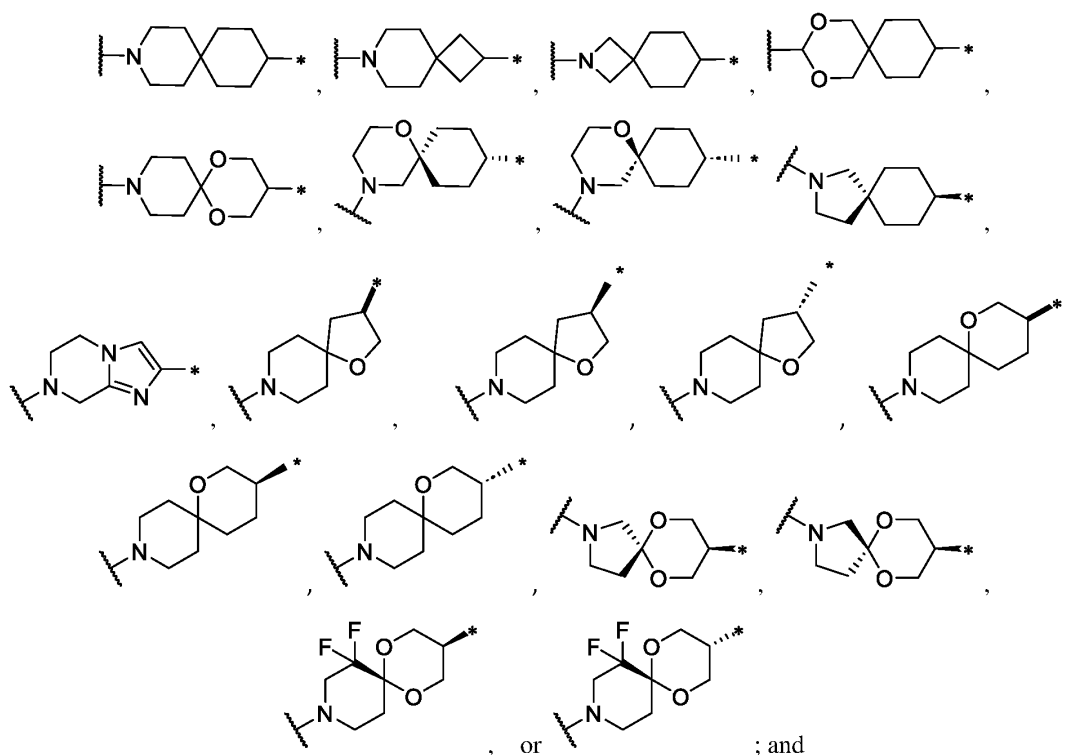
[1184] G^3 is:



[1185] x^a and y^a are independently 1 or 2 ; and

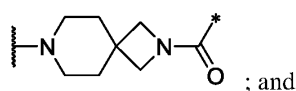
[1186] the bond marked with an "*" is attached to G⁴.

[1187] Embodiment A 67. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 59, wherein G³ is:



[1188] the bond marked with an “*” is attached to G⁴.

[1189] Embodiment A 68. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 1, wherein G^3 is



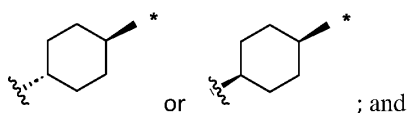
[1190] the bond marked with an “*” is attached to G⁴.

[1191] Embodiment A 69. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-68, wherein G⁴ is (C₁-C₆)alkylenyl.

[1192] Embodiment A 70. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 69, wherein G⁴ is -CH₂- or -CH₂CH₂-.

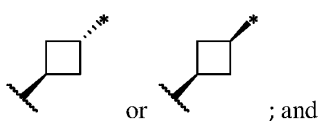
[1193] Embodiment A 71. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 1, wherein G^4 is (C₃-C₆)cycloalkylenyl.

[1194] Embodiment A 72. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 71, wherein G^4 is :



[1195] the bond marked with an “*” is attached to E.

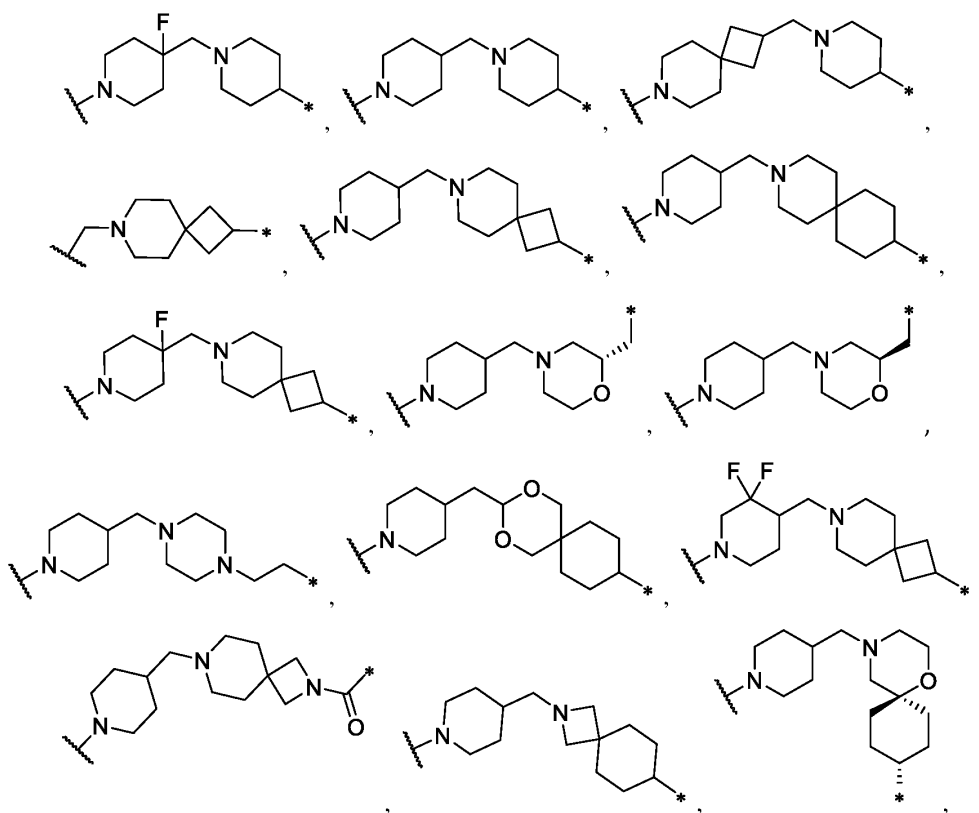
[1196] Embodiment A 73. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 71, wherein G^4 is:

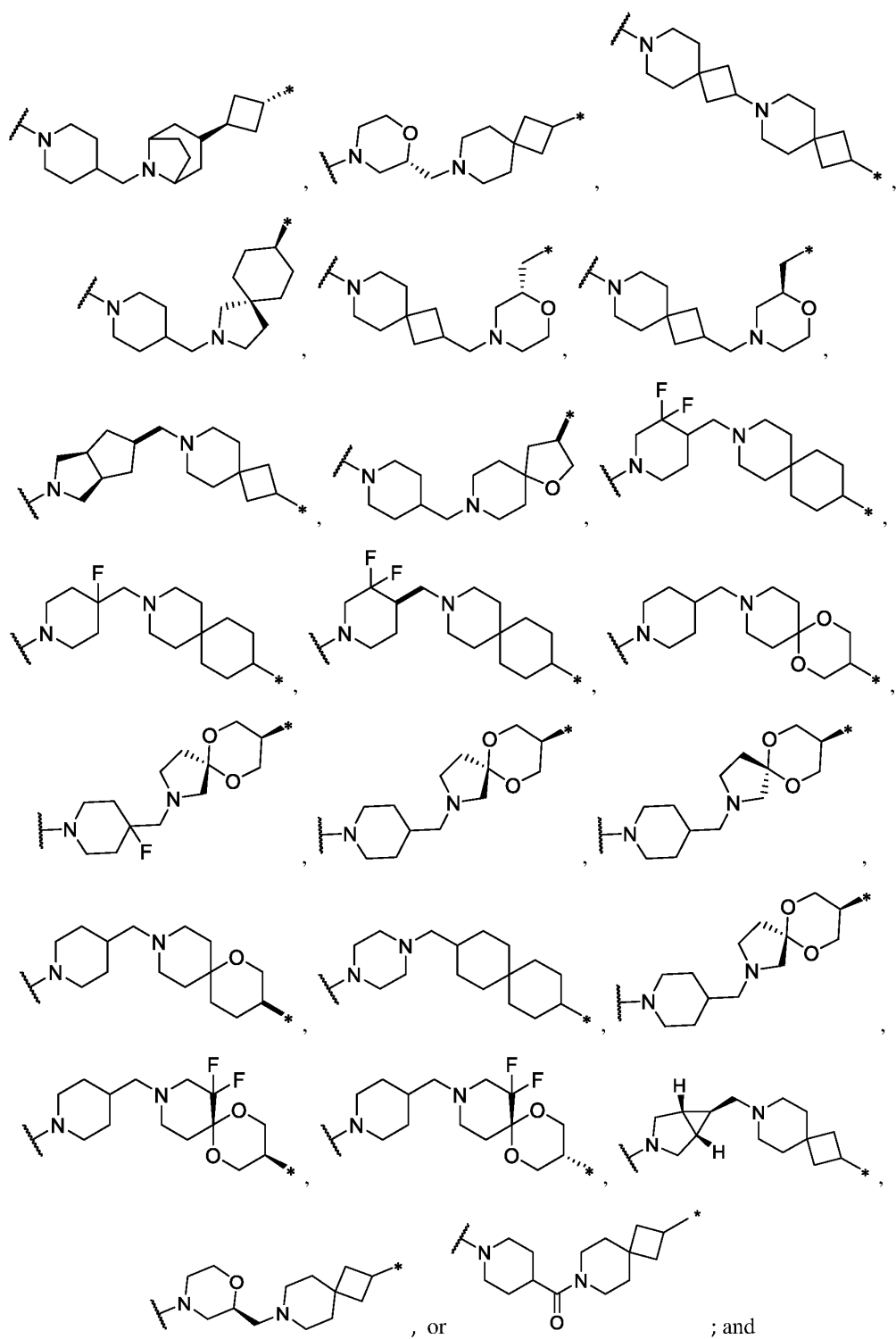


[1197] the bond marked with an “*” is attached to G^4 .

[1198] Embodiment A 74. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-68, wherein G^4 is a direct bond.

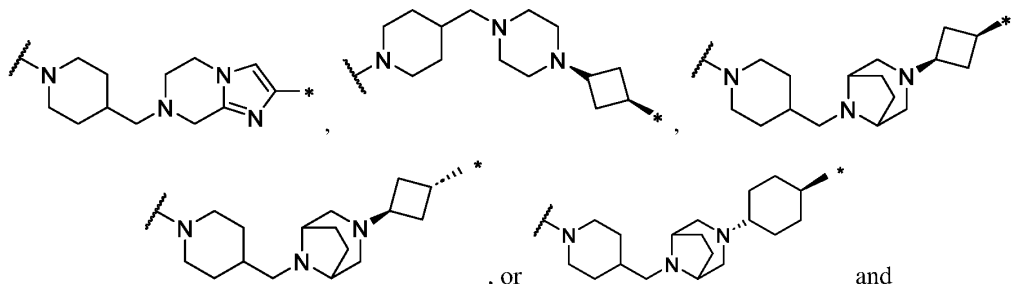
[1199] Embodiment A 75. The compound, or pharmaceutically acceptable salt thereof, of any one of Embodiments A 1-33, wherein L is:





[1200] the bond marked with an "*" is attached to E.

[1201] Embodiment A 76. The compound, or pharmaceutically acceptable salt thereof, of any one of Embodiments A 1-33, wherein L is:



[1202] the bond marked with an "*" is attached to E.

[1203] Embodiment A 77. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-76, wherein W is $\text{-C}\equiv\text{C-}$.

[1204] Embodiment A 78. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-76, wherein W is a direct bond.

[1205] Embodiment A The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-78, wherein R^7 , R^8 , R^9 , and R^{10} are H.

[1206] Embodiment A 80. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-78, wherein R^7 is halogen, $(\text{C}_1\text{-C}_6)\text{alkyl}$, cyano, or $(\text{C}_3\text{-C}_6)\text{cycloalkyl}$, wherein $(\text{C}_1\text{-C}_6)\text{alkyl}$ is optionally substituted with one, two, or three halogen.

[1207] Embodiment A 81. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 80, wherein R^7 is halogen or $(\text{C}_1\text{-C}_6)\text{alkyl}$.

[1208] Embodiment A 82. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 81, wherein R^7 is fluoro or methyl.

[1209] Embodiment A 83. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 80-82, wherein R^8 , R^9 , and R^{10} are hydrogen.

[1210] Embodiment A 84. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-78, wherein R^8 is halogen, $(\text{C}_1\text{-C}_6)\text{alkyl}$, cyano, or $(\text{C}_3\text{-C}_6)\text{cycloalkyl}$, wherein $(\text{C}_1\text{-C}_6)\text{alkyl}$ is optionally substituted with one, two, or three halogen.

[1211] Embodiment A 85. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 84, wherein R^8 is halogen or $(\text{C}_1\text{-C}_6)\text{alkyl}$.

[1212] Embodiment A 86. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 85, wherein R^8 is fluoro or methyl.

[1213] Embodiment A 87. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 84-86, wherein R^7 , R^9 , and R^{10} are hydrogen.

[1214] Embodiment A 88. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-78, wherein R^9 is halogen, (C_1-C_6) alkyl, cyano, or (C_3-C_6) cycloalkyl, wherein (C_1-C_6) alkyl is optionally substituted with one, two, or three halogen.

[1215] Embodiment A 89. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 88, wherein R^9 is halogen.

[1216] Embodiment A 90. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 89, wherein R^9 is fluoro.

[1217] Embodiment A 91. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 88-90, wherein R^7 , R^8 , and R^{10} are hydrogen.

[1218] Embodiment A 92. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-78, wherein R^{10} is halogen, (C_1-C_6) alkyl, cyano, or (C_3-C_6) cycloalkyl, wherein (C_1-C_6) alkyl is optionally substituted with one, two, or three halogen.

[1219] Embodiment A 93. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 92, wherein R^{10} is halogen.

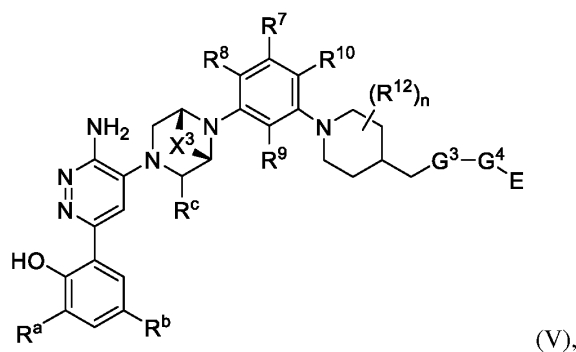
[1220] Embodiment A 94. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 93, wherein R^{10} is fluoro.

[1221] Embodiment A 95. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 92-94, wherein R^7 , R^9 , and R^9 are hydrogen.

[1222] Embodiment A 96. The compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-78, wherein R^{10} is cyano.

[1223] Embodiment A 97. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 96, wherein R^{10} is cyano; and R^7 , R^8 , and R^9 are hydrogen.

[1224] Embodiment A 98. A compound of Formula (V), or pharmaceutically acceptable salt thereof,

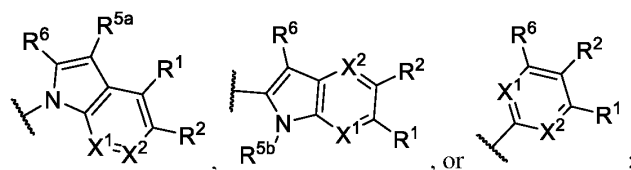


wherein:

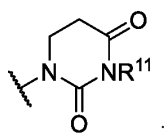
[1225] each R^{12} is fluoro or hydroxyl;

[1226] n is 0, 1, 2, or 3;

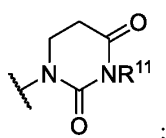
[1227] E is:



[1228] R^1 is hydrogen, halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or

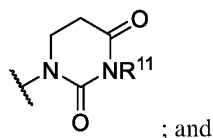


[1229] R^2 is hydrogen, halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or



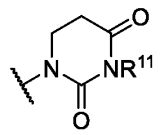
with the provisos:

[1230] (i) when R^1 is hydrogen, halogen, (C_1-C_6) alkyl, or (C_1-C_6) alkoxy, then R^2 is:



; and

[1231] (ii) when R^2 is hydrogen, halogen, (C_1-C_6) alkyl, or (C_1-C_6) alkoxy, then R^1 is:



[1232] R^{11} is hydrogen or $-(C_1-C_6)alkyl-O-P(=O)-(OH)_2$;

[1233] X^1 is CR^3 or N;

[1234] R^3 is hydrogen, halogen, or (C_1-C_6) alkyl;

[1235] X^2 is CR^4 or N;

[1236] R^4 is hydrogen, halogen, or (C_1-C_6) alkyl;

[1237] R^{5a} is hydrogen, halogen, (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, 4- to 6-membered heterocycloalkyl, cyano, aryl, or 5- or 6-membered heteroaryl, wherein (C_1-C_6) alkyl is optionally substituted with one, two, or three substituents independently selected from halogen or cyano; and 4- to 6-membered heterocycloalkyl, aryl, or 5- or 6-membered heteroaryl is optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or (C_1-C_6) alkyl;

[1238] R^{5b} is hydrogen, (C_1-C_6) alkyl, or (C_3-C_6) cycloalkyl;

[1239] R^6 is hydrogen, (C_1-C_6) alkyl, or cyano;

[1240] X^3 is $-CH_2CH_2-$ or absent;

[1241] G^3 is tetrahydronaphthalene; 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or cyano; 7- to 11-membered heterocycloalkyl-C(=O)-, or 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or cyano;

[1242] G^4 is absent or cyclobutylenyl;

[1243] R^7 , R^8 , R^9 , and R^{10} are independently hydrogen, fluoro, methyl, or cyano;

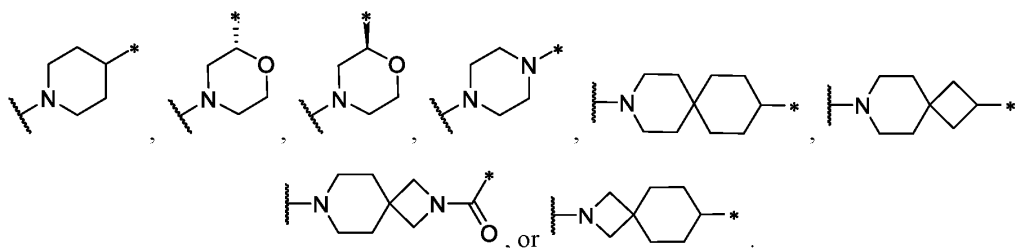
[1244] R^a is hydrogen, chloro, methyl, or fluoro;

[1245] R^b is hydrogen, chloro, methyl, or fluoro, and

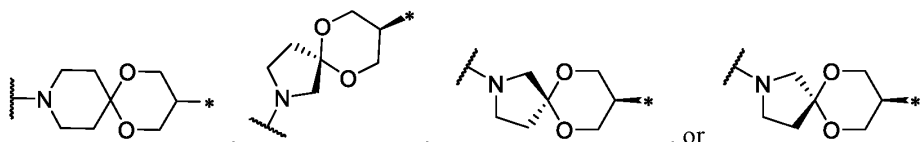
[1246] R^c is hydrogen or methyl.

[1247] Embodiment A 99. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 98, wherein:

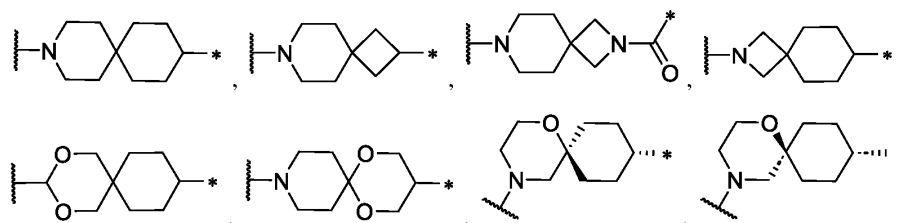
[1248] G^3 is:

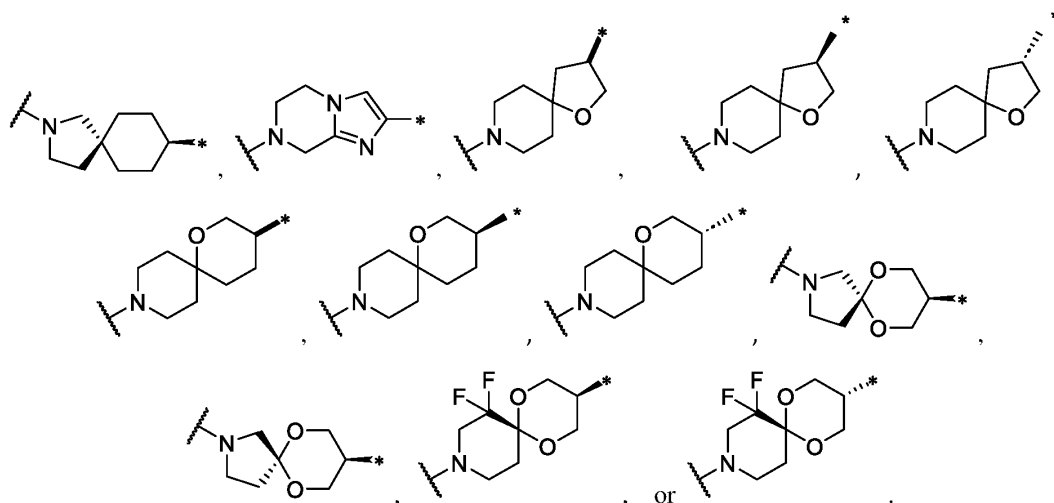


[1249] Embodiment A 100. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 98, wherein G^3 is:



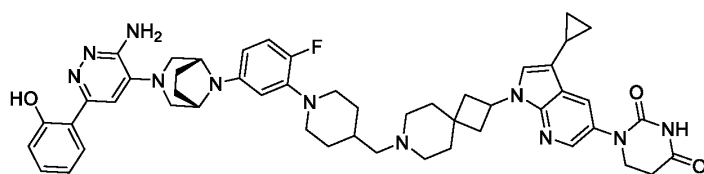
[1250] Embodiment A 101. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 98, wherein G^3 is:



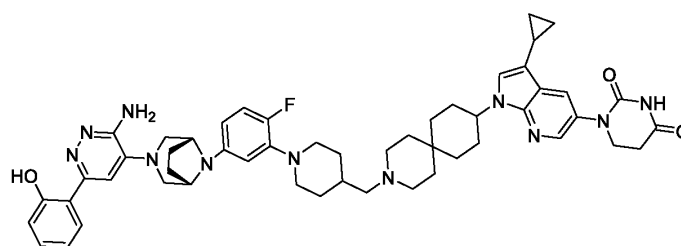


[1251] Embodiment A 102. The compound according to Embodiment A 1, or a pharmaceutically acceptable salt thereof, selected from any one or more of the compounds of Compound List 1, Compound List 2, Compound List 3, Compound List 4, and/or Compound List 5, or pharmaceutically acceptable salts thereof.

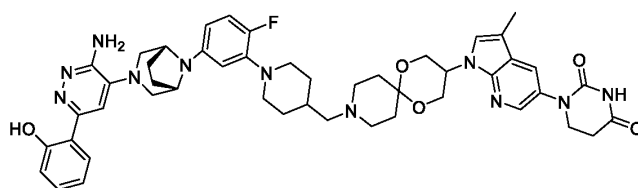
[1252] Embodiment A 103. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 1 or 102, wherein the compound is:



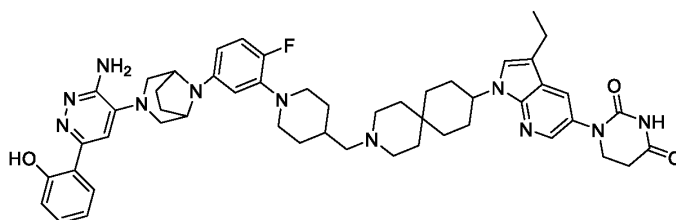
[1253] Embodiment A 104. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 1 or 102, wherein the compound is:



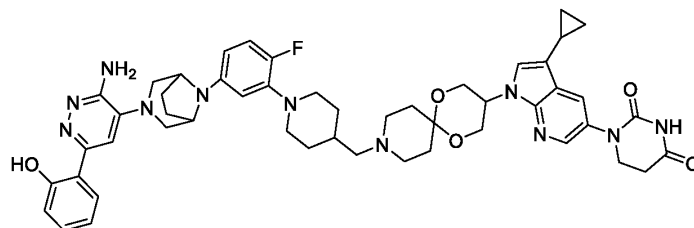
[1254] Embodiment A 105. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 1 or 102, wherein the compound is:



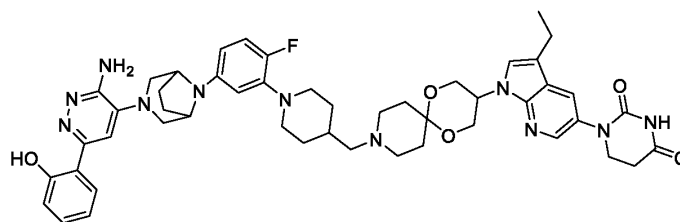
[1255] Embodiment A 106. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 1 or 102, wherein the compound is:



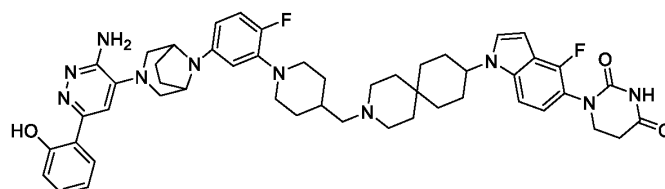
[1256] Embodiment A 107. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 1 or 102, wherein the compound is:



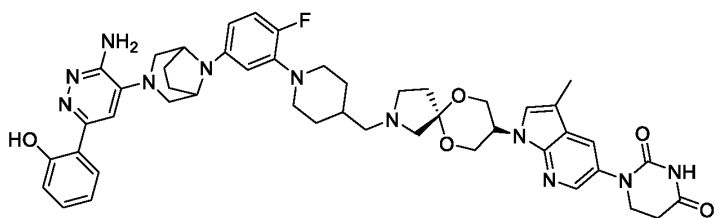
[1257] Embodiment A 108. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 1 or 102, wherein the compound is:



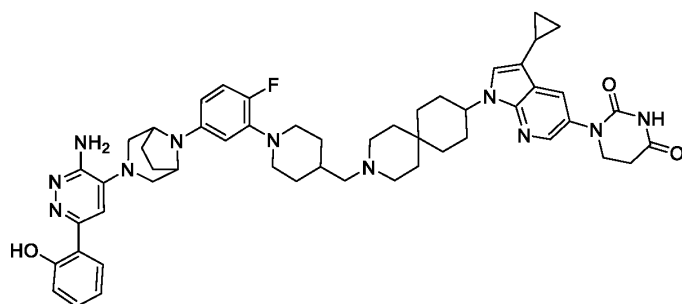
[1258] Embodiment A 109. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 1 or 102, wherein the compound is:



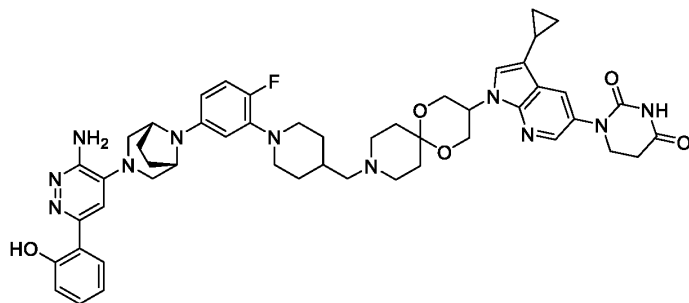
[1259] Embodiment A 110. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 1 or 102, wherein the compound is:



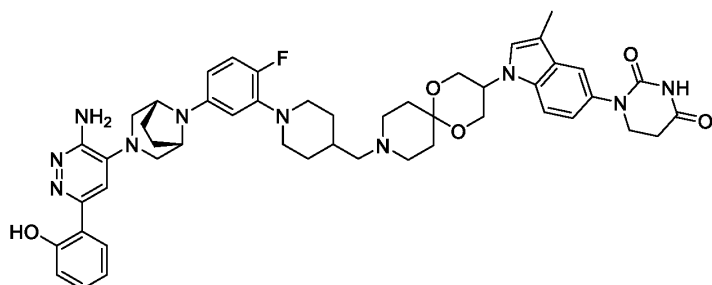
[1260] Embodiment A 111. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 1 or 102, wherein the compound is:



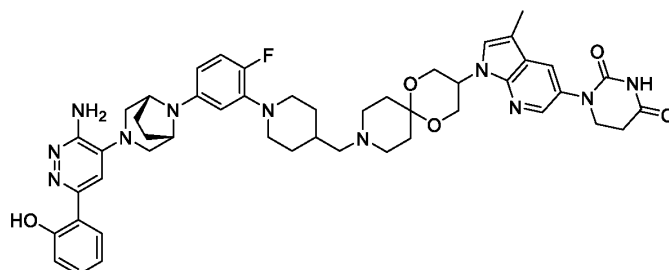
[1261] Embodiment A 112. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 1 or 102, wherein the compound is:



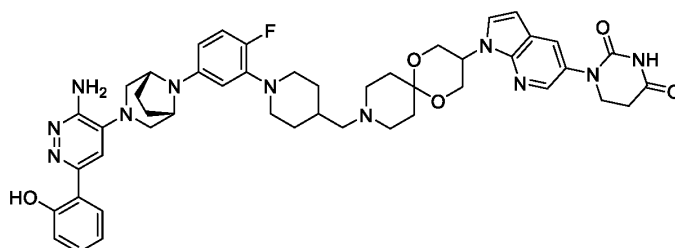
[1262] Embodiment A 113. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 1 or 102, wherein the compound is:



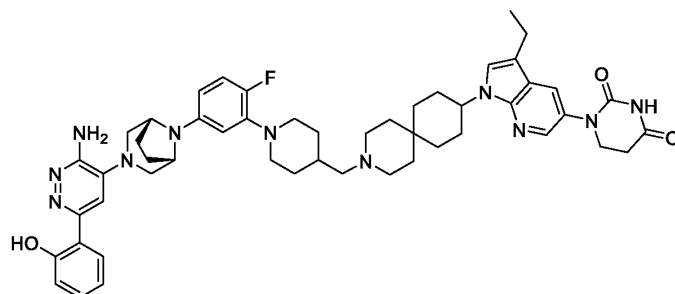
[1263] Embodiment A 114. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 1 or 102, wherein the compound is:



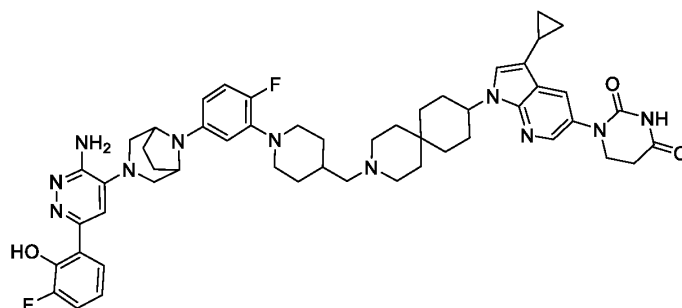
Embodiment A 115. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 1 or 102, wherein the compound is:



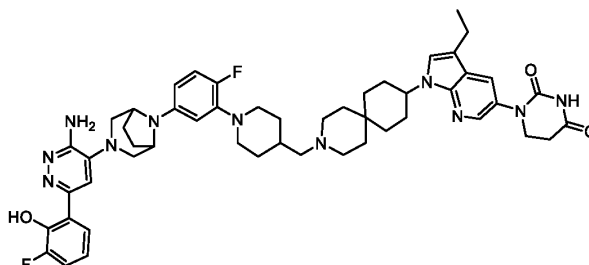
[1264] Embodiment A 116. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 1 or 102, wherein the compound is:



[1265] Embodiment A 117. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 1 or 102, wherein the compound is:



[1266] Embodiment A 118. The compound, or pharmaceutically acceptable salt thereof, according to Embodiment A 1 or 102, wherein the compound is:



[1267] Embodiment A 119. A pharmaceutical composition comprising the compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-118, and a pharmaceutically acceptable excipient.

[1268] Embodiment A 120. A method of degrading SMARCA2 protein in a human, comprising administering to a human in need thereof an effective amount of the compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-118, or the composition of Embodiment A 119.

[1269] Embodiment A 121. A method of reducing the level of SMARCA2 activity in a human, comprising administering to a human in need thereof an effective amount of the compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-118, or the composition of Embodiment A 119.

[1270] Embodiment A 122. A method of treating cancer in a human, comprising administering to a human in need thereof an effective amount of the compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-118, or the composition of Embodiment A 119.

[1271] Embodiment A 123. The method of Embodiment A 122, wherein the cancer is a SMARCA2-sensitive cancer.

[1272] Embodiment A 124. The method of Embodiment A 122, wherein the cancer is a SMARCA2-mutated cancer.

[1273] Embodiment A 125. The method of any one of Embodiments A 122-124, wherein the cancer is a solid tumor.

[1274] Embodiment A 126. The method of any one of Embodiments A 122-124, wherein the cancer is lung, liver, colon, skin, bladder, cervical or ovarian cancer.

[1275] Embodiment A 127. A compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-104, or the composition of Embodiment A 105 for use in degrading SMARCA2 protein in a human.

[1276] Embodiment A 128. A compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-118, or the composition of Embodiment A 119 for use in reducing the level of SMARCA2 activity in a human.

[1277] Embodiment A 129. A compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-118, or the composition of Embodiment A 119 for use in treating cancer in a human.

[1278] Embodiment A 130. The compound for use of Embodiment A 129, wherein the cancer is a SMARCA2-sensitive cancer.

[1279] Embodiment A 131. The compound for use of Embodiment A 129, wherein the cancer is a SMARCA2-mutated cancer.

[1280] Embodiment A 132. The compound for use of any one of Embodiments A 129-131, wherein the cancer is a solid tumor.

[1281] Embodiment A 133. The compound for use of any one of Embodiments A 129-131, wherein the cancer is lung, liver, colon, skin, bladder, cervical or ovarian cancer.

[1282] Embodiment A 134. Use of a compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-118, or the composition of Embodiment A 119 in the manufacture of a medicament for degrading SMARCA2 protein in a human.

[1283] Embodiment A 135. Use of a compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-118, or the composition of Embodiment A 119 in the manufacture of a medicament for reducing the level of SMARCA2 activity in a human.

[1284] Embodiment A 136. Use of a compound, or pharmaceutically acceptable salt thereof, according to any one of Embodiments A 1-118, or the composition of Embodiment A 119 in the manufacture of a medicament for treating cancer in a human.

[1285] Embodiment A 137. The compound, or pharmaceutically acceptable salt thereof, for use of Embodiment A 136, wherein the cancer is a SMARCA2-sensitive cancer.

[1286] Embodiment A 138. The compound, or pharmaceutically acceptable salt thereof, for use of Embodiment A 136, wherein the cancer is a SMARCA2-mutated cancer.

[1287] Embodiment A 139. The compound, or pharmaceutically acceptable salt thereof, for use of any one of Embodiments A 136-138, wherein the cancer is a solid tumor.

[1288] Embodiment A 140. The compound, or pharmaceutically acceptable salt thereof, for use of any one of Embodiments A 136-138, wherein the cancer is lung, liver, colon, skin, bladder, cervical or ovarian cancer.

EXAMPLES

General Experimental Conditions and Abbreviations

[1289] The following abbreviations are used: AcOH = acetic acid; aq = aqueous; BINAP = ($\pm$)-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene; Boc = *tert*-butoxycarbonyl; BrettPhos Pd G3 = [(2-dicyclohexylphosphino-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl)-2-(2'-amino-1,1'-biphenyl)]-

palladium(II) methanesulfonate; *t*-BuBrettPhos Pd G3 = [(2-di-*tert*-butylphosphino-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl)-2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate; (*t*Bu)PhCphos = 2-[(*tert*-Butyl)phenylphosphino]-2',6'-bis(*N,N*-dimethylamino)biphenyl; Cs₂CO₃ = cesium carbonate; CuI = copper (I) iodide; Cphos = 2-Dicyclohexylphosphino-2',6'-bis(*N,N*-dimethylamino)biphenyl; DCE = 1,2-dichloroethane; DCM = dichloromethane; DIBAL-H = diisobutylaluminum hydride; DIPEA = *N,N*-diisopropylethylamine; DMA = *N,N*-dimethylacetamide; DMAP = 4-dimethylaminopyridine; DMF = *N,N*-dimethylformamide; DMSO = dimethylsulfoxide; EtOAc = ethyl acetate; EtOH = ethanol; EPhos = dicyclohexyl(3-isopropoxy-2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphane; EPhos Pd G4 = palladium catalyst containing EPhos - CAS number: 2132978-44-8; FA = formic acid; FSC = flash silica chromatography; g = gram(s); h = hour(s); HATU = (dimethylamino)-*N,N*-dimethyl(3-oxido-1*H*-[1,2,3]triazolo[4,5-*b*]pyridinyl)methaniminium hexafluorophosphate; HCl = hydrochloric acid; HPLC = high-performance liquid chromatography; KO*t*Bu = potassium *tert*-butoxide; K₃PO₄ = potassium phosphate tribasic; LiHMDS = lithium hexamethyldisilazide; LiOH = lithium hydroxide; M = molar; mg = milligram(s); min = minute(s); mL = milliliter(s); mmol = millimole(s); MeCN = acetonitrile; MeOH = methanol; MTBE = methyl *tert*-butyl ether; N₂ = nitrogen gas; Na₂CO₃ = sodium carbonate; Na₂SO₄ = sodium sulfate; NEt₃ = triethylamine; NH₄Cl = ammonium chloride; NH₄HCO₃ = ammonium bicarbonate; NH₄OH = ammonium hydroxide; NMP = *N*-methyl pyrrolidinone; NMR = nuclear magnetic resonance; Na(OAc)₃BH = sodium triacetoxyborohydride; Pd/C = Palladium on carbon; PdCl₂(PPh₃)₂ = Bis(triphenylphosphine)palladium(II) dichloride; Pd(dba)₂ = Palladium(0) bis(dibenzylideneacetone); Pd₂(dba)₃ = tris(dibenzylideneacetone)dipalladium(0); Pd(dppf)Cl₂ = [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II); *i*PrOH = isopropyl alcohol; PyBOP = benzotriazol-1-yloxytripyrrolidino-phosphonium hexafluorophosphate; r.t. = room temperature (~18-25°C); RPC = reverse phase chromatography; RP-HPLC = reverse-phase high-performance liquid chromatography; RuPhos = 2-Dicyclohexylphosphino-2',6'-diisopropoxybiphenyl; RuPhos Pd G3 = (2-Dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate; SFC = supercritical fluid chromatography; SPhos Pd G2 = Chloro(2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II); TFA = trifluoroacetic acid; THF = tetrahydrofuran; TsOH = *p*-toluenesulfonic acid monohydrate; w.t.% = percentage by weight; Pd XPhos G3 = (2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate.

[1290] NMR: Proton NMR (¹H NMR) was carried out at 300-500 MHz at a temperature in the range from 15-30°C in deuterated-DMSO unless otherwise specified. ¹⁹F NMR was carried out in DMSO unless otherwise stated. Standard NMR abbreviations are used: s = single, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt doublet of triplets, m = multiplet, br = broad.

[1291] Chromatography methods: clean-appearing fractions containing the desired product are generally identified and combined together and then concentrated under reduced pressure. Flash

chromatography was performed using straight phase flash chromatography on a SP1™ Purification or SELEKT™ system from Biotage™, CombiFlash™ Rf from ISCO or on Gilson system from Thermo Fisher using normal phase silica FLASH+™ (40M, 25M or 12 M), Sfar Silica HC (5g, 10g, 25g, 100g) from Biotage™ or SNAP™ KP-Sil Cartridges (340, 100, 50 or 10), Flash Column silica-CS columns from Agela, with C18-flash columns or standard flash chromatography. RP-HPLC was performed using XSelect or XBridge columns.

[1292] In general, all solvents used were commercially available and of analytical grade. Anhydrous solvents were routinely used for reactions. Phase Separators used in the examples are ISOLUTE® Phase Separator columns.

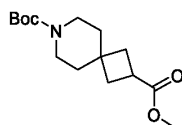
[1293] Concentration of solutions (to partly or fully remove solvent) are generally performed under reduced pressure at r.t. or slightly above.

[1294] The intermediates and examples named below were named using BIOVIA Draw 20.1 or Chem Draw. The starting materials were obtained from commercial sources or made via literature routes.

EXAMPLE 1

Intermediate 1a:

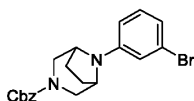
7-*tert*-Butyl 2-methyl 7-azaspiro[3.5]nonane-2,7-dicarboxylate



[1295] Cs₂CO₃ (4.84 g, 14.85 mmol) was added to iodomethane (1.054 g, 7.43 mmol) and 7-(*tert*-butoxycarbonyl)-7-azaspiro[3.5]nonane-2-carboxylic acid (2 g, 7.43 mmol) in DMF (10 mL). The resulting mixture was stirred at r.t for 6 h. Added 40 mL water and aqueous layer was extracted with ethyl acetate (2 x 75 mL). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated to afford the title compound (2.0 g, 95 %) as a white solid. ¹H NMR (DMSO-*d*₆) δ 1.32 – 1.42 (11H, m), 1.44 – 1.52 (2H, m), 1.85 – 1.95 (2H, m), 1.95 – 2.05 (2H, m), 3.05 – 3.20 (3H, m), 3.21 – 3.28 (2H, m), 3.58 (3H, s); *m/z* (ES⁺) [M+H]⁺ = 284.3.

Intermediate 1b:

Benzyl 8-(3-bromophenyl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate

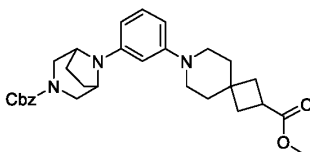


[1296] To a stirred solution of Cs₂CO₃ (5.29 g, 16.24 mmol), palladium(II) acetate (0.182 g, 0.81 mmol) and BINAP (0.506 g, 0.81 mmol) in 1,4-dioxane (20 mL) was added to 1,3-dibromobenzene (1.916 g, 8.12 mmol) and benzyl 3,8-diazabicyclo[3.2.1]octane-3-carboxylate (2.0 g, 8.12 mmol) at r.t. The resulting mixture was stirred at 100 °C for 16 h. The reaction mixture was diluted with water (100 mL), extracted with EtOAc (3 x 100 mL), the organic layer was dried (Na₂SO₄), filtered and evaporated.

Purification by FSC (gradient: 0 to 70 % EtOAc in petroleum ether) gave the title compound (1.3 g, 39.9 %) as a white solid. ^1H NMR (DMSO-*d*₆) δ 1.52 (2H, d), 1.83 – 1.93 (2H, m), 2.91 – 3.09 (4H, m), 4.28 (2H, d), 5.05 (2H, d), 6.26 (2H, d), 6.35 (1H, s), 6.97 (1H, t), 7.25 – 7.40 (5H, m); m/z (ES⁺) $[\text{M}+\text{H}]^+ = 366.1$.

Intermediate 1c:

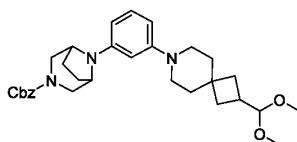
Methyl 7-[3-(3-benzyloxycarbonyl-3,8-diazabicyclo[3.2.1]octan-8-yl)phenyl]-7-azaspiro[3.5]nonane-2-carboxylate



[1297] 4M HCl in MeOH (5 mL, 164.57 mmol) was added to Intermediate 1a (318 mg, 1.12 mmol). The resulting mixture was stirred at r.t. for 2 h. The solvent was removed under reduced pressure and afford a white solid. To the crude product was added RuPhos Pd G3 (94 mg, 0.11 mmol), RuPhos (50.0 mg, 0.11 mmol), Cs₂CO₃ (1096 mg, 3.36 mmol) and Intermediate 1b (450 mg, 1.12 mmol) in dioxane (10 mL) under nitrogen. The resulting mixture was stirred at 100 °C for 2 h. The reaction mixture was filtered and concentrated. Purification by FSC (gradient: 0 to 100 % EtOAc in petroleum ether) gave the title compound (530 mg, 94 %) as a yellow solid. ^1H NMR (DMSO-*d*₆) δ 1.51 – 1.71 (6H, m), 1.83 – 2.07 (6H, m), 2.95 – 3.23 (7H, m), 3.52 – 3.56 (2H, m), 3.59 (3H, s), 4.25 (2H, d), 5.05 (2H, d), 6.21 – 6.42 (3H, m), 6.98 (1H, t), 7.21 – 7.47 (5H, m); m/z (ES⁺) $[\text{M}+\text{H}]^+ = 504.4$.

Intermediate 1d:

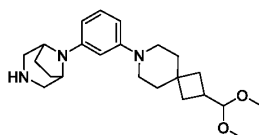
Benzyl 8-[3-[2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl]phenyl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



[1298] DIBAL-H (169 mg, 1.19 mmol) was added Intermediate 1c (300 mg, 0.60 mmol) in DCM (5 mL) at -50 °C under nitrogen. The resulting mixture was stirred at -50 °C for 1 h. Saturated NH₄Cl solution was added to the mixture. The aq. layer was back extracted with DCM (2 x 30 mL). Combined the organic layers were dried over Na₂SO₄, filtered and concentrated to afford the yellow solid. The product was used in the next step directly without further purification. To the residue TsOH (113 mg, 0.60 mmol) and trimethyl orthoformate (190 mg, 1.79 mmol) were added in DCM (5 mL). The resulting mixture was stirred at r.t. for 16 h. The reaction mixture was concentrated. Purification by FSC (gradient 0 to 100 % EtOAc in petroleum ether) gave the title compound (130 mg, 42.0 %) as a yellow solid. ^1H NMR (DMSO-*d*₆) δ 1.52 – 1.71 (6H, m), 1.80 – 2.10 (6H, m), 2.95 – 3.27 (5H, m), 3.34 (6H, s), 3.56 (1H, s), 3.61 (4H, s), 4.27 (2H, d), 5.07 (2H, d), 6.28 (2H, d), 6.38 (1H, s), 6.99 (1H, t), 7.18 – 7.46 (5H, m); m/z (ES⁺) $[\text{M}+\text{H}]^+ = 520$.

Intermediate 1e:

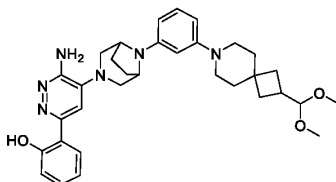
7-[3-(3,8-Diazabicyclo[3.2.1]octan-8-yl)phenyl]-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane



[1299] Pd/C (11.06 mg, 0.10 mmol) was added to Intermediate 1d (270 mg, 0.52 mmol) in MeOH (4 mL) under hydrogen. The resulting mixture was stirred at r.t. for 6 h. The reaction mixture was filtered through celite® and filtrate was concentrated to afford the title compound (80 mg, 39.9 %) as a white solid. m/z (ES⁺) [M+H]⁺ = 386.1.

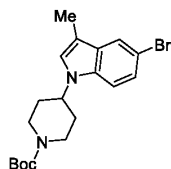
Intermediate 1f:

2-[6-Amino-5-[8-[3-[2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl]phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-yl]phenol



[1300] DIPEA (0.095 mL, 0.54 mmol) was added to Intermediate 1e (70 mg, 0.18 mmol) and 4-bromo-6-chloropyridazin-3-amine (37.8 mg, 0.18 mmol) in NMP (3 mL). The resulting mixture was stirred at 100 °C for 3 h. Reaction mixture diluted with water (10 mL) and extracted with EtOAc (30 mL x 2). The combined extracts were dried over Na₂SO₄, filtered and concentrated. The crude material was used for the next step. To the residue was added Cs₂CO₃ (177 mg, 0.54 mmol), XPhos Pd G3 (15.36 mg, 0.02 mmol), (2-hydroxyphenyl)boronic acid (37.6 mg, 0.27 mmol) dioxane (1 mL) and water (1 mL). The resulting mixture was stirred at 100 °C for 2 h. The solvent was removed. Purification by RPC (gradient 0 to 90 % MeOH in water with 0.5% NH₄HCO₃) gave the title compound (40.0 mg, 38.6 %) as a yellow solid. m/z (ES⁺) [M+H]⁺ = 571.

Intermediate 1g:

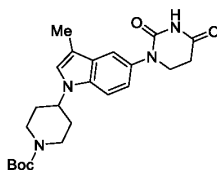
tert-Butyl 4-(5-bromo-3-methyl-indol-1-yl)piperidine-1-carboxylate

[1301] Cs₂CO₃ (16.20 g, 49.72 mmol) was added to a stirred solution of *tert*-butyl 4-methylsulfonyloxypiperidine-1-carboxylate (13.90 g, 49.74 mmol) and 5-bromo-3-methyl-1H-indole (5.50 g, 26.18 mmol) in DMF (30 mL) under N₂ at r.t. The resulting mixture was stirred at 95 °C for 8.5 h. The mixture was cooled to r.t. then additional *tert*-butyl 4-methylsulfonyloxypiperidine-1-carboxylate (14.00 g,

50.10 mmol) and Cs_2CO_3 (16.00 g, 49.11 mmol) were added under N_2 . The resulting mixture was stirred at 95°C for 14 h then cooled to r.t. and diluted with EtOAc (200 mL). The mixture was washed with water (2×50 mL) and brine (2×50 mL). The organic layer was dried (Na_2SO_4) and concentrated. Purification by FSC (gradient: 0-40% DCM in hexanes then 0-30% EtOAc in hexanes) gave the title compound (5.85 g, 57 %) as a white foam. ^1H NMR (CDCl_3): δ 1.50 (9H, s), 1.81-1.95 (2H, m), 2.00-2.07 (2H, m), 2.28 (3H, d), 2.82-2.99 (2H, m), 4.21-4.40 (3H, m), 6.95 (1H, s), 7.16-7.24 (1H, m), 7.28-7.30 (1H, m), 7.69 (1H, d); m/z (ES^+) $[\text{M}-t\text{Bu}+2\text{H}]^+ = 336.8$.

Intermediate 1h:

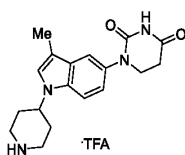
tert-Butyl 4-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-indol-1-yl]piperidine-1-carboxylate



[1302] 1,4-Dioxane (100 mL) was added to a degassed flask Intermediate 1g (4.20 g, 10.68 mmol), Cs_2CO_3 (6.96 g, 21.36 mmol), $\text{Pd}_2(\text{dba})_3$ (0.885 g, 0.97 mmol), EPhos (1.028 g, 1.92 mmol) and hexahydropyrimidine-2,4-dione (3.66 g, 32.03 mmol) at r.t. under argon. The mixture was sparged with argon for five minutes then stirred at 100°C for 14 h. The mixture was cooled to r.t., diluted with EtOAc (100 mL), and filtered through celite®. The filtrate was then concentrated. Purification by FSC (gradient: 0-100% EtOAc in hexanes) gave the title compound (3.06 g, 67 %) as an off-white solid. ^1H NMR (CDCl_3): δ 1.52 (9H, s), 1.85-1.97 (2H, m), 2.02-2.09 (2H, m), 2.32 (3H, d), 2.85-2.97 (4H, m), 3.93 (2H, t), 4.26-4.40 (3H, m), 7.02 (1H, s), 7.13 (1H, dd), 7.37 (1H, d), 7.40 (1H, s), 7.48 (1H, s); m/z (ES^+) $[\text{M}+\text{Na}]^+ = 449.2$.

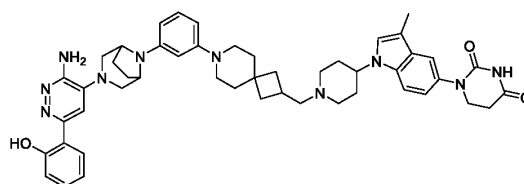
Intermediate 1i:

1-[3-Methyl-1-(4-piperidyl)indol-5-yl]hexahydropyrimidine-2,4-dione



[1303] TFA (0.289 mL, 3.75 mmol) was added to a solution of Intermediate 1h (80 mg, 0.19 mmol) in DCM (1.0 mL) at r.t. After 1h the mixture was concentrated. Diethyl ether (2 mL) was added and the resulting mixture was sonicated to yield a solid precipitate. The supernatant was removed and the solid dried under reduced pressure to give the title compound in the form of a trifluoroacetate salt (83 mg, 100 %) as a light pink solid. m/z (ES^+) $[\text{M}+\text{H}]^+ = 326.9$.

1-[1-[1-[7-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-7-azaspiro[3.5]nonan-2-yl]methyl]-4-piperidyl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione

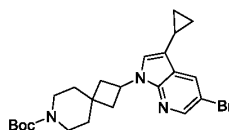


[1304] Formic acid (1 ml, 26.07 mmol) was added to Intermediate 1f (35 mg, 0.06 mmol). The resulting mixture was stirred at r.t. for 1h and the solvent was removed under reduced pressure. The crude material was dissolved in DMF (1.0 mL) and DCE (1.0 mL) and Intermediate 1i (20.0 mg, 0.06 mmol) was added. The resulting mixture was stirred at r.t. for 1h. Sodium triacetoxyborohydride (39.0 mg, 0.18 mmol) was added and stirred at r.t. for 1 h. The solvent was removed under reduced pressure. Purification by RPC (gradient: 0-60% MeCN in water with 0.1% FA) gave the title compound (5.60 mg, 10.01 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.45 (2H, t), 1.53 – 1.59 (2H, m), 1.65 – 1.71 (2H, m), 1.83 – 2.07 (8H, m), 2.08 – 2.21 (4H, m), 2.23 (3H, s), 2.46 (2H, d), 2.73 (2H, t), 2.91 – 3.04 (4H, m), 3.06 – 3.13 (2H, m), 3.25 (2H, d), 3.77 (3H, t), 4.25 (1H, d), 4.39 (2H, d), 5.95 (2H, s), 6.25 (1H, d), 6.26 (1H, d), 6.43 (1H, s), 6.83 – 6.90 (2H, m), 6.98 – 7.09 (2H, m), 7.19 – 7.26 (1H, m), 7.31 (1H, s), 7.39 (1H, d), 7.43 – 7.50 (2H, m), 7.92 (1H, d), 10.27 (1H, s) (OH proton not observed); *m/z* (ES⁺) [M+H]⁺ = 835.1.

EXAMPLE 2

Intermediate 2a:

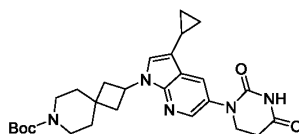
tert-Butyl 2-(5-bromo-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-1-yl)-7-azaspiro[3.5]nonane-7-carboxylate



[1305] A vial was charged with 5-bromo-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridine (600 mg, 2.53 mmol) and *tert*-butyl 2-hydroxy-7-azaspiro[3.5]nonane-7-carboxylate (611 mg, 2.53 mmol), 2-(tributyl-*l*-5-phosphaneylidene)acetonitrile (1222 mg, 5.06 mmol), and *m*-xylene (15 mL). The reaction was heated to 110 °C for 16 h then cooled to r.t. and concentrated *in vacuo*. Purification by RPC (gradient: 5-100% MeCN in water with 0.1% NH₄HCO₃) gave the title compound (1000 mg, 86 %) as a yellow solid. ¹H NMR (DMSO-*d*₆): δ 0.63 – 0.73 (2H, m), 0.82 – 0.90 (2H, m), 1.40 (9H, s), 1.57 – 1.67 (4H, m), 1.91 – 2.02 (1H, m), 2.16 – 2.27 (2H, m), 2.32 – 2.42 (2H, td), 3.21 – 3.34 (4H, m), 5.13 – 5.36 (1H, m), 7.59 (1H, s), 8.20 (1H, d), 8.26 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 460.2.

Intermediate 2b:

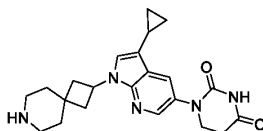
tert-Butyl 2-[3-cyclopropyl-5-(2,4-dioxohexahydropyrimidin-1-yl)pyrrolo[2,3-*b*]pyridin-1-yl]-7-azaspiro[3.5]nonane-7-carboxylate



[1306] A 40 mL vial was charged with hexahydropyrimidine-2,4-dione (873 mg, 7.65 mmol), *t*BuBrettPhos Pd G3 (327 mg, 0.38 mmol), Intermediate 2a (1762 mg, 3.83 mmol) and K₃PO₄ (1625 mg, 7.65 mmol), then the vial was capped and evacuated and backfilled with nitrogen. 1,4-dioxane (20 mL) was added, then the mixture was sparged with nitrogen for 15 min. The reaction was then warmed to 100 °C for 16 h. The reaction was cooled to r.t., then diluted with EtOAc (50 mL) and filtered through celite®. The filtrate was concentrated under reduced pressure. The resulting residue was purified by FSC (gradient: 0-100% EtOAc in hexanes then 0-30% MeOH in EtOAc) to give title compound (1446 mg, 77 %) as a brown dry film. ¹H NMR (DMSO-*d*₆): δ 0.65 – 0.72 (2H, m), 0.84 – 0.92 (2H, m), 1.41 (9H, s), 1.59 – 1.69 (4H, m), 1.91 – 1.98 (1H, m), 2.22 – 2.29 (2H, m), 2.32 – 2.43 (2H, m), 2.72 – 2.80 (2H, m), 3.21 – 3.30 (2H, m), 3.36 (2H, d), 3.78 – 3.87 (2H, m), 5.20 – 5.36 (1H, m), 7.57 (1H, s), 7.96 (1H, d), 8.17 (1H, d), 10.40 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 494.3.

Intermediate 2c:

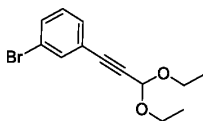
1-[1-(7-Azaspiro[3.5]nonan-2-yl)-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1307] TFA (6.00 mL) was added to a stirred solution of Intermediate 2b (1.974 g, 4 mmol) in DCM (24 mL). The resulting solution was stirred for 2h. The reaction mixture was concentrated. Purification by ion exchange chromatography (Porapak Rxn CX 50g cartridge) eluting with 2N NH₃ in MeOH gave the title compound (1.457 g, 93 %) as a white solid. ¹H NMR(DMSO-*d*₆): δ 0.67 - 0.74 (2H, m), 0.82 - 0.90 (2H, m), 1.60 (4H, dt), 1.88 - 2.00 (1H, m), 2.15 - 2.23 (2H, m), 2.30 - 2.38 (2H, m), 2.57 - 2.62 (2H, m), 2.67 - 2.72 (2H, m), 2.77 (2H, t), 3.82 (2H, t), 5.24 (1H, quin), 7.54 (1H, s), 7.95 (1H, d), 8.17 (1H, d), 10.37 (1H, br s) (NH proton not observed); *m/z* (ES⁺) [M+H]⁺ = 394.4.

Intermediate 2d:

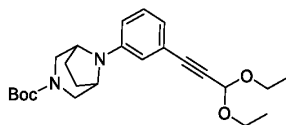
1-Bromo-3-(3,3-diethoxyprop-1-ynyl)benzene



[1308] A vial was charged with 3,3-diethoxyprop-1-yne (0.860 ml, 6.00 mmol), 1-bromo-3-iodobenzene (0.765 ml, 6 mmol), PdCl₂(PPh₃)₂ (0.632 g, 0.90 mmol), CuI (0.171 g, 0.90 mmol), DMF (20 mL) and NEt₃ (10 mL). The reaction was degassed and stirred at r.t. for 1.5 hours. The reaction was diluted with water, extracted with DCM (2 x 20 mL), washed with brine, dried with Na₂SO₄ and concentrated *in vacuo*. Purification by FCS (0-12% EtOAc in hexanes) gave the title compound (1.272 g, 74.9 %) as a colorless oil. ¹H NMR (CDCl₃): δ 1.28 (6H, t), 3.64 - 3.70 (2H, m), 3.81 (2H, dq), 5.48 (1H, s), 7.18 (1H, t), 7.40 (1H, d), 7.47 (1H, d), 7.63 (1H, s); *m/z* (ES⁺) [M-OEt]⁺ = 238.9.

Intermediate 2e:

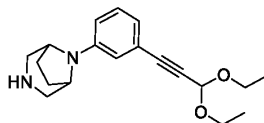
tert-Butyl 8-[3-(3,3-diethoxyprop-1-ynyl)phenyl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



[1309] *tert*-butyl (-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (0.954 g, 4.49 mmol) was added to a stirred solution of Intermediate 2d (1.272 g, 4.49 mmol), RuPhos Pd G3 (0.376 g, 0.45 mmol), dicyclohexyl(2',6'-diisopropoxy-[1,1'-biphenyl]-2-yl)phosphane (0.210 g, 0.45 mmol), and cesium carbonate (2.93 g, 8.98 mmol) in 1,4-dioxane (24 mL) under nitrogen. The vial was sealed and flushed with nitrogen for 5 minutes and heated at 90 °C for 4h. The reaction was filtered through a celite® plug and concentrated. Purification by FSC (gradient: 0-50% EtOAc in hexanes) gave the title compound (0.943 g, 50.6 %) as a brown viscous oil. ¹H NMR (CDCl₃): δ 1.30 (6H, t), 1.47 (9H, s), 1.77 - 1.94 (2H, m), 1.98 - 2.07 (2H, m), 3.20 (1H, br d), 3.30 (1H, br d), 3.59 - 3.78 (4H, m), 3.84 (2H, dq), 4.12 - 4.23 (2H, m), 5.50 (1H, s), 6.79 (1H, d), 6.89 (1H, d), 6.92 (1H, s), 7.19 (1H, t); *m/z* (ES⁺) [M+H]⁺ = 415.6.

Intermediate 2f:

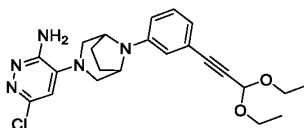
8-[3-(3,3-Diethoxyprop-1-ynyl)phenyl]-3,8-diazabicyclo[3.2.1]octane



[1310] A vial was charged with Intermediate 2e (0.803 g, 1.94 mmol), HCl solution (1.25M in EtOH, 15.50 mL, 19.37 mmol). The reaction was heated to 40 °C for 2h. Concentration in vacuo gave the title compound (609 mg, 100%) as a brown film. *m/z* (ES⁺) [M+H]⁺ = 315.5.

Intermediate 2g:

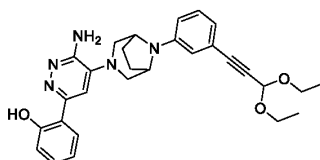
6-Chloro-4-[8-[3-(3,3-diethoxyprop-1-ynyl)phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-amine



[1311] A vial was charged with Intermediate 2f (610 mg, 1.94 mmol), 4-bromo-6-chloropyridazin-3-amine (809 mg, 3.88 mmol), *n*-butanol (8 mL), and DIPEA (1.694 mL, 9.70 mmol). The reaction was heated to 110 °C for 19 h. Purification by FCS (0-100% EtOAc in hexanes, then 0-25% MeOH in EtOAc) gave a mixture of acetal products. This material was stirred in HCl solution (1.25 M in EtOH, 0.3 mL, 0.4 mmol) and EtOH (10 mL) at 50 °C for 18 h. Concentration *in vacuo* gave the title compound (351 mg, 40.9 %) as a brown solid. ¹H NMR (DMSO-*d*₆): δ 1.17 (6H, t), 1.91 - 1.97 (2H, m), 2.04 - 2.14 (2H, m), 3.12 (2H, br d), 3.24 (2H, br d), 3.37 - 3.47 (1H, m), 3.50 - 3.62 (2H, m), 3.66 - 3.72 (2H, m), 4.45 (2H, br s), 5.51 (1H, s), 6.79 (1H, d), 6.95 - 7.05 (3H, m), 7.14 (1H, s), 7.22 (1H, t); *m/z* (ES⁺) [M+H]⁺ = 442.3.

Intermediate 2h:

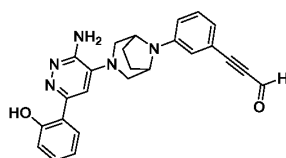
2-[6-Amino-5-[8-[3-(3,3-diethoxyprop-1-ynyl)phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-yl]phenol



[1312] Intermediate 2g (351 mg, 0.79 mmol) was added to (2-hydroxyphenyl)boronic acid (164 mg, 1.19 mmol), Cs₂CO₃ (518 mg, 1.59 mmol) and Xphos Pd G3 (67.2 mg, 0.08 mmol) in 1,4-dioxane (7 mL) and water (0.700 mL). The vial was degassed bubbling N₂ through the solution for 10 min. The vial was sealed and stirred at 100 °C for 30 min. The reaction was cooled to r.t. and concentrated under reduced pressure. The crude residue was partitioned between saturated NaHCO₃ (50 mL) and DCM (50 mL). The aqueous layer was extracted with DCM (2 x 20 mL) and the combined organic extracts were washed with brine, dried (Na₂SO₄), filtered and concentrated. Purification by FSC (gradient: 0-100% EtOAc in hexanes) gave the title compound (239 mg, 60.2 %) as a brown solid. ¹H NMR (DMSO-*d*₆): δ 1.14 - 1.21 (6H, m), 1.94 - 1.99 (2H, m), 2.09 - 2.25 (2H, m), 3.08 (2H, br d), 3.22 - 3.31 (2H, m), 3.49 - 3.61 (2H, m), 3.69 (2H, dq), 4.47 (2H, br s), 5.51 (1H, s), 5.94 (2H, s), 6.77 (1H, d), 6.83 - 6.90 (2H, m), 6.95 - 7.00 (2H, m), 7.15 - 7.29 (2H, m), 7.48 (1H, s), 7.92 (1H, d), 14.16 (1H, br s); *m/z* (ES⁺) [M+H]⁺ = 500.4.

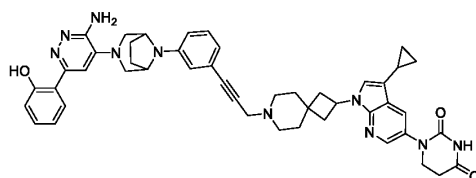
Intermediate 2i:

3-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]prop-2-ynal



[1313] A vial was charged with Intermediate 2h (153 mg, 0.31 mmol) and formic acid (0.5 mL). The reaction was stirred at 40 °C for 10 mins. The reaction was concentrated *in vacuo* and dried by lyophilization. The title compound was obtained (121 mg, 93 %) as a brown solid. *m/z* (ES⁺) [M+H]⁺ = 426.4.

1-[1-[7-[3-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]prop-2-ynyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

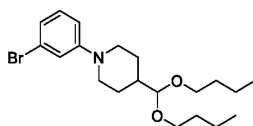


[1314] A vial was charged with Intermediate 2c (59.0 mg, 0.15 mmol), Intermediate 2i (63.8 mg, 0.15 mmol), and NMP (1.5 mL). The solution was stirred at r.t. for 30 min. Na(OAc)₃BH (95 mg, 0.45 mmol) was added and the reaction was stirred at r.t. for 15 min then concentrated *in vacuo*. Purification by RPC (0-50% MeCN in water with 0.1% FA) gave the title compound (12.12 mg, 9.84 %). ¹H NMR (DMSO-*d*₆): δ 0.66 - 0.70 (2H, m), 0.83 - 0.89 (2H, m), 1.70 - 1.80 (4H, m), 1.89 - 1.98 (3H, m), 2.14 (2H, br d), 2.20 - 2.28 (2H, m), 2.33 - 2.39 (2H, m), 2.43 - 2.48 (1H, m), 2.54 - 2.58 (1H, m), 2.76 (2H, t), 3.07 (2H, br d), 3.19 - 3.24 (2H, m), 3.45 (2H, s), 3.76 - 3.85 (4H, m), 4.44 (2H, br s), 5.26 (1H, quin), 5.92 (2H, s), 6.72 (1H, d), 6.83 (1H, t), 6.87 (1H, d), 6.89 - 6.96 (2H, m), 7.15 - 7.24 (2H, m), 7.47 (1H, s), 7.55 (1H, s), 7.91 (1H, dd), 7.94 (1H, d), 8.16 (1H, d), 10.37 (1H, s), 13.17 - 15.05 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 803.7.

EXAMPLE 3

Intermediate 3a:

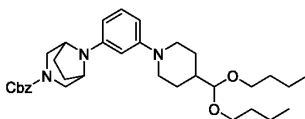
1-(3-Bromophenyl)-4-(dibutoxymethyl)piperidine



[1315] A mixture of Pd₂(dba)₃ (0.229 g, 0.25 mmol), xantphos (0.289 g, 0.50 mmol), and potassium *tert*-butoxide (1.122 g, 10.00 mmol) 1-bromo-3-iodobenzene (0.956 mL, 7.50 mmol) and 4-(dibutoxymethyl)piperidine (1.217 g, 5 mmol) and toluene (36 mL) was degassed, bubbling N₂ through the solution for 10 minutes. The reaction was heated to 85 °C for 1.75 h, Reaction was cooled to r.t. and concentrated under reduced pressure. Purification by FSC (gradient: 0-20% EtOAc in hexanes) gave the title compound (1.758 g, 88 %) as a yellow oil. ¹H NMR (CDCl₃): δ 0.94 (6H, t), 1.35 - 1.49 (6H, m), 1.53 - 1.63 (4H, m), 1.71 - 1.84 (1H, m), 1.87 (2H, br d), 2.65 - 2.73 (2H, m), 3.40 - 3.49 (2H, m), 3.64 (2H, dt), 3.69 (2H, br d), 4.19 (1H, d), 6.84 (1H, dd), 6.89 - 6.95 (1H, m), 7.03 - 7.06 (1H, m), 7.06 - 7.11 (1H, m); *m/z* (ES⁺) [M+Na]⁺ = 399.4.

Intermediate 3b:

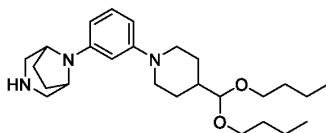
Benzyl 8-[3-[4-(dibutoxymethyl)-1-piperidyl]phenyl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



[1316] Prepared in an analogous manner to Intermediate 2e from benzyl 3,8-diazabicyclo[3.2.1]octane-3-carboxylate (0.927 g, 3.77 mmol) and Intermediate 3a (1.50 g, 3.77 mmol). Purification by FSC (gradient: 0-50% EtOAc in hexanes) gave the title compound (1.310 g, 61.7 %) as a light brown oil. ¹H NMR (CDCl₃): δ 0.96 (6H, t), 1.39 - 1.54 (6H, m), 1.55 - 1.64 (4H, m), 1.71 - 1.91 (5H, m), 2.00 - 2.06 (2H, m), 2.67 (2H, td), 3.32 - 3.53 (4H, m), 3.62 - 3.74 (6H, m), 3.79 (1H, br d), 4.19 - 4.25 (2H, m), 5.15 (2H, s), 6.29 - 6.35 (1H, m), 6.38 - 6.45 (2H, m), 7.13 (1H, t), 7.30 - 7.39 (5H, m); *m/z* (ES⁺) [M+Na]⁺ = 586.7.

Intermediate 3c:

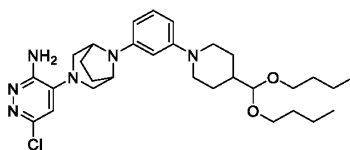
8-[3-[4-(Dibutoxymethyl)-1-piperidyl]phenyl]-3,8-diazabicyclo[3.2.1]octane



[1317] Pd/C (100 mg, 0.09 mmol) was added Intermediate 3b (1.3095 g, 2.32 mmol) and ammonium formate (1.465 g, 23.23 mmol) in MeOH (15 mL) was stirred at 50 °C for 30 min. The reaction was cooled to r.t. filtered through a celite® plug eluting with MeOH and EtOAc and concentrated. The resulting residue was partitioned between DCM (20 mL) and saturated aq. NaHCO₃ (20 mL). The layers were separated and the aqueous layer was extracted with DCM (2 x 20 mL). The combined organic extracts were washed with water and brine, dried (Na₂SO₄) and concentrated. Crude product has sufficient purity and taken onto next step without subsequent purification to give title compound (0.838 g, 84 %) as a yellow solid. ¹H NMR (DMSO-*d*₆): δ 0.89 (6H, t), 1.27 - 1.41 (6H, m), 1.45 - 1.55 (4H, m), 1.71 (3H, br d), 1.78 - 1.93 (4H, m), 2.39 (2H, br d), 2.49 - 2.59 (3H, m), 2.95 (2H, br d), 3.39 (2H, dt), 3.56 (2H, dt), 3.63 (2H, br d), 4.04 (2H, br s), 4.19 (1H, d), 6.18 - 6.25 (2H, m), 6.29 (1H, s), 6.96 (1H, t); *m/z* (ES⁺) [M+Na]⁺ = 452.2.

Intermediate 3d:

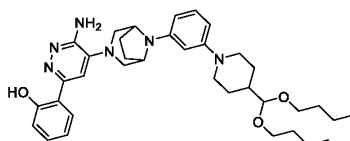
6-Chloro-4-[8-[3-[4-(dibutoxymethyl)-1-piperidyl]phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-amine



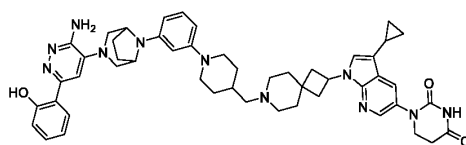
[1318] A mixture of Intermediate 3c (838.2 mg, 1.95 mmol), 4-bromo-6-chloropyridazin-3-amine (813 mg, 3.90 mmol), DIPEA (9.75 mmol, 1.704 mL), and *n*-butanol (10 mL) was heated at 110 °C for 8 h. The reaction was cooled to r.t. and concentrated. Purification by FSC (gradient: 0-100% EtOAc in hexanes) gave the title compound (657 mg, 60.4 %) as a brown solid. ¹H NMR (DMSO-*d*₆): δ 0.89 (6H, t), 1.27 - 1.40 (6H, m), 1.44 - 1.53 (4H, m), 1.61 - 1.74 (3H, m), 1.87 - 1.94 (2H, m), 2.05 - 2.11 (2H, m), 2.52 - 2.59 (2H, m), 2.95 (2H, br d), 3.17 (2H, br d), 3.34 - 3.43 (2H, m), 3.56 (2H, dt), 3.66 (2H, br d), 4.19 (1H, d), 4.34 (2H, br s), 5.79 (2H, s), 6.27 (1H, br d), 6.31 (1H, br d), 6.39 (1H, s), 6.85 (1H, s), 7.00 (1H, t); *m/z* (ES⁺) [M+H]⁺ = 557.2.

Intermediate 3e:

2-[6-Amino-5-[8-[3-[4-(dibutoxymethyl)-1-piperidyl]phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-yl]phenol

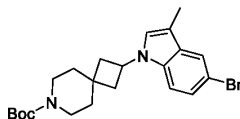


1-[1-[7-[[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



EXAMPLE 4

tert-Butyl 2-(5-bromo-3-methyl-indol-1-yl)-7-azaspiro[3.5]nonane-7-carboxylate

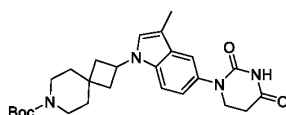


135

3.42 - 3.49 (2H, m), 4.80 (1H, quin), 7.02 (1H, s), 7.14 (1H, d), 7.23 - 7.26 (1H, m), 7.68 (1H, d); m/z (ES^+) $[M-tBu+2H]^+ = 377.1$.

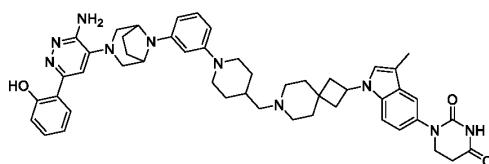
Intermediate 4b:

tert-Butyl 2-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-indol-1-yl]-7-azaspiro[3.5]nonane-7-carboxylate



[1322] The vial was charged with Intermediate 4a (824 mg, 1.90 mmol), hexahydropyrimidine-2,4-dione (651 mg, 5.70 mmol), CS_2CO_3 (1239 mg, 3.80 mmol), Ephos (102 mg, 0.19 mmol) and Ephos Pd G4 (175 mg, 0.19 mmol). The vial was evacuated and backfilled with nitrogen. 1,4-Dioxane (12 mL) was added and the reaction mixture was then degassed by bubbling nitrogen through the solution for 10 min. The vial was sealed and the resulting mixture was stirred at 100 °C for 16 h. The solvent was removed. Purification by FSC (gradient: 0-100% EtOAc in hexanes) gave the title compound (727 mg, 82 %) as an off-white solid. 1H NMR ($DMSO-d_6$): δ 1.39 (9H, s), 1.53 - 1.59 (2H, m), 1.64 - 1.71 (2H, m), 2.09 - 2.14 (2H, m), 2.24 (3H, s), 2.41 - 2.47 (2H, m), 2.71 (2H, t), 3.19 - 3.27 (2H, m), 3.32 - 3.36 (2H, m), 3.75 (2H, t), 4.98 (1H, quin), 7.03 (1H, dd), 7.36 - 7.43 (3H, m), 10.23 (1H, s); m/z (ES^+) $[M+Na]^+ = 489.2$.

1-[1-[7-[[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione

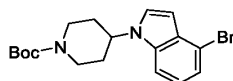


[1323] Prepared in an analogous manner to EXAMPLE 3 starting from Intermediate 3e (30.7 mg, 0.05 mmol) and Intermediate 4b (23.33 mg, 0.05 mmol). Purification by RPC (gradient: 0-100% MeCN in water with 0.1% NH_4OH) gave the title compound (11.30 mg, 25.5 %) as a pale yellow solid. 1H NMR ($DMSO-d_6$): δ 1.15 - 1.28 (6H, m), 1.62 - 1.68 (2H, m), 1.72 - 1.81 (3H, m), 1.89 - 1.97 (2H, m), 2.04 - 2.16 (4H, m), 2.19 - 2.22 (1H, m), 2.24 (3H, s), 2.29 - 2.34 (1H, m), 2.36 - 2.46 (3H, m), 2.61 (2H, br t), 2.71 (3H, br t), 3.08 (2H, br d), 3.25 (2H, br d), 3.64 (2H, br d), 3.75 (2H, br t), 4.38 (2H, br s), 4.88 - 5.01 (1H, m), 5.92 (2H, br s), 6.27 (1H, br d), 6.33 (1H, br d), 6.41 (1H, br s), 6.81 - 6.89 (2H, m), 6.94 - 7.09 (2H, m), 7.21 (1H, br t), 7.34 - 7.49 (4H, m), 7.90 (1H, br d), 10.23 (1H, s), 12.39 - 14.59 (1H, m); m/z (ES^+) $[M+H]^+ = 835.6$.

EXAMPLE 5

Intermediate 5a:

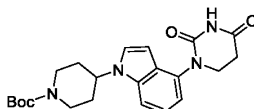
tert-Butyl 4-(4-bromoindol-1-yl)piperidine-1-carboxylate



[1324] 2-(Tributyl-*l*-5-phosphaneylidene)acetonitrile (92.0 g, 382.56 mmol) was added to a stirred solution of *tert*-butyl 4-hydroxypiperidine-1-carboxylate (77.0 g, 382.56 mmol) and 4-bromo-1*H*-indole (50.0 g, 255.04 mmol) in toluene (500 mL) under N₂ at r.t. The resulting mixture was stirred at 100°C for 18 h and then cooled to r.t. and concentrated under reduced pressure. Purification by RPC (gradient: 0-70% MeCN in water with 0.4% NH₄HCO₃) gave the title compound (20.0 g, 21 %) as a yellow solid. ¹H NMR (DMSO-*d*₆): δ 1.44 (9H, s), 1.76-2.00 (4H, m), 2.98 (2H, m), 4.13 (2H, d), 4.60 (1H, m), 6.42 (1H, d), 7.08 (1H, t), 7.23-7.28 (1H, m), 7.58-7.74 (2H, m); *m/z* (ES⁺) [M+H]⁺ = 379.1.

Intermediate 5b:

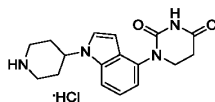
tert-Butyl 4-[4-(2,4-dioxohexahydropyrimidin-1-yl)indol-1-yl]piperidine-1-carboxylate



[1325] Prepared in an analogous method to Intermediate 4b starting from Intermediate 5a (5 g, 13.18 mmol). Purification by FSC (gradient: 0-60% EtOAc in petroleum ether) gave the title compound (5.20 g, 96 %) as a yellow solid. ¹H NMR (CDCl₃): δ 1.52 (9H, s), 1.86-2.01 (2H, m), 2.06-2.14 (2H, m), 2.86-3.00 (4H, m), 3.95 (2H, t), 4.23-4.50 (3H, m), 6.42 (1H, d), 7.06 (1H, d), 7.22-7.27 (2H, m), 7.38 (1H, d), 7.55 (1H, s); *m/z* (ES⁺) [M+Na]⁺ = 435.2.

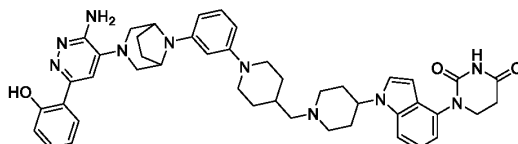
Intermediate 5c:

1-[1-(4-Piperidyl)indol-4-yl]hexahydropyrimidine-2,4-dione



[1326] Intermediate 5b (7.0 g, 16.97 mmol) was added to AcOH (20 mL). The resulting mixture was stirred at 100 °C for 72 h and then cooled to r.t. and concentrated under reduced pressure. Purification by RPC (gradient: 0-60% MeCN in water with 0.4% HCl) gave the title compound in the form of a hydrochloride salt (4.50 g, 85 %) as a red solid. ¹H NMR (DMSO-*d*₆): δ 1.89-2.30 (4H, m), 2.47-2.50 (2H, m), 2.75 (2H, t), 2.99-3.14 (2H, m), 3.76 (2H, t), 4.60-4.77 (1H, m), 6.44 (1H, d), 6.97 (1H, d), 7.16 (1H, t), 7.39 (1H, d), 7.57 (1H, d), 10.33 (1H, s) (NH protons not observed); *m/z* (ES⁺) [M+H]⁺ = 313.2.

1-[1-[1-[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl]methyl]-4-piperidyl]indol-4-yl]hexahydropyrimidine-2,4-dione

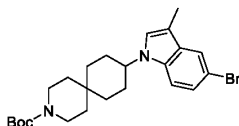


[1327] Prepared in an analogous manner to EXAMPLE 3 starting from Intermediate 3e (61.5 mg, 0.1 mmol) and Intermediate 5c (97 mg, 0.20 mmol). Purification by RPC (0-100% MeCN in water with 0.1% NH₄OH) gave the title compound (22.30 mg, 26.3 %) as a pale yellow solid. ¹H NMR (DMSO-*d*₆): δ 1.18 - 1.25 (2H, m), 1.61 - 1.72 (1H, m), 1.80 (2H, br d), 1.88 - 2.05 (6H, m), 2.09 - 2.15 (2H, m), 2.19 (2H, br t), 2.26 (2H, br d), 2.62 (2H, br t), 2.75 (2H, t), 3.00 (2H, br d), 3.09 (2H, br d), 3.25 (2H, br d), 3.66 (2H, br d), 3.77 (2H, t), 4.30 - 4.48 (3H, m), 5.92 (2H, s), 6.28 (1H, br d), 6.33 (1H, br d), 6.36 - 6.46 (2H, m), 6.81 - 6.88 (2H, m), 6.93 - 6.97 (1H, m), 7.01 (1H, t), 7.10 - 7.17 (1H, m), 7.21 (1H, t), 7.42 - 7.47 (1H, m), 7.48 - 7.54 (2H, m), 7.90 (1H, br d), 10.31 (1H, s), 12.34 - 14.69 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 781.4.

EXAMPLE 6

Intermediate 6a:

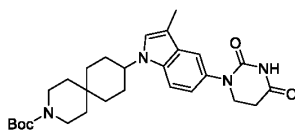
tert-Butyl 9-(5-bromo-3-methyl-indol-1-yl)-3-azaspiro[5.5]undecane-3-carboxylate



[1328] 2-(Tributyl-*l*5-phosphaneylidene)acetonitrile (3.74 mL, 14.28 mmol) was added to *tert*-butyl 9-hydroxy-3-azaspiro[5.5]undecane-3-carboxylate (2.56 g, 9.52 mmol) and 5-bromo-3-methylindole (1 g, 4.76 mmol) in toluene (20 mL) at r.t under nitrogen. The resulting mixture was stirred at 120 °C for 16 h. The reaction mixture was poured into water (200 mL), extracted with EtOAc (3 x 200 mL), the organic layer was dried over Na₂SO₄, filtered and concentrated. Purification by FSC (gradient 0 to 20% EtOAc in petroleum ether) gave the title compound (1.900 g, 86 %) as a white solid. ¹H NMR (DMSO-*d*₆) δ 1.24–1.38 (4H, m), 1.41 (9H, s), 1.58 (2H, t), 1.65–1.97 (7H, m), 2.22 (3H, d), 3.31 (2H, d), 3.34 (1H, s), 4.17–4.34 (1H, m), 7.20 (1H, dd), 7.38 (1H, s), 7.44 (1H, d), 7.64 (1H, d); *m/z* (ES⁺) [M-*t*Bu+2H]⁺ = 405.2.

Intermediate 6b:

tert-Butyl 9-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-indol-1-yl]-3-azaspiro[5.5]undecane-3-carboxylate

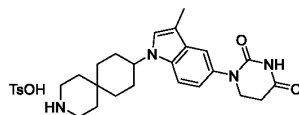


[1329] Di-μ-chlorobis[(1,2,3-4)-1-phenyl-2-propenyl]dipalladium(II) (0.057 g, 0.10 mmol) was added to Intermediate 6a (1.9 g, 4.12 mmol), hexahydropyrimidine-2,4-dione (1.409 g, 12.35 mmol), Cs₂CO₃ (4.02 g, 12.35 mmol) and 2-(di-*tert*-butylphosphino)-2',4',6'-triisopropyl-3,6-dimethoxy-1,1'-biphenyl (0.100 g, 0.21 mmol) in dioxane (40 mL) under nitrogen. The resulting mixture was stirred at 100 °C for 10 h. The reaction mixture was filtered through celite®. The filtrate was poured into water (500 mL), extracted with EtOAc (3 x 500 mL), the combined organic extracts were dried (Na₂SO₄), filtered and evaporated. The crude product was purified by FSC (gradient: 0 to 10% MeOH in DCM) gave the title compound (1.0 g, 49.1 %) as a brown solid. ¹H NMR (DMSO-*d*₆): δ 1.41 (13H, s), 1.60 (2H, t), 1.69–2 (6H, m), 2.24 (3H,

d), 2.51 (2H, t), 2.73 (2H, t), 3.77 (2H, t), 4.28 (1H, s), 5.76 (2H, s), 7.04 (1H, dd), 7.33–7.42 (2H, m), 7.45 (1H, d), 10.26 (1H, s); m/z (ES^+) $[M+H]^+ = 495.2$.

Intermediate 6c:

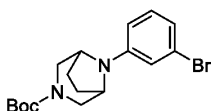
1-[1-(3-Azaspiro[5.5]undecan-9-yl)-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione



[1330] *para*-Toluenesulfonic acid (0.627 g, 3.64 mmol) was added to Intermediate 6b (1.5 g, 3.03 mmol) in MeCN (30 mL) was stirred at 70 °C for 3 h. The product was filtered to afford title compound (1.0 g, 58.2 %) as a white solid in the form of tosic salt. m/z (ES^+) $[M+H]^+ = 395.1$.

Intermediate 6d:

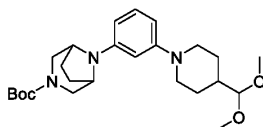
tert-Butyl 8-(3-bromophenyl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



[1331] Prepared in an analogous method to Intermediate 1b starting from 1,3-dibromobenzene (2.22 g, 9.42 mmol) and *tert*-butyl (3,8-diazabicyclo[3.2.1]octane-3-carboxylate (2 g, 9.42 mmol). Purification by FSC (gradient: 0 to 30% EtOAc in petroleum ether) gave the title compound (2.2 g, 63.6 %) as a white solid; m/z (ES^+) $[M+H]^+ = 367.0$.

Intermediate 6e:

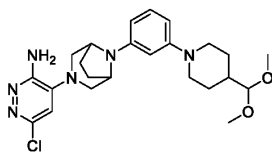
tert-Butyl 8-[3-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



[1332] The mixture of RuPhos (0.254 g, 0.54 mmol), RuPhos Pd G3 (0.455 g, 0.54 mmol), CS_2CO_3 (5.32 g, 16.34 mmol), 4-(dimethoxymethyl)piperidine (0.867 g, 5.45 mmol) and Intermediate 6d (2 g, 5.45 mmol) in 1,4-dioxane (40 mL) was stirred at 100 °C for 16 h. The reaction mixture was diluted with water (100 mL), extracted with EtOAc (3 x 500 mL), the organic layer was dried (Na_2SO_4), filtered and concentrated. Purification by FSC (gradient: 0 to 40% EtOAc in petroleum ether) gave the title compound (2.0 g, 82 %) as a yellow solid; m/z (ES^+) $[M+H]^+ = 446.2$.

Intermediate 6f:

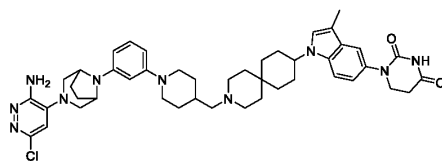
6-Chloro-4-[8-[3-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-amine



[1333] HCl in MeOH (10 mL, 40.00 mmol) was added to Intermediate 6c (1.3 g, 2.92 mmol) at r.t. The resulting mixture was stirred at r.t. for 2h. The solvent was removed under reduced pressure to afford the amine. To the crude amine was added 4-bromo-6-chloropyridazin-3-amine (0.608 g, 2.92 mmol), DIPEA (0.377 g, 2.92 mmol) and MeCN (15 mL) at r.t. The resulting mixture was stirred at 80 °C for 3 days. The reaction mixture was diluted with water (200 mL), extracted with EtOAc (3 x 200 mL), the organic layer was dried (Na₂SO₄), filtered and evaporated. Purification by RPC (gradient: 5 to 100% MeCN in water with 0.1% NH₄HCO₃) gave the title compound (0.900 g, 65.2 %) as a yellow solid. ¹H NMR (DMSO-*d*₆): δ 1.92 (1H, s), 2.29 (3H, s), 3.06–3.21 (8H, m), 3.36 (6H, s), 3.52–3.69 (7H, m), 5.77 (4H, s), 7.13 (2H, d), 7.42–7.53 (2H, m); *m/z* (ES⁺) [M+H]⁺ = 473.0.

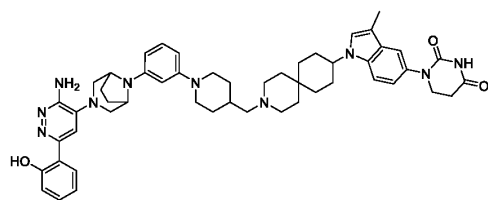
Intermediate 6g:

1-[1-[3-[[1-[3-[3-(3-Amino-6-chloro-pyridazin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione



[1334] Formic acid (1.0 mL) was added to Intermediate 6f (100 mg, 0.21 mmol). The resulting mixture was stirred at 40 °C for 30 min. The solvent was removed under reduced pressure to afford the aldehyde. To the crude aldehyde was added Intermediate 6c (120 mg, 0.21 mmol) and DCM (1 mL) at r.t. To the resulting solution was added sodium triacetoxyborohydride (67.2 mg, 0.32 mmol) and stirred at r.t. for 1 h. The reaction mixture was diluted with DCM (25 mL) and washed with saturated NH₄HCO₃ (3 x 25 mL). The organic layer was separated, dried (Na₂SO₄), filtered and evaporated. Purification by FCS (gradient: 0 to 10% MeOH in DCM) gave the title compound (60.0 mg, 35.2 %) as a yellow solid. ¹H NMR (DMSO-*d*₆): δ 1.15–1.51 (4H, m), 1.84 (14H, d), 2.09 (2H, d), 2.21–2.32 (5H, m), 2.57–2.77 (5H, m), 2.95 (2H, d), 3.17 (2H, d), 3.66 (3H, d), 3.77 (3H, t), 4.32 (4H, d), 5.82 (2H, s), 6.26–6.46 (3H, m), 6.87 (1H, s), 6.97–7.1 (2H, m), 7.3–7.49 (4H, m), 10.26 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 805.0.

1-[1-[3-[[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione

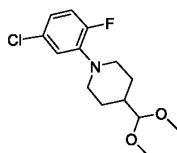


[1335] Prepared in an analogous method to Intermediate 2h starting from Intermediate 6g (45 mg, 0.06 mmol). Purification by RPC (Gradient: 0-50% MeCN in water with 0.1% FA) gave the title compound (6.80 mg, 14.10 %) as a white solid. ^1H NMR (DMSO- d_6): δ 1.12–1.26 (2H, m), 1.29–1.41 (4H, m), 1.67 (3H, s), 1.77 (6H, q), 1.88 (2H, d), 1.92–1.98 (2H, m), 2.17 (4H, dd), 2.23 (3H, d), 2.37 (4H, s), 2.62 (2H, t), 2.73 (2H, t), 3.10 (2H, d), 3.25 (1H, s), 3.27 (1H, d), 3.65 (2H, d), 3.77 (2H, t), 4.26 (1H, t), 4.39 (2H, d), 5.95 (2H, s), 6.25–6.37 (2H, m), 6.43 (1H, t), 6.81–6.91 (2H, m), 6.98–7.08 (2H, m), 7.19–7.27 (1H, m), 7.38 (2H, dd), 7.41–7.49 (2H, m), 7.92 (1H, dd), 8.19 (1H, d), 10.27 (1H, s); m/z (ES^+) $[\text{M}+\text{H}]^+ = 863.4$.

EXAMPLE 7

Intermediate 7a:

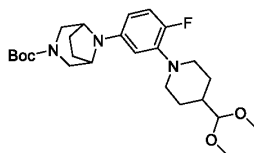
1-(5-Chloro-2-fluoro-phenyl)-4-(dimethoxymethyl)piperidine



[1336] Copper(I) iodide (0.074 g, 0.39 mmol) was added to *L*-proline (0.045 g, 0.39 mmol), K_3PO_4 (2.483 g, 11.70 mmol), 4-(dimethoxymethyl)piperidine (0.621 g, 3.90 mmol) and 4-chloro-1-fluoro-2-iodobenzene (1 g, 3.90 mmol) in DMF (13 mL) under nitrogen. The resulting mixture was stirred at 100 °C for 16h. Purification by RPC (gradient: 5 to 100% MeOH in water with 0.5% NH_4HCO_3) gave the title compound (0.470 g, 41.9 %) as a grey solid. ^1H NMR (DMSO- d_6) δ 1.21 – 1.46 (3H, m), 1.64 – 1.78 (3H, m), 2.57 – 2.68 (2H, m), 3.28 (6H, s), 3.43 (1H, s), 4.11 (1H, d), 6.93 – 7.03 (2H, m), 7.10 – 7.19 (1H, m); m/z (ES^+) $[\text{M}+\text{H}]^+ = 288.3$.

Intermediate 7b:

tert-Butyl 8-[3-[4-(dimethoxymethyl)-1-piperidyl]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate

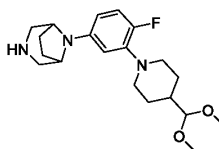


[1337] Prepared in an analogous method to Intermediate 2e from *tert*-butyl (3,8-diazabicyclo[3.2.1]octane-3-carboxylate (332 mg, 1.56 mmol) and Intermediate 7a (450 mg, 1.56 mmol). Purification by RPC (gradient: 5 to 100% MeOH in water with 0.5% NH_4HCO_3) gave the title compound (410 mg, 56.6 %) as a yellow solid. ^1H NMR (DMSO- d_6): δ 1.33 – 1.36 (1H, m), 1.33 (10H, m), 1.42 –

1.51 (1H, m), 1.60 – 1.76 (6H, m), 1.82 – 1.91 (2H, m), 2.52– 2.68 (2H, m), 2.96– 3.08 (1H, m), 3.10– 3.20 (1H, m), 3.28 (6H, s), 3.45 – 3.58 (2H, m), 4.12 (1H, d), 4.15– 4.25 (2H, m), 6.34 – 6.46 (2H, m), 6.79 – 6.59 (1H, m); m/z (ES⁺) [M+H]⁺ = 464.4.

Intermediate 7c:

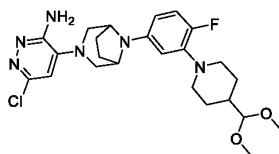
8-[3-[4-(Dimethoxymethyl)-1-piperidyl]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octane



[1338] HCl in MeOH (6 mL, 197.49 mmol, 4.0 M) was added to Intermediate 7b (400 mg, 0.86 mmol). The resulting mixture was stirred at r.t for 3 h. The reaction mixture was adjusted to pH to 9 with the 7 M ammonia methanol solution. The solvent was removed under reduced pressure. The reaction mixture was diluted with MeOH:DCM (1:3) (15 mL), solids were filtered off. The filtrate was concentrated under reduced pressure afford the title compound (300 mg, 87 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.27 – 1.49 (2H, m), 1.67 – 1.75 (3H, m), 1.95 – 2.16 (5H, m), 2.56 – 2.65 (2H, m), 2.88 – 2.95 (3H, m), 2.95 – 3.10 (2H, m), 3.26 (6H, s), 3.32 – 3.40 (1H, m), 4.12 (1H, d), 4.33 (2H, s), 6.36 – 6.49 (2H, m), 6.91 – 7.03 (1H, m); m/z (ES⁺) [M+H]⁺ = 364.2.

Intermediate 7d:

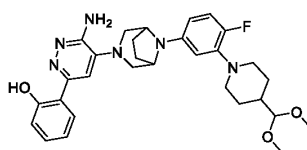
6-Chloro-4-[8-[3-[4-(dimethoxymethyl)-1-piperidyl]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-amine



[1339] Prepared in an analogous method to Intermediate 3d starting from Intermediate 7c (300 mg, 0.83 mmol). Purification by RPC (gradient 5 to 100% MeCN in water with 0.5% NH₄HCO₃) gave the title compound (200 mg, 45.3 %) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 1.50 – 1.60 (2H, m), 1.65 – 1.76 (1H, m), 1.77 – 1.84 (2H, m), 1.91 – 1.96 (2H, m), 2.02 – 2.15 (2H, m), 2.62 – 2.71 (3H, m), 3.02 – 3.18 (4H, m), 3.31 (6H, s), 3.39 – 3.46 (2H, m), 4.05 (1H, d), 4.16 – 4.27 (2H, m), 4.88 – 4.96 (1H, m), 6.31 (1H, s), 6.35 – 6.74 (2H, m), 6.78 – 6.91 (1H, m); m/z (ES⁺) [M+H]⁺ = 492.5.

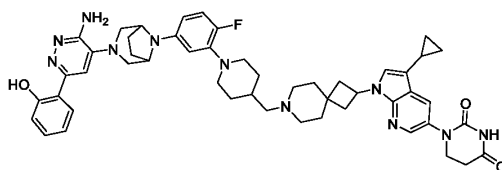
Intermediate 7e:

2-[6-Amino-5-[8-[3-[4-(dimethoxymethyl)-1-piperidyl]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-yl]phenol



[1340] Prepared in an analogous method to Intermediate 2h starting from Intermediate 7d. Purification by FSC (gradient: 0 to 10% MeOH in DCM) gave the title compound (160 mg, 82 %) as a yellow solid. ¹H NMR (DMSO-*d*₆) δ 1.23 – 1.27 (2H, m), 1.39 – 1.42 (2H, m), 1.62 – 1.81 (4H, m), 1.91 – 1.97 (3H, m), 2.10 – 2.20 (2H, m), 2.53 – 2.63 (3H, m), 3.05 – 3.13 (2H, m), 3.27 (6H, s), 4.25 – 4.31 (2H, m), 5.95 (2H, s), 6.44 – 6.49 (2H, m), 6.79 – 6.92 (3H, m), 7.02 – 7.27 (1H, m), 7.47 (1H, s), 7.91 (1H, d), 14.19 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 549.7

1-[1-[7-[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

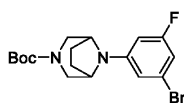


[1341] Prepared in an analogous method to EXAMPLE 3 starting from Intermediate 7c (40 mg, 0.07 mmol) and Intermediate 2b (28.7 mg, 0.07 mmol). Purification by RPC (Gradient: 10-50% MeCN in water with 0.1% FA) gave the title compound (11.0 mg, 16.46 %) as a white solid. ¹H NMR (DMSO-*d*₆) δ 0.66 – 0.73 (2H, m), 0.84 – 0.91 (2H, m), 1.21 – 1.29 (2H, m), 1.66 – 1.83 (7H, m), 1.90 – 1.98 (3H, m), 2.10 – 2.20 (5H, m), 2.19 – 2.36 (2H, m), 2.25 – 2.36 (5H, m), 2.59 – 2.68 (2H, m), 2.77 (2H, t), 3.05 – 3.18 (2H, m), 3.21 – 3.29 (2H, m), 3.34 – 3.40 (2H, m), 3.82 (2H, t), 4.25 – 4.41 (2H, m), 5.22 – 5.29 (1H, m), 5.96 (2H, s), 6.39 – 6.51 (2H, m), 6.84 – 6.97 (3H, m), 7.20 – 7.26 (1H, m), 7.47 (1H, s), 7.56 (1H, s), 7.89 – 7.97 (2H, m), 8.17 (1H, d), 10.40 (1H, s) (OH proton not observed); ¹⁹F NMR (DMSO-*d*₆) δ -136.41; *m/z* (ES⁺) [M+H]⁺ = 880.6.

EXAMPLE 8

Intermediate 8a:

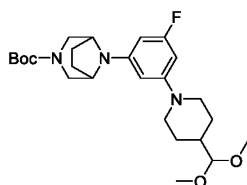
tert-Butyl 8-(3-bromo-5-fluoro-phenyl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



[1342] Prepared in an analogous method to Intermediate 1b starting from 1,3-dibromo-5-fluorobenzene (2 g, 7.88 mmol) and *tert*-butyl-(3,8-diazabicyclo[3.2.1]octane-3-carboxylate (1.672 g, 7.88 mmol). Purification by FSC (gradient 0 to 10% EtOAc in petroleum ether) gave the title compound (1.280 g, 42.2 %) as a white solid. ¹H NMR (DMSO-*d*₆) δ 1.39 (9H, s), 1.61 – 1.72 (2H, m), 1.86 – 1.96 (2H, m), 3.03 (2H, dd), 3.55 (2H, t), 4.33 (2H, s), 6.65 – 6.78 (2H, m), 6.86 – 6.91 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 385.

Intermediate 8b:

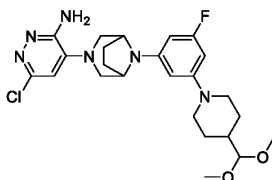
tert-Butyl 8-[3-[4-(dimethoxymethyl)-1-piperidyl]-5-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



[1343] Prepared in an analogous method to Intermediate 6e starting from Intermediate 8a (1.28 g, 3.32 mmol). Purification by FSC (gradient: 0 to 40 % EtOAc in petroleum ether) gave the title compound (0.790 g, 51.3 %) as a yellow solid. ¹H NMR (DMSO-*d*₆) δ 1.27 (2H, d), 1.39 (9H, s), 1.60 – 1.72 (5H, m), 1.84 – 1.95 (2H, m), 2.54 – 2.66 (2H, m), 3.06 (2H, dd), 3.27 (6H, s), 3.52 (2H, t), 3.70 (2H, d), 4.08 (1H, d), 4.26 (2H, s), 5.94 – 6.17 (3H, m); *m/z* (ES⁺) [M+H]⁺ = 464.

Intermediate 8c:

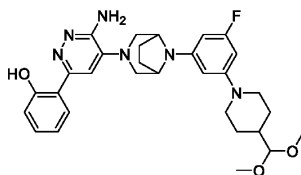
6-Chloro-4-[8-[3-[4-(dimethoxymethyl)-1-piperidyl]-5-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-amine



[1344] Prepared in an analogous method to Intermediate 6f starting from Intermediate 8b (490 mg, 1.06 mmol). Purification by RPC (gradient: 3 to 80% MeCN in water 0.1% NH₄HCO₃) gave the title compound (260 mg, 50.1 %) as a yellow solid. ¹H NMR (DMSO-*d*₆) δ 1.21 – 1.36 (2H, m), 1.62 – 1.74 (3H, m), 1.87 – 1.95 (2H, m), 2.05 – 2.15 (2H, m), 2.60 (2H, t), 2.93 (2H, d), 3.16 (2H, d), 3.27 (5H, s), 3.60 – 3.76 (3H, m), 4.08 (1H, d), 4.36 (2H, s), 5.82 (2H, s), 6.01 – 6.18 (3H, m), 6.89 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 491.2.

Intermediate 8d:

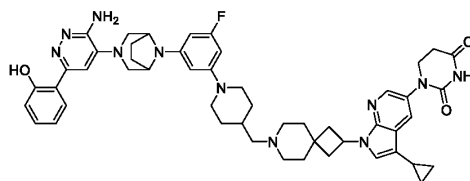
2-[6-Amino-5-[8-[3-[4-(dimethoxymethyl)-1-piperidyl]-5-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-yl]phenol



[1345] Prepared in an analogous method to Intermediate 2h starting from Intermediate 8c (200 mg, 0.41 mmol). Purification by FSC (gradient: 0 to 100 % DCM in petroleum ether and 0 to 10 % EtOH in DCM) gave the title compound (210 mg, 94 %) as a yellow solid. ¹H NMR (DMSO-*d*₆) δ 0.83 – 0.96 (2H, m), 1.22 – 1.28 (2H, m), 1.64 – 1.73 (3H, m), 1.91 – 2.00 (2H, m), 2.15 (2H, d), 2.61 (2H, t), 3.08 (2H, d), 3.25 (6H, s), 3.71 (2H, d), 4.08 (1H, d), 4.41 (2H, s), 5.96 (2H, s), 6.16 – 6.20 (1H, m), 6.73 – 6.78 (1H, m),

6.84 – 6.90 (2H, m), 7.10 – 7.20 (1H, m), 7.48 (1H, s), 7.89 – 7.96 (1H, m), 9.33 (1H, s), 14.17 (1H, s); m/z (ES⁺) $[M+H]^+ = 549$.

1-[1-[7-[[1-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-5-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

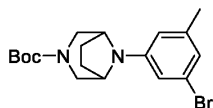


[1346] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 8d (60 mg, 0.11 mmol) and Intermediate 2c (51.6 mg, 0.13 mmol). Purification by RPC (gradient: 0-38 % MeCN water with 0.1 % FA) gave the title compound (14.88 mg, 14.72 %) as a white solid. ¹H NMR (DMSO-*d*₆) δ 0.66 – 0.71 (2H, m), 0.84 – 0.90 (2H, m), 1.17 (2H, dtd), 1.60 – 1.80 (6H, m), 1.93 (3H, dp), 2.05 – 2.25 (8H, m), 2.34 (5H, dd), 2.76 (2H, t), 3.09 (2H, d), 3.25 (3H, d), 3.63 (3H, d), 3.81 (2H, t), 4.34 – 4.40 (2H, m), 5.24 (1H, p), 5.94 (2H, s), 6.11 (1H, s), 6.21 (2H, d), 6.82 – 6.89 (2H, m), 7.23 (1H, t), 7.46 (1H, s), 7.56 (1H, s), 7.89 – 7.97 (2H, m), 8.17 (1H, d), 10.41 (1H, s); ¹⁹F NMR (DMSO-*d*₆) δ -73.44, -112.18; m/z (ES⁺) $[M+H]^+ = 880.6$.

EXAMPLE 9

Intermediate 9a:

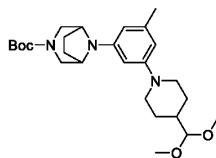
tert-Butyl 8-(3-bromo-5-methyl-phenyl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



[1347] Prepared in an analogous method to Intermediate 1b starting from 1,3-dibromo-5-methylbenzene (2 g, 8.00 mmol) and *tert*-butyl-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (1.7 g, 8.00 mmol). Purification by FSC (gradient: 0 to 7 % EtOAc in petroleum ether) gave the title compound (2.0 g, 65.5 %) as a white solid. ¹H NMR (DMSO-*d*₆) δ 1.39 (9H, s), 1.59 – 1.73 (2H, m), 1.82 – 1.96 (2H, m), 2.22 (3H, s), 2.92 – 3.19 (2H, m), 3.54 (2H, t), 4.28 (2H, s), 6.64 – 6.70 (2H, m), 6.83 (1H, d); m/z (ES⁺) $[M+H]^+ = 381$.

Intermediate 9b:

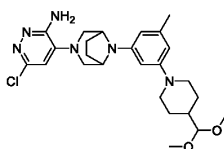
tert-Butyl 8-[3-[4-(dimethoxymethyl)-1-piperidyl]-5-methyl-phenyl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



[1348] Prepared in an analogous method to Intermediate 6e starting from Intermediate 9a (1 g, 2.62 mmol). Purification by FSC (gradient 0 to 30 % EtOAc in petroleum ether) gave the title compound (0.900 g, 74.7 %) as a yellow solid. ¹H NMR (DMSO-*d*₆) δ 1.22 – 1.33 (2H, m), 1.39 (9H, s), 1.58 – 1.73 (5H, m), 1.82 – 1.93 (2H, m), 2.16 (3H, s), 2.56 (2H, d), 3.01 (1H, d), 3.15 (1H, d), 3.20 (6H, s), 3.51 (2H, t), 3.64 (2H, d), 4.08 (1H, d), 4.22 (2H, s), 6.07 – 6.21 (3H, m); *m/z* (ES⁺) [M+H]⁺ = 460.

Intermediate 9c:

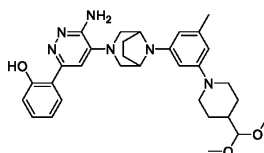
6-Chloro-4-[8-[3-[4-(dimethoxymethyl)-1-piperidyl]-5-methyl-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-amine



[1349] Prepared analogous method to Intermediate 6f starting from Intermediate 9b (500 mg, 1.09 mmol). Purification by RPC (gradient: 0 to 70 % MeCN in water with 0.1 % FA) gave the title compound (410 mg, 77 %). ¹H NMR (DMSO-*d*₆) δ 0.81 – 0.89 (2H, m), 1.22 – 1.36 (3H, m), 1.66 – 1.70 (2H, m), 1.85 – 1.93 (2H, m), 2.04 – 2.10 (1H, m), 2.16 (3H, s), 2.53 – 2.59 (1H, m), 2.94 (2H, d), 3.12 – 3.18 (2H, m), 3.27 (6H, s), 3.60 – 3.69 (2H, m), 4.08 (1H, d), 4.33 (2H, s), 5.81 (2H, s), 6.09 – 6.23 (3H, m), 6.87 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 487.0.

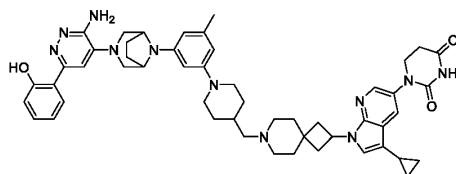
Intermediate 9d:

2-[6-Amino-5-[8-[3-[4-(dimethoxymethyl)-1-piperidyl]-5-methyl-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-yl]phenol



[1350] Prepared in an analogous method to Intermediate 2h starting from Intermediate 9c (200 mg, 0.41 mmol). Purification by FSC (gradient: 0 to 100 % DCM in petroleum ether and 0 to 10 % MeOH in DCM) gave the title compound (200 mg, 89 %) as a yellow solid. ¹H NMR (DMSO-*d*₆) δ 1.17 – 1.41 (4H, m), 1.60 – 1.73 (3H, m), 1.85 – 1.97 (2H, m), 2.11 (1H, d), 2.16 (3H, s), 2.55 (2H, d), 3.03 – 3.11 (2H, m), 3.21 (1H, s), 3.25 (6H, s), 3.59 – 3.68 (2H, m), 4.06 (1H, d), 4.35 (2H, s), 5.93 (1H, s), 6.09 (1H, s), 6.19 (2H, d), 6.80 – 6.89 (2H, m), 7.16 – 7.24 (1H, m), 7.44 (1H, s), 7.86 – 7.94 (1H, m), 14.15 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 545.

1-[1-[7-[[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)146yridine146e-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-5-methyl-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]146yridine-5-yl]hexahydropyrimidine-2,4-dione

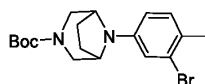


[1351] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 9d (60 mg, 0.11 mmol and Intermediate 2c (52.0 mg, 0.13 mmol). Purification by RPC (gradient: 0-38 % MeCN water with 0.1 % FA) gave the title compound (13.41 mg, 13.28 %) as a white solid. ^1H NMR (DMSO- d_6) δ 0.65 – 0.72 (2H, m), 0.83 – 0.91 (2H, m), 1.08 – 1.23 (2H, m), 1.57 – 1.81 (7H, m), 1.89 – 1.99 (3H, m), 2.10 – 2.25 (9H, m), 2.26 – 2.43 (6H, m), 2.59 – 2.70 (2H, m), 2.76 (2H, t), 3.07 (2H, d), 3.24 (2H, d), 3.69 (3H, d), 3.81 (2H, t), 4.41 (2H, d), 5.25 (1H, m), 5.96 (1H, s), 6.00 – 6.08 (1H, m), 6.10 – 6.23 (2H, m), 6.82 – 6.91 (2H, m), 7.19 – 7.26 (1H, m), 7.48 (1H, s), 7.56 (1H, s), 7.90 – 7.97 (2H, m), 8.14 – 8.18 (1H, m), 10.41 (1H, s); m/z (ES^+) $[\text{M}+\text{H}]^+ = 876.5$.

EXAMPLE 10

Intermediate 10a:

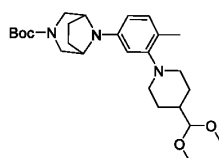
tert-Butyl 8-(3-bromo-4-methyl-phenyl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



[1352] 2-Bromo-4-iodo-1-methylbenzene (2 g, 6.74 mmol) was added to *tert*-butyl 3,8-diazabicyclo[3.2.1]octane-3-carboxylate (1.430 g, 6.74 mmol), palladium (II) acetate (0.151 g, 0.67 mmol), Cs_2CO_3 (4.39 g, 13.47 mmol) and BINAP (0.419 g, 0.67 mmol) in 1,4-dioxane (20 mL) under N_2 . The resulting mixture was stirred at 100 °C for 16 h. The reaction mixture was diluted with EtOAc (100 mL), and washed sequentially with saturated NH_4Cl (100 mL x 2) and saturated brine (100 mL x 2). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was purified by FSC (gradient: 0 to 7% EtOAc in petroleum ether) gave the title compound (2.280 g, 89 %) as a purple solid. ^1H NMR (DMSO- d_6) δ 1.39 (9H, s), 1.61 – 1.72 (2H, m), 1.83 – 1.94 (2H, m), 2.22 (3H, s), 2.93 – 3.17 (2H, m), 3.53 (2H, t), 4.25 (2H, s), 6.76 – 6.83 (1H, m), 7.07 (1H, d), 7.11 – 7.17 (1H, m); m/z (ES^+) $[\text{M}+\text{H}]^+ = 381.3$.

Intermediate 10b:

tert-Butyl 8-[3-[4-(dimethoxymethyl)-1-piperidyl]-4-methyl-phenyl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate

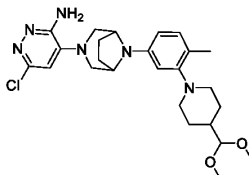


[1353] Prepared in an analogous method to Intermediate 6e starting from Intermediate 10a (1 g, 2.62 mmol). Purification by FSC (gradient: 0 to 30% MeCN in water with 0.1% NH_4HCO_3) gave the title

compound (750 g, 62.2 %) as a yellow solid. ^1H NMR (DMSO-*d*₆) δ 1.36 – 1.46 (11H, m), 1.59 – 1.75 (5H, m), 1.81 – 1.92 (2H, m), 2.09 (3H, s), 2.52 – 2.67 (2H, m), 2.95 – 3.10 (3H, m), 3.10 – 3.18 (1H, m), 3.28 (6H, s), 3.52 (2H, t), 4.12 (1H, d), 4.20 (2H, s), 6.44 (2H, d), 6.94 (1H, d); m/z (ES⁺) [M+H]⁺ = 460.

Intermediate 10c:

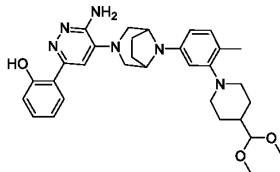
6-Chloro-4-[8-[3-[4-(dimethoxymethyl)-1-piperidyl]-4-methyl-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-amine



[1354] Prepared analogous method to Intermediate 6f starting from Intermediate 10b (370 mg, 0.80 mmol). Purification by RPC (gradient 3 to 80% MeCN in water with 0.1% NH₄HCO₃) gave the title compound (256 mg, 65.3 %) as a yellow solid. ^1H NMR (DMSO-*d*₆) δ 1.26 – 1.45 (2H, m), 1.61 – 1.77 (3H, m), 1.85 – 1.96 (2H, m), 2.00–2.12 (2H, m), 2.09 (3H, s), 2.53 – 2.64 (2H, m), 2.95 (2H, d), 3.06 (2H, d), 3.16 (2H, d), 3.28 (6H, s), 4.12 (1H, d), 4.30 (2H, s), 5.81 (2H, s), 6.42 – 6.48 (2H, m), 6.86 (1H, s), 6.94 (1H, d); m/z (ES⁺) [M+H]⁺ = 487.

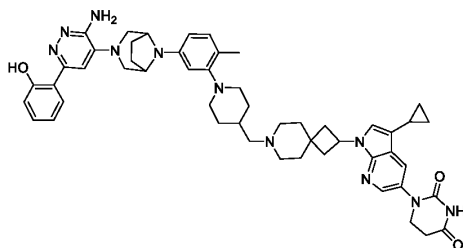
Intermediate 10d:

2-[6-Amino-5-[8-[3-[4-(dimethoxymethyl)-1-piperidyl]-4-methyl-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-yl]phenol



[1355] Prepared in an analogous method to Intermediate 2h starting from Intermediate 10c (200 mg, 0.41 mmol). Purification by FSC (gradient: 0 to 40 % DCM in petroleum ether) gave the title compound (215 mg, 96 %) as a yellow solid. ^1H NMR (DMSO-*d*₆) δ 1.32 – 1.46 (2H, m), 1.59 – 1.76 (4H, m), 1.87 – 2.05 (3H, m), 2.10 (3H, s), 2.11 – 2.16 (1H, m), 2.53 – 2.61 (1H, m), 3.00 – 3.13 (4H, m), 3.21 – 3.25 (1H, m), 3.28 (6H, s), 3.43 – 3.61 (1H, m), 4.13 (1H, d), 4.35 (2H, s), 5.95 (1H, s), 6.45 – 6.54 (2H, m), 6.81 – 6.91 (2H, m), 6.93 – 7.03 (2H, m), 7.18 – 7.26 (1H, m), 7.42 – 7.48 (1H, m), 7.91 (1H, d) (OH proton is not observed); m/z (ES⁺) [M+H]⁺ = 545.3.

1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-methyl-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

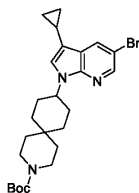


[1356] Prepared in an analogous method to EXAMPLE 1 starting from Intermediate 10d (60 mg, 0.11 mmol) and Intermediate 2c (52.0 mg, 0.13 mmol). Purification by RPC (Gradient: 0-50% MeCN in water with 0.1% FA) gave the title compound (14.05 mg, 14.23 %) as a white solid. ^1H NMR (DMSO- d_6) δ 0.66 – 0.72 (2H, m), 0.83 – 0.91 (2H, m), 1.18 – 1.31 (2H, m), 1.59 – 1.82 (6H, m), 1.89 – 1.98 (3H, m), 2.08 – 2.25 (10H, m), 2.27 – 2.39 (5H, m), 2.53 – 2.63 (2H, m), 2.76 (2H, t), 3.02 – 3.15 (5H, m), 3.25 (3H, d), 3.81 (2H, t), 4.34 (2H, s), 5.23 (1H, q), 5.93 (2H, s), 6.44 – 6.54 (2H, m), 6.86 (2H, t), 6.95 (1H, d), 7.23 (1H, t), 7.45 (1H, s), 7.55 (1H, s), 7.88 – 7.98 (2H, m), 8.17 (1H, d), 10.39 (1H, s); m/z (ES $^+$) $[\text{M}+\text{H}]^+ = 877.2$.

EXAMPLE 11

Intermediate 11a:

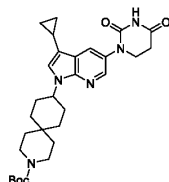
tert-Butyl 9-(5-bromo-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-1-yl)-3-azaspiro[5.5]undecane-3-carboxylate



[1357] Prepared in an analogous manner to Intermediate 2a starting from 5-bromo-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridine (593 mg, 2.5 mmol) and *tert*-butyl 9-hydroxy-3-azaspiro[5.5]undecane-3-carboxylate (1010 mg, 3.75 mmol). Purification by FSC (0-50 % EtOAc in hexanes) gave the title compound (816 mg, 66.8 %) as a colorless dry film. ^1H NMR (DMSO- d_6): δ 0.58 - 0.67 (2H, m), 0.76 - 0.91 (2H, m), 1.23 - 1.34 (4H, m), 1.39 (9H, s), 1.57 - 1.66 (4H, m), 1.78 (2H, br d), 1.89 - 1.97 (3H, m), 3.29 - 3.33 (4H, m), 4.56 (1H, tt), 7.52 (1H, s), 8.17 (1H, d), 8.24 (1H, d); m/z (ES $^+$) $[\text{M}+\text{H}]^+ = 490.2$.

Intermediate 11b:

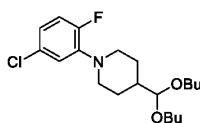
tert-Butyl 9-[3-cyclopropyl-5-(2,4-dioxohexahydropyrimidin-1-yl)pyrrolo[2,3-*b*]pyridin-1-yl]-3-azaspiro[5.5]undecane-3-carboxylate



[1000] Prepared in an analogous manner to Intermediate 2b starting from Intermediate 11a (816 mg, 1.67 mmol). Purification by FCS (0-100 % EtOAc in hexanes, then 0-30% MeOH in EtOAc) gave the title compound (420 mg, 48.2 %) as a brown solid. ¹H NMR (DMSO-*d*₆): δ 0.60 - 0.69 (2H, m), 0.79 - 0.90 (2H, m), 1.25 - 1.35 (4H, m), 1.39 (9H, s), 1.59 - 1.69 (4H, m), 1.80 (2H, br d), 1.87 - 1.94 (1H, m), 1.95 - 2.03 (2H, m), 2.75 (2H, t), 3.30 - 3.36 (4H, m), 3.80 (2H, t), 4.60 (1H, tt), 7.49 (1H, s), 7.92 (1H, d), 8.15 (1H, d), 10.35 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 522.7.

Intermediate 11c:

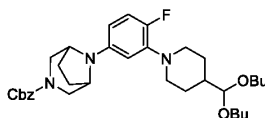
1-(5-Chloro-2-fluoro-phenyl)-4-(dibutoxymethyl)piperidine



[1359] A flask was charged with NaOtBu (27.5 g, 286.47 mmol) was added to 4-(dibutoxymethyl)piperidine (23.24 g, 95.49 mmol), 2-bromo-4-chloro-1-fluorobenzene (20 g, 95.49 mmol), Pd₂(dba)₃ (4.37 g, 4.77 mmol) and BINAP (5.95 g, 9.55 mmol) in toluene (300 mL). The resulting mixture was stirred at 60 °C for 20 h under nitrogen. The reaction mixture was diluted with EtOAc (500 mL), and washed sequentially with saturated NH₄Cl (500 mL) and saturated brine (500 mL). The organic layer was dried over Na₂SO₄, filtered and evaporate. Purification by FCS (0-5 % EtOAc in petroleum ether) gave the title compound (31.7 g, 89 %) as a pale yellow oil. ¹H NMR (CDCl₃): δ 0.96 (6H, t), 1.38 - 1.48 (4H, m), 1.49 - 1.65 (6H, m), 1.72 - 1.83 (1H, m), 1.89 (2H, br d), 2.53 - 2.73 (2H, m), 3.41 - 3.54 (4H, m), 3.61 - 3.73 (2H, m), 4.24 (1H, dd), 6.63 - 6.80 (1H, m), 6.88 - 6.99 (1H, m), 7.26 - 7.32 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 372.3.

Intermediate 11d:

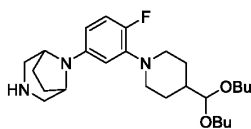
Benzyl 8-[3-[4-(dibutoxymethyl)-1-piperidyl]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



[1360] Prepared in an analogous manner to Intermediate 2e starting from Intermediate 11c (16.5 g, 44.36 mmol), and benzyl-3,8-diazabicyclo[3.2.1]octane-3-carboxylate, HCl (12.54 g, 44.36 mmol). Purification by FSC (0-25 % EtOAc in petroleum ether) gave the title compound (16.88 g, 65.4 %) as a red oil. ¹H NMR (DMSO-*d*₆): δ 0.89 (6H, t), 1.27 - 1.41 (6H, m), 1.43 - 1.56 (4H, m), 1.58 - 1.77 (5H, m), 1.84 - 1.96 (2H, m), 2.52 - 2.63 (2H, m), 3.07 - 3.28 (2H, m), 3.32 - 3.45 (4H, m), 3.50 - 3.63 (4H, m), 4.15 - 4.29 (3H, m), 5.00 - 5.14 (2H, m), 6.33 - 6.46 (2H, m), 6.85 - 6.98 (1H, dd), 7.24 - 7.48 (5H, m); *m/z* (ES⁺) [M+H]⁺ = 582.4.

Intermediate 11e:

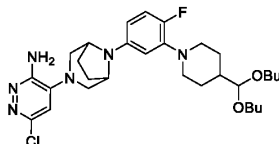
8-[3-[4-(Dibutoxymethyl)-1-piperidyl]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octane



[1361] A flask was charged with Intermediate 11d (9.8 g, 16.5 mmol), Pd/C (0.896 g, 0.84 mmol) and MeOH (300 mL) under a hydrogen atmosphere. The reaction was stirred at r.t. for 24 h. The solution was filtered and concentrated to give the title compound (7.10 g, 94 %) as a brown oil. ¹H NMR (DMSO-*d*₆): δ 0.89 (6H, t), 1.29 - 1.42 (6H, m), 1.45 - 1.53 (4H, m), 1.59 - 1.68 (1H, m), 1.68 - 1.76 (2H, m), 1.79 - 1.92 (4H, m), 2.38 (2H, br d), 2.52 - 2.60 (2H, m), 2.94 (2H, br d), 3.32 (2H, br d), 3.36 - 3.44 (2H, m), 3.53 - 3.60 (2H, m), 3.94 - 4.03 (2H, m), 4.22 (1H, d), 6.29 (1H, br d), 6.34 (1H, br d), 6.87 (1H, dd) (N-H not observed); *m/z* (ES⁺) [M+H]⁺ = 448.3.

Intermediate 11f:

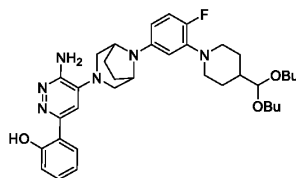
6-Chloro-4-[8-[3-[4-(dibutoxymethyl)-1-piperidyl]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-amine



[1362] A flask was charged with Intermediate 11e (12.7 g, 28.4 mmol), 4-bromo-6-chloropyridazin-3-amine (6.21 g, 29.79 mmol) DIPEA (14.87 mL, 85.1 mmol), and DMSO (100 mL). The resulting mixture was stirred at 100 °C for 16 h. The reaction mixture was diluted with EtOAc (300 mL), and washed sequentially with water (2 x 200 mL) and saturated brine (2 x 200 mL). The organic layer was dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 0-5 % MeOH in DCM) gave the title compound (13.49 g, 83 %) as a red oil. ¹H NMR (DMSO-*d*₆): δ 0.89 (6H, t), 1.30 - 1.42 (6H, m), 1.46 - 1.53 (4H, m), 1.60 - 1.68 (1H, m), 1.73 (2H, br d), 1.88 - 1.94 (2H, m), 2.04 - 2.12 (2H, m), 2.55 - 2.62 (2H, m), 2.95 (2H, br d), 3.16 (2H, br d), 3.33 - 3.43 (4H, m), 3.56 (2H, dt), 4.22 (1H, d), 4.27 - 4.33 (2H, m), 5.76 - 5.82 (2H, m), 6.38 - 6.45 (2H, m), 6.87 (1H, s), 6.91 (1H, dd). *m/z* (ES⁺) [M-OBu]⁺ = 501.4.

Intermediate 11g:

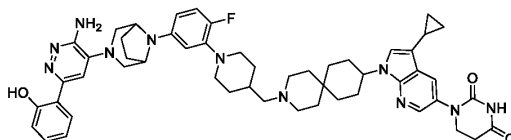
2-[6-Amino-5-[8-[3-[4-(dibutoxymethyl)-1-piperidyl]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-yl]phenol



[1363] Prepared in an analogous manner to Intermediate 2h starting from Intermediate 11f (281 mg, 0.49 mmol). Purification by FSC (gradient: 0-100 % EtOAc in hexanes) gave the title compound (202 mg, 65.2 %) as a light brown solid. ¹H NMR (DMSO-*d*₆): δ 0.88 (6H, t), 1.29 - 1.42 (6H, m), 1.43 - 1.52 (4H,

m), 1.58 - 1.68 (1H, m), 1.72 (2H, br d), 1.89 - 1.96 (2H, m), 2.07 - 2.15 (2H, m), 2.58 (2H, br t), 3.08 (2H, br d), 3.24 (2H, br d), 3.32 - 3.43 (4H, m), 3.55 (2H, dt), 4.21 (1H, d), 4.30 - 4.36 (2H, m), 5.92 (2H, s), 6.39 - 6.50 (2H, m), 6.80 - 6.98 (3H, m), 7.21 (1H, t), 7.45 (1H, s), 7.89 (1H, d), 14.15 (1H, s); m/z (ES^+) $[M+H]^+ = 633.6$.

1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

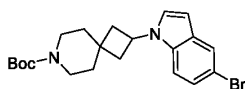


[1364] A vial was charged with Intermediate 11b (0.092 g, 0.18 mmol), Intermediate 11g (0.112 g, 0.18 mmol), and formic acid (2 mL, 52.15 mmol) was added and the mixture was stirred at 40 °C for 20 min. The reaction was concentrated under reduced pressure. Toluene (12 mL) was added and the reaction was evaporated to dryness. DMF (2 mL), and $MgSO_4$ (0.107 g, 0.88 mmol) were added. The mixture was stirred at 40 °C for 30 min. $Na(OAc)_3BH$ (0.075 g, 0.35 mmol) was added and the mixture was stirred at r.t. for 20 min. Purification by RPC (0-50% MeCN in water with 0.1% FA) gave the title compound (0.067 g, 41.2 %) as a white solid. 1H NMR ($DMSO-d_6$): δ 0.63 - 0.70 (2H, m), 0.81 - 0.90 (2H, m), 1.21 - 1.35 (4H, m), 1.36 - 1.44 (2H, m), 1.61 - 1.85 (9H, m), 1.89 - 2.04 (5H, m), 2.14 (2H, br d), 2.27 (2H, br d), 2.36 - 2.47 (4H, m), 2.65 (2H, br t), 2.77 (2H, t), 3.11 (2H, br d), 3.27 (2H, br d), 3.36 (2H, br d), 3.82 (2H, t), 4.35 (2H, br s), 4.59 (1H, br t), 5.94 (2H, s), 6.39 - 6.53 (2H, m), 6.83 - 6.98 (3H, m), 7.23 (1H, t), 7.49 (2H, d), 7.87 - 7.96 (2H, m), 8.13 - 8.20 (1H, m), 10.37 (1H, s), 13.30 - 14.81 (1H, m); m/z (ES^+) $[M+H]^+ = 908.7$.

EXAMPLE 12

Intermediate 12a:

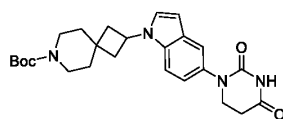
tert-Butyl 2-(5-bromoindol-1-yl)-7-azaspiro[3.5]nonane-7-carboxylate



[1365] Prepared in an analogous manner to Intermediate 4a from *tert*-butyl 2-hydroxy-7-azaspiro[3.5]nonane-7-carboxylate (2.462 g, 10.20 mmol) and 5-bromo-1*H*-indole (2 g, 10.20 mmol). Purification by RPC (gradient: 3 to 100% MeOH in MeOH (0.1% NH_4HCO_3) gave the title compound (4.15 g, 97 %) as an off-white solid. 1H NMR ($DMSO-d_6$) δ 1.41 (9H, s), 1.54 - 1.59 (2H, m), 1.66 - 1.72 (2H, m), 2.11 - 2.20 (2H, m), 2.44 - 2.50 (2H, m), 3.22 - 3.27 (2H, m), 3.34 - 3.39 (2H, m), 4.99 - 5.08 (1H, m), 6.48 (1H, d), 7.23 (1H, dd), 7.49 (1H, d), 7.65 (1H, d), 7.73 (1H, d); m/z (ES^+) $[M+H]^+ = 419.2$.

Intermediate 12b:

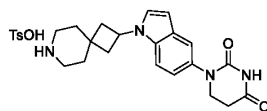
tert-Butyl 2-[5-(2,4-dioxohexahydropyrimidin-1-yl)indol-1-yl]-7-azaspiro[3.5]nonane-7-carboxylate



[1366] Prepared in an analogous manner to Intermediate 4b starting from Intermediate 12a (6.7 g, 15.98 mmol). Purification by FSC (gradient: 0 to 5% MeOH in DCM) gave the title compound (6.10 g, 84 %) as an off-white solid. ^1H NMR (DMSO-*d*₆) δ 1.41 (9H, s), 1.54 – 1.59 (2H, m), 1.67 – 1.74 (2H, m), 2.12 – 2.20 (2H, m), 2.46 – 2.51 (2H, m), 2.72 (2H, t), 3.23 – 3.29 (2H, m), 3.34 – 3.41 (2H, m), 3.76 (2H, t), 5.01 – 5.09 (1H, m), 6.49 (1H, d), 7.07 (1H, dd), 7.46 (1H, d), 7.50 (1H, d), 7.63 (1H, d), 10.27 (1H, s); m/z (ES^+) $[\text{M}+\text{H}]^+ = 453.3$.

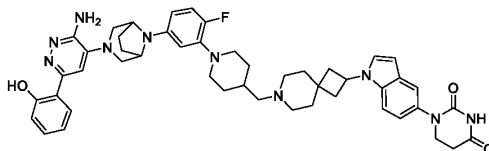
Intermediate 12c:

1-[1-(7-Azaspiro[3.5]nonan-2-yl)indol-5-yl]hexahydropyrimidine-2,4-dione



[1367] Prepared in an analogous manner to Intermediate 6c starting from Intermediate 12b (1.1 g, 2.43 mmol). The reaction mixture was diluted with MTBE (10 mL). The resulting mixture was stirred at room temperature for 10 mins. The precipitate was collected by filtration, washed with MTBE (10 mL) and dried under vacuum to afford the title compound (1.100 g, 86 %) as an off-white solid in the form of the TsOH salt. m/z (ES^+) $[\text{M}+\text{H}]^+ = 352.4$.

1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]indol-5-yl]hexahydropyrimidine-2,4-dione

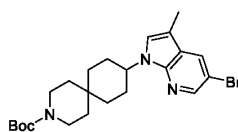


[1368] Prepared in an analogous manner to EXAMPLE 1 starting from Intermediate 11g (40 mg, 0.07 mmol) and Intermediate 12c (30.8 mg, 0.09 mmol). Purification by RPC (gradient: 0-50% MeCN in water with 0.1% FA) gave the title compound (8.00 mg, 12.78 %) as a white solid. ^1H NMR (DMSO-*d*₆) δ 1.17 – 1.29 (3H, m), 1.64 (3H, t), 1.73 – 1.82 (3H, m), 1.90 – 2.01 (2H, m), 2.09 – 2.20 (6H, m), 2.22 – 2.41 (4H, m), 2.45 (2H, t), 2.60 – 2.69 (2H, m), 2.69 – 2.77 (2H, m), 3.10 (2H, d), 3.23 – 3.28 (2H, m), 3.76 (2H, t), 4.35 (2H, d), 4.96 – 5.06 (1H, m), 5.96 (2H, s), 6.40 – 6.45 (1H, m), 6.46 – 6.51 (2H, m), 6.84 – 6.97 (3H, m), 7.04 – 7.09 (1H, m), 7.20 – 7.26 (1H, m), 7.44 – 7.52 (3H, m), 7.62 (1H, d), 7.89 – 7.93 (1H, m), 10.27 (1H, s), 14.19 (1H, s); ^{19}F NMR (DMSO-*d*₆) δ -136.4. m/z (ES^+) $[\text{M}+\text{H}]^+ = 839.5$.

EXAMPLE 13

Intermediate 13a:

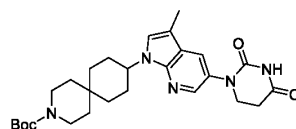
tert-Butyl 9-(5-bromo-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl)-3-azaspiro[5.5]undecane-3-carboxylate



[1369] Prepared in an analogous manner to Intermediate 4a starting 5-bromo-3-methyl-1H-pyrrolo[2,3-b]pyridine (800 mg, 3.79 mmol) and *tert*-butyl 9-hydroxy-3-azaspiro[5.5]undecane-3-carboxylate (1429 mg, 5.31 mmol). Purification by RPC (gradient: 2 to 80% MeCN in water with 0.1% NH₄CO₃) gave the title compound (910 mg, 51.9 %) as a yellow oil. ¹H NMR (CDCl₃) δ 1.34 – 1.44 (4 H, m), 1.47 (9 H, s), 1.61 – 1.67 (2 H, m), 1.82 – 1.94 (6 H, m), 2.27 (3 H, d), 3.38 – 3.44 (4 H, m), 4.61 – 4.69 (1 H, m), 7.07 (1 H, s), 7.94 (1 H, d), 8.28 (1 H, d); *m/z* (ES⁺) [M+H]⁺ = 462, 464.3.

Intermediate 13b:

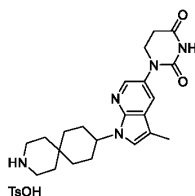
tert-Butyl 9-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-3-azaspiro[5.5]undecane-3-carboxylate



[1370] Prepared in an analogous method to Intermediate 6b starting from Intermediate 13a (530 mg, 1.15 mmol). Purification by FSC (gradient: 0 to 60% EtOAc in petroleum ether) gave the title compound (220 mg, 38.7 %) as a yellow solid. ¹H NMR (CDCl₃) δ 1.39 (3 H, d), 1.47 (9 H, s), 1.62 – 1.71 (3 H, m), 1.83 – 1.95 (6 H, m), 2.30 (3 H, d), 2.87 – 2.93 (2 H, m), 3.38 – 3.45 (4 H, m), 3.87 – 3.94 (2 H, m), 4.74 (1 H, s), 7.15 (1 H, s), 7.53 (1 H, s), 7.80 (1 H, s), 8.22 (1 H, d). *m/z* (ES⁺) [M+H]⁺ = 496.5.

Intermediate 13c:

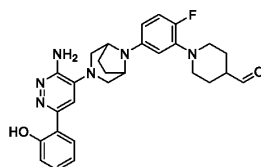
1-[1-(3-Azaspiro[5.5]undecan-9-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1371] Prepared in an analogous manner to Intermediate 6c starting from Intermediate 168b (190 mg, 0.38 mmol). The solvent was removed under reduced pressure gave the title compound (152 mg, 100%) as a white solid in the form of the TsOH salt. *m/z* (ES⁺) [M+H]⁺ = 396.5.

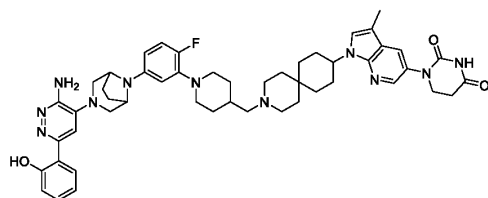
Intermediate 13d:

1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluorophenyl]piperidine-4-carbaldehyde



[1372] Formic acid (8 mL) was added to Intermediate 11g (300mg, 0.55 mmol). The resulting mixture was stirred at 40 °C for 1 h. The reaction mixture was evaporated. The reaction with quenched with saturated Na_2CO_3 , extracted with DCM (3 x 1 mL), the organic layer was dried over Na_2SO_4 , filtered and evaporated to afford the title compound (260 mg, 95 %) as a yellow solid. m/z (ES^+) $[\text{M}+\text{H}]^+ = 503.3$.

1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

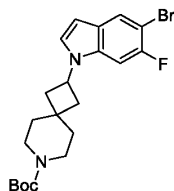


[1373] A mixture of Intermediate 13d (230 mg, 0.46 mmol) and Intermediate 13c (151 mg, 0.38 mmol) was heated at in 1,2-dichloroethane (4 mL) and NMP (4.00 mL) at 40 °C for 16 h. The reaction mixture was cooled r.t. and then added $\text{Na}(\text{OAc})_3\text{BH}$ (405 mg, 1.91 mmol) and stirred for 1 h. The reaction mixture was poured into saturated NaHCO_3 (50 mL), extracted with DCM (3 x 10 mL), the organic layer was dried over Na_2SO_4 , filtered and evaporated. Purification by RPC (gradient 2 to 100% MeCN in water with 0.1% NH_4CO_3) gave the title compound (37.4 mg, 11.33 %) as a white solid. ^1H NMR ($\text{DMSO}-d_6$) δ 0.80 – 0.89 (1 H, m), 1.17 – 1.45 (9 H, m), 1.62 – 1.73 (4 H, m), 1.74 – 1.85 (4 H, m), 1.89 – 2.05 (4 H, m), 2.10 – 2.27 (6 H, m), 2.35 (3 H, s), 2.58 – 2.69 (3 H, m), 2.72 – 2.78 (2 H, m), 3.09 (2 H, d), 3.25 (2 H, d), 3.73 – 3.86 (2 H, m), 4.28 – 4.40 (2 H, m), 4.52 – 4.66 (1 H, m), 5.95 (2 H, s), 6.36 – 6.55 (2 H, m), 6.80 – 6.98 (3 H, m), 7.16 – 7.28 (1 H, m), 7.50 (2 H, d), 7.78 – 7.99 (2 H, m), 8.16 (1 H, d), 10.39 (1 H, s), 14.18 (1 H, s); ^{19}F NMR ($\text{DMSO}-d_6$) δ : -136.4; m/z (ES^+), $[\text{M}+\text{H}]^+ = 882$.

EXAMPLE 14

Intermediate 14a:

tert-Butyl 2-(5-bromo-6-fluoro-indol-1-yl)-7-azaspiro[3.5]nonane-7-carboxylate

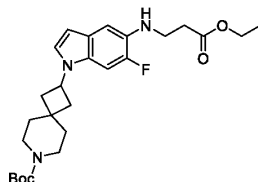


[1374] Prepared in an analogous manner to Intermediate 4a starting from 5-bromo-6-fluoro-1*H*-indole (535 mg, 2.5 mmol), *tert*-butyl 2-hydroxy-7-azaspiro[3.5]nonane-7-carboxylate (905 mg, 3.75 mmol).

Purification by FSC (0-30 % EtOAc in hexanes) gave the title compound (826 mg, 76 %) as a colorless solid. ^1H NMR (DMSO- d_6): δ 1.41 (9H, s), 1.54 - 1.59 (2H, m), 1.63 - 1.75 (2H, m), 2.09 - 2.17 (2H, m), 2.45 - 2.49 (2H, m), 3.22 - 3.27 (2H, m), 3.34 - 3.41 (2H, m), 5.03 (1H, quin), 6.50 (1H, d), 7.62 (1H, d), 7.70 (1H, d), 7.84 (1H, d); m/z (ES $^+$) $[\text{M}+\text{H}]^+ = 437.1$.

Intermediate 14b:

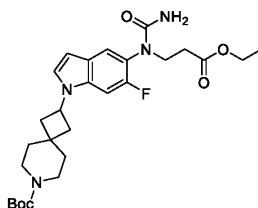
tert-Butyl 2-[5-[(3-ethoxy-3-oxo-propyl)amino]-6-fluoro-indol-1-yl]-7-azaspiro[3.5]nonane-7-carboxylate



[1375] Ethyl 3-aminopropanoate, HCl (435 mg, 2.83 mmol) was added to *t*BuBrettPhos Pd G3 (161 mg, 0.19 mmol), Intermediate 14a (826 mg, 1.89 mmol) and Cs_2CO_3 (1846 mg, 5.67 mmol) in 1,4-dioxane (10 mL). The vial was capped and evacuated and backfilled with nitrogen. The reaction was heated at 100 $^\circ\text{C}$ for 17 h. The reaction was cooled to r.t. then diluted with EtOAc and filtered through celite®. The filtrate was concentrated under reduced pressure. Purification by FSC (0-70% EtOAc in hexanes) gave the title compound (868 mg, 97 %) as a green liquid. ^1H NMR (DMSO- d_6): δ 1.19 (3H, t), 1.41 (9H, s), 1.49 - 1.60 (2H, m), 1.63 - 1.72 (2H, m), 2.05 - 2.12 (2H, m), 2.42 - 2.48 (2H, m), 2.63 (2H, t), 3.21 - 3.27 (2H, m), 3.30 - 3.34 (2H, m), 3.34 - 3.37 (2H, m), 4.08 (2H, q), 4.81 - 4.95 (2H, m), 6.30 (1H, d), 6.80 (1H, d), 7.28 (1H, d), 7.42 (1H, d); m/z (ES $^+$) $[\text{M}+\text{H}]^+ = 474.7$.

Intermediate 14c:

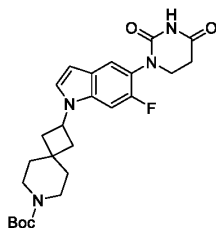
tert-Butyl 2-[5-[carbamoyl-(3-ethoxy-3-oxo-propyl)amino]-6-fluoro-indol-1-yl]-7-azaspiro[3.5]nonane-7-carboxylate



[1376] Intermediate 14b (868 mg, 1.83 mmol) was dissolved in DCM (5 mL) and acetic acid (5 mL). Potassium cyanate (743 mg, 9.16 mmol) was added and the reaction was stirred at r.t. for 20 min. The reaction was diluted with dichloromethane, then washed with water, saturated aq. NaHCO_3 solution, and brine solutions. The organic layer was separated, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to provide crude title compound (945 mg, 100 %) as a brown dry film, which was used in the next step without further purification. m/z (ES $^+$) $[\text{M}+\text{H}]^+ = 517.6$.

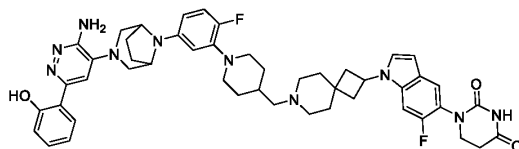
Intermediate 14d:

tert-Butyl 2-[5-(2,4-dioxohexahydropyrimidin-1-yl)-6-fluoro-indol-1-yl]-7-azaspiro[3.5]nonane-7-carboxylate



[1377] A mixture of Intermediate 14c (945 mg, 1.83 mmol), ethanol (8 mL) and sodium ethoxide solution (21 w.t.% in EtOH) (1.366 mL, 3.66 mmol) was stirred at r.t for 10 min. The reaction mixture precipitated out, ethanol (12 mL) was added to suspended the solid and stirring at r.t. continued for 1 h. The reaction was quenched with aq. NH₄Cl solution (20 mL) and water (100 mL) was added. The aqueous mixture was extracted with EtOAc (2 x 100 mL), then the organic layer was washed with brine (100 mL). The brine layer was extracted with DCM (50 mL), combined with the EtOAc extracts, dried (Na₂SO₄), filtered and concentrated. The resulting residue was suspended in ether and sonicated. The suspension was centrifuged and the liquid decanted (2x this trituration procedure). The resulting solid was dried under vacuum to afford the title compound (526 mg, 61.1 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.41 (9H, s), 1.53 - 1.61 (2H, m), 1.67 - 1.72 (2H, m), 2.09 - 2.18 (2H, m), 2.46 - 2.50 (2H, m), 2.73 (2H, t), 3.22 - 3.29 (2H, m), 3.35 - 3.41 (2H, m), 3.70 (2H, br t), 5.03 (1H, quin), 6.52 (1H, d), 7.50 (1H, d), 7.56 (1H, d), 7.68 (1H, d), 10.41 (1H, s). *m/z* (ES⁺) [M+Na]⁺ = 493.2.

1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-6-fluoro-indol-5-yl]hexahydropyrimidine-2,4-dione

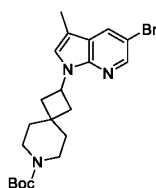


[1378] Prepared in an analogous manner to EXAMPLE 11 starting from Intermediate 14d (24 mg, 0.05 mmol) and Intermediate 11g (32 mg, 0.05 mmol). Purification by RPC (0-100% MeCN in water with 0.1% NH₄OH) gave the title compound (6.60 mg, 15.23 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.21 - 1.30 (2H, m), 1.64 (3H, br d), 1.73 - 1.83 (4H, m), 1.90 - 1.99 (2H, m), 2.06 - 2.19 (6H, m), 2.20 - 2.34 (2H, m), 2.35 - 2.40 (1H, m), 2.42 - 2.48 (2H, m), 2.53 - 2.56 (1H, m), 2.61 - 2.68 (2H, m), 2.73 (2H, t), 3.10 (2H, br d), 3.26 (2H, br d), 3.34 - 3.38 (2H, m), 3.70 (2H, t), 4.35 (2H, br s), 5.00 (1H, t), 5.96 (2H, s), 6.41 - 6.46 (1H, m), 6.46 - 6.50 (1H, m), 6.51 (1H, d), 6.84 - 6.90 (2H, m), 6.93 (1H, dd), 7.23 (1H, t), 7.47 (1H, s), 7.50 (1H, d), 7.56 (1H, d), 7.66 (1H, d), 7.92 (1H, d), 10.41 (1H, s), 14.20 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 857.6.

EXAMPLE 15

Intermediate 15a:

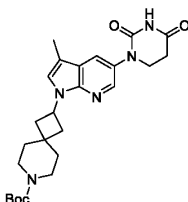
tert-Butyl 2-(5-bromo-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl)-7-azaspiro[3.5]nonane-7-carboxylate



[1379] Prepared in an analogous manner to Intermediate 4a starting from 5-bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (3.60 g, 17.06 mmol), *tert*-butyl 2-hydroxy-7-azaspiro[3.5]nonane-7-carboxylate (6.177 g, 25.60 mmol) Purification by FSC (gradient: 0-50 % EtOAc in hexanes) gave the title compound (6.44 g, 87 %) as a yellow solid. ¹H NMR (DMSO-*d*₆): δ 1.39 (9H, s), 1.56 - 1.66 (4H, m), 2.18 - 2.25 (5H, m), 2.35 - 2.41 (2H, m), 3.21 - 3.25 (2H, m), 3.31 - 3.35 (2H, m), 5.23 (1H, quin), 7.63 (1H, s), 8.14 (1H, d), 8.24 (1H, d); *m/z* (ES⁺) [M-*t*Bu+2H]⁺ = 378.4.

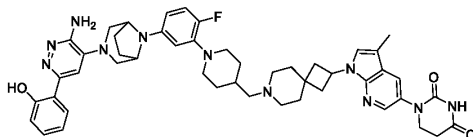
Intermediate 15b:

tert-Butyl 2-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-7-azaspiro[3.5]nonane-7-carboxylate



[1380] Prepared in an analogous manner to Intermediate 2b starting from Intermediate 15a (716 mg, 1.65 mmol). Purification by FSC (gradient: 0-100 % EtOAc in hexanes then 0-30% MeOH in EtOAc) gave the title compound (482 mg, 62.5 %) as a brown solid. ¹H NMR (DMSO-*d*₆): δ 1.41 (9H, s), 1.59 - 1.69 (4H, m), 2.22 - 2.27 (2H, m), 2.27 (3H, s), 2.37 - 2.44 (2H, m), 2.76 (2H, t), 3.23 - 3.29 (2H, m), 3.33 - 3.37 (2H, m), 3.81 (2H, t), 5.28 (1H, quin), 7.62 (1H, s), 7.89 (1H, d), 8.18 (1H, d), 10.38 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 468.5.

1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



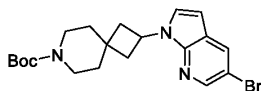
[1381] Prepared in an analogous manner to EXAMPLE 11 starting from Intermediate 15b (45.8 mg, 0.10 mmol) and Intermediate 11g (63.3 mg, 0.10 mmol). Purification by RPC (0-100% MeCN in water with 0.1% NH₄OH) gave the title compound (22.1 mg, 25.9%) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.08 - 1.32 (3H, m), 1.56 - 1.82 (5H, m), 1.83 - 1.99 (4H, m), 2.07 - 2.16 (3H, m), 2.18 - 2.24 (2H, m), 2.26 (3H, s), 2.44 (4H, br d), 2.51 - 2.69 (3H, m), 2.74 (2H, t), 2.95 - 3.16 (3H, m), 3.25 (2H, br d), 3.33 - 3.38 (2H,

m), 3.79 (2H, t), 4.33 (2H, br s), 5.17 - 5.34 (1H, m), 5.92 (2H, s), 6.39 - 6.54 (2H, m), 6.80 - 6.88 (2H, m), 6.92 (1H, br dd), 7.18 - 7.23 (1H, m), 7.41 - 7.50 (1H, m), 7.60 (1H, s), 7.85 - 7.91 (2H, m), 8.16 (1H, d), 10.36 (1H, s), 14.15 (1H, br s); m/z (ES^+) $[M+H]^+ = 854.6$.

EXAMPLE 16

Intermediate 16a:

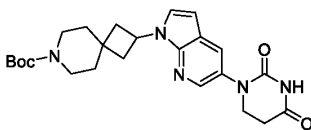
tert-Butyl 2-(5-bromopyrrolo[2,3-*b*]pyridin-1-yl)-7-azaspiro[3.5]nonane-7-carboxylate



[1382] Prepared in an analogous manner to Intermediate 4a starting from 7-*tert*-butoxycarbonyl-7-azaspiro[3.5]nonan-2-ol (500mg, 2.07 mmol) and 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (408 mg, 2.07 mmol). Purification by FSC (gradient: 0 to 30% EtOAc in petroleum ether) gave the title compound (660 mg, 75%) as a white solid. 1H NMR (DMSO- d_6): δ 1.39 (9H, s), 1.58-1.66 (4H, m), 2.22-2.29 (2H, m), 2.37-2.44 (2H, m), 3.22-3.25 (2H, m), 3.32 (1H, s), 3.35 (1H, s), 5.22-5.31 (1H, m), 6.50 (1H, d), 7.86 (1H, d), 8.19 (1H, d), 8.28 (1H, d); m/z (ES^+), $[M+H]^+ = 420.3$.

Intermediate 16b:

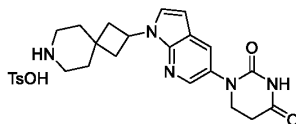
tert-butyl 2-[5-(2,4-dioxohexahydropyrimidin-1-yl)pyrrolo[2,3-*b*]pyridin-1-yl]-7-azaspiro[3.5]nonane-7-carboxylate



[1383] Prepared in an analogous method to Intermediate 6b starting from Intermediate 16a (300 mg, 0.71 mmol). Purification by FSC (gradient 50 to 100% EtOAc in petroleum ether) gave the title compound (172 mg, 45.5 %) as a pale yellow solid. 1H NMR (DMSO- d_6): δ 1.41 (9H, s), 1.61-1.70 (4H, m), 2.26-2.36 (2H, m), 2.37-2.48 (2H, m), 2.76 (2H, t), 3.25-3.30 (2H, m), 3.35-3.38 (2H, m), 3.81 (2H, t), 5.27-5.39 (1H, m), 6.54 (1H, d), 7.85 (1H, d), 7.92 (1H, d), 8.21 (1H, d), 10.40 (1H, s). m/z (ES^+) $[M+H]^+ = 454.5$.

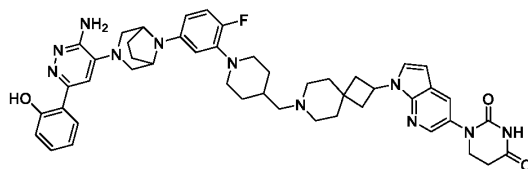
Intermediate 16c:

1-[1-(7-Azaspiro[3.5]nonan-2-yl)pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1384] Prepared in an analogous manner to Intermediate 6c starting from Intermediate 16b (168 mg, 0.37 mmol). The solvent was removed under reduced pressure gave the title compound (246 mg, 94%) as a yellow solid in the form of a 2 TsOH salt. m/z (ES^+) $[M+H]^+ = 353.4$.

1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

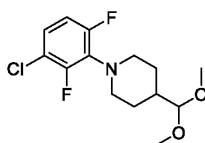


[1385] Prepared in an analogous method to EXAMPLE 13 starting from Intermediate 13d (166 mg, 0.33 mmol) and Intermediate 16c (230 mg, 0.33 mmol). Purification by RPC (gradient: 0-50% CH₃CN in water with 0.1% formic acid) gave the title compound (43.0 mg, 14.88 %) as a grey solid. ¹H NMR (DMSO-*d*₆): δ 1.21-1.33 (2H, m), 1.62-1.85 (7H, m), 1.90-2.00 (2H, m), 2.09-2.17 (2H, m), 2.22-2.31 (4H, m), 2.32-2.48 (6H, m), 2.60-2.68 (2H, m), 2.76 (2H, t), 3.10 (2H, d), 3.26 (2H, d), 3.36 (2H, d), 3.81 (2H, t), 4.35 (2H, s), 5.27-5.35 (1H, m), 5.95 (2H, s), 6.42-6.50 (2H, m), 6.53 (1H, d), 6.84-6.96 (3H, m), 7.21-7.25 (1H, m), 7.47 (1H, s), 7.84 (1H, d), 7.90-7.92 (2H, m), 8.17-8.23 (2H, m), 10.41 (1H, s). *m/z* (ES⁺) [M+H]⁺ = 840.5.

EXAMPLE 17

Intermediate 17a:

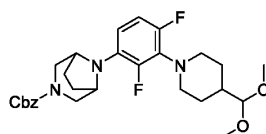
1-(3-Chloro-2,6-difluorophenyl)-4-(dimethoxymethyl)piperidine



[1386] A vial was charged with xantphos (0.211 g, 0.36 mmol), 1-chloro-2,4-difluoro-3-iodobenzene (1 g, 3.64 mmol), 4-(dimethoxymethyl)piperidine (0.696 g, 4.37 mmol), Pd₂(dba)₃ (0.167 g, 0.18 mmol), Cs₂CO₃ (2.374 g, 7.29 mmol) and 1,4-dioxane (5 mL). The resulting mixture was stirred at 100 °C for 12 h under nitrogen. The reaction mixture was diluted with EtOAc (50 mL), and washed sequentially with saturated NH₄Cl (50 mL) and saturated brine (50 mL). The organic layer was dried with Na₂SO₄, filtered and evaporated. Purification by FSC (gradient: 0 to 40% EtOAc in petroleum ether) gave the title compound (0.700 g, 62.8 %) as a pale yellow solid. ¹H NMR (CDCl₃) δ 1.39 – 1.56 (2H, m), 1.69 – 1.82 (3H, m), 3.01 – 3.13 (2H, m), 3.23 – 3.32 (2H, m), 3.37 (6H, s), 4.10 (1H, d), 6.72 – 6.82 (1H, m), 6.90 – 7.01 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 306.1.

Intermediate 17b:

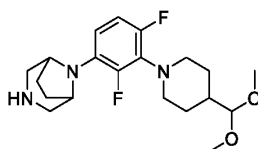
Benzyl 8-[3-[4-(dimethoxymethyl)-1-piperidyl]-2,4-difluoro-phenyl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



[1387] Prepared in an analogous manner to Intermediate 7b starting from Intermediate 17a (650 mg, 2.13 mmol). Purification by FSC (gradient 0 to 10% MeOH in DCM) gave the title compound (530 mg, 48.4 %) as a yellow solid. ^1H NMR (DMSO-*d*₆) δ 1.23 – 1.43 (2H, m), 1.55 – 1.74 (5H, m), 1.78 – 1.92 (2H, m), 2.98 (2H, t), 3.07 – 3.23 (4H, m), 3.28 (6H, s), 3.73 (2H, d), 3.98 (2H, s), 4.10 (1H, d), 5.10 (2H, d), 6.59 – 6.71 (1H, m), 6.78 – 6.88 (1H, m), 7.29 – 7.46 (5H, m); m/z (ES⁺) [M+H]⁺ = 516.

Intermediate 17c:

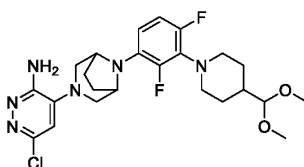
8-[3-[4-(Dimethoxymethyl)-1-piperidyl]-2,4-difluoro-phenyl]-3,8-diazabicyclo[3.2.1]octane



[1388] Prepared in an analogous manner to Intermediate 1e starting from Intermediate 17b (530 mg, 1.03 mmol). The reaction mixture was filtered and the filtrate was concentrated to afford title compound (370 mg, 94 %) as a yellow solid. ^1H NMR (DMSO-*d*₆) δ 1.22 – 1.42 (2H, m), 1.60 – 1.72 (3H, m), 1.72 – 1.86 (4H, m), 2.86 – 3.04 (4H, m), 3.08 – 3.16 (2H, m), 3.17 (2H, s), 3.27 (6H, s), 3.76 (2H, s), 4.10 (1H, d), 6.52 – 6.64 (1H, m), 6.73 – 6.84 (1H, m); m/z (ES⁺) [M+H]⁺ = 382.2.

Intermediate 17d:

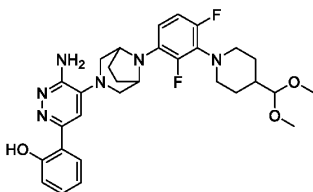
6-Chloro-4-[8-[3-[4-(dimethoxymethyl)-1-piperidyl]-2,4-difluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-amine



[1389] Prepared in an analogous manner to Intermediate 11f starting from Intermediate 17c (400 mg, 1.05 mmol). Purification by FSC (gradient: 0 to 9% MeOH in DCM) gave the title compound (320 mg, 60.0 %) as a yellow solid. ^1H NMR (DMSO-*d*₆) δ 1.25 – 1.42 (2H, m), 1.61 – 1.74 (3H, m), 1.81 – 1.92 (2H, m), 1.98 – 2.10 (2H, m), 2.89 – 3.06 (4H, m), 3.16 (2H, d), 3.28 (6H, s), 3.29 – 3.30 (2H, m), 4.05 – 4.15 (3H, m), 5.83 (2H, s), 6.62 – 6.74 (1H, m), 6.79 – 6.89 (1H, m), 6.94 (1H, s); m/z (ES⁺) [M+H]⁺ = 509.

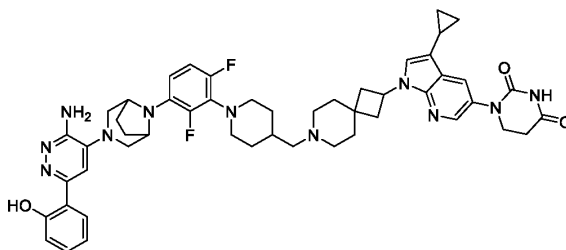
Intermediate 17e:

2-[6-Amino-5-[8-[3-[4-(dimethoxymethyl)-1-piperidyl]-2,4-difluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-yl]phenol



[1390] Prepared in an analogous manner to Intermediate 2h starting from Intermediate 17d (200 mg, 0.39 mmol). Purification by FSC (gradient: 0 to 10% MeOH in DCM) gave the title compound (130 mg, 58.4 %) as a yellow solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.31 – 1.40 (2H, m), 1.64 – 1.73 (3H, m), 1.86 – 1.95 (2H, m), 2.05 – 2.15 (2H, m), 2.97 – 3.04 (2H, m), 3.10 (2H, d), 3.15 – 3.20 (2H, m), 3.28 (6H, s), 3.34 – 3.39 (2H, m), 4.09 – 4.17 (3H, m), 5.98 (2H, s), 6.69 – 6.77 (1H, m), 6.82 – 6.92 (3H, m), 7.22 – 7.28 (1H, m), 7.55 (1H, s), 7.93 – 7.98 (1H, m), 14.18 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 567.4.

1-[1-[7-[[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2,6-difluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

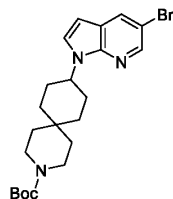


[1391] Formic acid (1 mL, 26.07 mmol) was added to Intermediate 17e (108 mg, 0.19 mmol). The resulting mixture was stirred at r.t. for 20 min. The solvent was removed under reduced pressure. The residue was dissolved in DCM (20 mL) and washed with NaHCO₃ solution. The organic layer was dried with Na₂SO₄, filtered and concentrated. To the residue was added Intermediate 2c (75 mg, 0.19 mmol), NMP (5 mL) and DCE (3 mL). The resulting mixture was stirred at r.t. for 1 h. Na(OAc)₃BH (121 mg, 0.57 mmol) was added and the reaction was stirred for 1 h. The reaction mixture diluted with DCM (20 mL) and washed with sat. NaHCO₃. The DCM layer collected and concentrated. Purification by RPC (gradient: 0-50% CH₃CN in water with 0.1% FA) gave the title compound (30.0 mg, 17.53 %) as a white solid. ¹H NMR (DMSO-*d*₆) δ 0.64 – 0.74 (2H, m), 0.83 – 0.92 (2H, m), 1.12 – 1.31 (2H, m), 1.60 – 1.81 (7H, m), 1.84 – 1.99 (3H, m), 2.05 – 2.13 (2H, m), 2.17 – 2.45 (10H, m), 2.76 (2H, t), 2.97 – 3.21 (5H, m), 3.46 – 3.27 (3H, s), 3.81 (2H, t), 4.07 – 4.20 (2H, m), 5.17 – 5.34 (1H, m), 5.97 (2H, s), 6.66 – 6.76 (1H, m), 6.78 – 6.95 (3H, m), 7.20 – 7.28 (1H, m), 7.55 (2H, d), 7.91 – 7.99 (2H, m), 8.14 – 8.19 (1H, m), 10.38 (1H, s), (OH proton not observed); ¹⁹F NMR (282 MHz, DMSO) δ -128.88, -128.89, -130.674, -130.68; *m/z* (ES⁺) [M+H]⁺ = 898.4.

EXAMPLE 18

Intermediate 18a:

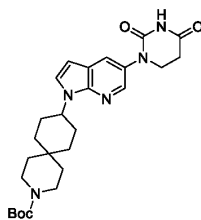
tert-Butyl 9-(5-bromopyrrolo[2,3-*b*]pyridin-1-yl)-3-azaspiro[5.5]undecane-3-carboxylate



[1392] Prepared in an analogous manner to Intermediate 4a starting from 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (700 mg, 3.55 mmol) and *tert*-butyl 9-hydroxy-3-azaspiro[5.5]undecane-3-carboxylate (1436 mg, 5.33 mmol). Purification by FSC (gradient: 0-50% EtOAc in hexanes) gave the title compound (900 mg, 56.5 %) as a colorless dry film. ¹H NMR (DMSO-*d*₆) δ 1.27 - 1.37 (5H, m), 1.38 - 1.45 (10H, m), 1.60 - 1.65 (2H, m), 1.73 (2H, br d), 1.83 (2H, br d), 1.95 - 2.06 (2H, m), 3.34- 3.40 (2H, m), 4.64 (1H, tt), 6.48 (1H, d), 7.82 (1H, br s), 8.20 (1H, d), 8.29 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 450.2.

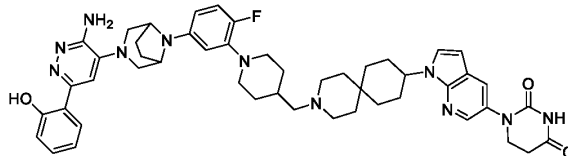
Intermediate 18b:

tert-Butyl 9-[5-(2,4-dioxohexahydropyrimidin-1-yl)pyrrolo[2,3-*b*]pyridin-1-yl]-3-azaspiro[5.5]undecane-3-carboxylate



[1393] Prepared in an analogous method to Intermediate 6b starting from Intermediate 18a (900mg, 2.01 mmol). Purification by FSC (gradient: 0-100% EtOAc in hexanes) gave the title compound (300 mg, 31.0 %) as a brown solid. ¹H NMR (DMSO-*d*₆) δ 1.28 - 1.45 (14H, m), 1.57 - 1.67 (2H, m), 1.70 - 1.77 (2H, m), 1.84 (2H, br d), 2.04 (2H, br dd), 2.76 (2H, t), 3.34 - 3.39 (3H, m), 3.81 (2H, t), 4.63 - 4.79 (1H, m), 6.50 (1H, d), 7.79 (1H, br d), 7.91 (1H, d), 8.20 (1H, d), 10.40 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 482.3.

1-[1-[3-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl)methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

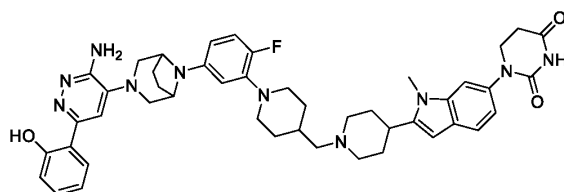


[1394] Prepared in an analogous manner to EXAMPLE 11 starting from Intermediate 11g (35mg, 0.06 mmol) and Intermediate 18b (26.6 mg, 0.06 mmol). Purification by RPC (gradient: 0-50% CH₃CN in water with 0.1% FA) gave the title compound (17.0 mg, 35.4 %) as a white solid. ¹H NMR (DMSO-*d*₆) δ 1.22 - 1.37 (4H, m), 1.43 (2H, br s), 1.64 - 1.86 (9H, m), 1.91 - 2.06 (4H, m), 2.14 (2H, br d), 2.32 (2H, br d), 2.48

(3H, br s), 2.65 (2H, br t), 2.76 (2H, t), 3.10 (2H, br d), 3.26 (2H, br d), 3.36 - 3.47 (3H, m), 3.81 (2H, t), 4.35 (2H, br s), 4.60 - 4.73 (1H, m), 5.95 (2H, s), 6.37 - 6.52 (3H, m), 6.81 - 6.98 (3H, m), 7.19 - 7.28 (1H, m), 7.47 (1H, s), 7.74 - 7.82 (1H, m), 7.86 - 7.94 (2H, m), 8.12 - 8.24 (1H, m), 10.40 (1H, s), 13.48 - 14.87 (1H, m); m/z (ES^+) $[M+H]^+ = 868.5$.

EXAMPLE 19

1-[2-[1-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indol-6-yl]hexahydropyrimidine-2,4-dione

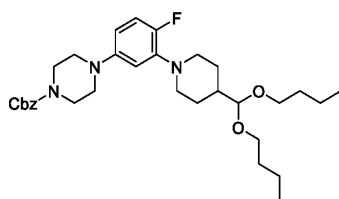


[1395] Prepared in an analogous manner to EXAMPLE 11 starting from Intermediate 11g (38.1 mg, 0.06 mmol) and 1-[1-methyl-2-(4-piperidyl)indol-6-yl]hexahydropyrimidine-2,4-dione TsOH salt (30 mg, 0.06 mmol) (prepared according to reported patent procedure WO 2022/069520 A1). Purification by RPC (gradient: 0-50% CH_3CN in water with 0.1% FA) gave the title compound (17.0 mg, 34.8 %) as a white solid. 1H NMR (500 MHz, $DMSO-d_6$) δ 1.25 - 1.32 (2H, m), 1.63 - 1.69 (2H, m), 1.79 - 1.85 (2H, m), 1.90 - 1.98 (4H, m), 2.05 - 2.15 (4H, m), 2.23 - 2.27 (2H, m), 2.63 - 2.68 (2H, m), 2.72 - 2.76 (2H, m), 2.76 - 2.84 (1H, m), 2.95 - 3.00 (2H, m), 3.11 (2H, br d), 3.27 (5H, br d), 3.69 (3H, s), 3.79 (2H, t), 4.35 (2H, br s), 5.93 (2H, s), 6.24 (1H, s), 6.41 - 6.52 (2H, m), 6.84 - 6.97 (4H, m), 7.21 - 7.26 (1H, m), 7.36 (1H, s), 7.41 - 7.49 (2H, m), 7.88 - 7.94 (1H, m), 10.27 (1H, s), 13.98 - 14.42 (1H, m); m/z (ES^+) $[M+H]^+ = 813.4$.

EXAMPLE 20

Intermediate 20a:

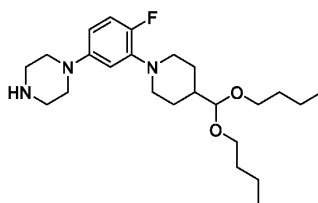
Benzyl 4-[3-[4-(dibutoxymethyl)-1-piperidyl]-4-fluoro-phenyl]piperazine-1-carboxylate



[1396] Prepared in an analogous manner to Intermediate 7b starting from Intermediate 11c (600mg, 1.63 mmol) and benzyl piperazine-1-carboxylate (359 mg, 1.63 mmol). Purification by FSC (gradient: 0-40% EtOAc in hexanes) gave the title compound (520 mg, 57.4 %) as a light yellow solid. 1H NMR ($DMSO-d_6$) δ 0.90 (6H, t), 1.30 - 1.44 (6H, m), 1.45 - 1.55 (4H, m), 1.73 (3H, br d), 2.58 (2H, s), 3.04 (4H, br d), 3.31 - 3.34 (3H, m), 3.38 - 3.45 (2H, m), 3.50 - 3.62 (6H, m), 4.22 (1H, d), 5.11 (2H, s), 6.40 - 6.51 (1H, m), 6.56 (1H, dd), 6.95 (1H, dd), 7.32 - 7.44 (4H, m); m/z (ES^+) $[M+H]^+ = 556.2$.

Intermediate 20b:

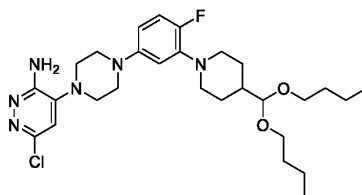
1-[3-[4-(Dibutoxymethyl)-1-piperidyl]-4-fluoro-phenyl]piperazine



[1397] Pd/C (105 mg, 0.10 mmol) was added to a solution of Intermediate 20a (550 mg, 0.99 mmol) in THF (8 mL) under N₂. The reaction was sparged with H₂ and stirred at r.t. under H₂ for 6 h. The reaction mixture was filtered through celite®, eluting with ethyl acetate. Concentration *in vacuo* gave the title compound (398 mg, 95 %) as an orange gum. m/z (ES⁺) [M+H]⁺ = 422.4.

Intermediate 20c:

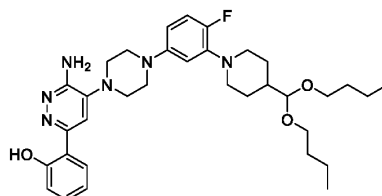
6-Chloro-4-[4-[3-[4-(dibutoxymethyl)-1-piperidyl]-4-fluoro-phenyl]piperazin-1-yl]pyridazin-3-amine



[1398] Prepared in an analogous manner to Intermediate 3d starting from Intermediate 20b (450mg, 1.07 mmol). Purification by FSC (gradient: 0-100% EtOAc in hexanes) gave the title compound (220 mg, 37.5 %) as an orange solid. m/z (ES⁺) [M+H]⁺ = 475.4.

Intermediate 20d:

2-[6-Amino-5-[4-[3-[4-(dibutoxymethyl)-1-piperidyl]-4-fluoro-phenyl]piperazin-1-yl]pyridazin-3-yl]phenol

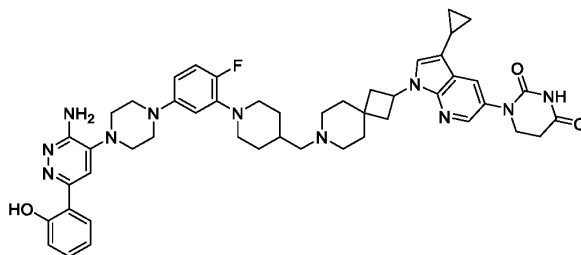


[1399] Prepared in an analogous manner to Intermediate 2h starting from Intermediate 20c (120 mg, 0.22 mmol). Purification by FSC (gradient: 0-100% EtOAc in hexanes) gave the title compound (70.0 mg, 52.8 %) as a light yellow solid. ¹H NMR (DMSO-*d*₆) δ 1.41 (9H, s), 1.52 - 1.69 (2H, m), 1.78 - 1.90 (4H, m), 1.96 (2H, br dd), 2.23 (3H, s), 2.39 (2H, br t), 2.55 - 2.64 (2H, m), 2.64 - 2.65 (1H, m), 2.73 (2H, t), 3.03 (4H, br d), 3.69 - 3.83 (4H, m), 4.27 (1H, br s), 7.05 (1H, dd), 7.32 (1H, s), 7.40 (1H, d), 7.47 (1H, d), 10.24 (1H, s); m/z (ES⁺) [M+H]⁺ = 607.6.

EXAMPLE 20

1-[1-[7-[[1-[5-[4-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]piperazin-1-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-

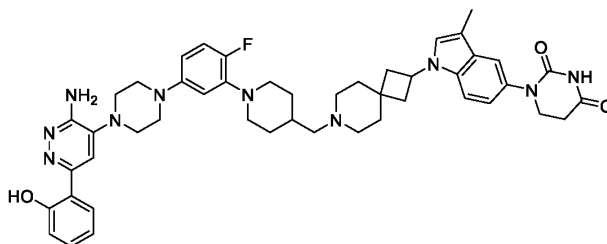
yl]hexahydropyrimidine-2,4-dione



[1400] Prepared in an analogous manner to EXAMPLE 11 starting from Intermediate 20d (30mg, 0.05 mmol) and Intermediate 2c (19.45 mg, 0.05 mmol). Purification by RPC (gradient: 0-50% CH₃CN in water with 0.1% FA) gave the title compound (17.0 mg, 40.3 %) as a white solid. ¹H NMR (DMSO-*d*₆) δ 0.62 - 0.73 (2H, m), 0.82 - 0.95 (2H, m), 1.28 (2H, q), 1.67 - 1.85 (7H, m), 1.91 - 1.97 (1H, m), 2.18 - 2.46 (8H, m), 2.52- 2.59 (1H, m), 2.66 (2H, br t), 2.77 (2H, t), 3.17 - 3.28 (5H, m), 3.33 - 3.36 (1H, m), 3.34 - 3.45 (4H, m), 3.81 (2H, t), 5.22 - 5.36 (1H, m), 6.36 (2H, br s), 6.51 - 6.67 (2H, m), 6.88 - 6.94 (2H, m), 6.99 (1H, br dd), 7.20 - 7.29 (1H, m), 7.57 (2H, s), 7.89 - 7.99 (2H, m), 8.17 (1H, d), 10.26 - 11.62 (1H, m), 10.41(1H, s), 13.51 - 14.73 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 854.5.

EXAMPLE 21

1-[1-[7-[[1-[5-[4-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]piperazin-1-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione

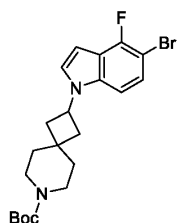


[1401] Prepared in an analogous manner to EXAMPLE 11 starting from Intermediate 20d (30mg, 0.05 mmol) and Intermediate 4b (23.07 mg, 0.05 mmol). Purification by RPC (gradient: 0-50% CH₃CN in water with 0.1% FA) gave the title compound (20.0 mg, 48.9 %) as a white solid. ¹H NMR (DMSO-*d*₆) δ 1.23 - 1.36 (2H, m), 1.69 (3H, br s), 1.81 (4H, br d), 2.13 (2H, br d), 2.25 (3H, s), 2.33 (2H, br d), 2.39 - 2.48 (3H, m), 2.51 - 2.54 (3H, m), 2.54 - 2.60 (1H, m), 2.67 (2H, br t), 2.73 (2H, t), 3.25 - 3.27 (2H, m), 3.28 - 3.43 (7H, m), 3.77 (2H, t), 4.98 (1H, br t), 6.36 (2H, s), 6.50- 6.69 (2H, m), 6.86 - 6.93 (2H, m), 6.95 - 7.10 (2H, m), 7.20 - 7.31 (1H, m), 7.36 - 7.47 (3H, m), 7.58 (1H, s), 7.95 (1H, dd), 10.28 (1H, s), 13.45 - 14.66(1H, m); *m/z* (ES⁺) [M+H]⁺ = 827.5.

EXAMPLE 22

Intermediate 22a:

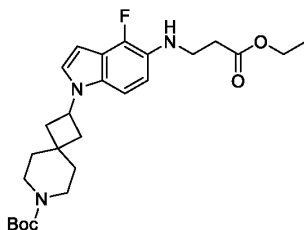
tert-Butyl 2-(5-bromo-4-fluoro-indol-1-yl)-7-azaspiro[3.5]nonane-7-carboxylate



[1402] Prepared in an analogous manner to Intermediate 4a starting from 5-bromo-4-fluoro-1*H*-indole (535 mg, 2.5 mmol) and *tert*-butyl 2-hydroxy-7-azaspiro[3.5]nonane-7-carboxylate (905 mg, 3.75 mmol). Purification by FSC (gradient: 0-30% EtOAc in hexanes) gave the title compound (963 mg, 88 %) as a pale yellow dry film. ¹H NMR (DMSO-*d*₆) δ 1.41 (9H, s), 1.55 - 1.60 (2H, m), 1.66 - 1.72 (2H, m), 2.12 - 2.21 (2H, m), 2.46 - 2.49 (1H, m), 3.21 - 3.28 (2H, m), 3.32 - 3.38 (3H, m), 5.07 (1H, quin), 6.59 (1H, d), 7.29 - 7.34 (1H, m), 7.35 - 7.39 (1H, m), 7.73 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 437.1.

Intermediate 22b:

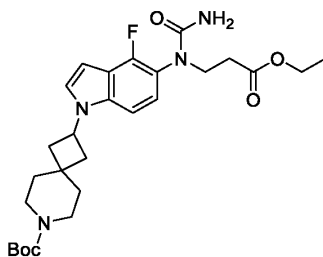
tert-Butyl 2-[5-[(3-ethoxy-3-oxo-propyl)amino]-4-fluoro-indol-1-yl]-7-azaspiro[3.5]nonane-7-carboxylate



[1403] Prepared in an analogous manner to Intermediate 14b starting from Intermediate 22a (962 mg, 2.20 mmol). Purification by FCS (gradient: 0-80% EtOAc in hexanes) gave the title compound (953 mg, 91 %) as a brown liquid. ¹H NMR (DMSO-*d*₆) δ 1.18 - 1.21 (3H, m), 1.41 (9H, s), 1.53 - 1.58 (2H, m), 1.65 - 1.69 (2H, m), 2.09 - 2.17 (2H, m), 2.42 - 2.49 (2H, m), 2.58 (2H, t), 3.22 - 3.27 (2H, m), 3.33 - 3.39 (4H, m), 4.05 - 4.10 (2H, m), 4.71 (1H, br s), 4.93 (1H, t), 6.34 (1H, d), 6.75 (1H, t), 7.15 (1H, d), 7.47 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 474.8.

Intermediate 22c:

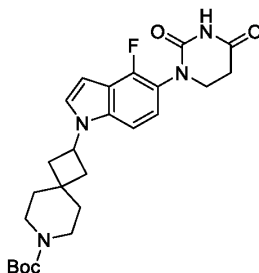
tert-Butyl 2-[5-[carbamoyl-(3-ethoxy-3-oxo-propyl)amino]-4-fluoro-indol-1-yl]-7-azaspiro[3.5]nonane-7-carboxylate



[1404] Prepared in an analogous manner to Intermediate 14c starting from Intermediate 22b (953 mg, 2.01 mmol). The title compound (1038 mg, 100%) was obtained as a brown dry film. m/z (ES⁺) [M+H]⁺ = 517.6.

Intermediate 22d:

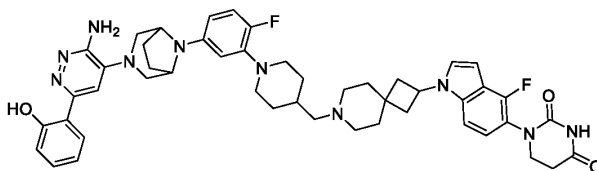
tert-Butyl 2-[5-(2,4-dioxohexahydropyrimidin-1-yl)-4-fluoro-indol-1-yl]-7-azaspiro[3.5]nonane-7-carboxylate



[1405] Prepared in an analogous manner to Intermediate 14d starting from Intermediate 22c (1038 mg, 2.01 mmol). Trituration with Et₂O gave the title compound (581 mg, 61.4 %) as a white solid. ¹H NMR (DMSO-*d*₆) δ 1.41 (9H, s), 1.55 - 1.61 (2H, m), 1.64 - 1.77 (2H, m), 2.14 - 2.21 (2H, m), 2.51 - 2.54 (2H, m), 2.74 (2H, t), 3.22 - 3.28 (2H, m), 3.35 - 3.40 (2H, m), 3.71 (2H, t), 5.07 (1H, quin), 6.59 (1H, d), 7.12 (1H, t), 7.38 (1H, d), 7.71 (1H, d), 10.42 (1H, s); m/z (ES⁺) [M-*t*Bu+2H]⁺ = 415.4.

EXAMPLE 22

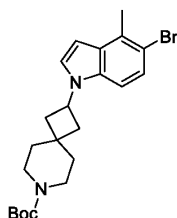
1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-4-fluoro-indol-5-yl]hexahydropyrimidine-2,4-dione



[1406] Prepared in an analogous manner to EXAMPLE 11 starting from Intermediate 22d (0.024 g, 0.05 mmol) and Intermediate 11g (0.032 g, 0.05 mmol). Purification by RPC (gradient: 0-50% MeCN in water with 0.1% FA) gave the title compound (0.022 g, 48.7 %) as a white solid. ¹H NMR (DMSO-*d*₆) δ 1.17 - 1.28 (2H, m), 1.62 (3H, br t), 1.70 - 1.81 (4H, m), 1.87 - 1.97 (2H, m), 2.07 - 2.18 (6H, m), 2.22 - 2.39 (3H, m), 2.44 (2H, br t), 2.56 - 2.68 (2H, m), 2.72 (2H, t), 3.08 (2H, br d), 3.24 (2H, br d), 3.34 (2H, br d), 3.69 (3H, t), 4.33 (2H, br s), 5.02 (1H, quin), 5.94 (2H, s), 6.37 - 6.49 (2H, m), 6.56 (1H, d), 6.81 - 6.95 (3H, m), 7.06 - 7.14 (1H, m), 7.18 - 7.25 (1H, m), 7.36 (1H, d), 7.45 (1H, s), 7.68 (1H, d), 7.90 (1H, dd), 10.40 (1H, s), 14.16 (1H, br s); m/z (ES⁻) [M-H]⁻ = 855.6.

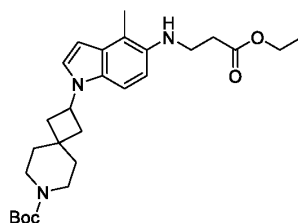
EXAMPLE 23

Intermediate 23a:

tert-Butyl 2-(5-bromo-4-methyl-indol-1-yl)-7-azaspiro[3.5]nonane-7-carboxylate

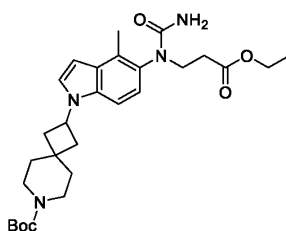
[1407] Prepared in an analogous manner to Intermediate 4a starting from 5-bromo-4-methyl-1*H*-indole (525 mg, 2.5 mmol) and *tert*-butyl 2-hydroxy-7-azaspiro[3.5]nonane-7-carboxylate (905 mg, 3.75 mmol). Purification by FCS (gradient: 0-30% EtOAc in hexanes) gave the title compound (757 mg, 69.9 %) as a pale yellow dry film. ¹H NMR (DMSO-*d*₆) δ 1.39 (9H, s), 1.50 - 1.57 (2H, m), 1.64 - 1.70 (2H, m), 2.07 - 2.17 (2H, m), 2.42 - 2.47 (2H, m), 2.48 (3H, s), 3.19 - 3.26 (2H, m), 3.31 - 3.38 (2H, m), 5.00 (1H, quin), 6.56 (1H, d), 7.24 (1H, d), 7.29 (1H, d), 7.62 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 433.2.

Intermediate 23b:

tert-Butyl 2-[5-[(3-ethoxy-3-oxo-propyl)amino]-4-methyl-indol-1-yl]-7-azaspiro[3.5]nonane-7-carboxylate

[1408] Prepared in an analogous manner to Intermediate 14b starting from Intermediate 23a (757 mg, 1.75 mmol). Purification by FCS (gradient: 0-100% EtOAc in hexanes) gave the title compound (314 mg, 38.3 %) as a brown liquid. ¹H NMR (CDCl₃): δ 1.29 (3H, t), 1.49 (9H, s), 1.62 (2H, br s), 1.76 (2H, br s), 2.20 - 2.27 (2H, m), 2.35 (3H, s), 2.56 (2H, ddd), 2.62 - 2.70 (2H, m), 3.31 - 3.39 (2H, m), 3.44 - 3.50 (2H, m), 3.50 - 3.57 (2H, m), 3.78 (1H, br s), 4.16 - 4.22 (2H, m), 4.83 (1H, t), 6.44 (1H, dd), 6.78 (1H, d), 7.12 (1H, d), 7.19 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 470.8.

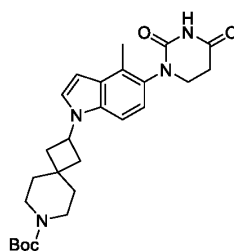
Intermediate 23c:

tert-Butyl 2-[5-[carbamoyl-(3-ethoxy-3-oxo-propyl)amino]-4-methyl-indol-1-yl]-7-azaspiro[3.5]nonane-7-carboxylate

[1409] Prepared in an analogous manner to Intermediate 14c starting from Intermediate 23b (314 mg, 0.67 mmol). The title compound (343 mg, 100%) was obtained as brown film. m/z (ES⁺) [M+H]⁺ = 513.6.

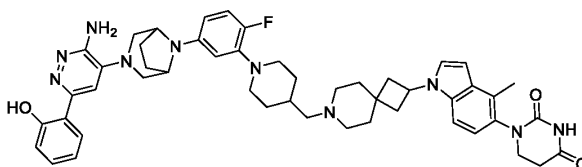
Intermediate 23d:

tert-Butyl 2-[5-(2,4-dioxohexahydropyrimidin-1-yl)-4-methyl-indol-1-yl]-7-azaspiro[3.5]nonane-7-carboxylate



[1410] Prepared in an analogous manner to Intermediate 14d starting from Intermediate 23c (343 mg, 0.67 mmol). Trituration with Et₂O and hexanes (1:1) gave the title compound (197 mg, 63.0 %) as a white solid. ¹H NMR (DMSO-*d*₆) δ 1.41 (9H, s), 1.55 - 1.60 (2H, m), 1.67 - 1.73 (2H, m), 2.09 - 2.21 (2H, m), 2.31 (3H, s), 2.45 - 2.50 (2H, m), 2.67 - 2.82 (2H, m), 3.23 - 3.28 (2H, m), 3.34 - 3.39 (2H, m), 3.53 (1H, dt), 3.74 (1H, ddd), 5.04 (1H, quin), 6.56 (1H, d), 7.01 (1H, d), 7.35 (1H, d), 7.63 (1H, d), 10.27 (1H, s); m/z (ES⁺) [M+H]⁺ = 467.3.

1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-4-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione

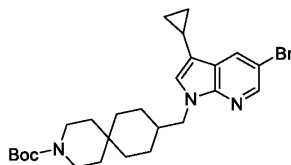


[1411] Prepared in an analogous manner to EXAMPLE 11 starting from Intermediate 23d (0.024 g, 0.05 mmol) and Intermediate 11g (0.032 g, 0.05 mmol). Purification by RPC (gradient: 0-50% MeCN in water with 0.1% FA) followed by purification by RPC (0-100% MeCN in water with 0.1% NH₄OH) gave the title compound (4.10 mg, 9.50 %) as a white solid. ¹H NMR (DMSO-*d*₆) δ 1.21 - 1.27 (2H, m), 1.59 - 1.68 (3H, m), 1.72 - 1.84 (4H, m), 1.88 - 2.01 (2H, m), 2.07 - 2.18 (6H, m), 2.26 (2H, br s), 2.31 (3H, s), 2.34 - 2.48 (4H, m), 2.59 - 2.67 (1H, m), 2.62 - 2.62 (1H, m), 2.68 - 2.82 (2H, m), 3.10 (2H, br d), 3.26 (2H, br d), 3.34 - 3.38 (2H, m), 3.54 (1H, dt), 3.74 (1H, ddd), 4.35 (2H, br s), 5.00 (1H, t), 5.96 (2H, s), 6.40 - 6.45 (1H, m), 6.48 (1H, dd), 6.55 (1H, d), 6.84 - 6.89 (2H, m), 6.93 (1H, dd), 7.00 (1H, d), 7.23 (1H, t), 7.35 (1H, d), 7.47 (1H, s), 7.61 (1H, d), 7.92 (1H, dd), 10.26 (1H, s), 14.20 (1H, s); m/z (ES⁺) [M+H]⁺ = 853.5.

EXAMPLE 24

Intermediate 24a:

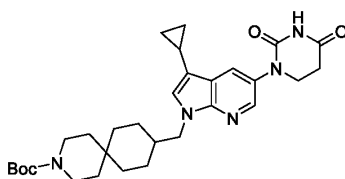
[1412] *tert*-Butyl 9-[(5-bromo-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-1-yl)methyl]-3-azaspiro[5.5]undecane-3-carboxylate



[1413] Prepared in an analogous manner to Intermediate 4a starting from 5-bromo-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridine (0.593 g, 2.5 mmol) and *tert*-butyl 9-(hydroxymethyl)-3-azaspiro[5.5]undecane-3-carboxylate (1.063 g, 3.75 mmol). Purification by FSC (gradient: 0-50% EtOAc in hexanes) gave the title compound (1.202 g, 96 %) as a yellow solid. ¹H NMR (DMSO-*d*₆) δ 0.57 - 0.65 (2H, m), 0.81 - 0.91 (2H, m), 0.94 - 1.03 (2H, m), 1.08 - 1.21 (5H, m), 1.22 - 1.30 (2H, m), 1.37 - 1.39 (10H, m), 1.61 (2H, br d), 1.75 - 1.85 (1H, m), 1.91 - 1.98 (1H, m), 3.21 - 3.29 (4H, m), 4.02 (2H, d), 7.30 (1H, s), 8.19 (1H, s), 8.27 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 504.2.

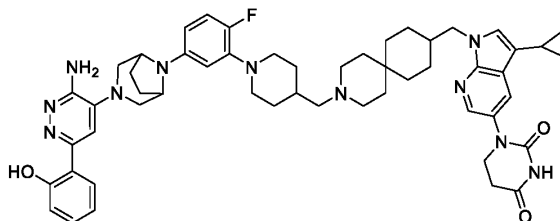
Intermediate 24b:

tert-Butyl 9-[[3-cyclopropyl-5-(2,4-dioxohexahydropyrimidin-1-yl)pyrrolo[2,3-*b*]pyridin-1-yl)methyl]-3-azaspiro[5.5]undecane-3-carboxylate



[1414] Prepared in an analogous manner to Intermediate 2b starting from Intermediate 24a (1.202 g, 2.39 mmol). Purification by FSC (gradient: 0-100% EtOAc in hexanes, then 0-30% MeOH in EtOAc) gave the title compound (0.831 g, 64.9 %) as a brown solid. ¹H NMR (DMSO-*d*₆) δ 0.57 - 0.68 (2H, m), 0.82 - 0.91 (2H, m), 0.96 - 1.05 (2H, m), 1.06 - 1.23 (5H, m), 1.25 - 1.33 (2H, m), 1.38 (9H, s), 1.40 - 1.43 (1H, m), 1.62 (2H, br d), 1.77 - 1.87 (1H, m), 1.89 - 1.96 (1H, m), 2.76 (2H, t), 3.20 - 3.30 (4H, m), 3.82 (2H, t), 4.04 (2H, br d), 7.28 (1H, s), 7.95 (1H, d), 8.17 (1H, d), 10.38 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 536.5.

1-[1-[[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl)methyl]-3-azaspiro[5.5]undecan-9-yl)methyl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

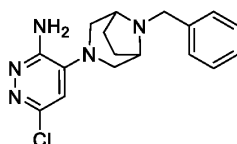


[1415] Prepared in an analogous manner to EXAMPLE 11 starting from Intermediate 24b (42.9 mg, 0.08 mmol) and Intermediate 11g (50.6 mg, 0.08 mmol). Purification by RPC (gradient: 0-50% MeCN in water with 0.1% FA) gave the title compound (19.60 mg, 25.6 %) as a white solid. ¹H NMR (DMSO-*d*₆) δ 0.62 (2H, q), 0.84 - 0.90 (2H, m), 0.96 (2H, br t), 1.11 - 1.30 (8H, m), 1.44 - 1.52 (2H, m), 1.56 - 1.66 (3H, m), 1.72 - 1.83 (3H, m), 1.89 - 1.98 (3H, m), 2.10 - 2.16 (2H, m), 2.20 (2H, br d), 2.28 - 2.36 (4H, m), 2.62 (2H, br t), 2.76 (2H, t), 3.09 (2H, br d), 3.25 (2H, br d), 3.33 (2H, br d), 3.82 (2H, t), 4.03 (2H, br d), 4.34 (2H, br s), 5.96 (2H, s), 6.39 - 6.49 (2H, m), 6.83 - 6.94 (3H, m), 7.19 - 7.26 (1H, m), 7.28 (1H, s), 7.46 (1H, s), 7.88 - 7.94 (1H, m), 7.95 (1H, d), 8.17 (1H, d), 10.41 (1H, s), 13.39 - 14.66 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 922.6.

EXAMPLE 25

Intermediate 25a:

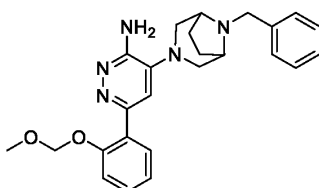
4-(8-Benzyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-chloro-pyridazin-3-amine



[1416] Prepared in an analogous manner to Intermediate 3d starting from 4-bromo-6-chloropyridazin-3-amine (6.02 g, 28.89 mmol) and 8-benzyl-3,8-diazabicyclo[3.2.1]octane (4.87 g, 24.07 mmol). Trituration with MeOH and collection by filtration provided clean product. The MeOH filtrate contained addition product and was concentrated and purified by FSC (gradient: 0-20% EtOAc in hexanes with 10% DCM additive). The solids were combined to give the title compound (6.81 g, 86 %) as an off-white solid. ¹H NMR (DMSO-*d*₆) δ 1.86 - 2.01 (4H, m), 2.81 (2H, br d), 3.17 - 3.23 (4H, m), 3.53 (2H, s), 5.71 - 5.79 (2H, m), 6.89 (1H, s), 7.21 - 7.29 (1H, m), 7.33 (2H, t), 7.37 - 7.41 (2H, m); *m/z* (ES⁺) [M+H]⁺ = 330.4.

Intermediate 25b:

4-(8-Benzyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-[2-(methoxymethoxy)phenyl]pyridazin-3-amine

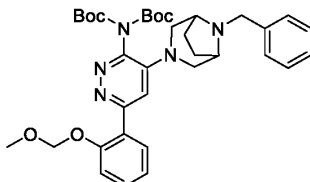


[1417] A flask was charged with Intermediate 25a (6.81 g, 20.65 mmol) and (2-(methoxymethoxy)phenyl)boronic acid (4.70 g, 25.81 mmol), K₂CO₃ (5.71 g, 41.29 mmol), XPhos Pd G3 (1.748 g, 2.06 mmol), dioxane (100 ml) and water (20 ml) under an N₂ atmosphere. The reaction was stirred at 100 °C for 1.25 h. The reaction was cooled to r.t. and partially concentrated under reduced pressure to remove excess THF. The reaction mixture was portioned between DCM (100 mL) and water (100 mL) and extracted with DCM (2 x 100 mL). The combined organic extracts were washed with brine, dried with Na₂SO₄, and concentrated under reduced pressure. Trituration with Et₂O gave the title compound (7.48 g,

84 %) as a beige solid. ^1H NMR (DMSO-*d*₆) δ 1.89 – 2.06 (4H, m), 2.80 (2H, br d), 3.15 – 3.20 (2H, m), 3.21 – 3.25 (2H, m), 3.34 (3H, s), 3.54 (2H, s), 5.21 (2H, s), 5.60 (2H, s), 7.09 (1H, t), 7.18 – 7.21 (2H, m), 7.21 – 7.27 (1H, m), 7.31 – 7.40 (5H, m), 7.62 (1H, dd); m/z (ES⁺) $[\text{M}+\text{H}]^+ = 432.5$.

Intermediate 25c:

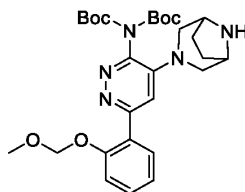
tert-Butyl *N*-[4-(8-benzyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-[2-(methoxymethoxy)phenyl]173ecarbonat-3-yl]-*N*-*tert*-butoxycarbonyl-carbamate



[1418] A flask was charged with Intermediate 25b (7.476 g, 17.32 mmol), DMAP (0.212 g, 1.73 mmol), NEt₃ (9.48 mL, 69.30 mmol) and DCM (100 mL). The reaction was cooled to 0 °C and di-*tert*-butyl 173ecarbonate (11.34 g, 51.97 mmol) was added. The reaction warmed to and stirred at r.t. for 1.5 h. The reaction was washed with 0.5 M HCl (2 x 150 mL), brine (150 mL), dried with Na₂SO₄ and concentrated. Trituration with Et₂O gave the title compound (10.16 g, 93 %) as a beige solid. ^1H NMR (DMSO-*d*₆) δ 1.41 (18H, s), 1.90 – 1.98 (2H, m), 2.34 – 2.46 (2H, m), 3.30 (3H, s), 3.51 (2H, br d), 3.80 (2H, br d), 4.02 (2H, br s), 4.24 (2H, br d), 5.26 (2H, s), 7.18 (1H, t), 7.29 (1H, d), 7.44 – 7.53 (4H, m), 7.62 (1H, s), 7.74 – 7.84 (3H, m); m/z (ES⁺) $[\text{M}+\text{H}]^+ = 632.5$.

Intermediate 25d:

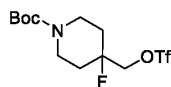
tert-Butyl *N*-*tert*-butoxycarbonyl-*N*-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6-[2-(methoxymethoxy)phenyl]pyridazin-3-yl]carbamate



[1419] A flask was charged with Intermediate 25c (10.156 g, 16.08 mmol), Pd/C (1.711 g, 1.61 mmol), EtOH (100 mL) and DCM (20 mL) under an H₂ atmosphere for 20 h. The reaction was sparged with N₂, filtered through celite®, eluting with DCM and EtOAc. The filtrate was concentrated under reduced pressure, triturated with Et₂O and collected by filtration. The resulting solid was taken up DCM (200 mL) and washed with NaHCO₃ solution (2 x 100 mL), brine (100 mL), dried Na₂SO₄ and concentrated. The resulting sticky solid was triturated with hexanes to give the title compound (6.67 g, 77 %) as a white solid. ^1H NMR (DMSO-*d*₆) δ 1.40 (18H, s), 1.68 (4H, br s), 2.99 (2H, br d), 3.29 – 3.32 (4H, m), 3.34 (2H, br d), 3.47 (2H, br s), 5.25 (2H, s), 7.16 (1H, br t), 7.27 (1H, br d), 7.42 – 7.50 (2H, m), 7.74 (1H, br d); m/z (ES⁺) $[\text{M}+\text{H}]^+ = 542.6$.

Intermediate 25e:

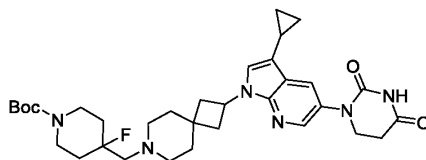
tert-Butyl 4-fluoro-4-(trifluoromethylsulfonyloxymethyl)piperidine-1-carboxylate



[1420] To a solution of *tert*-butyl 4-fluoro-4-(hydroxymethyl)piperidine-1-carboxylate (0.100 g, 0.43 mmol) and 2,6-lutidine (0.060 mL, 0.51 mmol) in DCM (0.72 mL) at -5°C was added trifluoromethanesulfonic anhydride (0.076 mL, 0.45 mmol) over 3 min. The mixture was stirred at -5°C for 50 min, then quenched with 1.0 M aq. NaHSO₄ (5 mL) and diluted with DCM (20 mL). The layers were separated. The organic layer was washed with 1.0 M aq. NaHSO₄ (5 mL), then saturated aq. NaHCO₃ (10 mL). The organic layer was dried (Na₂SO₄) and concentrated to give the title compound (0.142 g, 91 %) as a light brown oil. ¹H NMR (DMSO-*d*₆): δ 1.37-1.45 (9H, m), 1.56-1.76 (2H, m), 1.76-1.90 (2H, m), 2.99 (2H, br s), 3.65-3.96 (2H, m), 4.81-4.96 (2H, m); *m/z* (ES⁺) [M-*t*Bu+2H]⁺ = 309.8.

Intermediate 25f:

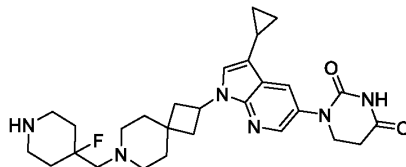
tert-Butyl 4-[[2-[3-cyclopropyl-5-(2,4-dioxohexahydropyrimidin-1-yl)pyrrolo[2,3-*b*]pyridin-1-yl]-7-azaspiro[3.5]nonan-7-yl]methyl]-4-fluoro-piperidine-1-carboxylate



[1421] Intermediate 25e (658 mg, 1.80 mmol) was added to Intermediate 2c (590 mg, 1.5 mmol), and DIPEA (1.310 mL, 7.50 mmol) in 1,4-dioxane (6 mL). The resulting mixture stirred at 85 °C for 24 h. Reaction was concentrated under reduced pressure. Purification by FSC (gradient: 1-10% MeOH in DCM with 0.1% NH₄OH) gave the title compound (674 mg, 73.8 %) as a beige solid. ¹H NMR (DMSO-*d*₆) δ 0.64 - 0.73 (2H, m), 0.82 - 0.92 (2H, m), 1.41 (9H, s), 1.49 - 1.64 (2H, m), 1.64 - 1.72 (4H, m), 1.75 - 1.82 (2H, m), 1.91 - 1.96 (1H, m), 2.16 - 2.24 (2H, m), 2.27 - 2.35 (2H, m), 2.36 - 2.42 (2H, m), 2.42 - 2.49 (4H, m), 2.76 (2H, t), 2.90 - 3.10 (2H, m), 3.72 (2H, br d), 3.81 (2H, t), 5.24 (1H, quin), 7.56 (1H, s), 7.95 (1H, d), 8.17 (1H, d), 10.40 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 609.6.

Intermediate 25g:

1-[3-Cyclopropyl-1-[7-[(4-fluoro-4-piperidyl)methyl]-7-azaspiro[3.5]nonan-2-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

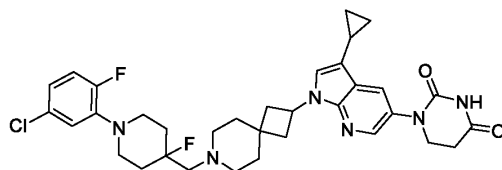


[1422] Prepared in an analogous manner to Intermediate 2c starting from Intermediate 25f (670 mg, 1.1 mmol). Purification by ion exchange chromatography (Porapak Rxn CX 5g cartridge) eluting with 2N NH₃ in MeOH gave the title compound (402 mg, 71.8 %) as a white solid. ¹H NMR (DMSO-*d*₆) δ 0.64 - 0.71

(2H, m), 0.84 - 0.87 (2H, m), 1.49 - 1.60 (2H, m), 1.63 - 1.72 (6H, m), 1.89 - 1.95 (1H, m), 2.15 - 2.22 (2H, m), 2.26 - 2.33 (2H, m), 2.33 - 2.48 (6H, m), 2.60 - 2.72 (4H, m), 2.75 (2H, t), 3.80 (2H, t), 5.22 (1H, quin), 7.53 (1H, s), 7.93 (1H, d), 8.15 (1H, d), 10.36 (1H, br s) (amine N-H not observed) ; m/z (ES⁺) [M+H]⁺ = 509.5.

Intermediate 25h:

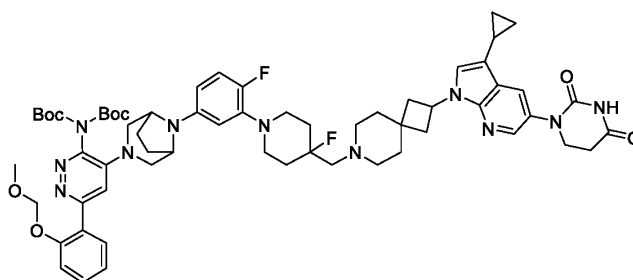
1-[1-[7-[[1-(5-Chloro-2-fluoro-phenyl)-4-fluoro-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1423] A vial was charged with Intermediate 25g (396 mg, 0.78 mmol), 2-bromo-4-chloro-1-fluorobenzene (190 μ l, 1.56 mmol), Pd(dba)₂ (90 mg, 0.16 mmol) (*t*Bu)PhCPhos (94 mg, 0.23 mmol), K₂CO₃ (323 mg, 2.34 mmol) and 1,4-dioxane (7.6 mL). The reaction was stirred at 100 °C for 16 h under an N₂ atmosphere. A second portion of Pd(dba)₂ (90 mg, 0.16 mmol) and (*t*Bu)PhCPhos (94 mg, 0.23 mmol) were added and the reaction was stirred at 100 °C for an additional 6 h under an N₂ atmosphere. The reaction was cooled to r.t. and concentrated *in vacuo* adsorbing the material onto silica. Purification by FSC (gradient: 0-6 % MeOH in DCM) gave the title compound (341 mg, 68.7 %) as a brown solid. ¹H NMR (DMSO-*d*₆) δ 0.67 - 0.72 (2H, m), 0.87 - 0.89 (2H, m), 1.67 - 1.75 (4H, m), 1.76 - 1.88 (2H, m), 1.94 (3H, ddd), 2.17 - 2.25 (2H, m), 2.29 - 2.37 (2H, m), 2.38 - 2.47 (2H, m), 2.48 - 2.58 (4H, m), 2.77 (2H, t), 2.94 (2H, br t), 3.17 - 3.25 (2H, m), 3.82 (2H, t), 5.25 (1H, quin), 6.96 - 7.02 (1H, m), 7.08 (1H, dd), 7.18 (1H, dd), 7.55 (1H, s), 7.95 (1H, d), 8.17 (1H, d), 10.37 (1H, s); m/z (ES⁺) [M+H]⁺ = 637.6.

Intermediate 25i:

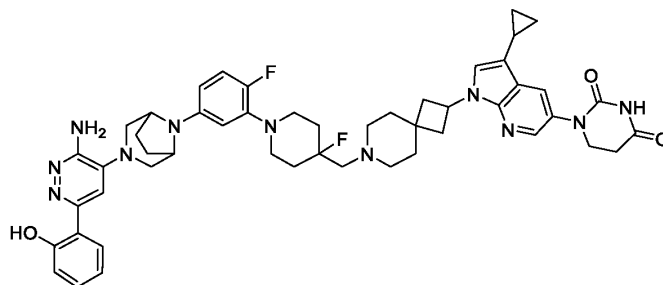
tert-Butyl *N*-*tert*-butoxycarbonyl-*N*-[4-[8-[3-[4-[[2-[3-cyclopropyl-5-(2,4-dioxohexahydropyrimidin-1-yl)pyrrolo[2,3-*b*]pyridin-1-yl]-7-azaspiro[3.5]nonan-7-yl]methyl]-4-fluoro-1-piperidyl]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]-6-[2-(methoxymethoxy)phenyl]pyridazin-3-yl]carbamate



[1424] A vial was charged with Intermediate 25d (342 mg, 0.63 mmol), Intermediate 25h (335 mg, 0.53 mmol), Cs₂CO₃ (514 mg, 1.58 mmol) and Pd-PEPSI-IPentCl 2-methylpyridine (88 mg, 0.11 mmol) and 1,4-dioxane (5.3 ml). The reaction was stirred at 100 °C for 2 h under an N₂ atmosphere. The reaction

was cooled to r.t. the reaction was partitioned between DCM (25 mL), H₂O (10 mL) and brine (20 mL) were added and the phases were separated. The aqueous layer was extracted with DCM (2 x 25 mL). The combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*. Purification by FSC (gradient: 0-6 % MeOH in DCM) gave the title compound (260 mg, 43.3 %) as a yellow solid. ¹H NMR (DMSO-*d*₆) δ 0.66 - 0.73 (2H, m), 0.81 - 0.90 (2H, m), 1.40 (18H, s), 1.68 - 1.74 (4H, m), 1.78 - 2.00 (9H, m), 2.18 - 2.25 (2H, m), 2.29 - 2.36 (2H, m), 2.39 - 2.57 (6H, m), 2.77 (2H, t), 2.92 (2H, br t), 3.12 - 3.20 (2H, m), 3.24 - 3.36 (7H, m), 3.82 (2H, t), 4.41 (2H, br s), 5.21 - 5.30 (3H, m), 6.48 (1H, dt), 6.55 (1H, br dd), 6.95 (1H, dd), 7.16 (1H, td), 7.26 (1H, d), 7.46 (1H, td), 7.54 (2H, d), 7.73 (1H, dd), 7.95 (1H, d), 8.17 (1H, d), 10.38 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 1142.9.

1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-fluoro-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

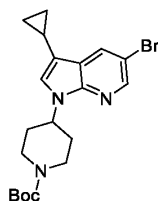


[1425] A vial was charged with Intermediate 25i (50 mg, 0.04 mmol), DCM (2 mL) and TFA (0.675 mL, 8.75 mmol). The mixture was stirred at r.t. for 60 min and concentrated under reduced pressure. The crude residue was purified by RPC (gradient: 50 % MeCN in water with 0.1% NH₄OH, then 0-60% MeCN in water with 0.1% FA). Product containing fractions were extracted with DCM (3x). The combined organic layers were dried over Na₂SO₄ and concentrated under *in vacuo*. The residue was dissolved in DCM (1.5 mL). TFA (0.5 mL) was added and the mixture was stirred at r.t. for 45 minutes. The mixture was diluted with DCM (20 mL), washed with sat. aq. K₂CO₃ (2 x 20 mL) and sat. aq. NH₄Cl (20 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Purification by RPC (0-60% MeCN in water with 0.1% FA) gave the title compound (11.0 mg, 28.0 %) as a white solid. ¹H NMR (DMSO-*d*₆) δ 0.65 - 0.71 (2H, m), 0.82 - 0.90 (2H, m), 1.65 - 1.96 (11H, m), 2.12 (2H, br d), 2.19 (2H, br t), 2.31 (2H, br t), 2.41 (2H, br s), 2.46 - 2.55 (4H, m), 2.75 (2H, t), 2.92 (2H, br t), 3.09 (2H, br d), 3.12 - 3.19 (2H, m), 3.24 (2H, br d), 3.76 - 3.84 (2H, m), 4.36 (2H, br s), 5.23 (1H, quin), 5.92 (2H, s), 6.39 - 6.47 (1H, m), 6.49 - 6.56 (1H, m), 6.81 - 6.89 (2H, m), 6.93 (1H, dd), 7.21 (1H, t), 7.45 (1H, s), 7.53 (1H, s), 7.89 (1H, d), 7.93 (1H, d), 8.15 (1H, d), 10.36 (1H, s), 13.43 - 14.83 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 898.7.

EXAMPLE 26

Intermediate 26a:

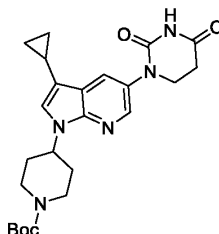
tert-Butyl 4-(5-bromo-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-1-yl)piperidine-1-carboxylate



[1426] Prepared in an analogous method to Intermediate 1g starting from 5-bromo-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridine (1.10 g, 4.64 mmol). Purification by RPC (gradient: 0-80% MeCN in water with 0.05% NH_4HCO_3) gave the title compound (1.40 g, 72 %) as a brown solid. ^1H NMR ($\text{DMSO}-d_6$): δ 0.46 – 0.58 (2H, m), 0.67 – 0.78 (2H, m), 1.31 (9H, s), 1.64 – 1.88 (5H, m), 2.60 – 3.00 (2H, m), 3.90 – 4.01 (2H, m), 4.60 – 4.71 (1H, m), 7.38 (1H, s), 8.09 (1H, d), 8.15 (1H, d); m/z (ES^+) $[\text{M}+\text{H}]^+ = 420.0$.

Intermediate 26b:

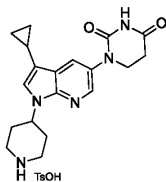
tert-butyl 4-[3-cyclopropyl-5-(2,4-dioxohexahydropyrimidin-1-yl)pyrrolo[2,3-*b*]pyridin-1-yl]piperidine-1-carboxylate



[1427] Prepared in an analogous method to Intermediate 4b starting from Intermediate 26a (0.700 g, 1.67 mmol). Purification by FSC (gradient: 0-70% EtOAc in petroleum ether) gave the title compound (0.400 g, 53 %) as a white solid. ^1H NMR ($\text{DMSO}-d_6$): δ 0.61 – 0.72 (2H, m), 0.80 – 0.92 (2H, m), 1.44 (9H, s), 1.79 – 2.03 (5H, m), 2.77 (2H, t), 2.80 – 3.00 (2H, m), 3.82 (2H, t), 3.99 – 4.24 (2H, m), 4.75 – 4.85 (1H, m), 7.48 (1H, s), 7.96 (1H, d), 8.18 (1H, d), 10.40 (1H, s); m/z (ES^+) $[\text{M}+\text{H}]^+ = 454.4$.

Intermediate 26c:

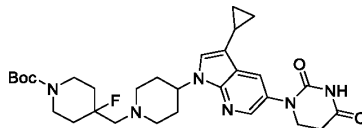
1-[3-Cyclopropyl-1-(4-piperidyl)pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1428] Prepared in an analogous method to Intermediate 6c starting from Intermediate 26b (5.6 g, 12.35 mmol). MTBE (100 mL) was added to the reaction mixture and stirred for 0.5 h. The product precipitate was collected by filtration and dried under vacuum to give title compound (6.00 g, 92 %) as a white solid in the form of a TsOH salt. m/z (ES^+) $[\text{M}+\text{H}]^+ = 354.3$.

Intermediate 26d:

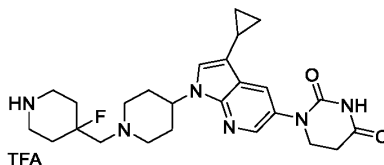
tert-butyl 4-[[4-[3-cyclopropyl-5-(2,4-dioxohexahydropyrimidin-1-yl)pyrrolo[2,3-*b*]pyridin-1-yl]-1-piperidyl]methyl]-4-fluoro-piperidine-1-carboxylate



[1429] Prepared in an analogous method to Intermediate 25f starting from Intermediate 26c (0.400 g, 0.76 mmol) and Intermediate 25e (0.473 g, 1.29 mmol). Purification by FSC (gradient: 0-100% EtOAc in hexanes) gave the title compound (0.189 g, 43.7 %) as a white foam. ¹H NMR (DMSO-*d*₆) 0.62 - 0.68 (2H, m), 0.80 - 0.87 (2H, m), 1.40 (9H, s), 1.50 - 1.67 (2H, m), 1.76 - 1.86 (4H, m), 1.86 - 1.94 (1H, m), 1.99 - 2.10 (2H, m), 2.29 - 2.37 (2H, m), 2.57 (2H, d), 2.75 (2H, t), 2.94 - 3.11 (4H, m), 3.67 - 3.76 (2H, m), 3.80 (2H, t), 4.49 - 4.64 (1H, m), 7.44 (1H, s), 7.93 (1H, d), 8.15 (1H, d), 10.35 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 569.3.

Intermediate 26e:

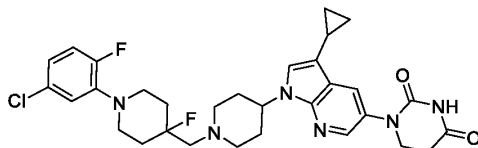
1-[3-cyclopropyl-1-[1-[(4-fluoro-4-piperidyl)methyl]-4-piperidyl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1430] Prepared in an analogous method to Intermediate 1i starting from Intermediate 26d (35 g, 61.6 mmol). The concentrate was pour into cold sat. aq. NaHCO₃ solution (1 L), extracted with DCM (4 x 1 L) and the organic layer was concentrated. The crude solid was triturated with DCM to give a solid which was collected by filtration and dried under vacuum to title compound (24.5 g, 71.4 %) as a white solid in the form of the 0.75 TF salt. *m/z* (ES⁺) [M+H]⁺ = 469.3.

Intermediate 26f:

1-[1-[1-[1-(5-Chloro-2-fluoro-phenyl)-4-fluoro-4-piperidyl]methyl]-4-piperidyl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

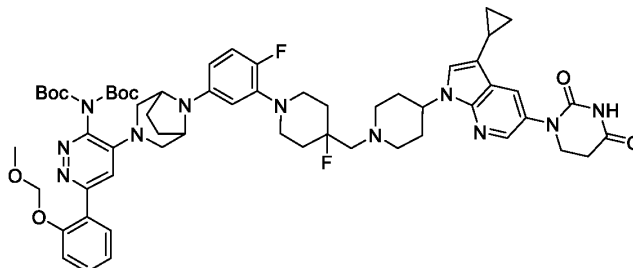


[1431] Prepared in an analogous manner to Intermediate 25h starting from Intermediate 26e (469 mg, 1 mmol) and 2-bromo-4-chloro-1-fluorobenzene (244 μl, 2 mmol). Purification by FSC (gradient: 0-5% MeOH in DCM) gave the title compound (556 mg, 93 %) as an orange solid. ¹H NMR (CDCl₃): δ 0.59 - 0.67 (2H, m), 0.81 - 0.97 (2H, m), 1.78 - 2.14 (10H, m), 2.47 (2H, td), 2.92 (2H, t), 3.00 - 3.12 (4H, m),

3.28 (2H, br d), 3.93 (2H, t), 4.68 - 4.81 (1H, m), 6.85 - 6.99 (3H, m), 7.11 (1H, s), 7.49 (1H, s), 7.90 (1H, d), 8.23 (1H, d) (N-H not observed); m/z (ES^+) $[M+H]^+ = 597.4$.

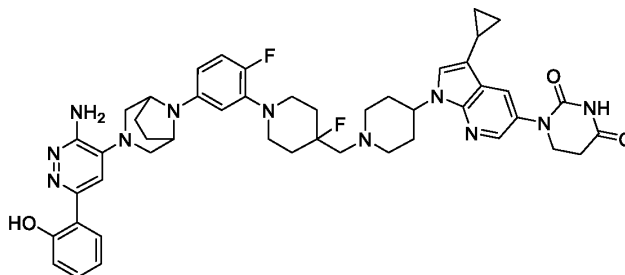
Intermediate 26g:

tert-Butyl *N*-*tert*-butoxycarbonyl-*N*-[4-[8-[3-[4-[[4-[3-cyclopropyl-5-(2,4-dioxohexahydropyrimidin-1-yl)pyrrolo[2,3-*b*]pyridin-1-yl]-1-piperidyl]methyl]-4-fluoro-1-piperidyl]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]-6-[2-(methoxymethoxy)phenyl]pyridazin-3-yl]carbamate



[1432] Prepared in an analogous manner to Intermediate 25i starting from Intermediate 26e (119 mg, 0.20 mmol) and Intermediate 26f (108 mg, 0.20 mmol). Purification by FSC (gradient: 0-3% MeOH in DCM with 0.1% NH_4OH) gave the title compound (40.0 mg, 18.14 %) as a yellow gum. 1H NMR ($CDCl_3$): δ 0.58 - 0.67 (2H, m), 0.84 - 0.94 (2H, m), 1.46 (18H, s), 1.84 - 2.11 (14H, m), 2.42 - 2.52 (2H, m), 2.56 - 2.65 (2H, m), 2.91 (2H, t), 2.97 - 3.05 (2H, m), 3.10 (2H, br d), 3.23 - 3.30 (2H, m), 3.38 (5H, s), 3.92 (2H, t), 4.22 (2H, br s), 4.74 (1H, br s), 5.17 (2H, s), 6.38 (1H, dt), 6.46 - 6.52 (1H, m), 6.89 - 6.96 (1H, m), 7.10 (1H, s), 7.13 - 7.21 (2H, m), 7.37 - 7.45 (2H, m), 7.57 (1H, s), 7.89 - 7.98 (2H, m), 8.23 (1H, d) (N-H not observed); m/z (ES^+) $[M+H]^+ = 1102.7$.

1-[1-[1-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-fluoro-4-piperidyl]methyl]-4-piperidyl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



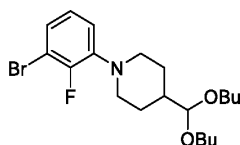
[1433] A vial was charged with Intermediate 26g (34 mg, 0.03 mmol), DCM (2 mL) and TFA (0.4 mL). The reaction was stirred at r.t. for 1.5 h, then concentrated *in vacuo*. Purification by RPC (gradient: 50-100% MeCN in water with 0.1% NH_4OH) gave the title compound (9.80 mg, 37.0 %) as a white solid. 1H NMR($DMSO-d_6$) δ 0.62 - 0.72 (2H, m), 0.80 - 0.89 (2H, m), 1.75 - 2.03 (9H, m), 2.04 - 2.20 (4H, m), 2.32 - 2.44 (2H, m), 2.58 - 2.69 (2H, m), 2.77 (2H, t), 2.96 (2H, br t), 3.04 - 3.13 (4H, m), 3.16 - 3.23 (2H, m), 3.27 (2H, br d), 3.82 (2H, t), 4.38 (2H, br d), 4.54 - 4.68 (1H, m), 5.94 (2H, s), 6.46 (1H, dt), 6.51 - 6.58

(1H, m), 6.83 - 6.91 (2H, m), 6.96 (1H, dd), 7.20 - 7.27 (1H, m), 7.47 (2H, s), 7.91 (1H, dd), 7.95 (1H, d), 8.18 (1H, d), 10.37 (1H, br s), 14.05 - 14.25 (1H, m); m/z (ES^+) $[M+H]^+ = 858.5$.

EXAMPLE 27

Intermediate 27a:

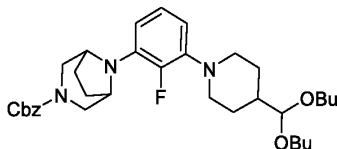
1-(3-Bromo-2-fluorophenyl)-4-(dibutoxymethyl)piperidine



[1434] A flask was charged with 4-(dibutoxymethyl)piperidine (2.57 g, 10.56 mmol), 1,3-dibromo-2-fluorobenzene (5.36 g, 21.12 mmol), BINAP (0.658 g, 1.06 mmol), $Pd_2(dba)_3$ (0.483 g, 0.53 mmol), and $KOtBu$ (1.185 g, 10.56 mmol) in toluene (52.8 ml). The reaction was degassed bubbling N_2 through the solution for 5 min. The reaction was heated to 105 °C for 3 h. The reaction was cooled to r.t. and concentrated *in vacuo*. Purification by FSC (gradient: 0-10% EtOAc in hexanes) gave the title compound (2.400 g, 54.6 %) as a colorless oil. 1H NMR (CD_2Cl_2): δ 0.91 - 0.96 (6H, m), 1.35 - 1.44 (4H, m), 1.52 - 1.60 (6H, m), 1.67 - 1.75 (1H, m), 1.84 (2H, br d), 2.61 - 2.68 (2H, m), 3.39 - 3.47 (4H, m), 3.61 (2H, dt), 4.19 (1H, d), 6.88 - 6.96 (2H, m), 7.08 - 7.14 (1H, m); m/z (ES^+) $[M+H]^+ = 416.2$.

Intermediate 27b:

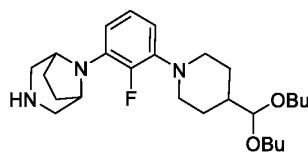
Benzyl 8-[3-[4-(dibutoxymethyl)-1-piperidyl]-2-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



[1435] A vial was charged with a solution of Intermediate 27a (1.249 g, 3 mmol), benzyl 3,8-diazabicyclo[3.2.1]octane-3-carboxylate (0.739 g, 3.00 mmol), and SPhos Pd G2 (0.216 g, 0.30 mmol) in THF (6.00 ml) was degassed with N_2 and LiHMDS solution (9.00 mL, 9.00 mmol, 1 M in THF) was added. The reaction mixture was heated to 60 °C for 2 h. The reaction was cooled to r.t. diluted with EtOAc (20 mL), and quenched with NH_4Cl solution (3 mL). The organic phase was separated, dried with $MgSO_4$, filtered, and concentrated. Purification by FSC (gradient: 0-30% EtOAc in hexanes) gave the title compound (1.100 g, 63.0 %) as a colorless oil. 1H NMR (CD_2Cl_2): δ 0.90 - 0.95 (6H, m), 1.20 - 1.29 (2H, m), 1.35 - 1.43 (4H, m), 1.43 - 1.51 (2H, m), 1.52 - 1.58 (4H, m), 1.70 - 1.73 (1H, m), 1.73 - 1.78 (2H, m), 1.79 - 1.85 (2H, m), 1.90 - 1.98 (2H, m), 2.60 (2H, br t), 3.34 - 3.40 (2H, m), 3.40 - 3.46 (2H, m), 3.61 (2H, dt), 3.74 - 3.85 (2H, m), 4.02 - 4.11 (2H, m), 4.18 (1H, d), 5.11 (2H, s), 6.49 - 6.56 (2H, m), 6.88 (1H, t), 7.26 - 7.31 (1H, m), 7.33 - 7.36 (4H, m); m/z (ES^+) $[M+H]^+ = 582.6$.

Intermediate 27c:

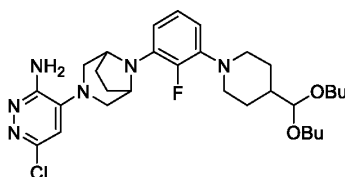
8-[3-[4-(Dibutoxymethyl)-1-piperidyl]-2-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octane



[1436] Prepared in an analogous manner to Intermediate 11e starting from Intermediate 27b (1.1 g, 1.89 mmol). The solids were filtered off and filtrate was concentrated to give title compound (0.500 g, 59.1 %) as a black gum. m/z (ES^+) $[M+H]^+ = 448.5$.

Intermediate 27d:

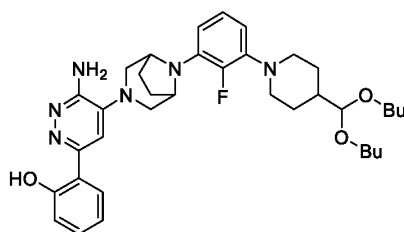
6-Chloro-4-[8-[3-[4-(dibutoxymethyl)-1-piperidyl]-2-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-amine



[1437] Prepared in an analogous manner to Intermediate 3d starting from Intermediate 27c (500 mg, 1.12 mmol) and 4-bromo-6-chloropyridazin-3-amine (233 mg, 1.12 mmol). Purification by FSC (gradient: 0-30% EtOAc in hexanes) gave the title compound (120 mg, 18.68 %) as a white solid. 1H NMR (CD_2Cl_2): δ 0.92 - 0.96 (6H, m), 1.38 - 1.44 (4H, m), 1.52 - 1.58 (6H, m), 1.66 - 1.75 (1H, m), 1.79 - 1.88 (2H, m), 1.96 - 1.99 (2H, m), 2.04 - 2.11 (2H, m), 2.61 (2H, br t), 3.10 (2H, d), 3.27 (2H, dd), 3.36 - 3.46 (4H, m), 3.61 (2H, dt), 4.17 - 4.21 (1H, m), 4.21 - 4.26 (2H, m), 4.68 (2H, s), 6.52 - 6.58 (2H, m), 6.75 (1H, s), 6.89 - 6.93 (1H, m); m/z (ES^+) $[M-OBu]^+ = 501.4$.

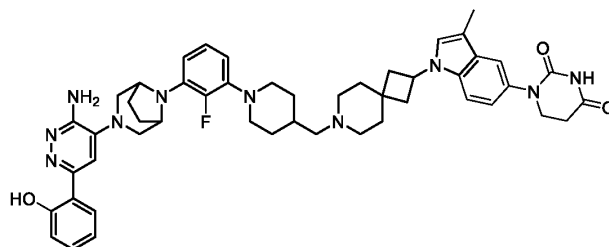
Intermediate 27e:

2-[6-Amino-5-[8-[3-[4-(dibutoxymethyl)-1-piperidyl]-2-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-yl]phenol



[1438] Prepared in an analogous method to Intermediate 2h starting from Intermediate 27d (120 mg, 0.21 mmol). Purification by FSC (gradient: 10-30% EtOAc in hexanes) gave the title compound (60 mg, 45% yield) as a yellow solid. 1H NMR (CD_2Cl_2): δ 0.93 (6H, t), 1.37 - 1.43 (4H, m), 1.46 - 1.51 (2H, m), 1.53 - 1.59 (4H, m), 1.66 - 1.74 (1H, m), 1.81 - 1.87 (2H, m), 1.99 - 2.05 (2H, m), 2.08 - 2.12 (2H, m), 2.58 - 2.66 (2H, m), 3.22 (2H, d), 3.32 - 3.37 (2H, m), 3.38 - 3.47 (4H, m), 3.62 (2H, dt), 4.19 (1H, d), 4.27 (2H, br s), 4.80 (2H, s), 6.57 (2H, t), 6.88 - 6.95 (2H, m), 6.97 (1H, dd), 7.23 - 7.29 (1H, m), 7.36 (1H, s), 7.61 - 7.64 (1H, m), 13.71 - 13.81 (1H, m); m/z (ES^+) $[M+H]^+ = 633.5$.

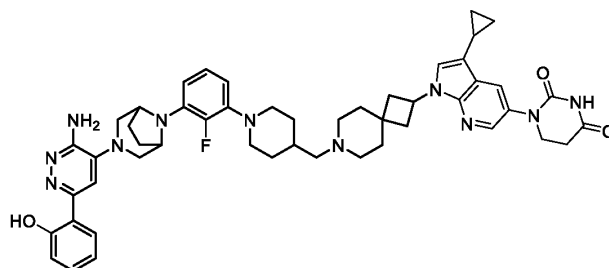
1-[1-[7-[[1-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione



[1439] Prepared in an analogous manner to EXAMPLE 11 starting from Intermediate 27e (32 mg, 0.05 mmol) and Intermediate 4b (24 mg, 0.05 mmol). Purification by RPC (gradient: 20-40% MeCN in water with 0.1% FA) gave the title compound (15 mg, 35%) as an amorphous white solid. ^1H NMR (DMSO- d_6) δ 1.20 - 1.30 (2H, m), 1.58 - 1.67 (3H, m), 1.71 - 1.81 (4H, m), 1.91 (2H, br d), 2.05 - 2.12 (4H, m), 2.12 - 2.16 (2H, m), 2.20 - 2.30 (5H, m), 2.30 - 2.43 (4H, m), 2.57 - 2.65 (2H, m), 2.71 (2H, t), 3.08 - 3.12 (2H, m), 3.36 - 3.46 (4H, m), 3.75 (2H, t), 4.22 (2H, br s), 4.95 (1H, quin), 5.94 (2H, s), 6.54 (1H, br t), 6.67 (1H, br t), 6.84 - 6.92 (3H, m), 7.03 (1H, dd), 7.23 (1H, t), 7.36 - 7.44 (3H, m), 7.53 (1H, s), 7.94 (1H, d), 10.22 (1H, s), 13.96 - 14.47 (1H, m); m/z (ES^+) $[\text{M}+\text{H}]^+ = 853.5$.

EXAMPLE 28

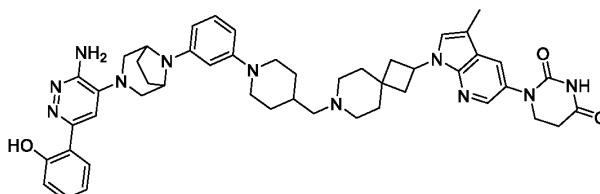
1-[1-[7-[[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1440] Prepared in an analogous manner to EXAMPLE 11 starting from Intermediate 27e (32 mg, 0.05 mmol) and Intermediate 2b (20 mg, 0.05 mmol). Purification by RPC (gradient: 20-40% MeCN in water with 0.1% FA) gave the title compound (16 mg, 36%) as an amorphous white solid. ^1H NMR (DMSO- d_6) δ 0.65 - 0.70 (2H, m), 0.83 - 0.88 (2H, m), 1.20 - 1.30 (2H, m), 1.59 - 1.65 (1H, m), 1.65 - 1.74 (4H, m), 1.74 - 1.82 (2H, m), 1.88 - 1.98 (3H, m), 2.05 - 2.19 (5H, m), 2.19 - 2.24 (2H, m), 2.29 - 2.42 (4H, m), 2.56 - 2.65 (2H, m), 2.75 (2H, t), 3.07 - 3.12 (2H, m), 3.38 - 3.47 (5H, m), 3.80 (2H, t), 4.22 (2H, br s), 5.23 (1H, quin), 5.94 (2H, s), 6.50 - 6.58 (1H, m), 6.68 (1H, br s), 6.82 - 6.96 (3H, m), 7.20 - 7.24 (1H, m), 7.53 (2H, d), 7.91 - 7.96 (2H, m), 8.15 (1H, d), 10.35 (1H, br s), 13.94 - 14.37 (1H, m); m/z (ES^+) $[\text{M}+\text{H}]^+ = 880.6$.

EXAMPLE 29

1-[1-[7-[[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

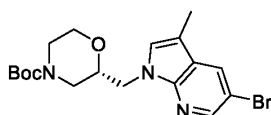


[1441] A vial was charged with Intermediate 3e (40 mg, 0.07 mmol) and Intermediate 15b (30.4 mg, 0.07 mmol) and formic acid (1 mL). The reaction was heated to 40 °C for 30 min. Toluene (2 mL) was added and solvents were concentrated *in vacuo*. To the mixture was added MeOH (1 mL), DCM (0.2 mL), and DIPEA (0.057 mL, 0.33 mmol). Decaborane (3.98 mg, 0.03 mmol) was added and the reaction was stirred at r.t. for 1 h. Acetone (1 mL) was added and stirred for 15 min. DMSO (1 mL) added and the volatiles were evaporated *in vacuo*. Purification by RPC (gradient: 0-80% CH₃CN in water with 0.1% formic acid) gave the title compound (18 mg, 33.1%) as an amorphous off-white solid. ¹H NMR (DMSO-*d*₆): δ 1.05 - 1.33 (3H, m), 1.51 - 1.87 (7H, m), 1.87 - 2.02 (2H, m), 2.13 (4H, br d), 2.18 - 2.24 (2H, m), 2.27 (3H, s), 2.35 (4H, br t), 2.62 (2H, br s), 2.76 (2H, t), 3.06 - 3.27 (4H, m), 3.65 (2H, br d), 3.81 (2H, t), 4.39 (2H, br s), 5.14 - 5.37 (1H, m), 6.24 - 6.38 (2H, m), 6.43 (1H, brs), 6.82 - 6.90 (2H, m), 7.02 (1H, t), 7.23 (1H, t), 7.46 (1H, s), 7.61 (1H, s), 7.85 - 7.94 (2H, m), 8.17 (1H, d), 10.38 (1H, s), 14.17 (1H, br s). *m/z* (ES⁺) [M+H]⁺ = 836.5.

EXAMPLE 30

Intermediate 30a:

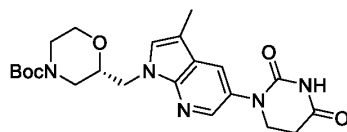
tert-Butyl (2*R*)-2-[(5-bromo-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl)methyl]morpholine-4-carboxylate



[1442] Prepared in an analogous manner to Intermediate 4a starting from 5-bromo-3-methyl-1*H*-indole (0.500 g, 2.37 mmol), *tert*-butyl (*S*)-2-(hydroxymethyl)morpholine-4-carboxylate (0.772 g, 3.55 mmol) and 2-(tributyl-*l*5-phosphaneylidene)acetonitrile (0.931 mL, 3.55 mmol). Purification by FSC (gradient: 0 to 50% EtOAc in hexanes) gave the title compound (821 mg, 84%) as an off-white foam. ¹H NMR (CDCl₃) δ 1.44 (9H, s), 2.27 (3H, s), 2.61 (1H, br s), 2.91 (1H, br s), 3.47 (1H, td), 3.71 - 4.08 (4H, m), 4.16 - 4.42 (2H, m), 7.06 (1H, br d), 7.95 (1H, s), 8.30 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 410.1.

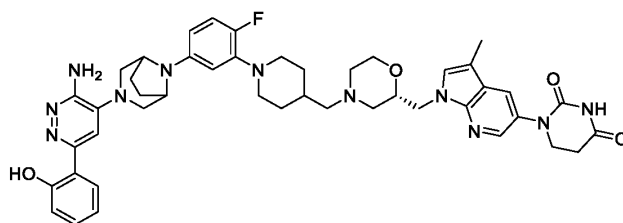
Intermediate 30b:

tert-Butyl (2*R*)-2-[[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl)methyl]morpholine-4-carboxylate



[1443] Prepared in an analogous manner to Intermediate 6b starting from Intermediate 30a (0.82 g, 1.99 mmol). The mixture was stirred at 90 °C for 21 h. After cooling to r.t., the mixture was filtered. The filter-cake was washed with DCM. The combined filtrates were concentrated *in vacuo*. Purification by FSC (first purification, gradient: 0 to 15% MeOH in DCM, second purification, elution gradient: 0 to 100% [3:1 EtOAc/EtOH] in hexanes) gave the title compound (0.66 g, 74%) as an off-white solid. ¹H NMR (DMSO-*d*₆) δ 1.36 (9H, s), 2.24 (3H, d), 2.53 - 2.68 (1H, m), 2.75 (2H, t), 2.85 (1H, br s), 3.27 - 3.35 (1H, m), 3.61 - 3.84 (6H, m), 4.27 (2H, br d), 7.33 (1H, d), 7.89 (1H, d), 8.18 (1H, d), 10.37 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 444.4.

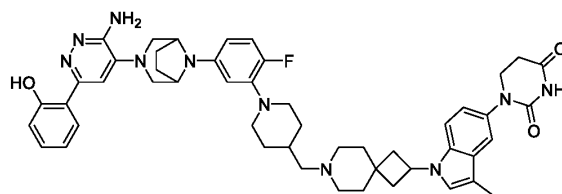
1-[1-[(2*S*)-4-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl)methyl]morpholin-2-yl)methyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1444] Formic acid (1 mL) was added to a mixture of Intermediate 11g (30 mg, 0.05 mmol) and Intermediate 30b (29 mg, 0.07 mmol). The resulting mixture was stirred at 40 °C for 30 min and concentrated under reduced pressure. The residue was azeotroped with toluene (2 mL). DMF (1 mL) was added and the mixture was stirred at 40 °C for 20 min. After cooling to r.t., Na(OAc)₃BH (20 mg, 0.09 mmol) was added and the mixture was stirred at r.t. for 20 min. Purification by RPC (gradient: 0 to 50% MeCN in water with 0.1% FA) gave the title compound (14.1 mg, 35%) as a white solid. ¹H NMR (DMSO-*d*₆) δ 1.16 - 1.30 (2H, m), 1.60 (1H, ddd), 1.71 - 1.84 (3H, m), 1.89 - 1.96 (2H, m), 1.96 - 2.02 (1H, m), 2.08 - 2.18 (4H, m), 2.23 (3H, s), 2.56 - 2.64 (3H, m), 2.69 - 2.77 (3H, m), 3.08 (2H, br d), 3.24 (2H, br d), 3.30 - 3.34 (2H, m), 3.38 - 3.43 (1H, m), 3.74 - 3.85 (4H, m), 4.24 (2H, br d), 4.33 (2H, br s), 5.93 (2H, s), 6.41 (1H, dt), 6.45 (1H, dd), 6.82 - 6.88 (2H, m), 6.90 (1H, dd), 7.17 - 7.26 (1H, m), 7.32 (1H, s), 7.45 (1H, s), 7.86 - 7.94 (2H, m), 8.17 (1H, d), 10.38 (1H, s), 13.15 - 14.96 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 830.4.

EXAMPLE 31

1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl)methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione

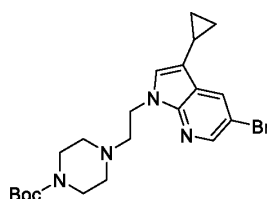


[1445] Prepared in an analogous manner to EXAMPLE 30 starting from Intermediate 11g (40 mg, 0.07 mmol) and Intermediate 4b (40.8 mg, 0.09 mmol). Purification by RPC (gradient: 0-60% MeCN in water with 0.1% FA) gave the title compound (3.50 mg, 5.53 %) as a white solid. ^1H NMR (DMSO-*d*₆) δ 0.85 (1H, d), 1.24 (4H, s), 1.64 (3H, s), 1.78 (4H, d), 1.95 (2H, s), 2.08 (1H, d), 2.12 (1H, d), 2.16 (3H, d), 2.25 (4H, d), 2.31 (1H, s), 2.41 (3H, d), 2.55 (1H, s), 2.63 (1H, d), 2.73 (2H, t), 3.10 (2H, d), 3.26 (3H, d), 3.77 (2H, t), 4.35 (2H, s), 4.92–5.01 (1H, m), 5.96 (2H, s), 6.4–6.51 (2H, m), 6.82–6.98 (3H, m), 7.01–7.08 (1H, m), 7.19–7.27 (1H, m), 7.37–7.5 (4H, m), 7.88–7.95 (1H, m), 10.26 (1H, s), 14.19 (1H, s); ^{19}F NMR (DMSO-*d*₆) δ -136.411; m/z (ES⁺) $[\text{M}+\text{H}]^+ = 853.1$.

EXAMPLE 32

Intermediate 32a:

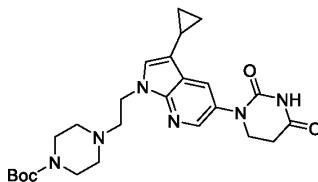
tert-Butyl 4-[2-(5-bromo-3-cyclopropyl-pyrrolo[2,3-*b*]pyridine-1-yl)ethyl]piperazine-1-carboxylate



[1446] A flask was charged with *tert*-butyl 4-(2-bromoethyl)piperazine-1-carboxylate (500 mg, 1.71 mmol), 5-bromo-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridine (270 mg, 1.14 mmol), Cs₂CO₃ (1111 mg, 3.41 mmol), and DMF (10 mL). The resulting mixture was stirred at 60 °C for 16 h. The reaction mixture was poured into water (100 mL), extracted with EtOAc (3 x 20 mL). The organic layer was separated, dried with Na₂SO₄, filtered and concentrated. Purification by FSC (gradient: 0 to 100% EtOAc in petroleum ether) gave the title compound (460 mg, 60.5 %) as a yellow oil. ^1H NMR (CDCl₃) δ 0.57 – 0.67 (2 H, m), 0.88 – 0.97 (2 H, m), 1.47 (9 H, s), 1.82 – 1.92 (1 H, m), 2.46 (4 H, s), 2.76 (2 H, s), 3.41 (4 H, s), 4.33 (2 H, s), 7.00 (1 H, s), 8.09 (1 H, d), 8.30 (1 H, d); m/z (ES⁺) $[\text{M}+\text{H}]^+ = 449.3$.

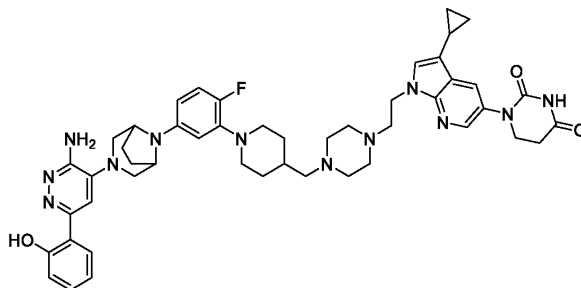
Intermediate 32b:

tert-Butyl 4-[2-[3-cyclopropyl-5-(2,4-dioxohexahydropyrimidin-1-yl)pyrrolo[2,3-*b*]pyridin-1-yl]ethyl]piperazine-1-carboxylate



[1447] Prepared in an analogous manner to Intermediate 6b starting from Intermediate 32a (450 mg, 1.00 mmol). Purification by FSC (gradient: 0 to 100% EtOAc in petroleum ether then 0 to 10% MeOH in DCM) gave the title compound (277 mg, 56.5 %) as a yellow solid. ¹H NMR (CDCl₃) δ 0.56 – 0.64 (2 H, m), 0.86 – 0.91 (2 H, m), 1.45 (9 H, s), 1.82 – 1.91 (1 H, m), 2.45 (4 H, s), 2.65 – 2.79 (2 H, m), 2.87 – 2.93 (2 H, m), 3.31 – 3.51 (4 H, m), 3.89 – 3.94 (2 H, m), 4.33 (2 H, s), 7.03 (1 H, s), 7.51 (1 H, s), 7.89 (1 H, d), 8.21 (1 H, d); *m/z* (ES⁺) [M+H]⁺ = 483.3.

1-[1-[2-[4-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]piperazin-1-yl]ethyl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

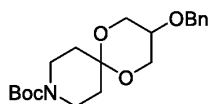


[1448] TsOH (58.9 mg, 0.31 mmol) was added to Intermediate 32b (115 mg, 0.24 mmol) in MeCN (2 mL). The resulting mixture was stirred at 70 °C for 16 h. The reaction mixture was evaporated. To the residue was added Intermediate 13d (143 mg, 0.29 mmol) and NMP (2.0 mL). The resulting mixture was stirred at 40 °C for 16 h, cooled to r.t., then Na(OAc)₃BH (303 mg, 1.43 mmol) was added and stirred at r.t. for 1 h. The reaction mixture was poured into saturated Na₂CO₃ (20 mL), extracted with DCM (3 x 10 mL), the organic layer was separated, dried with Na₂SO₄, filtered and concentrated. Purification by RPC (gradient: 0-70% CH₃CN in water with NH₄HCO₃ + 0.1% NH₄OH) gave the title compound (13.00 mg, 6.84 %) as a white solid. ¹H NMR (DMSO-*d*₆) δ 0.55 – 0.65 (2 H, m), 0.82 – 0.91 (2 H, m), 1.12 – 1.31 (3 H, m), 1.59 (1 H, s), 1.75 (2 H, d), 1.86 – 2.00 (3 H, m), 2.04 – 2.19 (4 H, m), 2.32 (4 H, s), 2.45 (3 H, s), 2.56 – 2.68 (4 H, m), 2.71 – 2.80 (2 H, m), 3.09 (2 H, d), 3.25 (2 H, d), 3.40 (2 H, s), 3.76 – 3.85 (2 H, m), 4.21 – 4.38 (4 H, m), 5.94 (2 H, s), 6.37 – 6.52 (2 H, m), 6.80 – 6.98 (3 H, m), 7.18 – 7.26 (1 H, m), 7.32 (1 H, s), 7.46 (1 H, s), 7.86 – 7.98 (2 H, m), 8.17 (1 H, d), 10.39 (1 H, s), 14.17 (1 H, s); ¹⁹F NMR (DMSO-*d*₆) δ: -136.40; *m/z* (ES⁺) [M+H]⁺ = 869.5.

EXAMPLE 33

Intermediate 33a:

tert-butyl 3-benzyloxy-1,5-dioxo-9-azaspiro[5.5]undecane-9-carboxylate

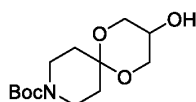


[1449] TsOH (0.19 g, 1.00 mmol) was added to a mixture of 2-benzyloxypropane-1,3-diol (2.01 g, 11.0 mmol) and *tert*-butyl 4-oxopiperidine-1-carboxylate (2.00 g, 10.0 mmol) in DCM (49 mL). The

resulting mixture was stirred at r.t. for 16 h. The mixture was washed with sat. aq. NaHCO_3 (50 mL), water (50 mL) and brine (50 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. Purification by FSC (gradient: 0 to 40% EtOAc in hexanes) gave the title compound (2.75 g, 75%) as a colorless oil. ^1H NMR ($\text{DMSO}-d_6$): δ 1.38 (9H, s), 1.66 - 1.77 (4H, m), 3.28 (4H, br s), 3.42 - 3.49 (1H, m), 3.71 (2H, dd), 3.94 (2H, dd), 4.52 (2H, s), 7.24 - 7.42 (5H, m); m/z (ES^+) $[\text{M}+\text{Na}]^+ = 386.3$.

Intermediate 33b:

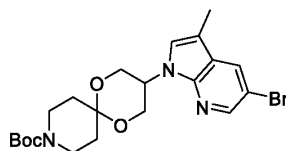
tert-Butyl 3-hydroxy-1,5-dioxo-9-azaspiro[5.5]undecane-9-carboxylate



[1450] EtOAc (50 mL) was added to a mixture of Intermediate 33a (2.74 g, 7.54 mmol) and Pd/C (0.80 g, 0.75 mmol). The mixture was sparged with H_2 for 5 min and stirred under an atmosphere of H_2 at r.t. for 4 h and at 50 °C for 17 h. After cooling to r.t., the mixture was filtered through a pad of Celite® with EtOAc. The combined filtrates were concentrated under reduced pressure. Purification by FSC (gradient: 0 to 100% EtOAc in hexanes) gave the title compound (1.30 g, 62%) as a white solid. ^1H NMR ($\text{DMSO}-d_6$) δ 1.39 (9H, s), 1.60 - 1.69 (2H, m), 1.74 - 1.83 (2H, m), 3.26 - 3.33 (4H, m), 3.48 - 3.59 (3H, m), 3.77 - 3.88 (2H, m), 5.00 (1H, br s); m/z (ES^+) $[\text{M}-t\text{Bu}+2\text{H}]^+ = 218.0$.

Intermediate 33c:

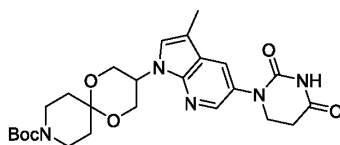
tert-Butyl 3-(5-bromo-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl)-1,5-dioxo-9-azaspiro[5.5]undecane-9-carboxylate



[1451] Prepared in an analogous manner to Intermediate 4a using 5-bromo-3-methyl-1*H*-indole (1.20 g, 5.66 mmol), Intermediate 33b (1.29 g, 4.72 mmol) and 2-(tributyl- λ^5 -phosphanylidene)acetonitrile (1.24 mL, 4.72 mmol). Purification by FSC (gradient: 0 to 50% EtOAc in hexanes) gave the title compound (339 mg, 15%) as an off-white solid. ^1H NMR ($\text{DMSO}-d_6$) δ 1.41 (9H, s), 1.80 - 1.88 (2H, m), 1.93 - 1.99 (2H, m), 2.27 (3H, d), 3.37 (4H, dt), 3.97 - 4.07 (2H, m), 4.34 (2H, dd), 4.80 (1H, quin), 7.74 (1H, s), 8.21 (1H, d), 8.28 (1H, d); m/z (ES^+) $[\text{M}+\text{H}]^+ = 466.3$.

Intermediate 33d:

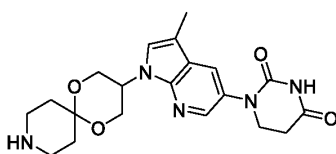
tert-Butyl 3-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-1,5-dioxo-9-azaspiro[5.5]undecane-9-carboxylate



[1452] Prepared in an analogous manner to Intermediate 6b using Intermediate 33c (334 mg, 0.72 mmol). The mixture was stirred at 95 °C for 23 h. After cooling to r.t., the mixture was filtered. The filter cake was washed with DCM. The combined filtrates were concentrated under reduced pressure. Purification by FSC (gradient: 0 to 100% [3:1 EtOAc/EtOH] in hexanes) gave the title compound (207g, 57%) as an off-white solid. ¹H NMR (DMSO-*d*₆) δ 1.40 (9H, s), 1.82 - 1.90 (2H, m), 1.91 - 1.98 (2H, m), 2.27 (3H, d), 2.75 (2H, t), 3.29 - 3.52 (4H, m), 3.80 (2H, t), 3.98 - 4.08 (2H, m), 4.31 (2H, br dd), 4.83 (1H, quin), 7.70 (1H, s), 7.91 (1H, d), 8.18 (1H, d), 10.37 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 500.2.

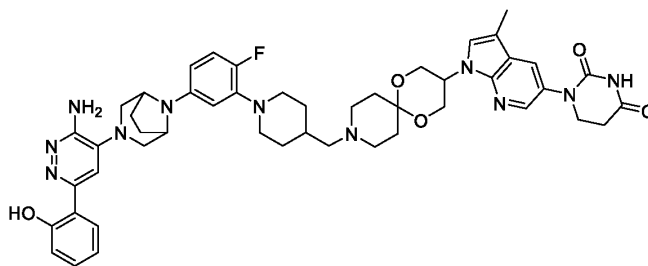
Intermediate 33e:

1-[1-(1,5-Dioxa-9-azaspiro[5.5]undecan-3-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1453] TFA (0.62 mL) was added to a solution of Intermediate 33d (199 mg, 0.40 mmol) in DCM (2.4 mL). The resulting mixture was stirred at r.t. for 30 min. The mixture was diluted with DCM-IPA (3:2, 30 mL), washed with sat. aq. K₂CO₃ (3 x 30 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give the title compound (115 mg, 72%) as an off-white solid. ¹H NMR (DMSO-*d*₆) δ 1.81 (2H, br s), 1.89 (2H, br s), 2.28 (3H, s), 2.66 - 2.78 (6H, m), 3.80 (2H, t), 4.01 (2H, dd), 4.26 - 4.35 (2H, m), 4.82 (1H, quin), 7.73 (1H, s), 7.91 (1H, d), 8.19 (1H, d), 9.92 - 10.86 (1H, m), NH proton not observed; *m/z* (ES⁺) [M+H]⁺ = 400.4.

1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxa-9-azaspiro[5.5]undecan-3-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



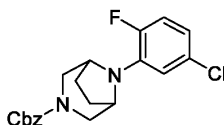
[1454] DMF (1 mL) was added to a mixture of Intermediate 33e (45 mg, 0.11 mmol) and Intermediate 13d (40 mg, 0.08 mmol). The resulting mixture was stirred at r.t. for 3 min. Na(OAc)₃BH (34 mg, 0.16 mmol) was added and the mixture was stirred at r.t. for 30 min. Purification by RPC (gradient: 40 to 100% MeCN in water with 0.1% NH₄OH) gave the title compound (21.5 mg, 30%) as an amorphous white solid, following lyophilization. ¹H NMR (DMSO-*d*₆) δ 1.18 - 1.32 (2H, m), 1.56 - 1.67 (1H, m), 1.78 (2H, br d), 1.85 - 2.08 (6H, m), 2.09 - 2.16 (2H, m), 2.19 (2H, br d), 2.27 (3H, s), 2.31 - 2.47 (4H, m), 2.58 - 2.68 (2H,

m), 2.75 (2H, t), 3.09 (2H, br d), 3.21 - 3.41 (4H, m), 3.80 (2H, t), 4.00 (2H, dd), 4.25 - 4.41 (4H, m), 4.81 (1H, quin), 5.92 (2H, s), 6.38 - 6.49 (2H, m), 6.81 - 6.97 (3H, m), 7.16 - 7.27 (1H, m), 7.46 (1H, s), 7.72 (1H, s), 7.84 - 7.97 (2H, m), 8.18 (1H, d), 9.85 - 10.91 (1H, m), 13.31 - 14.99 (1H, m); m/z (ES^+) $[M+H]^+ = 886.7$.

EXAMPLE 34

Intermediate 34a:

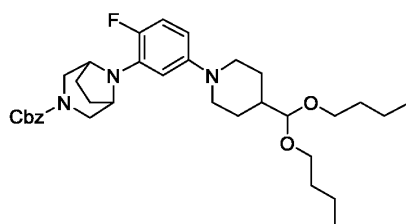
Benzyl 8-(5-chloro-2-fluoro-phenyl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



[1455] Benzyl 3,8-diazabicyclo[3.2.1]octane-3-carboxylate (1.232 g, 5.00 mmol) was added to a suspension of 2-bromo-4-chloro-1-fluorobenzene (1.047 g, 5 mmol), BINAP (0.311 g, 0.50 mmol), $Pd_2(dba)_3$ (0.229 g, 0.25 mmol), and $KOtBu$ (1.683 g, 15.00 mmol) in toluene (16 mL). The solution was degassed and purged with N_2 . The reaction was heated to 60 °C for 2 h. The reaction was cooled to r.t. and was quenched with NH_4Cl solution. The organic phase was dried ($MgSO_4$), filtered, and concentrated. Purification by FSC (gradient: 5-30% EtOAc in Hexanes) gave the title compound (1.140 g, 60.8 %) as a yellow liquid. 1H NMR (CD_2Cl_2): δ 1.75 - 1.82 (2H, m), 1.94 - 1.99 (2H, m), 3.16 - 3.26 (1H, m), 3.28 - 3.36 (1H, m), 3.76 - 3.86 (2H, m), 4.09 - 4.14 (1H, m), 4.14 - 4.19 (1H, m), 5.08 - 5.12 (2H, m), 6.74 - 6.78 (1H, m), 6.83 (1H, dd), 6.95 (1H, dd), 7.28 - 7.34 (1H, m), 7.34 - 7.39 (4H, m); m/z (ES^+) $[M+H]^+ = 375.1$.

Intermediate: 34b:

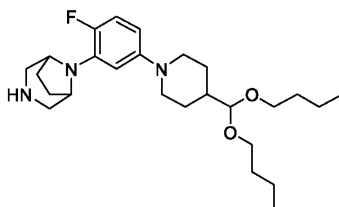
Benzyl 8-[5-[4-(dibutoxymethyl)-1-piperidyl]-2-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



[1456] Intermediate 34a (1.14 g, 3.04 mmol) was added to 4-(dibutoxymethyl)piperidine (0.740 g, 3.04 mmol), Ruphos Pd G3 (0.254 g, 0.30 mmol), and $KOtBu$ (0.444 g, 3.95 mmol) in toluene (15 mL). The reaction mixture was degassed and heated at 105 °C under N_2 for 1 h. The solvent was removed under reduced pressure. Purification by FSC (gradient: 5-35% EtOAc in Hexanes) gave the title compound (0.910 g, 51.4 %) as a colorless oil. 1H NMR (CD_2Cl_2) δ 0.92 (6H, t), 1.37 - 1.41 (4H, m), 1.51 - 1.58 (6H, m), 1.63 - 1.72 (1H, m), 1.73 - 1.85 (4H, m), 1.92 - 2.01 (2H, m), 2.57 (2H, br t), 3.22 - 3.28 (1H, m), 3.29 - 3.36 (1H, m), 3.39 - 3.45 (2H, m), 3.47 - 3.53 (2H, m), 3.57 - 3.63 (2H, m), 3.73 - 3.84 (2H, m), 4.05 - 4.19 (3H, m), 5.11 (2H, s), 6.32 - 6.43 (2H, m), 6.87 (1H, dd), 7.28 - 7.33 (1H, m), 7.33 - 7.38 (4H, m); m/z (ES^+) $[M+H]^+ = 582.8$.

Intermediate: 34c:

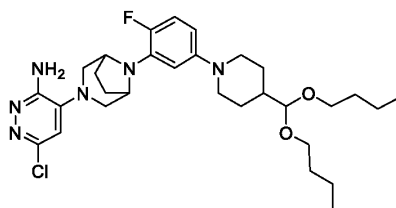
8-[5-[4-(Dibutoxymethyl)-1-piperidyl]-2-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octane



[1457] Prepared in an analogous manner to Intermediate 20b starting from Intermediate 34b (1.2 g, 2.06 mmol). The solids were filtered off and filtrate was concentrated to give title compound (0.897 g, 97 %) as a light black gum. ^1H NMR (DMSO- d_6): δ 0.87 (6H, t), 1.29 - 1.37 (6H, m), 1.44 - 1.51 (4H, m), 1.59 - 1.65 (1H, m), 1.64 - 1.72 (2H, m), 1.73 - 1.88 (4H, m), 2.40 - 2.48 (3H, m), 2.91 (2H, br d), 3.32 - 3.35 (2H, m), 3.35 - 3.41 (2H, m), 3.50 - 3.57 (4H, m), 3.94 (2H, br s), 4.17 (1H, d), 6.23 - 6.29 (1H, m), 6.39 (1H, dd), 6.86 (1H, dd); m/z (ES^+) $[\text{M}+\text{H}]^+ = 448.6$.

Intermediate 34d:

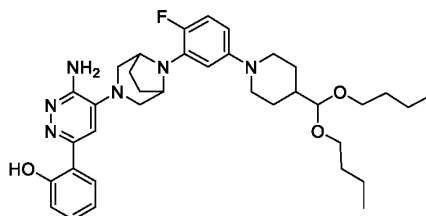
6-Chloro-4-[8-[5-[4-(dibutoxymethyl)-1-piperidyl]-2-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-amine



[1458] Prepared in an analogous manner to Intermediate 3d starting from Intermediate 34c (0.922 g, 2.06 mmol). Purification on FSC (gradient: 0-30% EtOAc in hexanes) gave the title compound (0.910 g, 77 %) as a white solid. ^1H NMR (CD_2Cl_2): δ 0.90 - 0.93 (6H, m), 1.37 - 1.41 (4H, m), 1.50 - 1.57 (6H, m), 1.67 (1H, dtd), 1.82 (2H, br d), 1.95 - 1.99 (2H, m), 2.05 - 2.11 (2H, m), 2.53 - 2.60 (2H, m), 3.08 (2H, d), 3.25 (2H, dd), 3.38 - 3.43 (2H, m), 3.51 (2H, br d), 3.58 - 3.62 (2H, m), 4.16 (1H, d), 4.26 (2H, br s), 4.68 (2H, s), 6.32 - 6.46 (2H, m), 6.73 (1H, s), 6.88 (1H, dd).

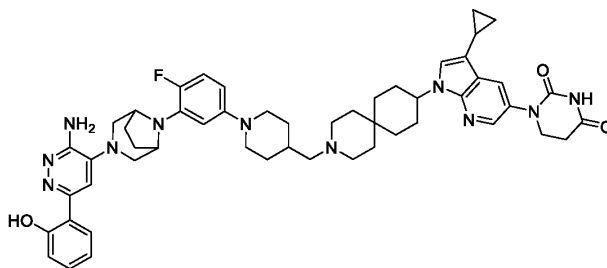
Intermediate 34e:

2-[6-Amino-5-[8-[5-[4-(dibutoxymethyl)-1-piperidyl]-2-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-yl]phenol



[1459] Prepared in an analogous method to Intermediate 2h starting from Intermediate 34d (0.87g, 1.82 mmol). Purification by FSC (gradient: 10-30% solvent B in hexanes [solvent B: 10% MeOH in EtOAc]) gave the title compound (0.760 g, 79 %) as a yellow solid. ¹H NMR (CD₂Cl₂): δ 0.91 - 0.94 (6H, m), 1.36 - 1.40 (4H, m), 1.49 - 1.57 (6H, m), 1.68 - 1.73 (1H, m), 1.81 - 1.85 (2H, m), 2.00 - 2.05 (2H, m), 2.09 - 2.16 (2H, m), 2.57 - 2.62 (2H, m), 3.20 - 3.25 (2H, m), 3.31 - 3.37 (2H, m), 3.40 - 3.45 (2H, m), 3.51 - 3.55 (2H, m), 3.58 - 3.63 (2H, m), 4.18 (1H, d), 4.31 (2H, br s), 4.81 (2H, s), 6.34 - 6.43 (1H, m), 6.47 (1H, dd), 6.88 - 6.95 (2H, m), 6.95 - 7.00 (1H, m), 7.26 (1H, ddd), 7.35 (1H, s), 7.62 (1H, dd), 13.66 - 13.92 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 633.7.

1-[1-[3-[[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-4-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

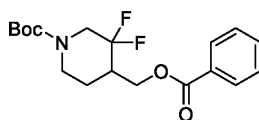


[1460] Prepared in an analogous manner to EXAMPLE 11 starting from Intermediate 34e (32 mg, 0.05 mmol) and Intermediate 11b (26 mg, 0.05 mmol). Purification by RPC (gradient: 50-100% MeCN in water with 0.1% NH₄OH) gave the title compound (21 mg, 46.2%) as an amorphous white solid. ¹H NMR (DMSO-*d*₆): 0.62 - 0.66 (2H, m), 0.83 - 0.88 (2H, m), 1.13 - 1.35 (6H, m), 1.37 - 1.47 (2H, m), 1.58 - 1.70 (4H, m), 1.74 - 1.85 (6H, m), 1.88 - 2.05 (6H, m), 2.08 - 2.13 (2H, m), 2.20 - 2.36 (2H, m), 2.51 - 2.64 (4H, m), 2.72 - 2.78 (2H, m), 3.07 - 3.13 (2H, m), 3.48 - 3.60 (2H, m), 3.73 - 3.84 (2H, m), 4.30 (2H, br s), 4.52 - 4.66 (1H, m), 5.94 (2H, s), 6.35 (1H, br d), 6.47 - 6.53 (1H, m), 6.82 - 6.89 (2H, m), 6.90 - 6.99 (1H, m), 7.21 - 7.25 (1H, m), 7.47 - 7.50 (1H, m), 7.50 - 7.55 (1H, m), 7.90 - 7.98 (2H, m), 8.13 - 8.17 (1H, m), 10.35 (1H, s), 14.02 - 14.32 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 908.6.

EXAMPLE 35

Intermediate 35a:

tert-Butyl 4-(benzyloxymethyl)-3,3-difluoro-piperidine-1-carboxylate

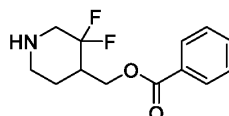


[1461] A mixture of *tert*-butyl 3,3-difluoro-4-(hydroxymethyl)piperidine-1-carboxylate (1.508 g, 6 mmol), DMAP (0.073 g, 0.60 mmol), DCM (25 mL) and DIPEA (3.14 mL, 18.00 mmol). The reaction was cooled to 0 °C. Benzoyl chloride (1.381 mL, 12.00 mmol) was added and the reaction was stirred at 0 °C for 5 min then stirred r.t. for 2.5 h. The reaction was quenched with sat. aq. NaHCO₃ (50 mL), extracted

with DCM (3 x 50 mL), washed with brine (100 mL), dried with Na₂SO₄ and concentrated *in vacuo*. Purification by FSC (gradient: 0-30% EtOAc in hexanes) gave the title compound (2.013 g, 94 %) as a colorless oil. ¹H NMR (CDCl₃): δ 1.50 (9H, s), 1.69 (1H, qd), 1.96 (1H, br d), 2.35 - 2.47 (1H, m), 2.73 - 2.93 (1H, m), 2.95 - 3.17 (1H, m), 4.16 - 4.45 (3H, m), 4.67 (1H, dd), 7.47 (2H, t), 7.59 (1H, t), 8.06 (2H, d); *m/z* (ES⁺) [M-*t*Bu+2H]⁺ = 300.1.

Intermediate 35b:

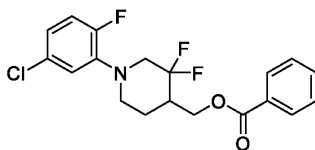
(3,3-Difluoro-4-piperidyl)methyl benzoate



[1462] A vial was charged with Intermediate 35a (2.013 g, 5.66 mmol), DCM (20 mL) and TFA (4 mL). The reaction was stirred at r.t. for 2.5 h then concentrated *in vacuo*. The crude material was purified by ion exchange chromatography (Porapak Rxn CX 5g cartridge) eluting with 2N NH₃ in MeOH gave the title compound (1.285 g, 89 %) as a light brown oil. ¹H NMR (DMSO-*d*₆): δ 1.46 (1H, qd), 1.78 - 1.90 (1H, m), 2.37 - 2.49 (2H, m), 2.52 - 2.56 (1H, m), 2.69 - 2.81 (1H, m), 2.91 (1H, br dd), 3.05 (1H, td), 4.28 (1H, dd), 4.52 (1H, dd), 7.54 (2H, t), 7.67 (1H, t), 7.98 (2H, d); *m/z* (ES⁺) [M+H]⁺ = 256.3.

Intermediate 35c:

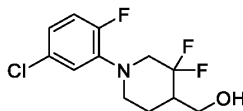
[1-(5-Chloro-2-fluoro-phenyl)-3,3-difluoro-4-piperidyl]methyl benzoate



[1463] A vial was charged with Intermediate 35b (1.2847 g, 5.03 mmol), Pd₂(dba)₃ (0.230 g, 0.25 mmol), (*t*Bu)PhCphos (0.204 g, 0.50 mmol), Cs₂CO₃ (4.92 g, 15.10 mmol), 1,4-dioxane (20 mL), and 2-bromo-4-chloro-1-fluorobenzene (0.613 mL, 5.03 mmol) under N₂. The reaction was heated to 100 °C for 1.5 h. The reaction was cooled to r.t., filtered through celite® eluting with DCM and concentrated *in vacuo*. Purification by FSC (0-20 % EtOAc in hexanes) gave the title compound (1.675 g, 87 %) as a yellow viscous liquid. ¹H NMR (DMSO-*d*₆): δ 1.75 (1H, qd), 1.99 - 2.06 (1H, m), 2.52 - 2.64 (1H, m), 2.89 - 2.98 (1H, m), 3.16 - 3.26 (1H, m), 3.47 (1H, br d), 3.65 (1H, td), 4.37 (1H, dd), 4.59 (1H, dd), 7.00 - 7.09 (1H, m), 7.12 (1H, dd), 7.21 (1H, dd), 7.55 (2H, t), 7.66 - 7.70 (1H, m), 8.00 (2H, d); *m/z* (ES⁺) [M+H]⁺ = 384.1.

Intermediate 35d:

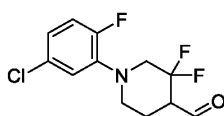
[1-(5-Chloro-2-fluoro-phenyl)-3,3-difluoro-4-piperidyl]methanol



[1464] A vial was charged with Intermediate 35c (1.6751 g, 4.36 mmol), lithium hydroxide (1.045 g, 43.65 mmol), MeOH (15 mL) and water (5 mL). The reaction was heated to 40 °C for 45 min. Reaction was partially concentrated *in vacuo* to remove excess MeOH. The reaction was quenched with sat. aq. NH₄Cl (100 mL), extracted with DCM (3 x 75 mL). The combined organic extracts were washed with sat. aq. NaHCO₃ (100 mL) and brine (100 mL), dried (Na₂SO₄) and concentrated *in vacuo*. The title compound (1.165 g, 95 %) was obtained as a yellow oil. ¹H NMR (DMSO-*d*₆): δ 1.52 - 1.62 (1H, m), 2.00 - 2.14 (2H, m), 2.87 (1H, br t), 3.07 - 3.17 (1H, m), 3.36 - 3.45 (2H, m), 3.48 - 3.61 (1H, m), 3.81 (1H, dt), 4.72 (1H, t), 7.00 - 7.06 (1H, m), 7.10 (1H, dd), 7.19 (1H, dd); *m/z* (ES⁺) [M+H]⁺ = 280.2.

Intermediate 35e:

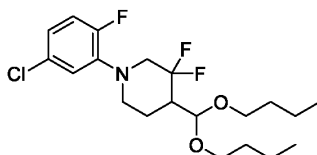
1-(5-Chloro-2-fluoro-phenyl)-3,3-difluoro-piperidine-4-carbaldehyde



[1465] Dess-Martin periodinane (1943 mg, 4.58 mmol) was added to a stirred solution of Intermediate 35d (1165 mg, 4.17 mmol) in DCM (25 mL). The reaction was stirred at r.t. for 1.5 h and quenched with aq. sodium thiosulfate (50 mL), extracted with DCM (2 x 75 mL). The combined organic extracts were washed sat. aq. NaHCO₃ (100 mL) and brine (100 mL), dried (Na₂SO₄) and concentrated *in vacuo*. Purification by FSC (gradient: 0-20% EtOAc in hexanes) gave the title compound (853 mg, 73.7 %) as a yellow oil. ¹H NMR (DMSO-*d*₆): δ 1.85 - 2.04 (2H, m), 2.89 - 3.00 (1H, m), 3.21 - 3.31 (1H, m), 3.32 - 3.44 (2H, m), 3.59 - 3.67 (1H, m), 7.05 (1H, ddd), 7.13 (1H, dd), 7.21 (1H, dd), 9.87 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 278.0.

Intermediate 35f:

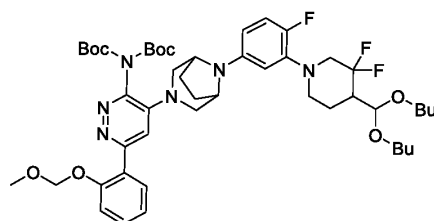
1-(5-Chloro-2-fluoro-phenyl)-4-(dibutoxymethyl)-3,3-difluoro-piperidine



[1466] A mixture of Intermediate 35e (853 mg, 3.07 mmol) and TsOH (58.4 mg, 0.31 mmol) in *n*-butanol (10 mL) was heated at 50 °C for 17 h then concentrated *in vacuo*. Purification by FSC (gradient: 0-10% EtOAc in hexanes) gave the title compound (985 mg, 79 %) as a pale yellow liquid. ¹H NMR (DMSO-*d*₆): δ 0.89 (6H, td), 1.31 - 1.41 (4H, m), 1.44 - 1.56 (4H, m), 1.60 - 1.74 (1H, m), 1.83 - 1.91 (1H, m), 2.27 - 2.39 (1H, m), 2.81 - 2.90 (1H, m), 3.06 - 3.16 (1H, m), 3.40 - 3.50 (3H, m), 3.52 - 3.63 (3H, m), 4.66 (1H, d), 7.01 - 7.04 (1H, m), 7.07 (1H, dd), 7.19 (1H, dd); *m/z* (ES⁺) [M+H]⁺ = 408.4.

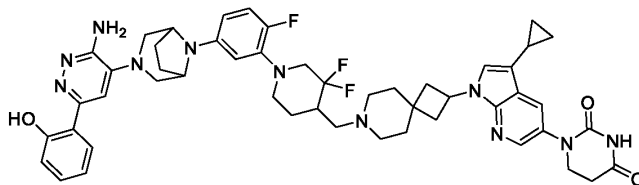
Intermediate 35g:

tert-Butyl *N*-*tert*-butoxycarbonyl-*N*-[4-[8-[3-[4-(dibutoxymethyl)-3,3-difluoro-1-piperidyl]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]-6-[2-(methoxymethoxy)phenyl]pyridazin-3-yl]carbamate



[1467] A vial was charged with Intermediate 35f (938 mg, 2.30 mmol), Intermediate 25d (1245 mg, 2.3 mmol), Cs₂CO₃ (2248 mg, 6.90 mmol), RuPhos Pd G3 (192 mg, 0.23 mmol), and 1,4-dioxane (20 mL) under an N₂ atmosphere. The reaction was heated to 100 °C for 1.5 h. A second portion of RuPhos Pd G3 (192 mg, 0.23 mmol) was added and the reaction was heated to 100 °C for 1.5 h. The reaction was cooled to r.t., filtered through celite®, eluting with DCM and concentrated *in vacuo*. Purification by FSC (gradient: 0-80% EtOAc in hexanes) gave the title compound (516 mg, 24.59 %) as a brown dry film. ¹H NMR (DMSO-*d*₆): δ 0.89 (6H, td), 1.31 - 1.41 (22H, m), 1.46 - 1.55 (4H, m), 1.63 - 1.76 (1H, m), 1.78 - 1.90 (3H, m), 1.92 - 1.99 (2H, m), 2.21 - 2.35 (1H, m), 2.76 (1H, br t), 2.97 - 3.10 (1H, m), 3.22 - 3.28 (5H, m), 3.29 - 3.31 (2H, m), 3.36 - 3.53 (4H, m), 3.59 (2H, ddt), 4.41 (2H, br s), 4.66 (1H, d), 5.22 (2H, s), 6.47 - 6.55 (2H, m), 6.97 (1H, dd), 7.12 - 7.19 (1H, m), 7.25 (1H, d), 7.43 - 7.49 (1H, m), 7.52 (1H, s), 7.72 (1H, dd); *m/z* (ES⁺) [M+H]⁺ = 913.6.

1-[1-[7-[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3-difluoro-4-piperidyl)methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



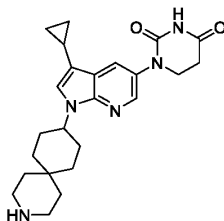
[1468] Intermediate 35g (0.377 g, 0.41 mmol) was added to a stirred solution of sulfuric acid (4.13 mL, 8.26 mmol, 2 M aq.) in THF (4 mL). The mixture was stirred at 50 °C for 2 h. The reaction was quenched with sat. aq. NaHCO₃ (50 mL) and extracted with DCM (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried (Na₂SO₄) and concentrated *in vacuo*. The crude aldehyde was dissolved in DCM (4 mL) and added to a vial containing Intermediate 2c (0.171 g, 0.43 mmol) and Na(OAc)₃BH (0.175 g, 0.83 mmol). The reaction was stirred at r.t. for 20 min. The reaction was quenched with sat. aq. NaHCO₃ (50 mL) and extracted with DCM (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried (Na₂SO₄) and concentrated. Purification by RPC (gradient: 50-100% MeCN in water with 0.1% NH₄OH) gave the title compound (0.030 g, 7.83 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 0.67 - 0.74 (2H, m), 0.83 - 0.91 (2H, m), 1.54 (1H, q), 1.64 - 1.80 (4H, m), 1.88 - 1.99 (3H, m), 2.00 - 2.07 (1H, m), 2.09 - 2.48 (12H, m), 2.73 - 2.86 (3H, m), 3.02 - 3.18 (3H, m), 3.22 - 3.29 (2H, m), 3.33 - 3.37 (1H, m), 3.38 - 3.44 (1H, m), 3.53 - 3.62 (1H, m), 3.82 (2H, t), 4.39 (2H, br s), 5.25 (1H, quin),

5.95 (2H, s), 6.47 - 6.52 (2H, m), 6.85 - 6.90 (2H, m), 6.97 (1H, dd), 7.21 - 7.26 (1H, m), 7.47 (1H, s), 7.56 (1H, s), 7.90 (1H, dd), 7.95 (1H, d), 8.17 (1H, d), 10.38 (1H, s), 14.17 (1H, s); m/z (ES⁺) [M+H]⁺ = 916.5

EXAMPLE 36

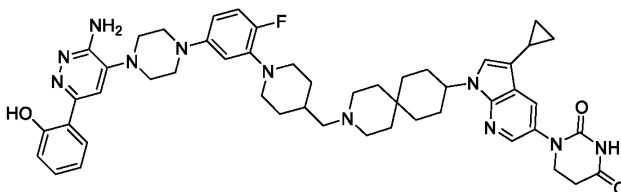
Intermediate 36a:

1-[1-(3-Azaspiro[5.5]undecan-9-yl)-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1469] Sulfuric acid (4.22 mL, 8.43 mmol, 2 M aq.) was added to Intermediate 11b (220 mg, 0.42 mmol) in THF (4.2 mL). The reaction was heated to 50 °C for 2 h. The crude mixture was cooled to 0 °C, quenched with sat. NaHCO₃. The crude mixture was extracted with 20% IPA/DCM (25 mL x 3). The combined organic layers were dried (Na₂SO₄), filtered and concentrated to give title compound (178 mg, 100%) as a white solid which was used in the next step without further purification. m/z (ES⁺) [M+H]⁺ = 422.5.

1-[1-[3-[[1-[5-[4-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]piperazin-1-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



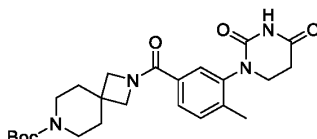
[1470] Formic acid (1 mL) was added to Intermediate 20d (40mg, 0.07 mmol). The reaction was heated at 40 °C for 30 min. The reaction was concentrated under reduced pressure. To the residue was added toluene (3 mL), then concentrated and dried under vacuum. The residue was dissolved in DMF (1 mL), then Intermediate 36a (27.8 mg, 0.07 mmol) was added and the reaction was stirred at r.t. for 20 min. Na(OAc)₃BH (27.9 mg, 0.13 mmol) was added and the reaction mixture was stirred at r.t. for 1 h. The reaction mixture was directly purified by RPC (0-50% MeCN in water with 0.1% FA) to give title compound (15.00 mg, 25.8 %) as a white solid. ¹H NMR (DMSO-*d*₆) δ 1.11-0.88 (1H, m), 0.37 - 0.50 (1H, m), 0.67 (2H, br s), 0.86 (5H, br s), 1.15 - 1.23 (4H, m), 1.39 (2H, br s), 1.60 -1.85 (9H, m), 1.90 - 2.03 (3H, m), 2.15 - 2.24 (2H, m), 2.29 - 2.40 (4H, m), 2.61 - 2.82 (4H, m), 3.25 (5H, br s), 3.82 (2H, br s), 4.51 - 4.71 (1H, m), 6.33 (2H, br s), 6.49 - 6.69 (2H, m), 6.85 - 7.04 (3H, m), 7.25 (1H, br d), 7.46 - 7.63 (2H, m), 7.94 (2H,

br s), 8.16 (1H, br s), 10.37 (1H, br s), 14.06 - 14.35 (1H, m); ^{19}F NMR (DMSO-*d*₆): 133.77; m/z ES⁺ [M+H]⁺ = 882.7.

EXAMPLE 37

Intermediate 37a:

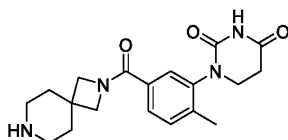
tert-Butyl 2-[3-(2,4-dioxohexahydropyrimidin-1-yl)-4-methyl-benzoyl]-2,7-diazaspiro[3.5]nonane-7-carboxylate



[1471] HATU (536 mg, 1.41 mmol) was added to a stirred solution of 3-(2,4-dioxohexahydropyrimidin-1-yl)-4-methyl-benzoic acid (500 mg, 2.01 mmol) (prepared according to reported patent procedure WO2022/206924 A1) and DIPEA (1.055 mL, 6.04 mmol) in DMF (5 mL). The resulting mixture was stirred at r.t. for 30 min then added *tert*-butyl 2,7-diazaspiro[3.5]nonane-7-carboxylate (684 mg, 3.02 mmol) in DMF (5 mL). The resulting mixture stirred at r.t. for 30 min. The reaction mixture was diluted with DCM:IPA (5:1, 50 mL), and washed sequentially with 0.3% NH₄OH (3 x 50 mL), brine (3 x 50 mL). The organic layer was separated, dried (Na₂SO₄), filtered and concentrated. Purification by RPC (elution gradient: 0 to 60% MeCN in water with 0.1% NH₄HCO₃) gave the title compound (760 mg, 83 %) as a white solid. ^1H NMR (DMSO-*d*₆) δ 1.39 (9H, s), 1.57–1.62 (2H, m), 1.65 (4H, t), 2.23 (3H, s), 2.63–2.74 (1H, m), 2.75–2.84 (1H, m), 3.21 (1H, d), 3.47–3.59 (2H, m), 3.76 (2H, s), 3.79–3.87 (1H, m), 4.05 (2H, s), 7.37 (1H, d), 7.51–7.53 (1H, m), 7.56 (1H, d), 10.39 (1H, s); m/z (ES⁺) [M+H]⁺ = 457.30.

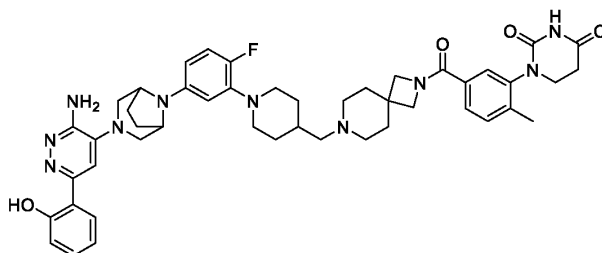
Intermediate 37b:

1-[5-(2,7-Diazaspiro[3.5]nonane-2-carbonyl)-2-methyl-phenyl]hexahydropyrimidine-2,4-dione



[1472] A vial was charged with Intermediate 37a (300 mg, 0.66 mmol), TsOH (187 mg, 0.99 mmol) and MeCN (5 mL). The resulting mixture was stirred at 70 °C for 2 h. The solvent was removed and residue dried under vacuum to afford title compound (300 mg, 74.3 %) as a white solid which was used in the next step directly without further purification. m/z (ES⁺) [M+H]⁺ = 357.1.

1-[5-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-2,7-diazaspiro[3.5]nonane-2-carbonyl]-2-methyl-phenyl]hexahydropyrimidine-2,4-dione

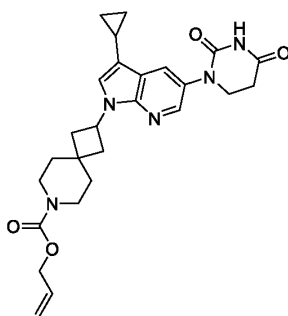


[1473] Formic acid (2 mL) was added to Intermediate 11g (100 mg, 0.18 mmol). The resulting mixture was stirred at 40 °C for 1 h. The solvent was removed under vacuum. To the residue was added Intermediate 37b (65.0 mg, 0.18 mmol) in DCE (2 mL) and NMP (2 mL). The resulting mixture was stirred at 40 °C for 30 min. The reaction cooled to r.t. and Na(OAc)₃BH (193 mg, 0.91 mmol) was added. The resulting mixture was stirred at r.t. for 30 min. The reaction mixture was diluted with DCM (50 mL), and washed sequentially with sat. NaHCO₃ (3 x 20 mL), brine (3 x 20 mL). The organic layer was separated, dried (Na₂SO₄), filtered and evaporated. Purification by RPC (elution gradient: 0-40% MeCN in water with 0.1% FA) gave the title compound (11.00 mg, 6.93 %) as a white solid. ¹H NMR (DMSO-*d*₆) δ 1.13–1.27 (4H, m), 1.57–1.65 (1H, m), 1.69–1.78 (6H, m), 1.91–1.97 (2H, m), 2.1–2.16 (4H, m), 2.23 (3H, s), 2.28 (2H, s), 2.59–2.66 (2H, m), 2.67–2.74 (1H, m), 2.76–2.83 (1H, m), 3.09 (2H, d), 3.24–3.27 (3H, m), 3.49–3.54 (2H, m), 3.73 (2H, s), 3.79–3.88 (1H, m), 4.01 (2H, s), 4.34 (2H, d), 5.95 (2H, s), 6.4–6.49 (2H, m), 6.83–6.95 (3H, m), 7.2–7.25 (1H, m), 7.36 (1H, d), 7.46 (1H, s), 7.51–7.56 (2H, m), 7.89–7.92 (1H, m), 8.21 (1H, s), 10.39 (1H, s). OH proton not observed; ¹⁹F NMR (471 MHz, DMSO) δ -136.42; *m/z* (ES⁺) [M+H]⁺ = 843.6.

EXAMPLE 38

Intermediate 38a:

Allyl 2-[3-cyclopropyl-5-(2,4-dioxohexahydropyrimidin-1-yl)pyrrolo[2,3-*b*]pyridin-1-yl]-7-azaspiro[3.5]nonane-7-carboxylate

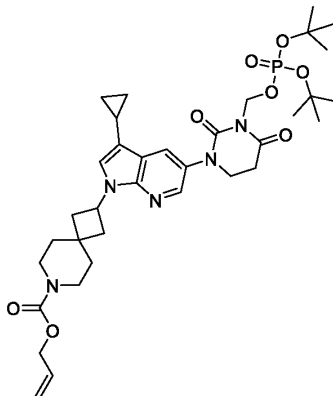


[1474] Allyl chloroformate (0.469 mL, 4.40 mmol) was added to a stirred solution of Intermediate 2c (0.787 g, 2 mmol) and NEt₃ (0.697 mL, 5 mmol) in DCM (20 mL) at 0 °C. The reaction was stirred at 0 °C for 1 h. The reaction was diluted with DCM (20 mL) and washed with sat. NH₄Cl solution, and Na₂CO₃ solution. The organic phase was separated, dried (MgSO₄), filtered and concentrated. The residue was triturated with ether (20 mL) to afford the title compound (0.875 g, 92 %) as an off-white solid. ¹H NMR (DMSO-*d*₆) δ 0.69 (2H, s), 0.84 - 0.88 (2H, m), 1.66 (4H, dt), 1.85 - 1.99 (1H, m), 2.22 - 2.30 (2H, m), 2.34

- 2.41 (2H, m), 2.75 (2H, t), 3.30 - 3.34 (2H, m), 3.40 - 3.46 (2H, m), 3.80 (2H, t), 4.52 (2H, d), 5.18 (1H, dd), 5.23 - 5.30 (2H, m), 5.83 - 6.01 (1H, m), 7.55 (1H, s), 7.94 (1H, d), 8.16 (1H, d), 10.36 (1H, s); m/z (ES⁺) [M+H]⁺ = 478.2.

Intermediate 38b:

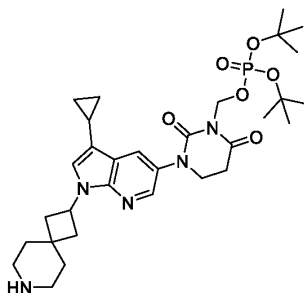
Allyl 2-[3-cyclopropyl-5-[3-(*di**tert*-butoxyphosphoryloxymethyl)-2,4-dioxo-hexahydropyrimidin-1-yl]pyrrolo[2,3-*b*]pyridin-1-yl]-7-azaspiro[3.5]nonane-7-carboxylate



[1475] LiHMDS (1.7 ml, 1.7 mmol) was added to a stirred solution of Intermediate 38a (0.67 g, 1.40 mmol) and sodium iodide (0.210 g, 1.40 mmol) in THF (10 ml) at 0°C. Then di-*tert*-butyl (chloromethyl) phosphate (0.726 g, 2.81 mmol) was added in one portion, and the reaction was stirred at 50 °C for 30 min. The reaction was cooled to r.t. and diluted with EtOAc (40 mL) and sat. NH₄Cl (20 mL) solution. The organic phase was separated, dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification by FSC (gradient: 10-50% EtOAc in hexane and 0-10% MeOH in EtOAc) gave the title compound (0.540 g, 55.0 %) as a white solid. ¹H NMR (DMSO-*d*₆) δ 0.65 - 0.70 (2H, m), 0.83 - 0.89 (2H, m), 1.40 - 1.43 (20H, m), 1.62 - 1.71 (4H, m), 1.89 - 1.96 (1H, m), 2.22 - 2.30 (2H, m), 2.35 - 2.42 (2H, m), 2.97 (2H, s), 3.37 - 3.47 (2H, m), 3.82 (2H, s), 4.52 (2H, d), 5.16 - 5.21 (1H, m), 5.23 - 5.32 (2H, m), 5.49 (2H, br d), 5.87 - 6.03 (1H, m), 7.59 (1H, s), 7.97 (1H, d), 8.18 (1H, d); m/z (ES⁺) [2M+2H]⁺ = 1400.

Intermediate 38c:

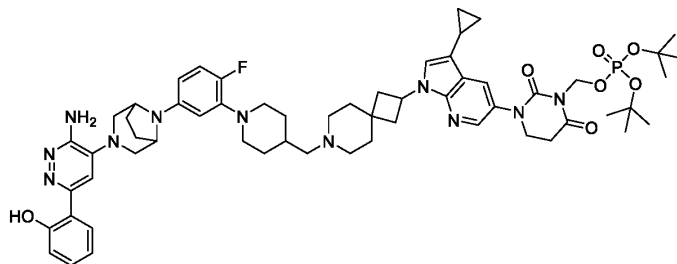
[3-[1-(7-Azaspiro[3.5]nonan-2-yl)-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]-2,6-dioxo-hexahydropyrimidin-1-yl]methyl di-*tert*-butyl phosphate



[1476] A mixture of Intermediate 38b (540 mg, 0.77 mmol), 1,3-dimethylhexahydropyrimidine-2,4,6-trione (120 mg, 0.77 mmol), and tetrakis(triphenylphosphine)-palladium(0) (44.6 mg, 0.04 mmol) in DCM (7.7 mL) was stirred under N₂ for 20 min. The solvent was removed *in vacuo* to give the title compound (475 mg, 100 %) as a yellow solid, which was used for the next step without further purification. *m/z* (ES⁺) [M+H]⁺ = 616.6.

Intermediate 38d:

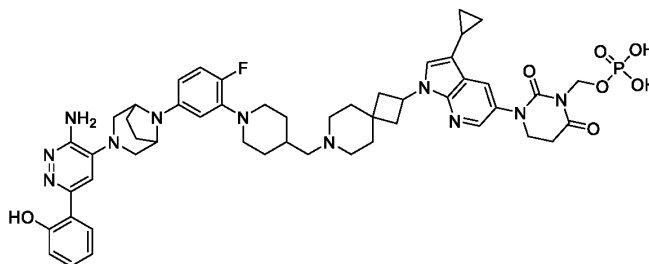
[3-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]-2,6-dioxo-hexahydropyrimidin-1-yl]methyl ditert-butyl phosphate



[1477] A mixture of Intermediate 11g (443 mg, 0.7 mmol) and TsOH (146 mg, 0.77 mmol) in acetone (6 mL) and water (0.6 mL) was heated at 80 °C in a microwave for 30 min. The solvent was removed, and the residue was partitioned between EtOAc (50 mL) and sat. NaHCO₃ solution. The organic phase was dried (MgSO₄), filtered and concentrated. To the residue was added Intermediate 38c (600 mg, 0.77 mmol) and DMF (5 mL). The reaction was stirred at r.t. for 20 min then Na(OAc)₃BH (445 mg, 2.10 mmol) was added. The reaction mixture was stirred at r.t for 30 min. The reaction was diluted with EtOAc (50 mL), washed with sat. NaHCO₃ solution, and 10% lithium chloride solution. The organic layer was separated, dried (MgSO₄), filtered and concentrated. Purification by FSC (elution gradient: 20-50% EtOAc in hexanes then 10% MeOH in EtOAc) gave the title compound (270 mg, 35.0 %) as a colorless foam. ¹H NMR (DMSO-*d*₆) δ 0.68 (2H, dd), 0.83 - 0.88 (2H, m), 1.36 - 1.43 (18H, m), 1.57 - 1.65 (1H, m), 1.65 - 1.73 (4H, m), 1.73 - 1.80 (2H, m), 1.86 - 1.97 (3H, m), 2.06 - 2.15 (4H, m), 2.17 - 2.29 (4H, m), 2.29 - 2.37 (4H, m), 2.59 - 2.67 (2H, m), 2.97 (2H, t), 3.09 (2H, br d), 3.19 - 3.27 (4H, m), 3.33 - 3.39 (2H, m), 3.82 (2H, t), 4.33 (2H, br s), 5.21 - 5.29 (1H, m), 5.49 (2H, d), 5.92 (2H, s), 6.38 - 6.51 (2H, m), 6.81 - 6.95 (3H, m), 7.17 - 7.24 (1H, m), 7.45 (1H, s), 7.57 (1H, s), 7.87 - 7.92 (1H, m), 7.94 - 7.97 (1H, m), 8.17 (1H, d), OH proton not observed; *m/z* (ES⁺) [M+H]⁺ = 1103.

[3-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]-2,6-dioxo-hexahydropyrimidin-1-yl]methyl ditert-butyl phosphate

2,6-dioxo-hexahydropyrimidin-1-yl)methyl dihydrogen phosphate

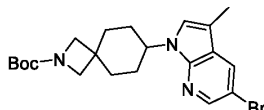


[1478] Intermediate 38d (230 mg, 0.21 mmol) in DCM (4 mL) was added TFA (0.8 mL, 10.43 mmol). The reaction was stirred at r.t. for 2 h then the solvent was removed under reduced pressure. Purification by RPC (elution gradient: 20-50% MeCN in water with 0.1% NH₄OH) gave the title compound (151 mg, 73.1 %) as a white solid. ¹H NMR (CD₂Cl₂): δ 0.66 (2H, br d), 0.80 - 0.90 (2H, m), 1.22 - 1.35 (2H, m), 1.79 - 1.85 (4H, m), 1.85 - 2.00 (4H, m), 2.01 - 2.14 (2H, m), 2.14 - 2.21 (2H, m), 2.25 - 2.37 (2H, m), 2.63 - 2.68 (2H, m), 2.86 - 2.93 (2H, m), 3.07 - 3.11 (2H, m), 3.17 - 3.28 (10H, m), 3.76 - 3.82 (2H, m), 4.30 - 4.38 (2H, m), 5.10 - 5.24 (1H, m), 5.41 (2H, br d), 5.91 (2H, s), 6.38 - 6.50 (2H, m), 6.82 - 6.96 (3H, m), 7.19 - 7.23 (1H, m), 7.43 - 7.48 (1H, m), 7.48 - 7.54 (1H, m), 7.88 (1H, d), 7.92 - 7.99 (1H, m), 8.16 (1H, d), OH and NH₂ protons not observed; *m/z* (ES⁺) [M+H]⁺ = 990.7

EXAMPLE 39

Intermediate 39a:

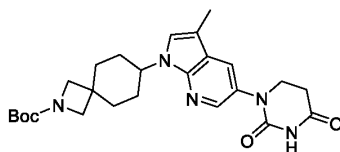
tert-Butyl 7-(5-bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-2-azaspiro[3.5]nonane-2-carboxylate



[1479] Prepared in an analogous manner to Intermediate 4a starting from 5-bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (0.700 g, 3.31 mmol) and *tert*-butyl 7-hydroxy-2-azaspiro[3.5]nonane-2-carboxylate (1 g, 4.14 mmol), and 2-(tributyl-1*l*-phosphaneylidene)acetonitrile (1.303 mL, 4.97 mmol). Purification by FSC (elution gradient: 0 - 20% EtOAc in hexanes) and RPC (elution gradient: 0-50% MeCN in water with 0.2% NH₄OH) to afford title compound (0.514 g, 35.7 %) as a white solid. ¹H NMR (CD₂Cl₂) δ 1.47 (9H, s), 1.71 - 1.81 (4H, m), 1.99 - 2.13 (4H, m), 2.30 (3H, s), 3.64 (2H, s), 3.76 (2H, s), 4.64 - 4.73 (1H, m), 7.10 (1H, s), 8.00 (1H, d), 8.29 (1H, d); *m/z* (ES⁺) [M+2H]⁺ = 436.3.

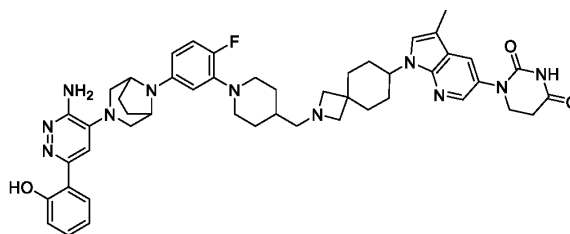
Intermediate 39b:

tert-Butyl 7-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-2-azaspiro[3.5]nonane-2-carboxylate



[1480] A vial was charged with *t*BuBrettPhos Pd G3 (0.049 g, 0.06 mmol), di-*tert*-butyl(2',4',6'-triisopropyl-3,6-dimethoxy-[1,1'-biphenyl]-2-yl)phosphane (0.028 g, 0.06 mmol), hexahydropyrimidine-2,4-dione (0.131 g, 1.15 mmol), Intermediate 39a (0.25 g, 0.58 mmol) and K₃PO₄ (0.305 g, 1.44 mmol). The solids were evacuated and backfilled with N₂ and 1,4-dioxane (2.88 mL) was added. The mixture was stirred at 95 °C for 19 h. The reaction mixture was filtered through Celite®, washing with EtOAc and MeOH. The filtrate was concentrated. Purification by FSC (elution gradient: 0- 100% EtOAc in hexanes) gave the title compound (0.149 g, 55.4 %) as a tan solid. ¹H NMR (CD₂Cl₂) δ 1.47 (9H, s), 1.72 - 1.84 (4H, m), 2.01 - 2.14 (4H, m), 2.33 (3H, d), 2.89 (2H, t), 3.64 (2H, s), 3.77 (2H, s), 3.91 (2H, t), 4.67 - 4.79 (1H, m), 7.15 (1H, s), 7.68 (1H, s), 7.78 (1H, d), 8.21 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 468.5.

1-[1-[2-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-2-azaspiro[3.5]nonan-7-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

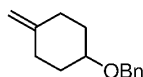


[1481] A solution of sulfuric acid (0.5 mL, 1.01 mmol, 2.0 M aq.) was added to a solution Intermediate 11g in THF (0.5 mL) and heated at 40 °C for 1 h and cooled to r.t. In a separate reaction vessel, a solution of sulfuric acid (0.5 mL, 1.01 mmol, 2 M aq.) was added to a suspension of Intermediate 39b (28.4 mg, 0.06 mmol) in THF (0.5 mL) at r.t. The reaction solution was stirred at 50 °C for 2 h. The reaction contents from both deprotections were combined, neutralized by addition of sat aq. NaHCO₃ while stirring at 0 °C, and diluted with DCM (20 mL) and extracted with DCM/IPA (4:1) (2x) The combined organic phase was dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The resulting solids were dissolved in DCM (1 mL) and stirred at r.t for 2 mins. Na(OAc)₃BH (12.86 mg, 0.06 mmol) was added while the mixture stirred at 0 °C for 5 min and r.t. 1h, quenched with sat. aq. NaHCO₃; diluted with water and DCM; and the layers were separated. The aqueous layer was extracted with DCM/IPA (4:1) (2 x 25 mL). The combined organic layers were dried (Na₂SO₄), filtered and concentrated. Purification by FSC (elution gradient: 0 - 50% MeOH in DCM) and lyophilization gave the title compound (30.3 mg, 70.2 %) as a white solid. ¹H NMR (DMSO-*d*₆) δ 1.22 - 1.35 (2H, m), 1.46 (1H, br s), 1.57 - 1.70 (2H, m), 1.73 - 1.87 (6H, m), 1.90 - 1.99 (2H, m), 2.00 - 2.09 (2H, m), 2.09 - 2.18 (2H, m), 2.25 (3H, s), 2.48 (2H, br s), 2.62 (2H, br t), 2.76 (2H, t), 3.05 (2H, br s), 3.11 (2H, br d), 3.20 (2H, br s), 3.23 - 3.29 (2H, m), 3.35 (2H, br s), 3.81 (2H, t), 4.35 (2H, br s), 4.54 - 4.65 (1H, m), 5.94 (2H, s), 6.40 - 6.52 (2H, m), 6.82 - 6.97 (3H, m), 7.23 (1H, t), 7.46 (2H, d), 7.87 (1H, d), 7.91 (1H, d), 8.17 (1H, d), 10.38 (1H, s), 14.17 (1H, br s); ¹⁹F NMR (DMSO-*d*₆) - 136.46; *m/z* (ES⁺) [M+H]⁺ = 854.7.

Example 40

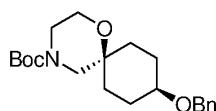
Intermediate 40a:

(4-Methylenecyclohexoxy)methylbenzene



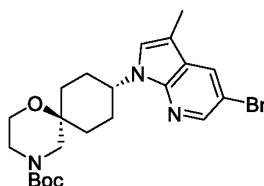
[1482] KO^tBu (10.99 g, 97.91 mmol) was added slowly to methyltriphenylphosphonium iodide (39.6 g, 97.91 mmol) in THF (200 mL). The resulting mixture was stirred at r.t. for 1 h. Then 4-(benzyloxy)cyclohexan-1-one (10 g, 48.96 mmol) was added in dropwise in THF (100 mL) and stirred at r.t. for 16 h. The reaction mixture was filtered and filtrate was concentrated. Purification by RPC (elution gradient: 2 to 100% MeCN in water with 0.1% NH₃HCO₃) to afford the title compound (8.00 g, 81 %) as a yellow oil. ¹H NMR (DMSO-d₆): δ 1.42 – 1.57 (2H, m), 1.78 – 1.92 (2H, m), 1.94 – 2.09 (2H, m), 2.21 – 2.35 (2H, m), 3.49 – 3.59 (1H, m), 4.51 (2H, s), 4.60 – 4.66 (2H, m), 7.20 – 7.40 (5H, m).

Intermediate 40b:

tert-Butyl (6*s*,9*s*)-9-benzyloxy-1-oxa-4-azaspiro[5.5]undecane-4-carboxylate

[1483] NIS (5.56 g, 24.72 mmol) was added to Intermediate 40a (5 g, 24.72 mmol) and *tert*-butyl (2-hydroxyethyl)carbamate (3.98 g, 24.72 mmol) in MeCN (100 mL). The resulting mixture was stirred at 70 °C for 2 h. The reaction mixture was filtered and filtrate was evaporated to afford crude product and used in the next step directly without further purification. NaH (9.89 g, 247.16 mmol) was added to the crude product in DMF (40 mL). The resulting mixture was stirred at r.t. for 1 h. The reaction mixture was poured into sat. aq. NH₄Cl (150 mL), extracted with EtOAc (3 x 50 mL), the organic layer was dried over Na₂SO₄, filtered and evaporated. Purification by FSC (elution gradient 0 to 80% EtOAc in petroleum ether) gave the title compound (0.600 g, 40.8 %) as a yellow gum. ¹H NMR (CDCl₃): δ 1.20 – 1.32 (2H, m), 1.45 (9H, s), 1.62 – 1.72 (2H, m), 1.76 – 1.84 (2H, m), 1.90 – 2.00 (2H, m), 3.21 (2H, s), 3.35 – 3.46 (3H, m), 3.65 (2H, s), 4.55 (2H, s), 7.23 – 7.29 (1H, m), 7.30 – 7.39 (4H, m); *m/z* (ES⁺) [M-*t*Bu+H]⁺ = 306.

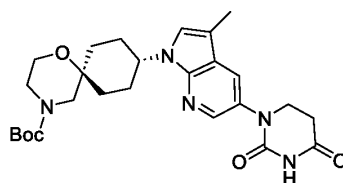
Intermediate 40c:

tert-Butyl (6*r*,9*r*)-9-(5-bromo-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl)-1-oxa-4-azaspiro[5.5]undecane-4-carboxylate

[1484] DDQ (628 mg, 2.77 mmol) was added to a solution of Intermediate 40b (500 mg, 1.38 mmol) in DCM (10 mL). The resulting mixture was stirred at r.t for 2 h. The reaction mixture was poured into sat. aq. Na₂CO₃ (50 mL), extracted with DCM (3 x 20 mL), the organic layer was dried over Na₂SO₄, filtered and evaporated to afford crude product. The product was used in the next step directly without further purification. (Tributylphosphoranylidene)acetonitrile (401 mg, 1.66 mmol) was added to the crude product and 5-bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (350 mg, 1.66 mmol) in toluene (10 mL) under nitrogen. The resulting mixture was stirred at 100 °C for 16 h then cooled to r.t. and concentrated. Purification by FSC (elution gradient: 0 to 70% EtOAc in petroleum ether) gave the title compound (250 mg, 38.9 %) as a yellow gum. ¹H NMR (DMSO-*d*₆): δ 1.40 (9H, s), 1.44 – 1.51 (2H, m), 1.79 – 2.01 (6H, m), 2.23 (3H, s), 3.47 – 3.63 (7H, m), 7.32 – 7.62 (1H, m), 8.16 (1H, d), 8.24 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 464.

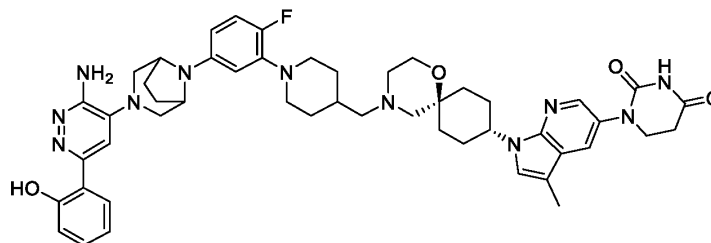
Intermediate 40d:

tert-Butyl (6*r*,9*r*)-9-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-1-oxa-4-azaspiro[5.5]undecane-4-carboxylate



[1485] GPhos Pd G6 TES (40.8 mg, 0.04 mmol) was added to Intermediate 40c (200 mg, 0.43 mmol), dihydrouracil (197 mg, 1.72 mmol), EPhos (23.03 mg, 0.04 mmol) and Cs₂CO₃ (421 mg, 1.29 mmol) in 1,4-dioxane (4 mL) under nitrogen. The resulting mixture was stirred at 100 °C for 16 h. The reaction mixture was poured into sat. aq. NH₄Cl (20 mL), extracted with EtOAc (3 x 10 mL), the organic layer was separated, dried over Na₂SO₄, filtered and evaporated. Purification by FCS (elution gradient: 0 to 40% EtOAc in petroleum ether, then 0 to 10% MeOH in DCM) gave the title compound (94 mg, 43.9 %) as a yellow solid. ¹H NMR (DMSO-*d*₆): δ 1.41 (9H, s), 1.46 – 1.59 (4H, m), 1.86 (2H, d), 1.98 (2H, d), 2.24 (3H, s), 2.73 – 2.78 (2H, m), 3.49 – 3.67 (6H, m), 3.77 – 3.83 (2H, m), 4.63 (1H, s), 7.38 (1H, s), 7.87 (1H, d), 8.16 (1H, s), 10.38 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 498.

1-[1-[(6*r*,9*r*)-4-[[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl]methyl]-1-oxa-4-azaspiro[5.5]undecan-9-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

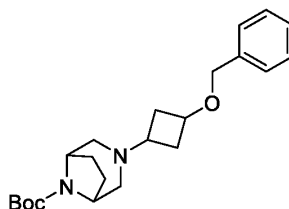


[1486] p-Toluenesulfonic acid monohydrate (30.6 mg, 0.16 mmol) was added to Intermediate 40d (80 mg, 0.16 mmol) in MeCN (1.5 mL). The resulting mixture was stirred at 80 °C for 16 h. The reaction mixture was evaporated and the crude product was used in the next step directly without further purification. Formic acid (3 mL) was added to Intermediate 11g (142 mg, 0.23 mmol) and stirred at 40 °C for 20 min. The reaction mixture was evaporated. Then quenched with sat. aq. Na₂CO₃ (10 mL), extracted with EtOAc (3 x 5 mL), the organic layer was dried over Na₂SO₄, filtered and evaporated to afford crude product. Both crude products were dissolved in DCE (1.00 mL) and NMP (1.00 mL). The resulting mixture was stirred at 40 °C for 2 h. Then sodium triacetoxyhydroborate (136 mg, 0.64 mmol) was added and stirred at r.t. for 2 h. The crude product was purified by RPC (elution gradient: 0-77% ACN in water with 10 mM NH₄HCO₃+ 0.05% NH₃H₂O) to afford title compound (32.0 mg, 22.86 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.23 – 1.33 (2H, m), 1.42 – 1.52 (2H, m), 1.74 – 1.86 (5H, m), 1.89 – 1.98 (4H, m), 2.07 – 2.13 (2H, m), 2.14 – 2.28 (8H, m), 2.30 – 2.39 (3H, m), 2.54 (1H, s), 2.63 – 2.69 (2H, m), 2.71 – 2.76 (2H, m), 3.08 (2H, d), 3.24 (2H, d), 3.36 – 3.38 (1H, m), 3.61 – 3.69 (2H, m), 3.75 – 3.82 (2H, m), 4.33 (2H, s), 4.61 – 4.70 (1H, m), 5.93 (2H, s), 6.38 – 6.43 (1H, m), 6.44 – 6.49 (1H, m), 6.81 – 6.95 (3H, m), 7.18 – 7.25 (1H, m), 7.45 (1H, s), 7.55 (1H, s), 7.85 (1H, d), 7.87 – 7.91 (1H, m), 8.17 (1H, d), 10.38 (1H, s), 14.17 (1H, s); ¹⁹F NMR (DMSO-*d*₆) δ -136.33; *m/z* (ES⁺), [M+H]⁺ = 884.5.

Example 41

Intermediate 41a:

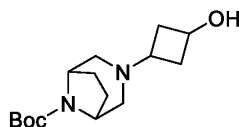
tert-Butyl 3-(3-benzyloxycyclobutyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[1487] 3-(Benzyloxy)cyclobutan-1-one (6g, 34.05 mmol) was added to *tert*-butyl 3,8-diazabicyclo[3.2.1]octane-8-carboxylate (7.95 g, 37.45 mmol) in DCE (50 mL) and NMP (50 mL) at r.t.. The resulting mixture was stirred at 40 °C for 30 min. then sodium triacetoxyborohydride (28.9 g, 136.20 mmol) was added. The resulting mixture was stirred at r.t. for 2 h. The reaction mixture was diluted with EtOAc (150 mL), and washed sequentially with sat. aq. NaHCO₃ (75 mL x 2) and sat. brine (75 mL). The organic layer was separated, dried over Na₂SO₄, filtered and evaporated. The crude solid was triturated with hexane, the solids were collected by filtration and dried under vacuum to give title compound (8.00 g, 63.1 %) as a yellow solid. ¹H NMR (DMSO-*d*₆): δ 1.40 (9H, s), 1.60 – 1.67 (2H, m), 1.69 – 1.76 (3H, m), 1.87 – 1.94 (2H, m), 2.16 – 2.20 (1H, m), 2.24 – 2.36 (3H, m), 2.55 (1H, d), 2.70 (1H, s), 3.67 – 3.77 (1H, m), 4.03 (2H, s), 4.35 (2H, s), 7.25 – 7.38 (5H, m); *m/z* (ES⁺), [M+H]⁺ = 373.3.

Intermediate 41b:

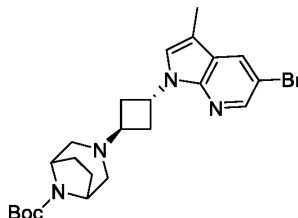
tert-Butyl 3-(3-hydroxycyclobutyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[1488] Palladium hydroxide on carbon powder (1.508 g, 2.15 mmol) was added to Intermediate 41a (8 g, 21.48 mmol) in MeOH (300 mL) under hydrogen. The resulting mixture was stirred at r.t. for 16 h. The reaction mixture was filtered through celite®. The filtrate was evaporated to dryness to afford the title compound (6.00 g, 99 %) as a yellow solid. ¹H NMR (CDCl₃): δ 1.44 (9H, s), 1.64 – 1.71 (2H, m), 1.75 – 1.83 (4H, m), 1.96 – 2.05 (2H, m), 2.20 – 2.27 (1H, m), 2.36 (1H, t), 2.39 – 2.46 (2H, m), 2.55 – 2.58 (2H, m), 3.94 – 4.01 (1H, m), 4.13 (2H, d); *m/z* (ES⁺) [M+H]⁺ = 283.1.

Intermediate 41c:

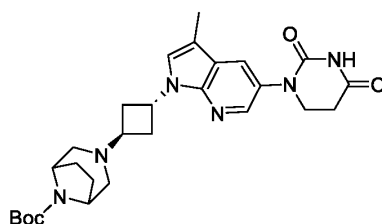
tert-Butyl 3-[(1*r*,3*r*)-3-(5-bromo-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl)cyclobutyl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[1489] Prepared in an analogous manner to Intermediate 4a from Intermediate 41b (5 g, 17.71 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in petroleum ether) gave the title compound as a mixture of *cis* (minor) and *trans* isomers (2.5 g). To remove minor isomer, the material further purified by SFC (Column: CHIRALPAK ID, 3x25 cm, 5 μm. Mobile Phase A: CO₂, Mobile Phase B: (1:1) IPA/(ACN with 0.1% 2M NH₃ in MeOH); Flow rate: 100 mL/min; Gradient: isocratic 45% B). Fractions containing the pure *trans* isomer were evaporated to dryness to a gave the title compound (2.0 g, 35.6 %). ¹H NMR (DMSO-*d*₆): δ 1.41 (9H, s), 1.54 – 1.63 (2H, m), 1.73– 1.78 (2H, m), 1.82– 1.86 (2H, m), 1.95 (1H, d), 2.26 (3H, d), 2.39 – 2.47 (3H, m), 2.79 (2H, d), 2.99 – 3.06 (1H, m), 4.06– 4.10 (2H, m), 5.21 – 5.29 (1H, m), 7.67 (1H, d), 8.17 (1H, d), 8.27 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 475.3.

Intermediate 41d:

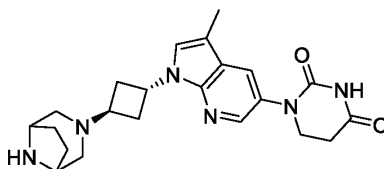
tert-Butyl 3-[(1*r*,3*r*)-3-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]cyclobutyl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[1490] Prepared in an analogous manner to Intermediate 4b from Intermediate 41c (0.500 g, 46.7 %). Purification by FSC (elution gradient: 0 to 50% EtOAc in petroleum ether then 0 to 20% MeOH in DCM) gave the title compound (0.500 g, 46.7 %) as a yellow solid. ¹H NMR (DMSO-*d*₆): δ 1.42 (9H, s), 1.75 – 1.78 (1H, m), 1.84 – 1.87 (2H, m), 1.93 – 2.00 (2H, m), 2.28 (3H, d), 2.43 – 2.49 (4H, m), 2.72 – 2.82 (4H, m), 3.00 – 3.08 (1H, m), 3.16 – 3.23 (1H, m), 3.81 (2H, t), 4.09 (2H, s), 5.22 – 5.34 (1H, m), 7.63 (1H, d), 7.89 (1H, d), 8.18 (1H, d), 10.40 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 509.6.

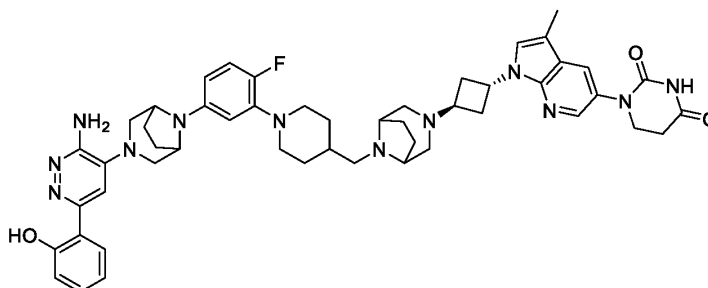
Intermediate 41e:

1-[1-[(1*r*,3*r*)-3-(3,8-Diazabicyclo[3.2.1]octan-3-yl)cyclobutyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1491] Prepared in an analogous manner to Intermediate 1i from Intermediate 41d (500 mg, 0.98 mmol). The crude product was purified by RPC (elution gradient: 5 to 60% MeCN in water with 0.1% NH₄HCO₃). Pure fractions were evaporated to dryness to afford the title compound (300 mg, 74.7 %) as a yellow solid. ¹H NMR (DMSO-*d*₆): δ 1.54 – 1.66 (2H, m), 1.71 – 1.82 (2H, m), 1.91 (2H, d), 2.27 (3H, s), 2.35 – 2.47 (4H, m), 2.67 – 2.79 (4H, m), 2.95 – 3.04 (1H, m), 3.80 (2H, t), 5.21 – 5.31 (1H, m), 7.63 (1H, s), 7.88 (1H, d), 8.17 (1H, d), 10.21 – 10.56 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 409.2.

1-[1-[(1*r*,3*r*)-3-[8-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)206yridine206e-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]cyclobutyl]-3-methyl-pyrrolo[2,3-*b*]206yridine-5-yl]hexahydropyrimidine-2,4-dione



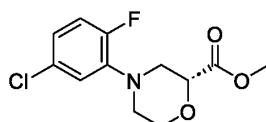
[1492] Formic acid was added to Intermediate 11g (81 mg, 0.15 mmol) at r.t. The resulting mixture was stirred at 40 °C for 1 h. The solvent was removed under reduced pressure. To the residue was added

Intermediate 41e (60 mg, 0.15 mmol) in DCE (3.00 mL) and NMP (3.00 mL) then sodium triacetoxyborohydride (187 mg, 0.88 mmol) was added.. The resulting mixture was stirred at r.t. for 2 h. The reaction mixture was diluted with EtOAc (20 mL), and washed sequentially with sat. aq. NaHCO₃ (10 mL x 2) and sat. brine (10 mL x 2). The organic layer was dried over Na₂SO₄, filtered and evaporated. Purification by RPC (elution gradient: 0-70% CH₃CN in water with 0.1% NH₄HCO₃+0.05% NH₃H₂O) gave the title compound (20.0 mg, 15.21 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.19 – 1.23 (1H, m, 1.25 – 1.31 (1H, m), 1.50 (1H, s), 1.74 (2H, d), 1.75 – 1.80 (2H, m), 1.81 – 1.86 (2H, m), 1.92 – 1.98 (2H, m), 2.04 (2H, d), 2.13 (2H, t), 2.21 (2H, d), 2.25 – 2.29 (3H, m), 2.38 – 2.48 (4H, m), 2.60 – 2.68 (2H, m), 2.70 (2H, d), 2.76 (2H, t), 3.05 (1H, d), 3.08 – 3.15 (4H, m), 3.26 (2H, d), 3.36 – 3.39 (2H, m), 3.81 (2H, t), 4.31 – 4.36 (2H, m), 5.23 – 5.32 (1H, m), 5.95 (2H, s), 6.39 – 6.55 (2H, m), 6.83 – 6.99 (3H, m), 7.20 – 7.27 (1H, m), 7.47 (1H, s), 7.62 – 7.65 (1H, m), 7.87 – 7.94 (2H, m), 8.18 (1H, d), 10.39 (1H, s), 14.18 (1H, s); ¹⁹F NMR (DMSO-*d*₆): δ -136.379; *m/z* (ES⁺), [M+H]⁺ = 895.7.

Example 42

Intermediate 42a:

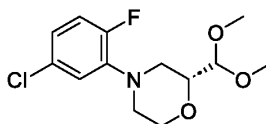
Methyl (2*R*)-4-(5-chloro-2-fluoro-phenyl)morpholine-2-carboxylate



[1493] Methyl (*R*)-morpholine-2-carboxylate, HCl (0.954 g, 5.25 mmol) was added to mixture of 2-bromo-4-chloro-1-fluorobenzene (1 g, 4.77 mmol), RuPhos Pd G3 (0.399 g, 0.48 mmol), RuPhos (0.223 g, 0.48 mmol) and Cs₂CO₃ (6.22 g, 19.10 mmol) in 1,4-dioxane (20 mL) under nitrogen. The resulting mixture was stirred at 100 °C for 16 h. The reaction mixture was poured into water (150 mL), extracted with EtOAc (3 x 50 mL), the organic layer was dried over Na₂SO₄, filtered and evaporated. Purification by FSC (elution gradient: 0 to 20% EtOAc in petroleum ether) gave the title compound (1.700 g, 65.4 %) as a yellow solid. ¹H NMR (DMSO-*d*₆): δ 2.91 – 2.99 (1H, m), 3.06 – 3.15 (2H, m), 3.32 – 3.38 (1H, m), 3.69 (3H, s), 3.70 – 3.76 (1H, m), 3.96 – 4.05 (1H, m), 4.37 – 4.45 (1H, m), 7.01 – 7.09 (2H, m), 7.15 – 7.24 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 274.

Intermediate 42b:

(2*R*)-4-(5-Chloro-2-fluoro-phenyl)-2-(dimethoxymethyl)morpholine

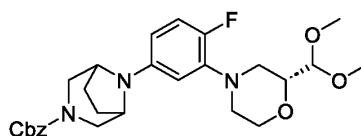


[1494] DIBAL-H solution (9.32 mL, 9.32 mmol, 1M in DCM) was added dropwise to Intermediate 42a (1.7 g, 6.21 mmol) in DCM (40 mL) at -60°C under N₂. The resulting mixture was stirred at -60°C for 30 mins. The reaction mixture was quenched with sat. aq. NH₄Cl (200 mL), extracted with DCM (3 x 50 mL), the organic layer was dried over Na₂SO₄, filtered and evaporated. The crude product was dissolved in

MeOH (40.0 mL) then trimethyl orthoformate (1.977 g, 18.63 mmol) and *p*-TsOH·H₂O (0.118 g, 0.62 mmol) were added. The resulting mixture was stirred at 40 °C for 2 h and quenched with water (5 mL), extracted with EtOAc (3 x 60 mL), the organic layer was dried over Na₂SO₄, filtered and evaporated. Purification by FSC (elution gradient: 0 to 30% EtOAc in petroleum ether) gave the title compound (1.380 g, 77 %) as a yellow solid. ¹H NMR (DMSO-*d*₆): δ 2.58 – 2.67 (1H, m), 2.76 – 2.86 (1H, m), 3.12 – 3.19 (1H, m), 3.24 – 3.30 (1H, m), 3.32 (3H, s), 3.32 (3H, s), 3.60 – 3.70 (2H, m), 3.88 – 3.95 (1H, m), 4.31 (1H, d), 6.99 – 7.05 (2H, m), 7.15 – 7.23 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 290.

Intermediate 42c:

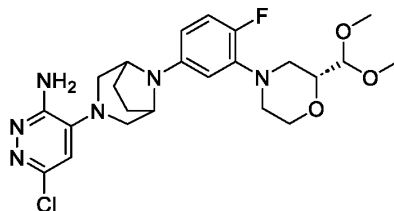
Benzyl 8-[3-[(2*R*)-2-(dimethoxymethyl)morpholin-4-yl]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



[1495] To a vial was added RuPhos Pd G3 (188 mg, 0.22 mmol), RuPhos (105 mg, 0.22 mmol), Intermediate 42b (650 mg, 2.24 mmol), benzyl 3,8-diazabicyclo[3.2.1]octane-3-carboxylate, HCl (698 mg, 2.47 mmol) and Cs₂CO₃ (2924 mg, 8.97 mmol) in 1,4-dioxane (13 mL) under nitrogen. The resulting mixture was stirred at 80 °C for 16 h. The reaction mixture was filtered and poured into water (100 mL), extracted with DCM (3 x 25 mL), the organic layer was dried over Na₂SO₄, filtered and evaporated. Purification by FSC (elution gradient: 0 to 30% EtOAc in petroleum ether and 0 to 6% MeOH in DCM) gave the title compound (2.0 g, 89 %) as a brown gum. ¹H NMR (DMSO-*d*₆): δ 1.60 – 1.68 (2H, m), 1.80 – 1.95 (2H, m), 2.53 – 2.62 (1H, m), 2.75 – 2.85 (1H, m), 3.05 – 3.16 (2H, m), 3.19 – 3.28 (2H, m), 3.31 (6H, s), 3.32 – 3.33 (2H, m), 3.54 – 3.69 (4H, m), 3.87 – 3.95 (1H, m), 4.23 (2H, d), 5.07 (1H, d), 6.39 – 6.42 (1H, m), 6.42 – 6.45 (1H, m), 6.90 – 6.99 (1H, m), 7.28 – 7.40 (5H, m); *m/z* (ES⁺) [M+H]⁺ = 500.

Intermediate 42d:

6-Chloro-4-[8-[3-[(2*R*)-2-(dimethoxymethyl)morpholin-4-yl]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-amine

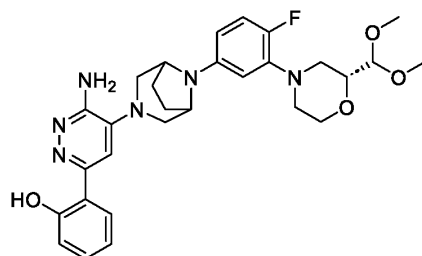


[1496] Pd/C (0.160 g, 0.15 mmol) was added to Intermediate 42c (1.5 g, 3.00 mmol) in MeOH (30 mL) under hydrogen. The resulting mixture was stirred at r.t. for 16 h. The catalyst was filtered off and filtrate evaporated to afford crude product. To the crude product was added DIPEA (1.573 mL, 9.01 mmol),

4-bromo-6-chloropyridazin-3-amine (0.688 g, 3.30 mmol) and DMSO (20 mL). The resulting mixture was stirred at 100 °C for 16 h. The reaction mixture was poured into water (100 mL), extracted with EtOAc (3 x 50 mL), the organic layer was dried over Na₂SO₄, filtered and evaporated. Purification by FSC (elution gradient: 0 to 80% EtOAc in petroleum ether) gave the title compound (0.880 g, 59.5 %) as a yellow gum. ¹H NMR (DMSO-*d*₆): δ 1.85 – 1.95 (2H, m), 2.08 (2H, d), 2.57 – 2.63 (1H, m), 2.76 – 2.85 (1H, m), 2.90 – 2.99 (2H, m), 3.08 – 3.20 (3H, m), 3.26 (1H, d), 3.31 – 3.32 (6H, m), 3.60 – 3.68 (2H, m), 3.91 (1H, d), 4.26 – 4.36 (3H, m), 5.81 (2H, s), 6.40 – 6.48 (2H, m), 6.87 (1H, s), 6.91 – 6.99 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 493.

Intermediate 42e:

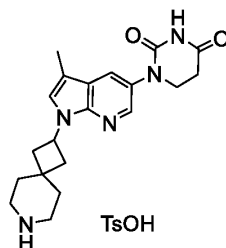
2-[6-Amino-5-[8-[3-[(2*R*)-2-(dimethoxymethyl)morpholin-4-yl]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-yl]phenol



[1497] Prepared in an analogous manner to Intermediate 2h from Intermediate 42d (860 mg, 1.74 mmol). Purification by FSC (elution gradient: 0 to 10% MeOH in DCM) gave the title compound (600 mg, 62.5 %) as a yellow gum. ¹H NMR (DMSO-*d*₆): δ 1.90 – 1.97 (2H, m), 2.13 (2H, d), 2.58 – 2.61 (1H, m), 2.78 – 2.85 (1H, m), 3.05 – 3.15 (3H, m), 3.22 – 3.29 (3H, m), 3.32 (6H, s), 3.60 – 3.68 (2H, m), 3.88 – 3.95 (1H, m), 4.31 (1H, d), 4.34 – 4.38 (2H, m), 5.95 (2H, s), 6.43 – 6.52 (2H, m), 6.83 – 6.89 (2H, m), 6.93 – 6.99 (1H, m), 7.19 – 7.26 (1H, m), 7.46 (1H, s), 7.87 – 7.92 (1H, m), 14.17 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 551.

Intermediate 42f:

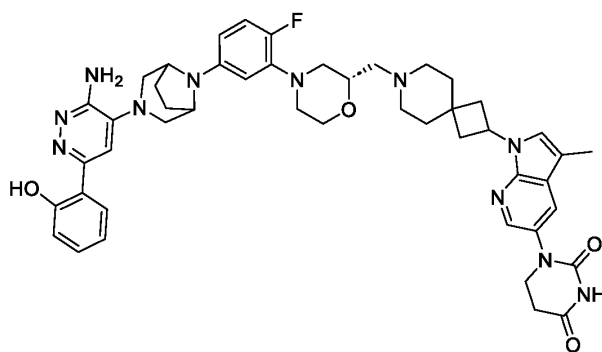
1-[1-(7-Azaspiro[3.5]nonan-2-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1498] *p*-TsOH·H₂O (177 mg, 1.03 mmol) was added to Intermediate 15b (400 mg, 0.86 mmol) in MeCN (10 mL) at r.t.. The resulting mixture was stirred at 80 °C for 16 h. The reaction mixture was diluted

with MTBE (200 mL). The solids were filtered and washed with ether, dried under vacuum to give the title compound (450 mg, 84 %) as a white solid in the form of the TsOH salt. m/z (ES⁺) [M+H]⁺ = 368.2.

1-[1-[7-[(2S)-4-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]morpholin-2-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione

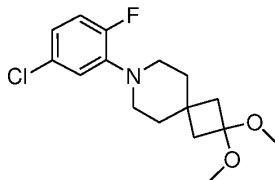


[1499] *p*-TsOH·H₂O (62.2 mg, 0.33 mmol) was added to Intermediate 42c (60 mg, 0.11 mmol) in acetone (1 mL) and water (0.111 mL). The resulting mixture was stirred at 80 °C for 2 h. The reaction mixture was poured into sat. aq. NaHCO₃ (5 mL), extracted with EtOAc (3 x 10 mL), the organic layer was dried over Na₂SO₄, filtered and evaporated. To the crude product was added Intermediate 42f (22.01 mg, 0.05 mmol) in DCE (0.5 mL) and NMP (0.5 mL). The resulting mixture was stirred at 40 °C for 16 h. Sodium triacetoxyborohydride (69.3 mg, 0.33 mmol) was added to the mixture and stirred at r.t. for 2 h. The reaction mixture was poured into sat. aq. NaHCO₃ (5 mL), extracted with DCM (3 x 10 mL), the organic layer was dried over Na₂SO₄, filtered and evaporated. Purification by RPC (elution gradient: 0-70% CH₃CN in H₂O with 10mM NH₄HCO₃+0.05% NH₃H₂O) gave the title compound (7.70 mg, 7.70 %) as a brown solid. ¹H NMR (DMSO-*d*₆): δ 1.22 – 1.24 (1H, m), 1.61 – 1.74 (4H, m), 1.94 (2H, d), 2.13 (2H, d), 2.16 – 2.22 (2H, m), 2.26 (3H, s), 2.30 – 2.40 (6H, m), 2.43 – 2.48 (2H, m), 2.73 – 2.77 (2H, m), 2.78 – 2.82 (1H, m), 3.06 – 3.13 (2H, m), 3.17 (1H, d), 3.21 – 3.29 (3H, m), 3.62 – 3.69 (1H, m), 3.71 – 3.77 (1H, m), 3.77 – 3.82 (2H, m), 3.88 (1H, d), 4.36 (2H, s), 5.19 – 5.29 (1H, m), 5.94 (2H, s), 6.43 – 6.50 (2H, m), 6.83 – 6.90 (2H, m), 6.92 – 7.00 (1H, m), 7.17 – 7.26 (1H, m), 7.46 (1H, s), 7.60 (1H, s), 7.85 – 7.93 (2H, m), 8.16 (1H, d), 10.38 (1H, s), 14.16 (1H, s); ¹⁹F NMR (DMSO-*d*₆) δ -136.80; m/z (ES⁺) [M+H]⁺ = 856.

Example 43

Intermediate 43a:

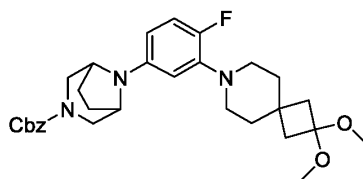
7-(5-Chloro-2-fluoro-phenyl)-2,2-dimethoxy-7-azaspiro[3.5]nonane



[1500] *tert*-Butyl 2-oxo-7-azaspiro[3.5]nonane-7-carboxylate (5 g, 20.89 mmol) was added to HCl in MeOH (30 mL, 120.00 mmol) under air. The resulting mixture was stirred at r.t. for 2 h. The solvent was removed under reduced pressure. The reaction mixture was adjusted to pH=8 with 7 M NH₃ in MeOH. The solvent was removed under reduced pressure. The reaction mixture was diluted with 15 mL 5:1 MeOH/DCM. The reaction mixture was filtered and concentrated under reduced pressure. The crude product (3.6 g, 19.43 mmol) was added to 2-bromo-4-chloro-1-fluorobenzene (4.07 g, 19.43 mmol), Pd₂(dba)₃ (1.778 g, 1.94 mmol), BINAP (1.210 g, 1.94 mmol) and NaOtBu (5.60 g, 58.29 mmol) in toluene (20 mL) under nitrogen. The resulting mixture was stirred at 80 °C for 16 h. The reaction mixture was diluted with EtOAc (300 mL) and washed sequentially with water (3 x 200 mL). The organic layer was dried over Na₂SO₄, filtered and evaporated. Purification by FSC (elution gradient: 0 to 20% EtOAc in petroleum ether) gave the title compound (0.480 g, 7.87 %) as a yellow solid. ¹H NMR (DMSO-*d*₆): δ 1.63–1.70 (4H, m), 1.91 (4H, s), 2.90–2.96 (4H, m), 3.05 (6H, s), 6.93–7.03 (2H, m), 7.1–7.19 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 314.2.

Intermediate 43b:

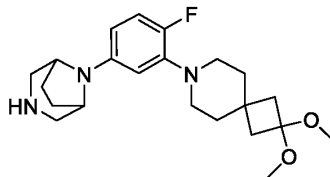
Benzyl 8-[3-(2,2-dimethoxy-7-azaspiro[3.5]nonan-7-yl)-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



[1501] Prepared in an analogous manner to Intermediate 42c from Intermediate 43a (380 mg, 1.21 mmol). Purification by RPC (elution gradient: 0 to 90% MeOH in water with 0.1% NH₄HCO₃) gave the title compound (560 mg, 88 %) as a dark colored solid. ¹H NMR (DMSO-*d*₆): δ 1.62–1.67 (6H, m), 1.90 (4H, s), 2.85–2.91 (5H, m), 3.04 (6H, s), 3.09–3.26 (3H, m), 3.56–3.62 (2H, m), 4.19–4.26 (2H, m), 5.02–5.13 (2H, m), 6.35–6.4 (1H, m), 6.41–6.45 (1H, m), 6.86–6.95 (1H, m), 7.30–7.40 (5H, m); *m/z* (ES⁺) [M+H]⁺ = 524.3.

Intermediate 43c:

7-[5-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-2-fluoro-phenyl]-2,2-dimethoxy-7-azaspiro[3.5]nonane

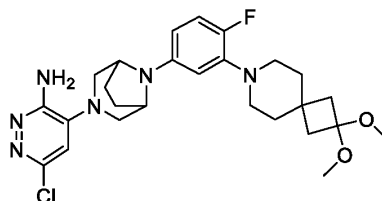


[1502] Intermediate 43b (370 mg, 0.71 mmol) was added to Pd/C (75 mg, 0.07 mmol) in DCM (25 mL) under hydrogen. The resulting mixture was stirred at r.t. for 4 h. The reaction was filtered through celite®, the filtrate was collected, and the solvent was removed by reduced pressure to afford the title

compound (260 mg, 94 %) as a white solid. The product was used in the next step directly without further purification. ¹H NMR (DMSO-*d*₆): δ 1.62–1.69 (4H, m), 1.88–1.93 (4H, m), 1.98–2.11 (4H, m), 2.92 (6H, s), 2.98–3.09 (8H, m), 6.37–6.47 (2H, m), 6.92–7.00 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 390.4.

Intermediate 43d:

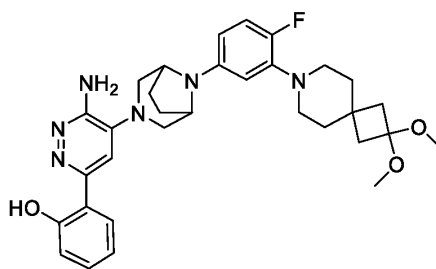
6-Chloro-4-[8-[3-(2,2-dimethoxy-7-azaspiro[3.5]nonan-7-yl)-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-amine



[1503] A mixture of Intermediate 43c (250mg, 0.64 mmol), 4-bromo-6-chloropyridazin-3-amine (134 mg, 0.64 mmol) and DIPEA (0.336 mL, 1.93 mmol) in DMSO (10 mL) was heated at 100 °C for 16 h. The reaction mixture was diluted with DCM (100 mL) and washed sequentially with saturated brine (3 x 75 mL), water (3 x 75 mL). The organic layer was dried over Na₂SO₄, filtered, and evaporated. Purification by RPC (elution gradient 0 to 70% MeCN in water (0.1%NH₄HCO₃)) gave the title compound (180 mg, 54.2 %) as a brown solid. ¹H NMR (DMSO-*d*₆): δ 1.62–1.68 (4H, m), 1.87–1.93 (6H, m), 2.05–2.11 (2H, m), 2.87–2.91 (4H, m), 2.94 (2H, d), 3.04 (6H, s), 3.14–3.18 (2H, m), 4.29–4.32 (2H, m), 5.82 (2H, s), 6.38–6.42 (1H, m), 6.43–6.46 (1H, m), 6.88 (1H, d), 6.90–6.93 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 517.1.

Intermediate 43e:

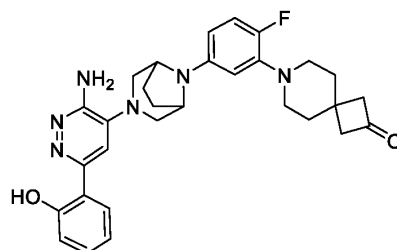
2-[6-Amino-5-[8-[3-(2,2-dimethoxy-7-azaspiro[3.5]nonan-7-yl)-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-yl]phenol



[1504] Intermediate 43d (160 mg, 0.31 mmol) was added to (2-hydroxyphenyl)boronic acid (85 mg, 0.62 mmol), Pd(dppf)Cl₂•DCM (25.3 mg, 0.03 mmol) and Cs₂CO₃ (302 mg, 0.93 mmol) in 1,4-dioxane (10 mL) and water (1.0 mL) under nitrogen. The resulting mixture was stirred at 100 °C for 8 h. The solvent was removed under reduced pressure. Purification by FSC (elution gradient 0 to 10% MeOH in DCM) gave the title compound (160 mg, 90 %) as a brown solid. ¹H NMR (DMSO-*d*₆): δ 1.63–1.68 (4H, m), 1.89–1.97 (6H, m), 2.11–2.15 (2H, m), 2.88–2.92 (4H, m), 3.04 (6H, s), 3.07–3.11 (2H, m), 3.23–3.28 (2H, m), 4.33–4.37 (2H, m), 5.96 (2H, s), 6.41–6.5 (2H, m), 6.84–6.95 (3H, m), 7.21–7.25 (1H, m), 7.47 (1H, s), 7.9–7.93 (1H, m), 14.19 (1H, s); *m/z* (ES⁺), [M+H]⁺ = 575.2.

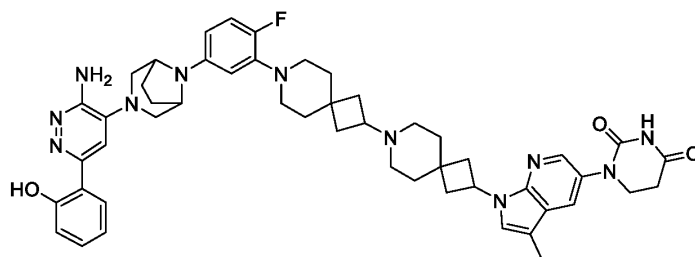
Intermediate 43f:

7-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-7-azaspiro[3.5]nonan-2-one



[1505] Formic acid (5 mL) was added to Intermediate 43e (120 mg, 0.21 mmol). The resulting mixture was stirred at 40 °C for 1 h. The solvent was removed under reduced pressure to afford the title compound (95 mg, 86 %) as a brown solid. The product was used in the next step directly without further purification. ¹H NMR (DMSO-*d*₆): δ 1.22–1.26 (2H, m), 1.78–1.85 (4H, m), 1.92–1.98 (2H, m), 2.07–2.13 (2H, m), 2.84 (4H, s), 2.95–3.01 (4H, m), 3.14–3.23 (2H, m), 4.34–4.38 (2H, m), 6.13 (2H, d), 6.43–6.48 (1H, m), 6.49–6.52 (1H, m), 6.87–6.98 (3H, m), 7.28 (1H, d), 7.46 (1H, s), 7.80 (1H, s); *m/z* (ES⁺), [M+H]⁺ = 529.6.

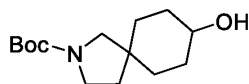
1-[1-[7-[7-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-7-azaspiro[3.5]nonan-2-yl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1506] Intermediate 43f (90 mg, 0.17 mmol) was added to Intermediate 42f (75 mg, 0.20 mmol) in DCE (3 mL) and NMP (3 mL). The resulting mixture was stirred at 40 °C for 1 h then sodium triacetoxyborohydride (289 mg, 1.36 mmol) was added. The resulting mixture was stirred at r.t. for 16 h. The reaction mixture was diluted with DCM (50 mL) and washed sequentially with sat. aq. NaHCO₃ (2 x 50 mL) and brine (2 x 50 mL). The organic layer was dried over Na₂SO₄, filtered, and evaporated. Purification by RPC (elution gradient: 0-60% ACN in water with 0.1% FA) gave the title compound (17.89 mg, 11.94 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.51–1.62 (4H, m), 1.63–1.77 (6H, m), 1.91–2.01 (4H, m), 2.10–2.14 (3H, mt), 2.18–2.24 (3H, m), 2.27 (3H, s), 2.31–2.37 (2H, m), 2.57–2.65 (1H, m), 2.76 (2H, t), 2.87 (2H, t), 2.92–2.97 (2H, m), 3.10 (2H, d), 3.25 (2H, d), 3.29–3.32 (1H, m), 3.34–3.37 (1H, s), 3.80 (2H, t), 4.33–4.36 (2H, m), 5.21–5.3 (1H, m), 5.95 (2H, s), 6.39–6.5 (2H, m), 6.84–6.95 (3H, m), 7.2–7.26 (1H, m), 7.47 (1H, s), 7.61 (1H, s), 7.86–7.93 (2H, m), 8.17 (1H, d), 10.40 (1H, s), 14.19 (1H, s); ¹⁹F NMR (DMSO-*d*₆): δ -136.44; *m/z* (ES⁺), [M+H]⁺ = 880.7.

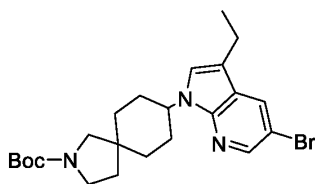
Example 44

Intermediate 44a:

tert-Butyl 8-hydroxy-2-azaspiro[4.5]decane-2-carboxylate

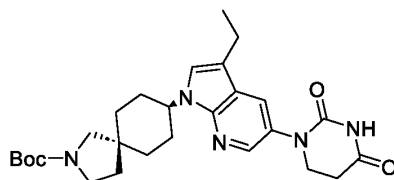
[1507] Sodium borohydride (0.164 g, 4.34 mmol) was added portion wise to *tert*-butyl 8-oxo-2-azaspiro[4.5]decane-2-carboxylate (1 g, 3.95 mmol) in MeOH (10 mL) at 0 °C under nitrogen. The resulting mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched with sat. aq. NH₄Cl (10 mL), extracted with EtOAc (3 x 30 mL), the organic layer was dried over MgSO₄, filtered, and evaporated. Purification by FSC (elution gradient: 0 to 100% ethyl acetate in hexane) gave the title compound (0.850 g, 84 %) as an oil as a mixture of *cis* and *trans* isomers. ¹H NMR (DMSO-*d*₆): δ 1.22 - 1.34 (5H, m), 1.36 - 1.42 (17H, m), 1.48 - 1.72 (11H, m), 2.97 - 2.99 (1H, m), 3.00 - 3.06 (2H, m), 3.26 (3H, br d), 3.41 - 3.51 (1H, m), 4.44 - 4.52 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 241.1.

Intermediate 44b:

tert-Butyl 8-(5-bromo-3-ethyl-pyrrolo[2,3-*b*]pyridin-1-yl)-2-azaspiro[4.5]decane-2-carboxylate

[1508] A vial was charged with Intermediate 44a (1021 mg, 4.00 mmol), 5-bromo-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridine (900 mg, 4.00 mmol) and 2-(tributyl-1*l*-phosphaneylidene)acetonitrile (1.572 mL, 6.00 mmol). Toluene (14mL) was added, and the reaction was heated at 80 °C for 16 h. The reaction was concentrated under reduced pressure. Purification by FSC (elution gradient: 0-50% EtOAc/Hexane) gave the title compound (500 mg, 27.0 %) as an orange solid as a mixture of *cis* and *trans* isomers. ¹H NMR (DMSO-*d*₆): δ 1.25 (4H, t), 1.39 - 1.47 (10H, m), 1.56 (3H, br d), 1.64 - 1.73 (4H, m), 1.75 - 1.87 (3H, m), 1.87 - 1.98 (3H, m), 2.69 (2H, br d), 3.25 - 3.32 (4H, m), 4.54 - 4.72 (1H, m), 7.59 (1H, s), 8.18 (1H, d), 8.26 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 462, 464.1.

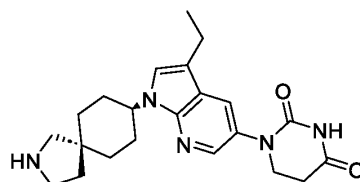
Intermediate 44c:

tert-Butyl (5*r*,8*r*)-8-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-ethyl-pyrrolo[2,3-*b*]pyridin-1-yl]-2-azaspiro[4.5]decane-2-carboxylate

[1509] Prepared in an analogous method to Intermediate 2b starting from Intermediate 44b (500 mg, 1.08 mmol). Purification by FSC (elution gradient: 0-100% EtOAc/hexane) to give title compound (200 mg, 37.3 %) as a brown solid. The isomers were separated by SFC (Chiralcel OJ 21 x 250mm, 5 μ m, CO₂ with 15% (methanol with 0.2% NH₄OH), 85 ml/ min, 120 bar, 40 °C) gave the title compound (65 mg, 40.6%) as a white solid which eluted first off of the column. Relative stereochemistry assigned by ROESY NMR. ¹H NMR (CDCl₃): δ 1.33 (3H, br t), 1.48 - 1.55 (9H, m), 1.65 (1H, br s), 1.67 (1H, br d), 1.71 - 1.92 (6H, m), 2.02 (2H, br d), 2.70 - 2.80 (2H, m), 2.92 (2H, t), 3.32 (1H, s), 3.38 - 3.50 (3H, m), 3.92 (2H, t), 4.73 - 4.91 (1H, m), 7.08 - 7.20 (1H, m), 7.54 (1H, br s), 7.80 (1H, br s), 8.23 (1H, br s); m/z (ES⁺) [M+H]⁺ = 496.4

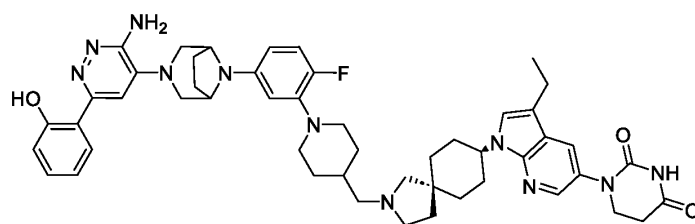
Intermediate 44d:

1-[1-((5*r*,8*r*)-2-Azaspiro[4.5]decan-8-yl)-3-ethyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1510] TFA (0.187 mL, 2.42 mmol) was added to a stirred solution of Intermediate 44c (60mg, 0.12 mmol) in DCM (2 mL). The resulting solution was stirred at r.t. for 2 h. The solvent was removed under reduced pressure. The residue was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and pure fractions were evaporated to dryness to afford title compound (42.0 mg, 88 %) as an orange gum. m/z (ES⁺) [M+H]⁺ = 396.3.

1-[1-[1-((5*r*,8*r*)-2-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl)methyl]-2-azaspiro[4.5]decan-8-yl)-3-ethyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



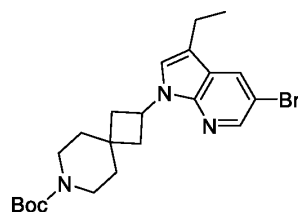
[1511] DCM (1.0mL) and *i*-PrOH (0.2 mL) were added to Intermediate 44d (27.5 mg, 0.07 mmol) and Intermediate 13d (35 mg, 0.07 mmol). The resulting mixture was stirred at r.t. for 10 min, then Na(OAc)₃BH (29.5 mg, 0.14 mmol) was added and the mixture was stirred at r.t. for 4 h. The solvent was removed under reduced pressure. Purification by RPC (elution gradient: 0 to 60% MeCN in water with 0.1% formic acid) gave the title compound (33.0 mg, 53.7 %) as an amorphous white solid, following lyophilization. ¹H NMR (DMSO-*d*₆): δ 1.28 (3H, t), 1.38 - 1.46 (2H, m), 1.59 - 1.74 (2H, m), 1.80 - 2.00 (14H, m), 2.08 (2H, br d),

2.67 - 2.80 (6H, m), 3.04 - 3.09 (1H, m), 3.19 - 3.31 (5H, m), 3.41 - 3.44 (1H, m), 3.45 - 3.51 (2H, m), 3.66 - 3.73 (1H, m), 3.81 (3H, br t), 4.38 (2H, br s), 4.64 - 4.74 (1H, m), 6.47 - 6.53 (2H, m), 6.57 (1H, br s), 6.91 - 7.01 (3H, m), 7.34 (1H, br t), 7.45 (1H, s), 7.52 (1H, s), 7.67 (1H, br d), 7.93 (1H, d), 8.18 (1H, d), 9.89 - 9.97 (1H, m), 10.37 - 10.40 (1H, m); ^{19}F NMR (DMSO-*d*₆): -73.66 (1F, s); m/z (ES⁺) [M+H]⁺ = 868.6.

Example 45

Intermediate 45a:

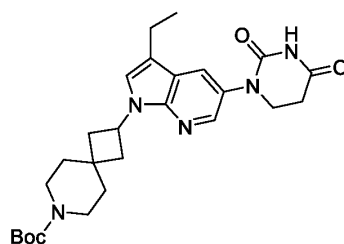
tert-Butyl 2-(5-bromo-3-ethyl-pyrrolo[2,3-*b*]pyridin-1-yl)-7-azaspiro[3.5]nonane-7-carboxylate



[1512] Prepared in an analogous method to Intermediate 1b starting from 5-bromo-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridine (500 mg, 2.22 mmol) and *tert*-butyl 2-hydroxy-7-azaspiro[3.5]nonane-7-carboxylate (804 mg, 3.33 mmol). Purification by FSC (elution gradient: 0-50% EtOAc/Hexane) gave the title compound (900 mg, 90 %) as a colorless dry film. ^1H NMR (DMSO-*d*₆): δ 1.26 (3H, t), 1.40 (9H, s), 1.63 (4H, dt), 2.21 - 2.30 (2H, m), 2.35 - 2.43 (2H, m), 2.70 (2H, q), 3.21 - 3.27 (2H, m), 3.33 (2H, s), 5.26 (1H, t), 7.66 (1H, s), 8.19 (1H, d), 8.26 (1H, d); m/z (ES⁺) [M+H]⁺ = 448.4 450.2.

Intermediate 45b:

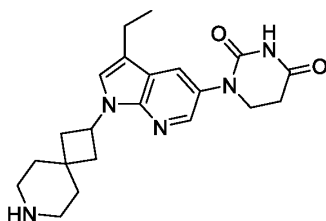
tert-Butyl 2-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-ethyl-pyrrolo[2,3-*b*]pyridin-1-yl]-7-azaspiro[3.5]nonane-7-carboxylate



[1513] Prepared in an analogous method to Intermediate 2b starting from Intermediate 45a (900 mg, 2.01 mmol). Purification by FSC (elution gradient: 0-100% EtOAc in hexane) gave the title compound (410 mg, 42.4 %) as a brown solid. ^1H NMR (DMSO-*d*₆): δ 1.28 (3H, t), 1.41 (9H, s), 1.60 - 1.71 (4H, m), 2.21 - 2.30 (2H, m), 2.34 - 2.45 (2H, m), 2.66 - 2.83 (4H, m), 3.26 - 3.29 (1H, m), 3.30 - 3.41 (3H, m), 3.81 (2H, t), 5.17 - 5.42 (1H, m), 7.63 (1H, s), 7.92 (1H, d), 8.17 (1H, d), 10.40 (1H, s); m/z (ES⁺) [M+H]⁺ = 481.9.

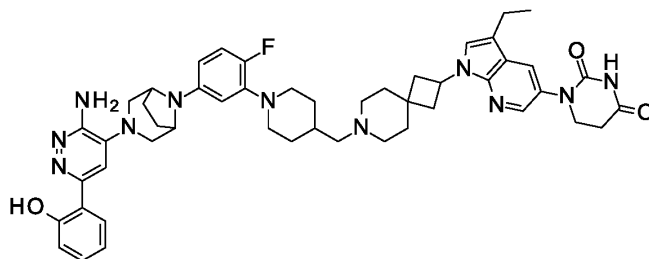
Intermediate 45c:

1-[1-(7-Azaspiro[3.5]nonan-2-yl)-3-ethyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1514] Prepared in an analogous method to Intermediate 44e starting from Intermediate 45b (200mg, 0.42 mmol) to give the title compound (120 mg, 76 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.28 (3H, t), 1.62 (4H, dt), 2.17 - 2.26 (2H, m), 2.33 - 2.42 (2H, m), 2.58 - 2.65 (2H, m), 2.68 - 2.80 (6H, m), 3.81 (2H, t), 5.26 (1H, br t), 7.60 (1H, s), 7.91 (1H, d), 8.17 (1H, d), 10.24 - 10.69 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 382.3.

1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-ethyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

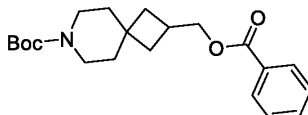


[1515] Prepared in an analogous method to Example 35 starting from Intermediate 11g (50mg, 0.08 mmol) and Intermediate 45c (30.1 mg, 0.08 mmol). Purification by RPC (elution gradient: 0-80% MeCN in water with 0.1% NH₄OH) gave the title compound (22.0 mg, 32.1 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.20 - 1.31 (5H, m), 1.59 - 1.85 (8H, m), 1.95 (2H, br d), 2.15 (4H, br dd), 2.24 (4H, br s), 2.36 (4H, br d), 2.62 - 2.68 (2H, m), 2.71 (2H, br d), 2.76 (2H, br s), 3.08 - 3.14 (2H, m), 3.24 - 3.29 (2H, m), 3.34 - 3.37 (2H, m), 3.81 (2H, br t), 4.35 (2H, br s), 5.26 (1H, br t), 5.94 (2H, br s), 6.38 - 6.53 (2H, m), 6.82 - 6.98 (3H, m), 7.20 - 7.27 (1H, m), 7.47 (1H, s), 7.61 (1H, s), 7.86 - 7.95 (2H, m), 10.38 (1H, s), 13.87 - 14.59 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 868.6.

Example 46

Intermediate 46a:

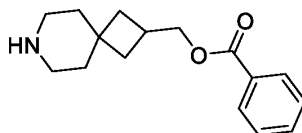
tert-Butyl 2-(benzoyloxymethyl)-7-azaspiro[3.5]nonane-7-carboxylate



[1516] In a 100 mL flask, *tert*-butyl 2-(hydroxymethyl)-7-azaspiro[3.5]nonane-7-carboxylate (1.532 g, 6 mmol) and DMAP (0.073 g, 0.60 mmol) were dissolved in DCM (25 mL). DIPEA (3.14 mL, 18.00 mmol) was added, and the reaction was cooled to 0 °C. Benzoyl chloride (1.381 mL, 12.00 mmol) was added, and the reaction was stirred at 0 °C for 5 mins then warmed to r.t. stirred for 2.5 h. The reaction was quenched with sat.aq. NaHCO₃, extracted with DCM, dried over Na₂SO₄, and concentrated. Purification by FSC (elution gradient: 0-40% EtOAc in hexanes) gave the title compound (1.940 g, 90 %) as a yellow oil. ¹H NMR (CDCl₃): δ 1.45 (9H, s), 1.47 - 1.53 (2H, m), 1.57 - 1.63 (2H, m), 1.64 - 1.70 (2H, m), 1.96 - 2.03 (2H, m), 2.68 - 2.78 (1H, m), 3.26 - 3.31 (2H, m), 3.34 - 3.39 (2H, m), 4.30 (2H, d), 7.45 (2H, t), 7.57 (1H, t), 8.04 (2H, d); *m/z* (ES⁺) [M-*t*Bu+2H]⁺ = 304.1.

Intermediate 46b:

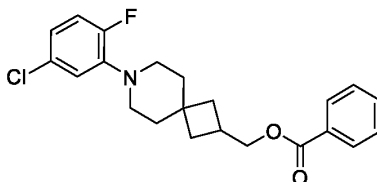
7-Azaspiro[3.5]nonan-2-ylmethyl benzoate



[1517] Prepared in an analogous method to Intermediate 44e starting from Intermediate 46a (1.9396 g, 5.40 mmol) gave the title compound (1.276 g, 91 %) as a yellow oil. ¹H NMR (CDCl₃): δ 1.48 - 1.53 (2H, m), 1.56 (1H, br s), 1.59 - 1.69 (4H, m), 1.93 - 2.04 (2H, m), 2.67 - 2.76 (3H, m), 2.80 (2H, br t), 4.31 (2H, d), 7.46 (2H, t), 7.57 (1H, t), 8.06 (2H, d); *m/z* (ES⁺) [M+H]⁺ = 260.6.

Intermediate 46c:

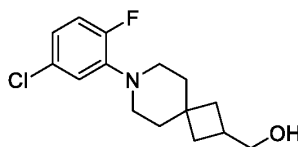
[7-(5-Chloro-2-fluoro-phenyl)-7-azaspiro[3.5]nonan-2-yl]methyl benzoate



[1518] A mixture of Pd₂dba₃ (0.218 g, 0.24 mmol), Intermediate 46b (1.2336 g, 4.76 mmol), and Cs₂CO₃ (4.65 g, 14.27 mmol) 2-bromo-4-chloro-1-fluorobenzene (0.580 mL, 4.76 mmol) and *t*BuPhCphos (0.192 g, 0.48 mmol) and 1,4-dioxane (20 mL) was degassed for 5 min. The reaction was heated to 100 °C for 2.5h. Reaction was cooled to r.t., filtered through celite® eluting with DCM and concentrated. Purification by FSC (elution gradient: 0-30% EtOAc/hexane) gave the title compound (1.673 g, 91 %) as a colorless viscous liquid. ¹H NMR (CDCl₃): δ 1.70 - 1.77 (4H, m), 1.83 - 1.87 (2H, m), 1.99 - 2.12 (2H, m), 2.73 - 2.84 (1H, m), 2.92 - 2.97 (2H, m), 3.00 - 3.05 (2H, m), 4.35 (2H, d), 6.85 - 6.89 (1H, m), 6.90 - 6.99 (2H, m), 7.47 (2H, t), 7.54 - 7.64 (1H, m), 8.08 (2H, d); *m/z* (ES⁺) [M+H]⁺ = 388.5.

Intermediate 46d:

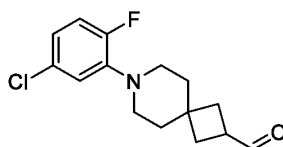
[7-(5-Chloro-2-fluoro-phenyl)-7-azaspiro[3.5]nonan-2-yl]methanol



[1519] A mixture of Intermediate 46c (1.1263 g, 2.90 mmol), LiOH (0.695 g, 29.04 mmol), MeOH (10 mL) and water (5 mL) was heated to 40 °C for 1.5h. Reaction was quenched with 1M HCl (50 mL), extracted with DCM (3 x 50 mL). The combined organic extracts were washed with brine, dried by Na₂SO₄, filtered, and concentrated. Purification by FSC (elution gradient: 0-50% EtOAc in hexanes) afforded title compound (0.717 g, 87 %) as a colorless oil. ¹H NMR (CDCl₃): δ 1.55 - 1.63 (2H, m), 1.69 - 1.73 (2H, m), 1.80 - 1.85 (2H, m), 1.94 - 2.00 (2H, m), 2.47 - 2.56 (1H, m), 2.92 - 2.96 (2H, m), 2.99 - 3.05 (2H, m), 3.65 (2H, d), 6.84 - 6.88 (1H, m), 6.90 - 6.96 (2H, m) (OH not observed); *m/z* (ES⁺) [M+H]⁺ = 285.2.

Intermediate 46e:

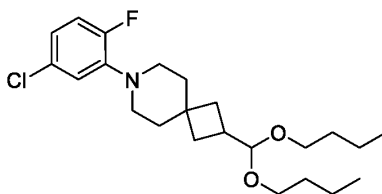
7-(5-Chloro-2-fluoro-phenyl)-7-azaspiro[3.5]nonane-2-carbaldehyde



[1520] To a stirred solution of Intermediate 46d (666 mg, 2.35 mmol) in DCM (20 mL) was added Dess–Martin periodinane (1095 mg, 2.58 mmol) in one portion. The mixture was stirred at r.t. for 2.5 h. The reaction was quenched with sodium thiosulfate soln., extracted with DCM (2 x 25 mL). The combined organic extracts were washed with sat. aq. NaHCO₃ and brine, dried with Na₂SO₄, filtered, and concentrated. Purification by FSC (elution gradient: 0-30% EtOAc/hexanes) afforded the title compound (494 mg, 74.7 %) as a white solid. ¹H NMR (CDCl₃): δ 1.67 - 1.71 (2H, m), 1.81 - 1.86 (2H, m), 2.01 - 2.14 (4H, m), 2.92 - 2.96 (2H, m), 2.99 - 3.03 (2H, m), 3.11 - 3.22 (1H, m), 6.83 - 6.97 (3H, m), 9.79 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 282.3.

Intermediate 46f:

7-(5-Chloro-2-fluoro-phenyl)-2-(dibutoxymethyl)-7-azaspiro[3.5]nonane

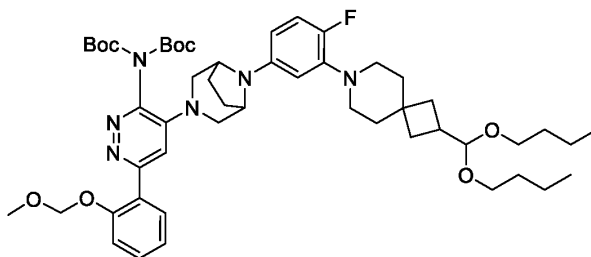


[1521] A mixture of Intermediate 46e (494 mg, 1.75 mmol) and *p*-TsOH•H₂O (33.3 mg, 0.18 mmol) in 1-butanol (5 mL) was stirred at 50 °C for 2.25 h. The reaction was concentrated under reduced pressure. Purification by FSC (elution gradient: 0-10% EtOAc/hexane) to give title compound (521 mg, 72.1 %) as a colorless liquid. ¹H NMR (CDCl₃): δ 0.95 (6H, t), 1.41 (4H, sxt), 1.53 - 1.64 (4H, m), 1.67 - 1.73 (4H, m),

1.76 - 1.82 (2H, m), 1.88 - 1.95 (2H, m), 2.56 - 2.65 (1H, m), 2.90 - 2.95 (2H, m), 2.97 - 3.03 (2H, m), 3.45 (2H, dt), 3.58 (2H, dt), 4.43 (1H, d), 6.80 - 6.87 (1H, m), 6.88 - 6.95 (2H, m); m/z (ES^+) $[M+H]^+ = 412.6$.

Intermediate 46g:

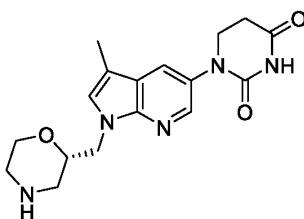
tert-Butyl *N*-*tert*-butoxycarbonyl-*N*-[4-[8-[3-[2-(dibutoxymethyl)-7-azaspiro[3.5]nonan-7-yl]-4-fluorophenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]-6-[2-(methoxymethoxy)phenyl]pyridazin-3-yl]carbamate



[1522] A mixture of Intermediate 25d (632 mg, 1.17 mmol), Intermediate 46f (481 mg, 1.17 mmol), CS_2CO_3 (1141 mg, 3.50 mmol) and RuPhos Pd G3 (98 mg, 0.12 mmol), in 1,4-dioxane (12 mL) was sparged with N_2 for 10 mins. The reaction was heated to 100 °C for 1.5 h, conversion had stalled. A second portion of RuPhos Pd G3 (98 mg, 0.12 mmol) was added. The reaction was sparged with N_2 for 5 min. and continued to stir at 100 °C for 5 h. The reaction was cooled to r.t., filtered through celite® and concentrated. Purification by FSC (elution gradient: 0-80% EtOAc/Hexane) gave the title compound (404 mg, 37.7 %) as a brown dry film. 1H NMR (DMSO-*d*6): δ 0.88 (5H, t), 0.91 - 0.94 (1H, m), 1.29 - 1.37 (5H, m), 1.37 - 1.42 (18H, m), 1.43 - 1.51 (5H, m), 1.55 - 1.64 (4H, m), 1.65 - 1.71 (2H, m), 1.77 - 1.88 (4H, m), 1.93 - 2.00 (2H, m), 2.78 - 2.85 (2H, m), 2.87 - 2.93 (2H, m), 3.21 - 3.30 (5H, m), 3.32 - 3.42 (3H, m), 3.50 (2H, dt), 4.37 - 4.42 (3H, m), 5.14 - 5.27 (2H, m), 6.41 - 6.52 (2H, m), 6.91 (1H, dd), 7.16 (1H, t), 7.25 (1H, d), 7.46 (1H, t), 7.51 (1H, s), 7.73 (1H, dd); m/z (ES^+) $[M+H]^+ = 917.7$.

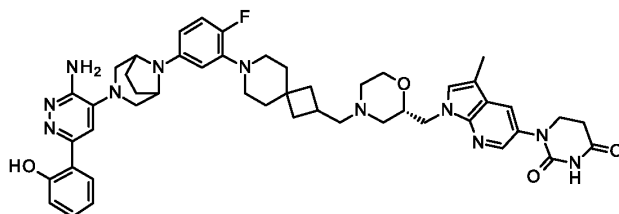
Intermediate 46h:

1-[3-Methyl-1-[(2*S*)-morpholin-2-yl]methyl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1523] HCl solution (4M in dioxane, 4.51 mL, 18.04 mmol) was added to a stirred solution of Intermediate 30b (400 mg, 0.90 mmol) in DCM (1 mL). The resulting mixture was stirred at r.t. for 1 h. The solvent was removed under reduced pressure and residue was dissolved in DCM/*i*PrOH (3:1, 100 mL) and basified with sat. aq. $NaHCO_3$ (10 mL). The aqueous layer separated, extracted with DCM/*i*PrOH mixture (2 x 50 mL). The combined extracts were dried over Na_2SO_4 , filtered, and concentrated to give title compound (260 mg, 84 %) as a white solid. The crude material was used for the next step without further purification. m/z (ES^+) $[M+H]^+ = 344.3$.

1-[1-[(2*S*)-4-[[7-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-7-azaspiro[3.5]nonan-2-yl)methyl]morpholin-2-yl)methyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

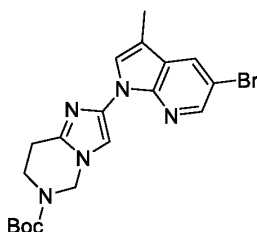


[1524] Prepared in an analogous manner to Example 35 starting from Intermediate 46g (50mg, 0.05 mmol) and Intermediate 46h (18.72 mg, 0.05 mmol). Purification by RPC (elution gradient: 0-60% CH₃CN/water with 0.1% formic acid) gave the title compound (10.00 mg, 21.08 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.40 (2H, br t), 1.57 (2H, br s), 1.69 (2H, br s), 1.81 (1H, br t), 1.89 - 1.96 (4H, m), 1.99 - 2.04 (1H, m), 2.10 - 2.16 (2H, m), 2.25 (3H, s), 2.32 - 2.39 (2H, m), 2.41 - 2.45 (1H, m), 2.56 (2H, br s), 2.64 - 2.69 (1H, m), 2.75 (2H, br t), 2.81 - 2.86 (2H, m), 2.93 (2H, br s), 3.06 - 3.13 (2H, m), 3.26 (2H, br d), 3.38 - 3.42 (1H, m), 3.75 - 3.84 (4H, m), 4.19 - 4.27 (2H, m), 4.31 - 4.39 (2H, m), 5.93 (2H, br s), 6.39 - 6.50 (2H, m), 6.81 - 6.97 (3H, m), 7.22 (1H, br s), 7.33 (1H, s), 7.44 - 7.49 (1H, m), 7.85 - 7.93 (2H, m), 8.15 - 8.22 (1H, m), 10.32 - 10.44 (1H, br s), 14.02 - 14.31 (1H, br s); *m/z* (ES⁺) [M+H]⁺ = 870.7.

Example 47

Intermediate 47a:

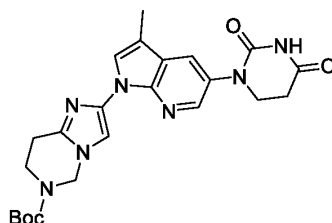
tert-Butyl 2-(5-bromo-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl)-7,8-dihydro-5*H*-imidazo[1,2-*c*]pyrimidine-6-carboxylate



[1525] A mixture of 5-bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (50mg, 0.24 mmol), *tert*-butyl 2-bromo-5,6-dihydroimidazo[1,2-*a*]pyrazine-7(8*H*)-carboxylate (71.6 mg, 0.24 mmol), copper(I) iodide (9.02 mg, 0.05 mmol), (1*S*,2*S*)-*N*1,*N*2-dimethylcyclohexane-1,2-diamine (13.48 mg, 0.09 mmol) and K₂CO₃ (98 mg, 0.71 mmol) in 1,4-dioxane (3 mL) was heated at 100 °C for 16 h. The reaction mixture cooled to r.t. and the solids were filtered off. Filtrate was diluted with DCM and washed with sat. aq. NaHCO₃ (20 mL), organic layer was separated, dried over Na₂SO₄, filtered, and concentrated. Purification by FSC (elution gradient: 0-100% EtOAc in hexane) gave the title compound (70.0 mg, 68.3 %) as a light-yellow solid. ¹H NMR (DMSO-*d*₆): δ 1.46 (9H, s), 2.31 (3H, d), 3.83 (2H, br d), 4.08 (2H, br d), 4.60 (2H, br s), 7.66 (1H, s), 7.86 (1H, s), 8.29 (1H, d), 8.39 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 432.1.

Intermediate 47b:

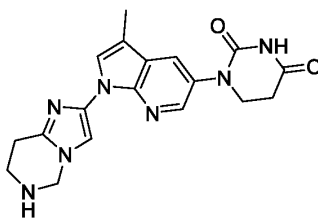
tert-Butyl 2-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-7,8-dihydro-5*H*-imidazo[1,2-*c*]pyrimidine-6-carboxylate



[1526] Prepared in an analogous manner to Intermediate 4b starting from Intermediate 47a (70 mg, 0.16 mmol). Purification by FSC (elution gradient: 0-100% EtOAc in hexane) gave the title compound (40.0 mg, 53.1 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.46 (8H, s), 2.32 (3H, d), 2.78 (2H, s), 3.79 - 3.91 (5H, m), 4.09 (3H, br s), 4.59 - 4.62 (3H, m), 7.65 - 7.76 (1H, m), 7.84 - 7.90 (1H, m), 7.97 - 8.07 (1H, m), 8.28 - 8.36 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 466.0.

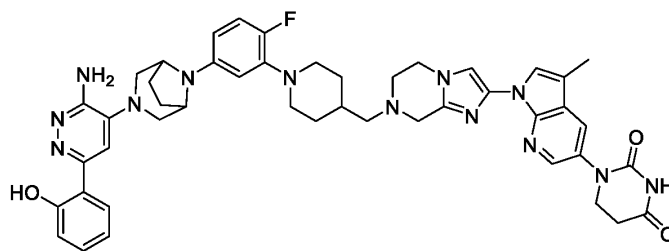
Intermediate 47c:

1-[3-Methyl-1-(5,6,7,8-tetrahydroimidazo[1,2-*c*]pyrimidin-2-yl)pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1527] TFA (0.248 mL, 3.22 mmol) was added to a stirred solution of Intermediate 47b (50mg, 0.11 mmol) in DCM (1.5 mL). The resulting solution was stirred at r.t. for 1 h. The reaction mixture was concentrated. The crude product was dissolved in MeOH and solid supported bicarbonate was added and stirred for 1 h, filtered and concentrated to give the title compound (30.0 mg, 76 %) as a gum. The crude product used for the next step without further purification. *m/z* (ES⁺) [M+H]⁺ = 366.1.

1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazin-2-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

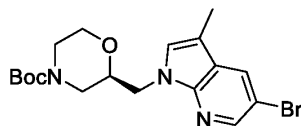


[1528] Prepared in an analogous manner to Example 39 starting from Intermediate 11g (34.6 mg, 0.05 mmol) and Intermediate 47c (20 mg, 0.05 mmol). Purification by RPC (elution gradient: 0-80% MeCN in water with 0.2% NH₄OH) gave the title compound (15 mg, 32.2 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.32 (2H, br d), 1.72 - 1.79 (1H, m), 1.84 (2H, br d), 1.92 - 1.99 (2H, m), 2.13 (2H, br d), 2.32 (3H, s), 2.46 (2H, br d), 2.69 (2H, br t), 2.78 (2H, br t), 2.90 (2H, br s), 3.11 (2H, br d), 3.27 (2H, br d), 3.38 (2H, br d), 3.65 (2H, s), 3.86 (2H, t), 4.07 (2H, br s), 4.35 (2H, br s), 5.94 (2H, s), 6.38 - 6.54 (2H, m), 6.82 - 6.98 (3H, m), 7.23 (1H, t), 7.47 (1H, s), 7.65 (1H, s), 7.85 (1H, s), 7.91 (1H, br d), 8.00 (1H, d), 8.30 (1H, d), 10.43 (1H, s), 14.17 (1H, br s). *m/z* (ES⁺) [M+H]⁺ = 852.4.

Example 48

Intermediate 48a:

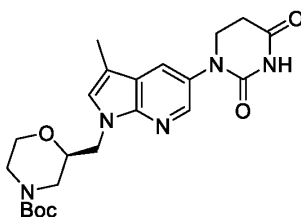
tert-Butyl (2*S*)-2-[(5-bromo-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl)methyl]morpholine-4-carboxylate



[1529] Prepared in an analogous manner to Intermediate 4a starting from 5-bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (0.500 g, 2.37 mmol) and *tert*-butyl (*R*)-2-(hydroxymethyl)morpholine-4-carboxylate (0.772 g, 3.55 mmol). Purification by FSC (elution gradient: 0 to 50% EtOAc in hexane) gave the title compound (0.845 g, 87 %) as an off-white foam. ¹H NMR (CDCl₃): δ 1.44 (9H, s), 2.27 (3H, s), 2.61 (1H, br s), 2.91 (1H, br s), 3.47 (1H, td), 3.71 - 4.08 (4H, m), 4.16 - 4.42 (2H, m), 7.06 (1H, br d), 7.95 (1H, s), 8.30 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 410.1, 412.0.

Intermediate 48b:

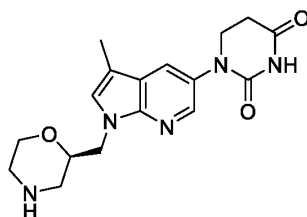
tert-Butyl (2*S*)-2-[[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl)methyl]morpholine-4-carboxylate



[1530] Prepared in an analogous manner to Intermediate 6b starting from Intermediate 48a (0.838 g, 2.04 mmol), Purification by FSC (elution gradient: 0 to 15% MeOH in DCM and 0 to 100% [3:1 EtOAc/EtOH] in hexane) gave the title compound (0.625 g, 69.0 %) as an orange solid. ¹H NMR (DMSO-*d*₆): δ 1.36 (9H, s), 2.24 (3H, d), 2.51 - 2.71 (1H, m), 2.75 (2H, t), 2.78 - 2.92 (1H, m), 3.27 - 3.35 (1H, m), 3.65 (1H, br d), 3.68 - 3.76 (2H, m), 3.80 (3H, t), 4.27 (2H, br d), 7.33 (1H, d), 7.89 (1H, d), 8.18 (1H, d), 10.37 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 444.4.

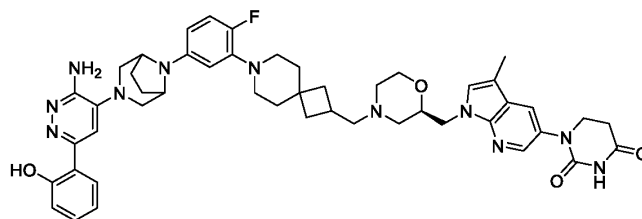
Intermediate 48c:

1-[3-Methyl-1-[(2*R*)-morpholin-2-yl]methyl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1531] Prepared in an analogous manner to Intermediate 46h starting from Intermediate 48b (400mg, 0.90 mmol). The reaction mixture was concentrated to give title compound (270 mg, 87 %) as a white solid. The crude material was used for the next step without further purification. m/z (ES^+) $[M+H]^+ = 344.3$.

1-[1-[(2*R*)-4-[[7-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-7-azaspiro[3.5]nonan-2-yl]methyl]morpholin-2-yl]methyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

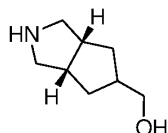


[1532] Prepared in an analogous manner to Example 46 starting from Intermediate 46g (50 mg, 0.05 mmol) and Intermediate 48c (18.72 mg, 0.05 mmol). Purification by RPC (elution gradient: 0-60% CH_3CN /water with 0.1% formic acid) gave the title compound (13.00 mg, 27.4 %) as a white solid. 1H NMR ($DMSO-d_6$): δ 1.40 (2H, br t), 1.57 (2H, br s), 1.69 (2H, br s), 1.81 (1H, s), 1.87 - 1.97 (4H, m), 1.98 - 2.04 (1H, m), 2.08 (1H, s), 2.13 (2H, br d), 2.25 (3H, s), 2.30 - 2.38 (2H, m), 2.40 - 2.46 (1H, m), 2.54 - 2.60 (1H, m), 2.63 - 2.69 (1H, m), 2.75 (2H, t), 2.84 (2H, br s), 2.93 (2H, br s), 3.10 (2H, br d), 3.25 - 3.28 (1H, m), 3.37 - 3.43 (1H, m), 3.74 - 3.85 (4H, m), 4.20 - 4.28 (2H, m), 4.35 (2H, br s), 5.93 (2H, s), 6.40 - 6.50 (2H, m), 6.82 - 6.95 (3H, m), 7.22 (1H, t), 7.33 (1H, s), 7.47 (1H, s), 7.89 (2H, d), 8.19 (1H, d), 10.32 - 10.46 (1H, br s), 13.90 - 14.47 (1H, br s); m/z (ES^+) $[M+H]^+ = 870.7$.

Example 49

Intermediate 49a:

[(3*aR*,6*aS*)-1,2,3,3*a*,4,5,6,6*a*-Octahydrocyclopenta[*c*]pyrrol-5-yl]methanol

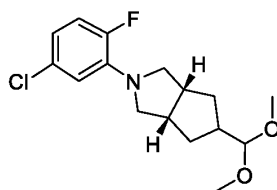


[1533] *tert*-Butyl (3*aR*,6*aS*)-5-(hydroxymethyl)hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate (5 g, 20.72 mmol) was added to 4M HCl in dioxane (15 mL, 493.72 mmol). The resulting mixture was stirred at r.t. for 1 h. The reaction mixture was diluted with MTBE forming a precipitate. The solid was collected

by filtration and dried under vacuum. The solid was suspended in MeCN (15 mL) and MeOH (6 mL) and K_2CO_3 (2 g) was added. The resulting mixture was stirred at r.t. for 1 h. The reaction mixture was filtered, and the filtrate was concentrated to afford the title compound (2.30 g, 79 %) as colorless oil. 1H NMR (DMSO-*d*₆): δ 0.84 – 0.96 (2H, m), 1.36 – 1.47 (1H, m), 1.81 – 1.87 (1H, m), 1.88 – 1.94 (2H, m), 2.46 – 2.49 (1H, m), 2.63 – 2.67 (2H, m), 2.68 – 2.74 (2H, m), 3.25 – 3.35 (3H, m), 4.69 (1H, brs); m/z (ES^+) $[M+H]^+ = 142.2$.

Intermediate 49b:

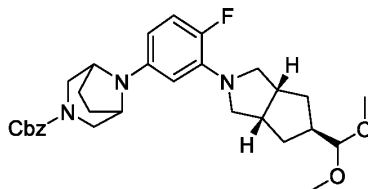
(3*aR*,6*aS*)-2-(5-Chloro-2-fluoro-phenyl)-5-(dimethoxymethyl)-3,3*a*,4,5,6,6*a*-hexahydro-1*H*-cyclopenta[*c*]pyrrole



[1534] DMSO (3.29 mL, 46.34 mmol) was added to oxalyl dichloride (3.53 g, 27.80 mmol) in DCM (20 mL) at -78 °C under nitrogen. The resulting mixture was stirred at -78 °C for 30 min. then a solution of Intermediate 49a (2.5 g, 9.27 mmol) in DCM (2 mL) was added. The resulting mixture was stirred at -78 °C for 1 h. Et₃N (7.75 mL, 55.61 mmol) was added and resulting mixture was stirred at -40 °C for 1 h. The reaction mixture was diluted with DCM (100 mL) and washed sequentially with sat. aq. NH₄Cl (2 x 50 mL), brine (2 x 50 mL). The organic layer was dried over Na₂SO₄, filtered, and evaporated. To the crude aldehyde was added *p*TsOH (0.353 g, 1.85 mmol) and trimethoxymethane (1.967 g, 18.54 mmol) in MeOH (30 mL). The resulting mixture was stirred at r.t. for 6 h. The solvent was removed under reduced pressure. Purification by RPC (elution gradient: 5 to 100% MeCN in water with 0.5% NH₄HCO₃) gave the title compound (2.10 g, 72.2 %) as a yellow oil. 1H NMR (CDCl₃): δ 1.24 – 1.36 (1H, m), 1.64 – 1.72 (1H, m), 2.04 – 2.15 (1H, m), 2.22 – 2.54 (1H, m), 2.64 – 2.86 (2H, m), 2.99 – 3.08 (1H, m), 3.16 – 3.23 (1H, m), 3.27 – 3.33 (2H, m), 3.34 (6H, s), 3.43 – 3.52 (1H, m), 4.12 – 4.24 (1H, m), 6.63 – 6.72 (2H, m), 6.84 – 6.96 (1H, m); m/z (ES^+) $[M+H]^+ = 314.2$.

Intermediate 49c:

Benzyl 8-[3-[(3*aR*,6*aS*)-5-(dimethoxymethyl)-3,3*a*,4,5,6,6*a*-hexahydro-1*H*-cyclopenta[*c*]pyrrol-2-yl]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate

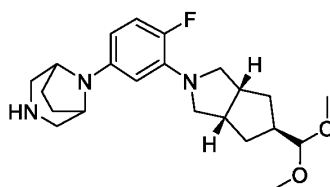


[1535] Prepared in an analogous manner to Intermediate 42c from Intermediate 49b (2.1 g, 6.69 mmol) and benzyl-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (1.648 g, 6.69 mmol). Purification by FSC (elution

gradient 0 to 50% EtOAc in petroleum ether) gave the title compound (3.20 g, 91 %, mixture of trans and cis isomers) as a yellow oil. The mixture was purified by SFC (Column: CHIRAL ART Cellulose-SB, 3.0 x 100mm, 3 μ m; Mobile Phase A: CO₂, Mobile Phase B: MeOH; Flow rate: 100 mL/min; Gradient: isocratic 15% B; Back Pressure(bar): 100; wave length: 220 nm). The fractions containing the desired compound were evaporated to dryness to afford the title compound (0.800 g, 25.00 %) as a dark oil. ¹H NMR (CDCl₃): δ 1.65 – 1.71 (4H, m), 1.75 – 1.89 (2H, m), 1.97 – 2.07 (2H, m), 2.46 – 2.55 (1H, m), 2.78 – 2.87 (2H, m), 2.95 – 3.02 (2H, m), 3.29 – 3.31 (1H, m), 3.35 (6H, s), 3.38 – 3.43 (1H, m), 3.45 – 3.52 (2H, m), 3.68 – 3.74 (1H, m), 3.76 – 3.82 (1H, m), 4.05 – 4.14 (2H, m), 4.16 (1H, d), 5.15 (2H, s), 6.12 – 6.20 (2H, m), 6.82 – 6.91 (1H, m), 7.31 – 7.40 (5H, m). m/z (ES⁺) [M+H]⁺ = 524.3.

Intermediate 49d:

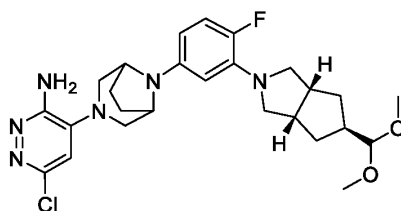
8-[3-[(3*aR*,6*aS*)-5-(Dimethoxymethyl)-3,3*a*,4,5,6,6*a*-hexahydro-1*H*-cyclopenta[*c*]pyrrol-2-yl]-4-fluorophenyl]-3,8-diazabicyclo[3.2.1]octane



[1536] Pd/C (10%) (15.24 mg, 0.14 mmol) was added to Intermediate 49c (750 mg, 1.43 mmol) in MeOH (25 mL) under nitrogen. The resulting mixture was flushed with hydrogen and stirred at r.t. under hydrogen atmosphere for 16 h. The reaction was filtered through celite®, and the filtrate concentrated under reduced pressure to afford title compound (486 mg, 87 %) as a colorless gum. ¹H NMR (DMSO-*d*₆): δ 1.48 – 1.61 (4H, m), 1.93 – 2.09 (4H, m), 2.29 – 2.42 (1H, m), 2.67 – 2.76 (2H, m), 2.79 – 2.86 (2H, m), 2.88 – 2.96 (2H, m), 3.01 – 3.05 (2H, m), 3.23 (6H, s), 3.34 – 3.41 (2H, m), 4.11 (1H, d), 4.22 – 4.28 (2H, m), 6.12 – 6.25 (2H, m), 6.85 – 6.94 (1H, m); m/z (ES⁺) [M+H]⁺ = 390.4.

Intermediate 49e:

4-[8-[3-[(3*aR*,6*aS*)-5-(Dimethoxymethyl)-3,3*a*,4,5,6,6*a*-hexahydro-1*H*-cyclopenta[*c*]pyrrol-2-yl]-4-fluorophenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]-6-chloro-pyridazin-3-amine

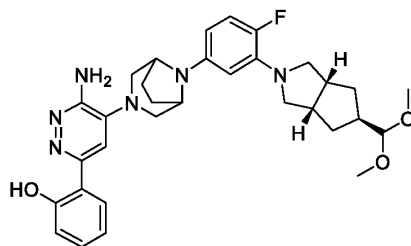


[1537] Intermediate 49d (476 mg, 1.22 mmol) was added to 4-bromo-6-chloropyridazin-3-amine (306 mg, 1.47 mmol) and DIPEA (0.640 mL, 3.67 mmol) in DMSO (7 mL). The resulting mixture was stirred at 80 °C for 24 h. The crude product was purified by RPC (elution gradient: 5 to 80% MeCN in water (0.1% NH₄HCO₃)) to afford the title compound (400 mg, 63.3 %) as a yellow solid. ¹H NMR (DMSO-*d*₆): δ 1.50

– 1.63 (4H, m), 1.85 – 1.96 (2H, m), 2.03 – 2.12 (2H, m), 2.33 – 2.44 (1H, m), 2.65 – 2.78 (2H, m), 2.89 – 3.01 (4H, m), 3.14 – 3.18 (1H, m), 3.24 (6H, s), 3.35 – 3.43 (2H, m), 4.13 (1H, d), 4.24 – 4.29 (2H, m), 5.80 (2H, s), 6.17 – 6.30 (2H, m), 6.82 – 6.93 (2H, m); m/z (ES⁺) [M+H]⁺ = 517.2.

Intermediate 49f:

2-[5-[8-[3-[(3*aR*,6*aS*)-5-(dimethoxymethyl)-3,3*a*,4,5,6,6*a*-hexahydro-1*H*-cyclopenta[*c*]pyrrol-2-yl]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]-6-amino-pyridazin-3-yl]phenol



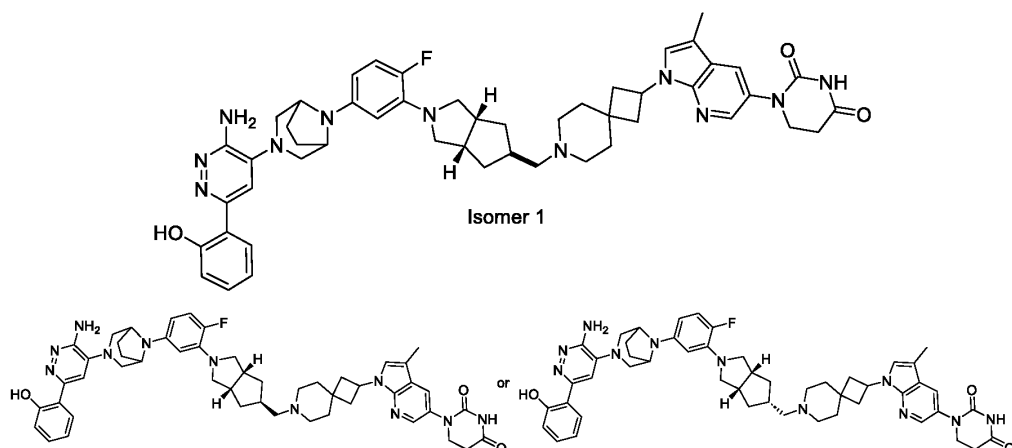
[1538] Prepared in an analogous manner to Intermediate 2h from Intermediate 49e (450 mg, 0.87 mmol). Purification by FSC (elution gradient: 0 to 40% EtOAc in petroleum ether, then 0 to 10% MeOH in DCM) gave the title compound (330 mg, 66.0 %) as a white solid. ¹H NMR (DMSO-*d*₆) δ 1.51 – 1.60 (4H, m), 1.87 – 1.98 (2H, m), 2.06 – 2.15 (2H, m), 2.32 – 2.43 (1H, m), 2.66 – 2.73 (2H, m), 2.88 – 2.97 (2H, m), 3.04 – 3.12 (2H, m), 3.21 (6H, s), 3.34 – 3.42 (2H, m), 3.22 – 3.27 (2H, m), 4.11 (1H, d), 4.29 – 4.36 (2H, m), 5.92 (2H, s), 6.18 – 6.31 (2H, m), 6.80 – 6.93 (3H, m), 7.17 – 7.26 (1H, m), 7.45 (1H, s), 7.90 (1H, d), 14.17 (1H, s); m/z (ES⁺) [M+H]⁺ = 575.

1-[3-Methyl-1-[7-[[*rel*-(3*aR*,5*r**,6*aS*)-2-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3*a*,4,5,6,6*a*-hexahydro-1*H*-cyclopenta[*c*]pyrrol-5-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione
(ISOMER 1)

[*absolute configuration not yet confirmed]

1-[3-Methyl-1-[7-[[3*aR*,5*s*,6*aS*)-2-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3*a*,4,5,6,6*a*-hexahydro-1*H*-cyclopenta[*c*]pyrrol-5-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione
or

1-[3-Methyl-1-[7-[[3*aR*,5*r*,6*aS*)-2-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3*a*,4,5,6,6*a*-hexahydro-1*H*-cyclopenta[*c*]pyrrol-5-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1539] A vial was charged with Intermediate 49f (100 mg, 0.17 mmol) and formic acid (2 mL). The mixture was stirred at 40 °C for 30 mins. The reaction mixture was evaporated to dryness, redissolved in DCM (5 mL), and washed with sat. aq. NaHCO₃ (2 x 2 mL). The organic layer was dried over Na₂SO₄, filtered, and evaporated to afford crude yellow solid. The crude aldehyde was taken up in DCM (6 mL) and LiBH₄ (7.58 mg, 0.35 mmol) was added. The resulting mixture was stirred at r.t., for 1 h. The reaction mixture was evaporated to dryness, redissolved in DCM (5 mL), and washed with sat. aq. NH₄Cl (2 x 2 mL). The organic layer was dried over Na₂SO₄, filtered, and evaporated to afford crude yellow solid. The crude alcohol was dissolved in DCM (6 mL) and methanesulfonic anhydride (39.4 mg, 0.23 mmol) and NEt₃ (0.073 mL, 0.52 mmol) were added. The resulting mixture was stirred at r.t. for 2 h. The reaction mixture was evaporated to dryness, redissolved in DCM (10 mL), and washed with sat. aq. NH₄Cl (2 x 2 mL). The organic layer was dried over Na₂SO₄, filtered, and evaporated to afford crude yellow solid. The crude mesylate was dissolved in dioxane (6 mL) and KI (28.9 mg, 0.17 mmol) and Intermediate 42f (63.9 mg, 0.17 mmol) were added. The resulting mixture was stirred at 80 °C for 16 h. The reaction was cooled to r.t. and concentrated. Purification by RPC (elution gradient: 0-70% CH₃CN in water with 0.1% formic acid) gave a mixture of two isomers. The isomers were separated by prep HPLC (Column: Xselect CSH Prep C18 OBD, 19x250mm, 5 µm; Mobile Phase A: water with 0.1% FA, Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 26% B to 33% B in 10 min). The title compound (8 mg, 4.96 %), which eluted from the column first, was obtained as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.41 – 1.49 (2H, m), 1.60 – 1.74 (6H, m), 1.90 – 1.98 (2H, m), 2.13 (2H, d), 2.16 – 2.22 (4H, m), 2.25 – 2.28 (4H, m), 2.29 – 2.39 (5H, m), 2.69 – 2.78 (4H, m), 2.91 – 2.98 (2H, m), 3.11 (2H, d), 3.26 (2H, d), 3.51 – 3.53 (3H, m), 3.77 – 3.83 (2H, t), 4.31 – 4.38 (2H, m), 5.20 – 5.29 (1H, m), 5.9 – 5.98 (2H, m), 6.23 – 6.32 (2H, m), 6.84 – 6.92 (3H, m), 7.23 (1H, t), 7.47 (1H, s), 7.60 (1H, s), 7.86 – 7.95 (2H, m), 8.16 (1H, s), 8.30 (1H, s), 10.39 (1H, s), 14.22 (1H, s); ¹⁹F NMR (DMSO-*d*₆): δ -136.691. *m/z* (ES+) [M+H]⁺ = 880.5.

Example 50:

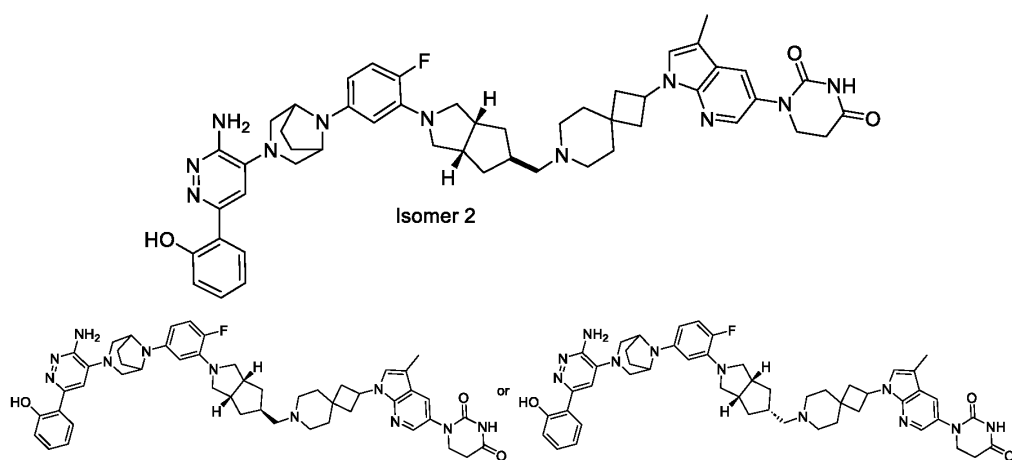
1-[3-Methyl-1-[7-[[*rel*-(3*aR*,5*r**,6*aS*)-2-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3*a*,4,5,6,6*a*-hexahydro-1*H*-cyclopenta[*c*]pyrrol-5-

yl)methyl]-7-azaspiro[3.5]nonan-2-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione
(ISOMER 2)

[*absolute configuration not yet confirmed]

1-[3-Methyl-1-[7-[(3*aR*,5*s*,6*aS*)-2-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3*a*,4,5,6,6*a*-hexahydro-1*H*-cyclopenta[*c*]pyrrol-5-yl)methyl]-7-azaspiro[3.5]nonan-2-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione
or

1-[3-Methyl-1-[7-[(3*aR*,5*r*,6*aS*)-2-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3*a*,4,5,6,6*a*-hexahydro-1*H*-cyclopenta[*c*]pyrrol-5-yl)methyl]-7-azaspiro[3.5]nonan-2-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

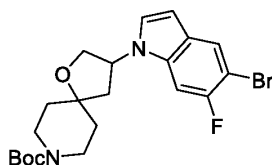


[1540] Prepared with an analogous method to Example 49 starting with Intermediate 49f (100 mg, 0.17 mmol). Purification prep HPLC (Column: Xselect CSH Prep C18 OBD, 19x250mm, 5 μ m; Mobile Phase A: water with 0.1% FA, Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 26% B to 33% B in 10 min) gave the title compound (5 mg, 3.04 %), which eluted second from the column, as a white solid. ^1H NMR (DMSO-*d*₆): δ 0.97 – 1.08 (2H, m), 1.66 – 1.73 (4H, m), 1.92 – 1.97 (2H, m), 2.06 – 2.15 (5H, m), 2.17 – 2.23 (3H, m), 2.22 – 2.30 (6H, m), 2.30 – 2.39 (5H, m), 2.59 – 2.64 (2H, m), 2.76 (2H, t), 3.07 – 3.12 (3H, m), 3.21 – 3.29 (3H, m), 3.44 – 3.54 (1H, m), 3.78 – 3.80 (2H, m), 4.31 – 4.36 (2H, m), 5.23 – 5.27 (1H, m), 5.95 (2H, s), 6.25 – 6.31 (2H, m), 6.85 – 6.91 (3H, m), 7.23 (1H, t), 7.47 (1H, s), 7.61 (1H, s), 7.87 – 7.93 (2H, m), 8.17 (1H, s), 8.32 (1H, s), 10.39 (1H, s), 14.22 (1H, s); ^{19}F NMR (DMSO-*d*₆) δ -136.823 1; m/z (ES⁺), [M+H]⁺ = 880.4.

Example 51

Intermediate 51a:

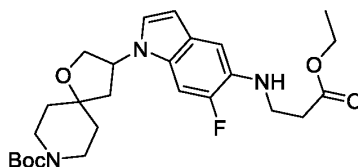
tert-Butyl 3-(5-bromo-6-fluoro-indol-1-yl)-1-oxa-8-azaspiro[4.5]decane-8-carboxylate



[1541] Prepared with an analogous method to Intermediate 4a starting from 5-bromo-6-methyl-1*H*-indole (0.6g, 2.80 mmol) and *tert*-butyl 3-hydroxy-1-oxa-8-azaspiro[4.5]decane-8-carboxylate (1.37 g, 5.32 mmol). Purification by FSC (elution gradient: 0-70% EtOAc in hexanes) gave the title compound (856mg, 67%) as an off-white solid. ¹H NMR (CD₂Cl₂): δ 1.47 (9H, s), 1.56 - 1.70 (2H, m, overlaps with residual water), 1.71 - 1.81 (2H, m), 1.99 (1H, dd), 2.43 (1H, dd), 3.37 (2H, ddt), 3.64 (2H, ddt), 4.21 - 4.29 (2H, m), 4.98 - 5.03 (1H, m), 6.50 (1H, d), 7.25 (1H, d), 7.38 (1H, d), 7.80 (1H, d); ¹⁹F NMR (CD₂Cl₂): δ -115.78 (1F, s); *m/z* (ES⁺) [M-*t*Bu+H]⁺ = 397.1.

Intermediate 51b:

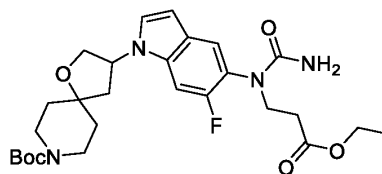
tert-Butyl 3-[5-[(3-ethoxy-3-oxo-propyl)amino]-6-fluoro-indol-1-yl]-1-oxa-8-azaspiro[4.5]decane-8-carboxylate



[1542] Prepared with an analogous method to Intermediate 14b with addition of *t*BuBrettPhos (42.8 mg, 0.09 mmol) starting from Intermediate 51a (0.40 g, 0.88 mmol). Purification by FSC (elution gradient: 0-50% EtOAc/hexanes) afforded the title compound, (0.361 g, 84%) as a yellow gum. ¹H NMR (CD₂Cl₂): δ 1.29 (3H, t), 1.47 (9H, s), 1.56 - 1.71 (2H, m, overlaps with residual water), 1.75 (2H, br s), 2.00 (1H, dd), 2.39 (1H, dd), 2.69 (2H, t), 3.30 - 3.43 (2H, m), 3.51 (2H, br t), 3.56 - 3.68 (2H, m), 4.05 (1H, br s), 4.18 (3H, q), 4.22 - 4.28 (1H, m), 4.93 - 5.00 (1H, m), 6.39 (1H, d), 6.92 (1H, d), 7.12 (1H, d), 7.23 (1H, d); ¹⁹F NMR (CD₂Cl₂): δ -139.89 (1F, s); *m/z* (ES⁺) [M+H]⁺ = 490.6.

Intermediate 51c:

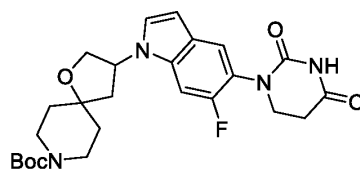
tert-Butyl 3-[5-[carbamoyl-(3-ethoxy-3-oxo-propyl)amino]-6-fluoro-indol-1-yl]-1-oxa-8-azaspiro[4.5]decane-8-carboxylate



[1543] Prepared with an analogous method to Intermediate 14c starting from Intermediate 51b (361 mg, 0.74 mmol) to afford the title compound. The crude product was used for the next step without purification and quantitative yield was assumed. *m/z* (ES⁺) [M+H]⁺ = 533.4.

Intermediate 51d:

tert-Butyl 3-[5-(2,4-dioxohexahydropyrimidin-1-yl)-6-fluoro-indol-1-yl]-1-oxa-8-azaspiro[4.5]decane-8-carboxylate



[1544] Prepared with an analogous method to Intermediate 14d starting from Intermediate 51c (394 mg, 0.74 mmol) to give title compound (338 mg, 94 %) as an off-white solid. ¹H NMR (CD₂Cl₂): δ 1.47 (9H, s), 1.59 (2H, s), 1.72 - 1.83 (2H, m), 1.99 - 2.05 (1H, m), 2.44 (1H, dd), 2.87 (2H, t), 3.33 - 3.43 (2H, m), 3.58 - 3.70 (2H, m), 3.83 (2H, t), 4.21 - 4.32 (2H, m), 5.00 - 5.07 (1H, m), 6.57 (1H, d), 7.25 - 7.30 (1H, m), 7.39 - 7.43 (1H, m), 7.56 (1H, d), 7.63 (1H, s); *m/z* (ES⁺) [M-tBu+H]⁺ = 431.2.

Intermediate 51c:

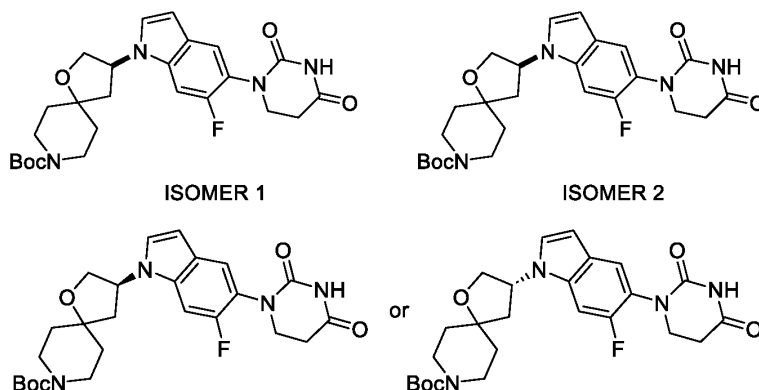
tert-Butyl *rel*-(3*S**)-3-[5-(2,4-dioxohexahydropyrimidin-1-yl)-6-fluoro-indol-1-yl]-1-oxa-8-azaspiro[4.5]decane-8-carboxylate

[*absolute configuration not yet confirmed]

tert-Butyl (3*S*)-3-[5-(2,4-dioxohexahydropyrimidin-1-yl)-6-fluoro-indol-1-yl]-1-oxa-8-azaspiro[4.5]decane-8-carboxylate

or

tert-Butyl (3*R*)-3-[5-(2,4-dioxohexahydropyrimidin-1-yl)-6-fluoro-indol-1-yl]-1-oxa-8-azaspiro[4.5]decane-8-carboxylate



[1545] Intermediate 51d (0.338 g, 0.69 mmol) was purified by chiral SFC (Column: IH 21mm × 250 5μm, MeOH/0.2% NH₄OH) to give the title compound, Isomer 1, that eluted first from the column (136 mg) as an off-white solid and Isomer 2 (133 mg) that eluted second from the column as a white solid.

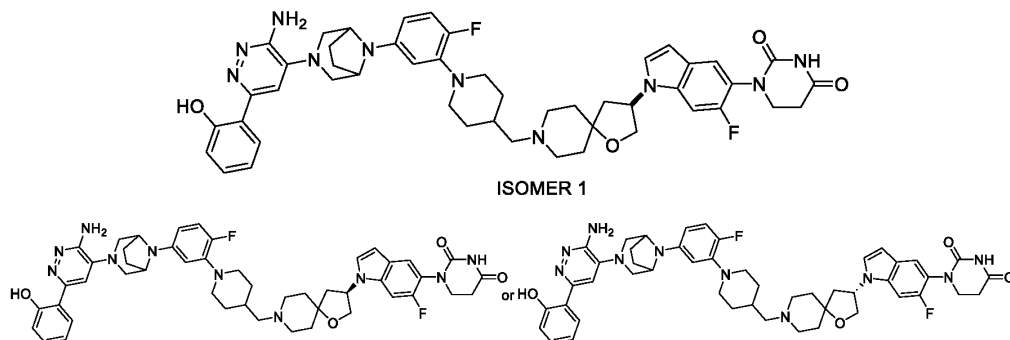
1-[6-Fluoro-1-[*rel*-(3*R**)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]indol-5-yl]hexahydropyrimidine-2,4-dione (ISOMER 1)

[*absolute configuration not yet confirmed]

1-[6-Fluoro-1-[(3*R*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]indol-5-yl]hexahydropyrimidine-2,4-dione

or

1-[6-Fluoro-1-[(3*S*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]indol-5-yl]hexahydropyrimidine-2,4-dione



[1546] H₂SO₄ 2M aq. (719 μ l, 1.44 mmol) was added to a solution of Intermediate 51e, Isomer 1 (35 mg, 0.07 mmol) in THF (719 μ l), stirred at 50 °C for 2.5 h, and cooled to r.t. The reaction mixture was combined with a solution of Intermediate 11g (29 mg, 0.06 mmol) in 1M H₂SO₄ in THF/H₂O (1:1) were quenched with sat. aq. NaHCO₃ and diluted with DCM. The layers were separated, and the aq. layer was extracted with DCM/IPA (4:1). The combined organic extracts, were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting solids were dissolved in DCM (1.85 mL) and *i*PrOH (250 μ L) and stirred at r.t. for 5 min. Na(OAc)₃BH (14.7 mg, 0.07 mmol) was added and the mixture was stirred at r.t. for 5 min. and then held at 4 °C overnight. The reaction mixture was quenched with sat. aq. NaHCO₃, diluted with water and DCM, and the layers were separated. The aqueous layer was extracted with 20% IPA in DCM (2 x 20 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated. Purification by FSC (elution gradient: 80-100% MeOH in EtOAc and then 0 - 25% MeOH in EtOAc) followed by lyophilization gave the title compound (33.4 mg, 66.3 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.19 - 1.31 (2H, m), 1.55 - 1.84 (7H, m), 1.85 - 1.99 (3H, m), 2.09 - 2.22 (4H, m), 2.25 - 2.51 (5H, m, overlaps with residual solvent), 2.64 (2H, br t), 2.74 (2H, t), 3.10 (2H, br d), 3.23 - 3.29 (2H, m), 3.29 - 3.38 (2H, m, overlaps with residual water), 3.67 - 3.75 (2H, m), 4.00 (1H, dd), 4.17 (1H, dd), 4.34 (2H, br s), 5.23 (1H, dt), 5.93 (2H, s), 6.40 - 6.50 (2H, m), 6.52 (1H, d), 6.83 - 6.96 (3H, m), 7.23 (1H, t), 7.47 (1H, s), 7.54 (1H, d), 7.57 (2H, d), 7.91 (1H, d), 10.40 (1H, s), 14.15 (1H, br s); ¹⁹F NMR (DMSO-*d*₆) δ -136.37 (1F, s), -128.92 (1F, s); *m/z* ES⁺ [M+H]⁺ 873.5.

Example 52

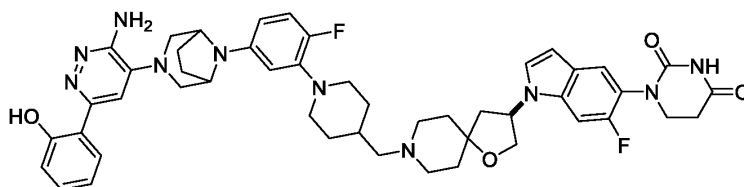
1-[6-Fluoro-1-[(*rel*-(3*R**)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl)methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]indol-5-yl]hexahydropyrimidine-2,4-dione (ISOMER 2)

[*absolute configuration not yet confirmed]

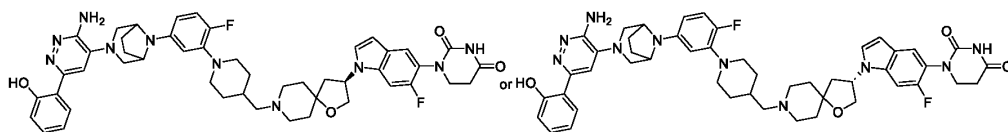
1-[6-Fluoro-1-[(3*R*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl)methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]indol-5-yl]hexahydropyrimidine-2,4-dione

or

1-[6-Fluoro-1-[(3*S*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl)methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]indol-5-yl]hexahydropyrimidine-2,4-dione



ISOMER 2

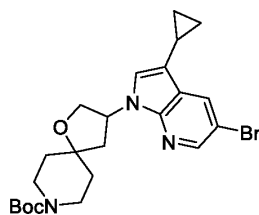


[1547] Prepared in an analogous method to Example 51 starting from Intermediate 51e, Isomer 2 (35 mg, 0.07 mmol) and Intermediate 11g (28 mg, 0.06 mmol). Purification by FSC (elution gradient: 0-20% MeOH in EtOAc) followed by lyophilization gave the title compound (36.7 mg, 75 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.19 - 1.32 (2H, m), 1.57 - 1.84 (7H, m), 1.85 - 2.00 (3H, m), 2.13 (2H, br d), 2.17 - 2.29 (2H, m), 2.30 - 2.45 (3H, m), 2.47 - 2.55 (2H, m, overlaps with residual solvent), 2.64 (2H, br t), 2.74 (2H, br t), 3.10 (2H, br d), 3.22 - 3.29 (2H, m, overlaps with residual water), 3.30 - 3.39 (2H, m, overlaps with residual water), 3.71 (2H, br t), 4.00 (1H, br dd), 4.17 (1H, dd), 4.34 (2H, br s), 5.23 (1H, dt), 5.93 (2H, s), 6.39 - 6.45 (1H, m), 6.45 - 6.50 (1H, m), 6.52 (1H, d), 6.83 - 6.95 (3H, m), 7.23 (1H, t), 7.46 (1H, s), 7.53 (1H, d), 7.56 (1H, d), 7.58 (1H, s), 7.90 (1H, d), 10.40 (1H, s), 14.15 (1H, br s); ¹⁹F NMR (DMSO-*d*₆) δ -136.37 (1F, s), -128.91 (1F, s); *m/z* ES⁺ [M+H]⁺ 873.5.

Example 53

Intermediate 53a:

tert-Butyl 3-(5-bromo-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-1-yl)-1-oxa-8-azaspiro[4.5]decane-8-carboxylate



[1548] Prepared in an analogous method to Intermediate 4a starting from 5-bromo-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridine (0.6 g, 2.53 mmol) and *tert*-butyl 3-hydroxy-1-oxa-8-azaspiro[4.5]decane-8-carboxylate (1.24 g, 4.81 mmol). Purification by FSC (elution gradient: 0-30% EtOAc in hexanes) gave the title compound (1.0911 g, 91 %) an off-white solid. ¹H NMR (CD₂Cl₂): δ 0.61 - 0.70 (2H, m), 0.89 - 0.97 (2H, m), 1.47 (9H, s), 1.56 - 1.64 (1H, m), 1.67 - 1.83 (3H, m), 1.87 - 1.94 (1H, m), 1.98 (1H, dd), 2.43 (1H, dd), 3.33 - 3.46 (2H, m), 3.61 (2H, br d), 4.08 (1H, dd), 4.25 (1H, dd), 5.52 - 5.58 (1H, m), 7.18 (1H, s), 8.13 (1H, d), 8.30 (1H, d); *m/z* ES⁺ [M+2H]⁺ = 478.2.

Intermediate 53b:

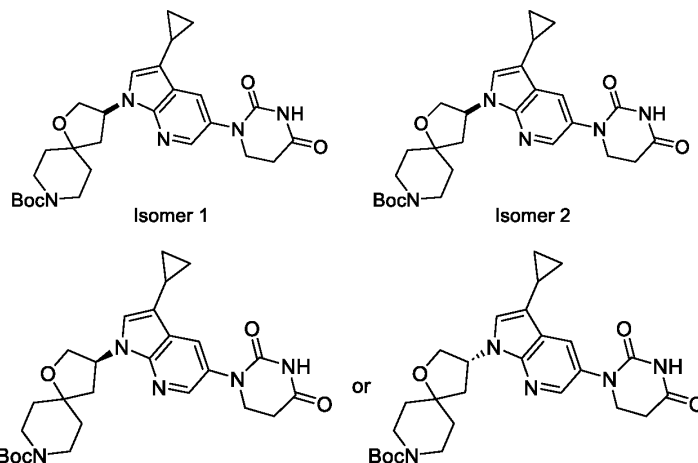
tert-Butyl (3*S**)-3-[3-cyclopropyl-5-(2,4-dioxohexahydropyrimidin-1-yl)pyrrolo[2,3-*b*]pyridin-1-yl]-1-oxa-8-azaspiro[4.5]decane-8-carboxylate

[*absolute configuration not yet confirmed]

tert-Butyl (3*S*)-3-[3-cyclopropyl-5-(2,4-dioxohexahydropyrimidin-1-yl)pyrrolo[2,3-*b*]pyridin-1-yl]-1-oxa-8-azaspiro[4.5]decane-8-carboxylate

or

tert-Butyl (3*R*)-3-[3-cyclopropyl-5-(2,4-dioxohexahydropyrimidin-1-yl)pyrrolo[2,3-*b*]pyridin-1-yl]-1-oxa-8-azaspiro[4.5]decane-8-carboxylate



[1549] Prepared in an analogous method to Intermediate 35b with the addition of *t*BuBrettPhos (41.7 mg, 0.09 mmol) starting from Intermediate 53a (410 mg, 0.86 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes and then 0 to 4% MeOH in EtOAc) gave a racemic mixture of the title compound (290 mg, 66.1 %) as a tan solid. The racemate was further purified by chiral SFC (Column: IH

21mm × 250 5µm, MeOH/0.2% NH₄OH) to give the title compound, Isomer 1, that eluted first from the column (127 mg, 29.0%) as a clear film, which turned to a white solid upon scraping the sides of the vial, and Isomer 2 (119 mg, 27.1%) that eluted second from the column as an off white solid. Isomer 1: ¹H NMR (CD₂Cl₂): δ 0.64 - 0.71 (1H, m), 0.91 - 0.97 (2H, m), 1.47 (9H, s), 1.57 - 1.65 (1H, m, overlaps with residual water), 1.68 - 1.86 (3H, m), 1.90 - 1.98 (1H, m), 1.94 - 1.94 (1H, m), 2.01 (1H, dd), 2.44 (1H, dd), 2.90 (2H, t), 3.33 - 3.48 (2H, m), 3.61 (2H, br d), 3.92 (2H, t), 4.10 (1H, dd), 4.26 (1H, dd), 5.56 - 5.64 (1H, m), 7.22 (1H, s), 7.60 (1H, br s), 7.92 (1H, d), 8.23 (1H, d); *m/z* ES⁺ [M+H]⁺ = 510.3. Isomer 2: ¹H NMR (CD₂Cl₂): δ 0.63 - 0.73 (2H, m), 0.88 - 0.99 (2H, m), 1.47 (9H, s), 1.56 - 1.65 (1H, m, overlaps with residual water), 1.66 - 1.85 (3H, m), 1.91 - 1.98 (1H, m), 2.01 (1H, dd), 2.44 (1H, dd), 2.90 (2H, t), 3.33 - 3.47 (2H, m), 3.61 (2H, br d), 3.92 (2H, t), 4.10 (1H, dd), 4.26 (1H, dd), 5.57 - 5.64 (1H, m), 7.22 (1H, s), 7.74 (1H, br s), 7.92 (1H, d), 8.23 (1H, d); *m/z* ES⁺ [M+H]⁺ 510.3.

Intermediate 53c

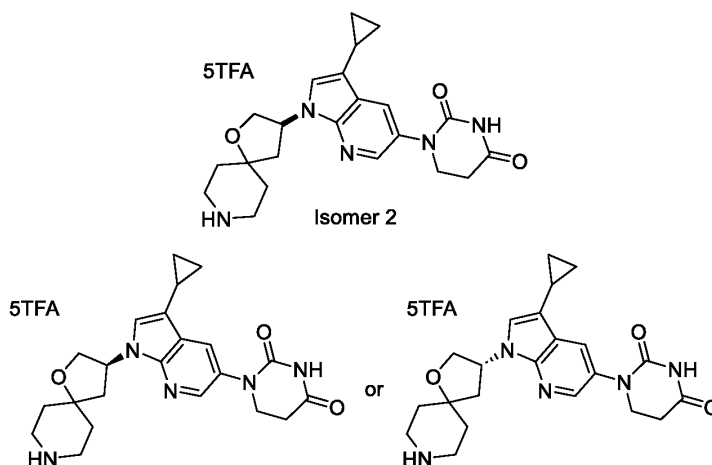
1-[3-Cyclopropyl-1-[(3*S**)-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione (ISOMER 2)

[*absolute configuration not yet confirmed]

1-[3-Cyclopropyl-1-[(3*S*)-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

or

1-[3-Cyclopropyl-1-[(3*R*)-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1550] TFA (360 µl, 4.67 mmol) was added to a solution of Intermediate 53b, Isomer 2 (119 mg, 0.23 mmol) in DCM (808 µl). The reaction was stirred at r.t. for 2 h and concentrated under reduced pressure. The residue was azeotroped with DCM (3x) and dried in vacuo to give the title compound (243 mg, 107 %) in the form of a *penta* TFA salt. Quantitative yield assumed. *m/z* ES⁺ [M+H]⁺ = 410.6.

1-[3-Cyclopropyl-1-*rel*-(3*R**)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

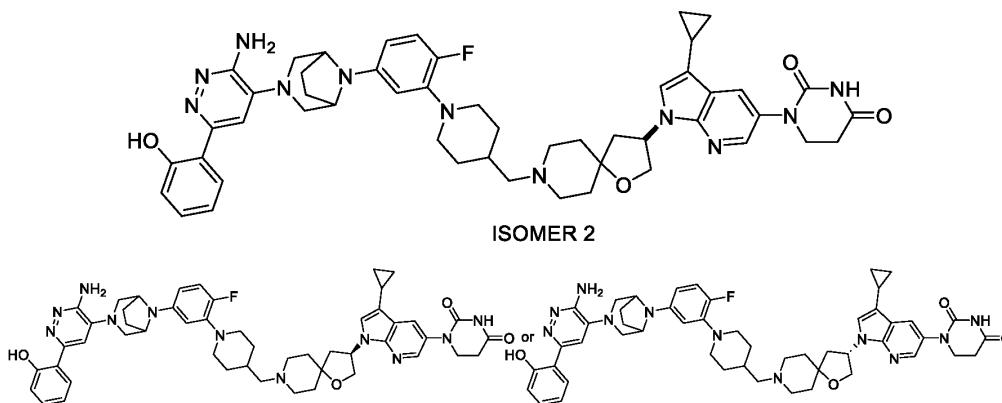
(ISOMER 2)

[*absolute configuration not yet confirmed]

1-[3-Cyclopropyl-1-[(3*R*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

or

1-[3-Cyclopropyl-1-[(3*S*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

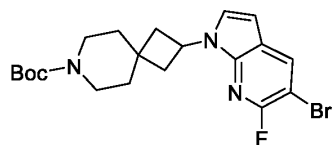


[1551] Prepared in an analogous method to Example 51 starting from Intermediate 53c (Isomer 2) (65.2 mg, 0.07 mmol) and Intermediate 11g (28 mg, 0.06 mmol). Purification by FSC (elution gradient: 80-100% EtOAc in hexanes and then 0 - 40% MeOH in EtOAc) followed by lyophilization gave the title compound (38.6 mg, 77 %) as a white solid. ¹H NMR (DMSO-*d*₆) δ 0.63 - 0.69 (2H, m), 0.83 - 0.91 (2H, m), 1.17 - 1.30 (2H, m), 1.54 - 1.83 (7H, m), 1.87 - 2.03 (4H, m), 2.10 - 2.20 (4H, m), 2.23 - 2.40 (3H, m), 2.51 (2H, br s), 2.63 (2H, br t), 2.77 (2H, t), 3.10 (2H, br d), 3.23 - 3.29 (2H, m), 3.34 (2H, s), 3.82 (2H, t), 3.95 (1H, dd), 4.13 (1H, dd), 4.34 (2H, br s), 5.43 (1H, quin), 5.93 (2H, s), 6.40 - 6.45 (1H, m), 6.48 (1H, br d), 6.82 - 6.97 (3H, m), 7.23 (1H, t), 7.40 (1H, s), 7.47 (1H, s), 7.90 (1H, d), 7.97 (1H, d), 8.20 (1H, d), 10.39 (1H, s), 14.16 (1H, br s). ¹⁹F NMR (DMSO-*d*₆) δ -136.36 (1F, s); *m/z* ES+ [M+H]⁺ 896.7.

Example 54

Intermediate 54a:

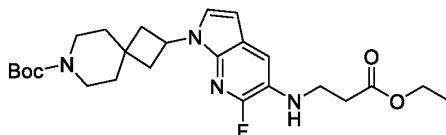
tert-Butyl 2-(5-bromo-6-fluoro-pyrrolo[2,3-*b*]pyridin-1-yl)-7-azaspiro[3.5]nonane-7-carboxylate



[1552] Prepared in an analogous manner to Intermediate 4a starting from *tert*-butyl 2-hydroxy-7-azaspiro[3.5]nonane-7-carboxylate (1.122 g, 4.65 mmol) and 5-bromo-6-fluoro-1*H*-pyrrolo[2,3-*b*]pyridine (1 g, 4.65 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in petroleum ether) gave the title compound (0.900 g, 44.1 %) as a yellow solid. ¹H NMR (DMSO-*d*₆): δ 1.41 (9H, s), 1.59 – 1.64 (2H, m), 1.64 – 1.69 (2H, m), 2.24 – 2.29 (2H, m), 2.40 – 2.46 (2H, m), 3.24 – 3.27 (2H, m), 3.34 – 3.36 (2H, m), 5.10 – 5.17 (2H, m), 6.56 (1H, d), 7.84 (1H, d), 8.44 (1H, d); *m/z* (ES⁺) [M-*t*Bu+H]⁺ = 381.8.

Intermediate 54b:

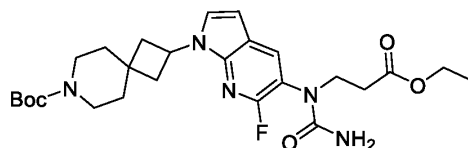
tert-Butyl 2-[5-[(3-ethoxy-3-oxo-propyl)amino]-6-fluoro-pyrrolo[2,3-*b*]pyridin-1-yl]-7-azaspiro[3.5]nonane-7-carboxylate



[1553] A vial was charged with Cs₂CO₃ (1338 mg, 4.11 mmol), Pd-PEPPS-IheptCl (87 mg, 0.11 mmol), Intermediate 54a (600 mg, 1.37 mmol) and ethyl 3-aminopropanoate, HCl (273 mg, 1.78 mmol) and 1,4-dioxane (20 mL) under nitrogen. The resulting mixture was stirred at 100 °C for 16 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.4% NH₄HCO₃) gave the title compound (400 mg, 61.6 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.18 (3H, t), 1.40 (9H, s), 1.56 – 1.68 (4H, m), 2.18 – 2.25 (2H, m), 2.35 – 2.41 (2H, m), 2.63 (2H, t), 3.25 (2H, t), 3.30 – 3.36 (4H, m), 4.07 (2H, q), 5.00 – 5.13 (2H, m), 6.35 (1H, d), 7.33 (1H, d), 7.54 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 475.2.

Intermediate 54c:

tert-Butyl 2-[5-[carbamoyl-(3-ethoxy-3-oxo-propyl)amino]-6-fluoro-pyrrolo[2,3-*b*]pyridin-1-yl]-7-azaspiro[3.5]nonane-7-carboxylate

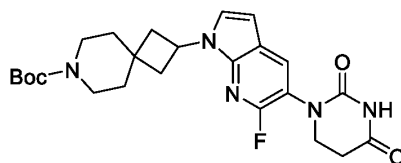


[1554] Prepared in an analogous manner to Intermediate 14c starting from Intermediate 54b (400 mg, 0.84 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.4% NH₄HCO₃) gave the title compound (300 mg, 68.8 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.06 (3H, t), 1.41 (9H, s), 1.62 – 1.69 (4H, m), 2.26 – 2.31 (2H, m), 2.40 – 2.45 (2H, m), 2.47 – 2.51 (2H, m), 3.24 – 3.29 (2H, m), 3.35

–3.38 (2H, m), 3.90 (2H, q), 5.14 – 5.21 (1H, m), 5.84 (2H, s), 6.57 – 6.62 (1H, m), 7.80 (1H, d), 7.99 (1H, d); m/z (ES^+) $[M+H]^+ = 518.3$.

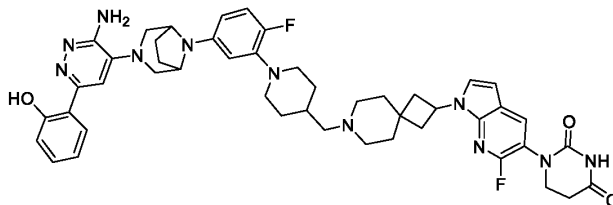
Intermediate 54d:

tert-Butyl 2-[5-(2,4-dioxohexahydropyrimidin-1-yl)-6-fluoro-pyrrolo[2,3-*b*]pyridin-1-yl]-7-azaspiro[3.5]nonane-7-carboxylate



[1555] Prepared in an analogous manner to Intermediate 14d starting from Intermediate 54c (300mg, 0.58 mmol). The reaction mixture was diluted with EtOAc (25 mL) and washed sequentially with saturated NH_4Cl (10 mL). The organic layer was dried over Na_2SO_4 , filtered, and evaporated to afford the title compound (240 mg, 88 %) as a yellow solid. The product was used in the next step directly without further purification. 1H NMR ($DMSO-d_6$): δ 1.39 (9H, s), 1.59 – 1.67 (4H, m), 2.22 – 2.30 (2H, m), 2.39 – 2.45 (2H, m), 2.74 (2H, t), 3.22 – 3.26 (2H, m), 3.31 – 3.35 (2H, m), 3.72 (2H, t), 5.09 – 5.19 (1H, m), 6.58 (1H, d), 7.80 (1H, d), 8.15 (1H, d); m/z (ES^+) $[M-tBu+H]^+ = 416.1$.

1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-6-fluoro-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1556] Step-1- Intermediate 54d (100 mg, 0.21 mmol) was added to para-Toluenesulfonic acid (91 mg, 0.53 mmol) in MeCN (4.0 mL). The resulting mixture was stirred at 80°C for 16 h. The solvent was removed under reduced pressure. The crude product was triturated with TBME (50 mL), solids were collected by filtration and dried under vacuum to give intermediate 1. Step-2- Formic acid (4.0 mL) was added to Intermediate 11g (116 mg, 0.21 mmol). The resulting mixture was stirred at 40 °C for 30 min. The solvent was removed under reduced pressure. To the residue was added the intermediate 1 in NMP (4 mL) and DCE (4.0 mL). The resulting mixture was stirred at 40 °C for 30 min. then Sodium triacetoxyborohydride (225 mg, 1.06 mmol) was added. The reaction mixture was stirred for 1 h at r.t. The solvent was removed under reduced pressure and the residue was diluted with EtOAc (25 mL), and washed sequentially with saturated $NaHCO_3$ (10 mL x 2) and saturated brine (10 mL). The organic layer was dried over Na_2SO_4 , filtered and evaporated. Purification by preparative HPLC (Column: Sunfire Prep C18 OBD column, 30*150mm, 5um; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min

mL/min; Gradient: 17% B to 31% B in 8 min) gave the title compound (16.89 mg, 9.09 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.22 – 1.26 (3H, m), 1.60 – 1.85 (7H, m), 1.92 – 1.97 (2H, m), 2.10 – 2.19 (4H, m), 2.23 – 2.27 (3H, m), 2.36 – 3.40 (3H, m), 2.64 (2H, t), 2.75 (2H, t), 3.10 (2H, d), 3.24 – 3.29 (3H, m), 3.33 – 3.37 (2H, m), 3.74 (2H, t), 4.35 (2H, s), 5.08 – 5.19 (1H, m), 5.95 (2H, s), 6.40 – 6.51 (2H, m), 6.59 (1H, d), 6.83 – 6.90 (2H, m), 6.90 – 6.97 (1H, m), 7.23 (1H, t), 7.47 (1H, s), 7.81 (1H, d), 7.91 (1H, d), 8.15 (1H, d), 10.51 (1H, s), 14.18 (1H, s). ¹⁹F NMR (DMSO-*d*₆): δ -83.288, -136.400; *m/z* (ES⁺) [M+H]⁺ = 858.4.

Example 55

Intermediate 55a:

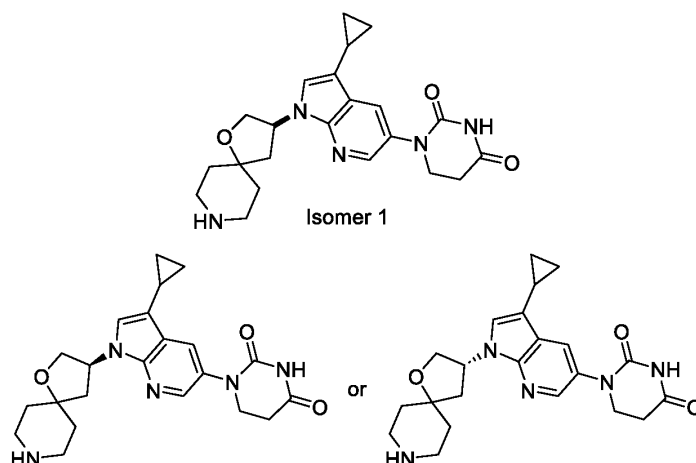
tert-Butyl *rel*-(3*S**)-3-[3-cyclopropyl-5-(2,4-dioxohexahydropyrimidin-1-yl)pyrrolo[2,3-*b*]pyridin-1-yl]-1-oxa-8-azaspiro[4.5]decan-8-carboxylate (Isomer 1)

[*absolute configuration not yet confirmed]

1-[3-Cyclopropyl-1-[(3*S*)-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

or

1-[3-Cyclopropyl-1-[(3*R*)-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1557] Preparation in an analogous method to Intermediate 53c starting from Intermediate 53b, Isomer 1 (125 mg, 0.25 mmol) gave the title compound (188 mg, 102 %) in the form of a *tris* TFA salt, as a goo. Quantitative yield assumed. *m/z* ES⁺ [M+H]⁺ = 410.3.

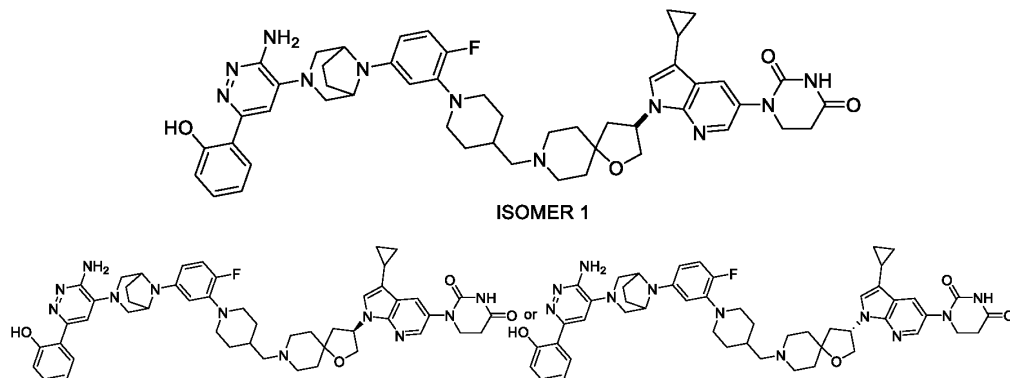
1-[3-Cyclopropyl-1-[(*rel*-(3*R**)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione (ISOMER 1)

[*absolute configuration not yet confirmed]

1-[3-Cyclopropyl-1-[(3*R*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

or

1-[3-Cyclopropyl-1-[(3*S*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

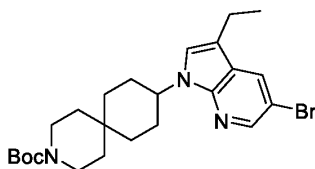


[1558] Prepared in an analogous method to Example 51 starting from Intermediate 55a (Isomer 1) (65.2 mg, 0.07 mmol) and Intermediate 11g (28 mg, 0.06 mmol). Purification by FSC (elution gradient: 0-100% MeOH in EtOAc and then 0 - 40% MeOH in EtOAc) followed by lyophilization gave the title compound (42.3 mg, 85 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 0.63 - 0.70 (2H, m), 0.83 - 0.91 (2H, m), 1.18 - 1.30 (2H, m), 1.56 - 1.81 (7H, m), 1.88 - 2.04 (4H, m), 2.09 - 2.22 (4H, m), 2.26 - 2.40 (3H, m), 2.42 - 2.53 (2H, m, overlaps with residual solvent), 2.64 (2H, br t), 2.77 (2H, t), 3.10 (2H, br d), 3.24 - 3.29 (2H, m), 3.30 - 3.40 (2H, m, overlaps with water), 3.82 (2H, t), 3.95 (1H, dd), 4.13 (1H, dd), 4.35 (2H, br s), 5.43 (1H, quin), 5.94 (2H, s), 6.39 - 6.45 (1H, m), 6.48 (1H, br d), 6.82 - 6.96 (3H, m), 7.23 (1H, t), 7.41 (1H, s), 7.47 (1H, s), 7.91 (1H, d), 7.97 (1H, d), 8.20 (1H, d), 10.39 (1H, s), 14.16 (1H, br s). ¹⁹F NMR (DMSO-*d*₆): δ -136.36 (1F, s); *m/z* ES⁺ [M+H]⁺ = 896.9.

Example 56

Intermediate 56a:

tert-Butyl 9-(5-bromo-3-ethyl-pyrrolo[2,3-*b*]pyridin-1-yl)-3-azaspiro[5.5]undecane-3-carboxylate

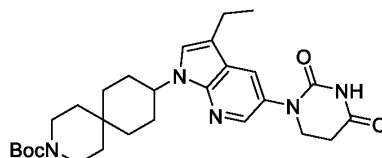


[1559] Prepared with an analogous method to Intermediate 4a starting from 5-bromo-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridine (484 mg, 2.15 mmol) and *tert*-butyl 9-hydroxy-3-azaspiro[5.5]undecane-3-carboxylate (1.10 g, 4.09 mmol). Purification by FSC (elution gradient: 0 - 45% EtOAc in hexanes) gave

the title compound (853 mg, 83 %) as an off-white solid. ^1H NMR (CD_2Cl_2): δ 1.33 (3H, t), 1.39 - 1.51 (13H, m), 1.64 - 1.72 (2H, m), 1.85 - 2.05 (6H, m), 2.75 (2H, q), 3.39 - 3.48 (4H, m), 4.65 - 4.74 (1H, m), 7.17 (1H, s), 8.03 (1H, d), 8.29 (1H, d); m/z ES^+ $[\text{M}+\text{H}]^+ = 476.2$.

Intermediate 56b:

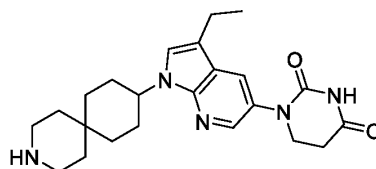
tert-Butyl 9-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-ethyl-pyrrolo[2,3-*b*]pyridin-1-yl]-3-azaspiro[5.5]undecane-3-carboxylate



[1560] Prepared in an analogous method to Intermediate 2b starting from Intermediate 56a (837 mg, 1.76 mmol). Purification by FSC (elution gradient: 0-100% EtOAc in hexanes and then 0-5% MeOH in EtOAc) gave the title compound (512 mg, 57.2 %) as a white solid. ^1H NMR ($\text{DMSO}-d_6$): δ 1.24 - 1.38 (7H, m), 1.41 (9H, s), 1.61 - 1.67 (2H, m), 1.71 (2H, br d), 1.83 (2H, br d), 1.96 - 2.08 (2H, m), 2.70 (2H, q), 2.76 (2H, t), 3.28 - 3.38 (4H, m, overlaps with residual water), 3.81 (2H, t), 4.63 (1H, ddd), 7.56 (1H, s), 7.90 (1H, d), 8.16 (1H, d), 10.36 (1H, s); m/z ES^+ $[\text{M}+\text{H}]^+ = 510.4$.

Intermediate 56c:

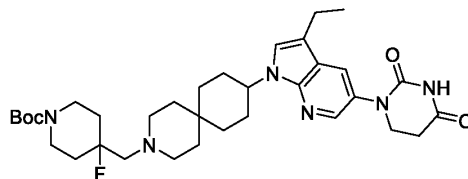
1-[1-(3-Azaspiro[5.5]undecan-9-yl)-3-ethyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1561] Prepared in an analogous manner to Intermediate 2c starting from Intermediate 56b (213 mg, 0.42 mmol). Purification by ion exchange chromatography (PoraPak Rxn CX cartridge) eluting with 2.9 N NH_3 in MeOH and 2.9 N NH_3 in MeOH/DCM gave the title compound (187 mg, 100 %) as a white solid. ^1H NMR ($\text{DMSO}-d_6$): δ 1.23 - 1.33 (7H, m), 1.62 (2H, br s), 1.69 (2H, br d), 1.84 (2H, br d), 1.97 - 2.08 (2H, m), 2.65 - 2.73 (6H, m), 2.76 (2H, t), 3.81 (2H, t), 4.56 - 4.65 (1H, m), 7.55 (1H, s), 7.90 (1H, d), 8.16 (1H, d), 10.33 (1H, br s); m/z ES^+ $[\text{M}+\text{H}]^+ = 410.4$.

Intermediate 56d:

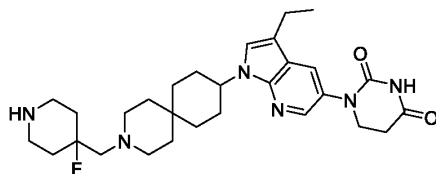
tert-Butyl 4-[[9-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-ethyl-pyrrolo[2,3-*b*]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl]methyl]-4-fluoro-piperidine-1-carboxylate



[1562] Intermediate 56c (186 mg, 0.45 mmol), Intermediate 25e (232 mg, 0.64 mmol), DIPEA (238 μ l, 1.36 mmol), and 1,4-dioxane (2 mL) were stirred together at 95 °C for 16 h. The reaction mixture was concentrated under reduced pressure. Purification by FSC (elution gradient: 15-100% EtOAc in hexanes and then 0-20% MeOH in EtOAc) gave the title compound (248 mg, 87 %) as an orange-brown solid. ¹H NMR (DMSO-*d*₆): δ 1.23 - 1.31 (5H, m), 1.34 - 1.43 (11H, m), 1.48 - 1.73 (6H, m), 1.80 (4H, br d), 1.95 - 2.05 (2H, m), 2.43 - 2.55 (6H, m, overlaps with residual solvent), 2.69 (2H, q), 2.76 (2H, t), 3.03 (2H, br s), 3.71 (2H, br d), 3.80 (2H, t), 4.60 (1H, br t), 7.55 (1H, s), 7.90 (1H, d), 8.16 (1H, d), 10.36 (1H, s); *m/z* ES⁺ [M+H]⁺ = 625.5.

Intermediate 56e:

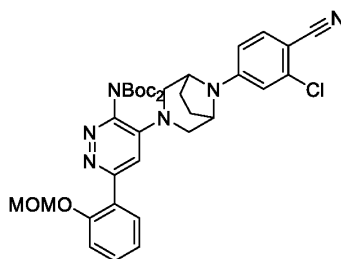
1-[3-Ethyl-1-[3-[(4-fluoro-4-piperidyl)methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1563] TFA (304 μ l, 3.97 mmol) was added to a solution of Intermediate 56d (248 mg, 0.40 mmol) in DCM (1.3 ml). The reaction was stirred at r.t. for 1.25 h then concentrated under reduced pressure. Purification by ion exchange chromatography (PoraPak Rxn CX cartridge) eluting with 2.9 N NH₃ in MeOH and 2.9 N NH₃ in MeOH/DCM gave the title compound (192 mg, 92 %) as a tan solid. ¹H NMR (DMSO-*d*₆): δ 1.23 - 1.32 (5H, m), 1.33 - 1.41 (2H, m), 1.49 - 1.64 (2H, m), 1.64 - 1.75 (6H, m), 1.80 (2H, br d), 1.93 - 2.07 (2H, m), 2.42 - 2.50 (6H, m), 2.64 - 2.79 (8H, m), 3.80 (2H, t), 4.55 - 4.65 (1H, m), 7.55 (1H, s), 7.90 (1H, d), 8.16 (1H, d), 10.36 (1H, br s) (NH not observed); *m/z* ES⁺ [M+H]⁺ = 525.4.

Intermediate 56f:

tert-butyl *N*-*tert*-butoxycarbonyl-*N*-[4-[8-(3-chloro-4-cyano-phenyl)-3,8-diazabicyclo[3.2.1]octan-3-yl]-6-[2-(methoxymethoxy)phenyl]pyridazin-3-yl]carbamate

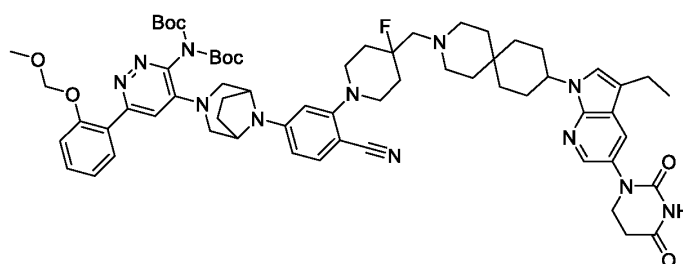


[1564] Intermediate 25d (0.750 g, 1.38 mmol), CPhos Pd G3 (0.112 g, 0.14 mmol), 4-bromo-2-chlorobenzonitrile (0.450 g, 2.08 mmol), and Cs₂CO₃ (1.128 g, 3.46 mmol) were sealed in a vial. The vial was evacuated and backfilled with nitrogen three times and toluene (6.9 ml) was added. The resulting suspension was stirred at 100 °C for 18 h then cooled to r.t. The reaction mixture was diluted with

DCM/MeOH, filtered with Celite® and concentrated under reduced pressure. Purification by FSC (elution gradient: 0-100% EtOAc and then 0-19% MeOH in EtOAc) gave the title compound (0.340 g, 36.3 %) as an off-white dry film. ¹H NMR (CD₂Cl₂): δ 1.50 (18H, s), 2.07 - 2.19 (4H, m), 3.27 (2H, d), 3.35 - 3.42 (5H, m), 4.42 (2H, br s), 5.22 (2H, s), 6.74 (1H, dd), 6.88 - 6.92 (1H, m), 7.20 (1H, t), 7.25 (1H, d), 7.42 - 7.49 (2H, m), 7.52 (1H, d), 7.86 - 7.92 (1H, m); *m/z* ES⁺ [M+H]⁺ = 677.5.

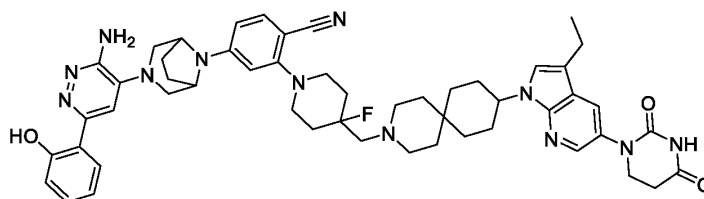
Intermediate 56g:

tert-butyl *N*-*tert*-butoxycarbonyl-*N*-[4-[8-[4-cyano-3-[4-[[9-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-ethyl-pyrrolo[2,3-*b*]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl]methyl]-4-fluoro-1-piperidyl]phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]-6-[2-(methoxymethoxy)phenyl]pyridazin-3-yl]carbamate



[1565] Intermediate 56f (97 mg, 0.14 mmol), Intermediate 56e (62.6 mg, 0.12 mmol), K₂CO₃ (49.5 mg, 0.36 mmol), and Pd-PEPPSI-IPentCl 2-methylpyridine (20.06 mg, 0.02 mmol) were sealed in a vial and evacuated/backfilled with nitrogen three times. Dioxane (955 µl) was added and the reaction mixture was stirred and heated at 100 °C for 15 h. The reaction was diluted with DCM/MeOH, filtered with Celite®, and concentrated under reduced pressure. Purification by FSC (elution gradient: 75-100% EtOAc in hexanes and then 0 to 20% MeOH in EtOAc) gave the title compound (47.8 mg, 34.4 %) as a pale-yellow solid. *m/z* ES⁺ [M+H]⁺ = 1164.6.

4-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-[4-[[9-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-ethyl-pyrrolo[2,3-*b*]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl]methyl]-4-fluoro-1-piperidyl]benzonitrile



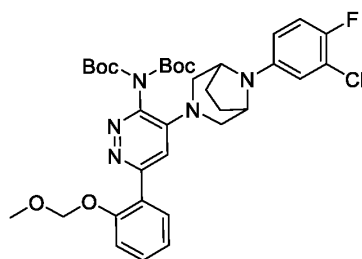
[1566] 2M aq. H₂SO₄ (820 µL, 1.64 mmol) was added to a stirred solution of Intermediate 56g (47.8 mg, 0.04 mmol) in THF (820 µL). The resulting solution was stirred at 50 °C for 4.5 h. The reaction was diluted in DCM (50 mL), quenched with sat. aq. NaHCO₃ and extracted with DCM/IPA (4:1). The organic layers were combined, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 75-100% EtOAc in hexanes and then 0 to 12% MeOH in EtOAc) followed by

lyophilization gave the title compound (18.9 mg, 50.0 %) as a white solid. ^1H NMR (DMSO- d_6): δ 1.21 - 1.34 (5H, m), 1.39 (2H, br s), 1.63 - 1.90 (8H, m), 1.99 (6H, br s), 2.21 (2H, br d), 2.48 - 2.62 (6H, m, overlaps with residual solvent), 2.69 (2H, q), 2.76 (2H, t), 2.99 - 3.09 (4H, m), 3.25 - 3.43 (4H, m, overlaps with residual water), 3.81 (2H, t), 4.54 - 4.66 (3H, m), 5.97 (2H, s), 6.51 (1H, s), 6.58 (1H, br d), 6.83 - 6.92 (2H, m), 7.23 (1H, t), 7.44 (1H, d), 7.50 (1H, s), 7.55 (1H, s), 7.87 - 7.92 (2H, m), 8.16 (1H, d), 10.37 (1H, s), 14.13 (1H, br s). ^{19}F NMR (DMSO- d_6): -155.90 (1F, br s); m/z ES $^+$ [M+H] $^+$ = 921.8.

Example 57

Intermediate 57a:

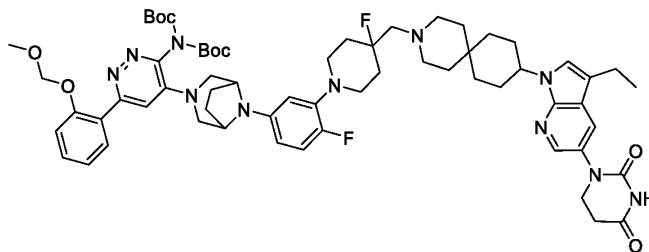
tert-Butyl *N*-*tert*-butoxycarbonyl-*N*-[4-[8-(3-chloro-4-fluoro-phenyl)-3,8-diazabicyclo[3.2.1]octan-3-yl]-6-[2-(methoxymethoxy)phenyl]pyridazin-3-yl]carbamate



[1567] A vial was charged with Intermediate 25d (812 mg, 1.5 mmol), 4-bromo-2-chloro-1-fluorobenzene (0.364 mL, 3.00 mmol), Cs₂CO₃ (1466 mg, 4.50 mmol), Cphos (85 mg, 0.20 mmol), CPhosPdG3 (157 mg, 0.20 mmol), and toluene (10 mL). The vial was sparged with N₂ and heated at 100 °C for 3 h. Reaction was cooled to r.t., filtered through celite® eluting with EtOAc/DCM and concentrated. Purification by FSC (elution gradient: 0-80% EtOAc in hexanes) gave the title compound (668 mg, 66.5 %) as an off white dry film. ^1H NMR: δ 1.39 (18H, s), 1.81 - 1.89 (2H, m), 1.94 - 1.99 (2H, m), 3.21 - 3.26 (2H, m), 3.27 (3H, s), 3.29 - 3.31 (2H, m), 4.45 (2H, br s), 5.22 (2H, s), 6.92 (1H, dt), 7.10 - 7.19 (2H, m), 7.21 - 7.29 (2H, m), 7.43 - 7.49 (1H, m), 7.54 (1H, s), 7.72 (1H, dd); m/z (ES $^+$) [M+H] $^+$ = 670.3.

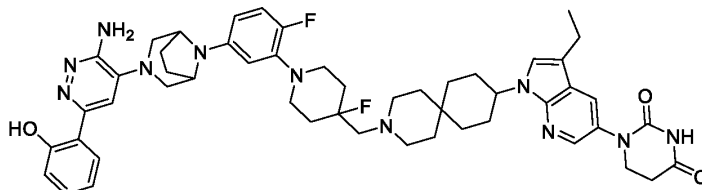
Intermediate 57b:

tert-Butyl *N*-*tert*-butoxycarbonyl-*N*-[4-[8-[3-[4-[9-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-ethyl-pyrrolo[2,3-*b*]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl)methyl]-4-fluoro-1-piperidyl]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]-6-[2-(methoxymethoxy)phenyl]pyridazin-3-yl]carbamate



[1568] Prepared in an analogous method to Intermediate 56f starting with Intermediate 57a (97 mg, 0.14 mmol) and Intermediate 56e (63.3 mg, 0.12 mmol). Purification by FSC (25-100% EtOAc in hexanes and then 0-20% MeOH in EtOAc) gave the title compound (56.2 mg, 40.2 %) as a pale-yellow solid. m/z $ES^+ [M+H]^+ = 1158.7$.

1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-fluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-ethyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

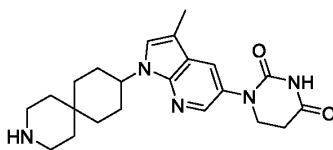


[1569] Prepared from an analogous method to Example 56 starting with Intermediate 57b (49 mg, 0.04 mmol). Purification by FSC (elution gradient: 0-100% EtOAc in hexanes and then 0 to 20% MeOH in EtOAc) followed by lyophilization gave the title compound (7.4 mg, 19.14 %) as an off-white solid. 1H NMR (DMSO- d_6): δ 1.21 – 1.34 (5H, m), 1.39 (2H, br s), 1.71 (4H, br s), 1.75 – 2.07 (10H, m), 2.14 (2H, br d), 2.44 – 2.61 (6H, m, overlaps with residual solvent), 2.70 (2H, q), 2.76 (2H, br t), 2.94 (2H, br t), 3.11 (2H, br d), 3.18 (2H, br d), 3.23 – 3.29 (2H, m), 3.81 (2H, br t), 4.38 (2H, br s), 4.61 (1H, br t), 5.94 (2H, br s), 6.46 (1H, br d), 6.53 (1H, br d), 6.82 – 6.91 (2H, m), 6.95 (1H, br dd), 7.23 (1H, br t), 7.47 (1H, s), 7.56 (1H, s), 7.86 – 7.98 (2H, m), 8.16 (1H, d), 10.37 (1H, s), 14.17 (1H, br s). ^{19}F NMR (DMSO- d_6) δ -155.94 (1F, br s), -136.60 (1F, s); m/z $ES^+ [M+H]^+ = 913.5$.

Example 58

Intermediate 58a:

1-[1-(3-Azaspiro[5.5]undecan-9-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

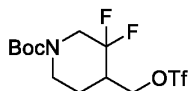


[1570] TFA (2.3 mL, 30.26 mmol) was added to a solution of Intermediate 13b (1.5 g, 3.03 mmol) in DCM (10 mL). The mixture was stirred at r.t. for 3 h and concentrated under reduced pressure. DCM (100 mL), IPA (30 mL), and 5 M K_2CO_3 were added, and the phases were separated. The organic layer was washed with sat. aq. K_2CO_3 (2 x 100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Solids from the leftover aqueous layers from extraction were filtered, redissolved in MeOH/DCM (1:3), and concentrated and combined with solid from the extraction to give title compound (1.09 g, 91 %) as a white solid. 1H NMR (DMSO- d_6): δ 1.23 - 1.34 (4H, m), 1.61 (2H, br s), 1.69 (2H, br d), 1.84 (2H, br d), 1.94 -

2.07 (2H, m), 2.25 (3H, s), 2.70 (4H, br s), 2.76 (2H, t), 3.81 (2H, t), 4.53 - 4.67 (1H, m), 7.54 (1H, s), 7.87 (1H, d), 8.16 (1H, d), 10.37 (1H, br s) (NH not observed); m/z ES⁺ [M+H]⁺ = 396.4.

Intermediate 58b:

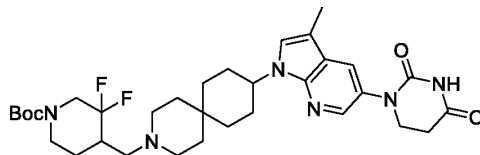
tert-Butyl 3,3-difluoro-4-(trifluoromethylsulfonyloxymethyl)piperidine-1-carboxylate



[1571] A 100 mL round-bottom flask was charged with *tert*-butyl 3,3-difluoro-4-(hydroxymethyl)piperidine-1-carboxylate (1.56 g, 6.21 mmol), 2,6-dimethylpyridine (0.863 ml, 7.45 mmol) and DCM (17.33 ml) and the mixture was cooled to 0 °C. Trifluoromethanesulfonic anhydride (1.149 ml, 6.83 mmol) was added dropwise over 5 mins. The resulting mixture was stirred at 0 °C for 2 h, quenched by slow addition of 1 M aq. NaHSO₄ (7 mL). The layers were separated. The organic layer was washed with 1 M aq. NaHSO₄ (2 x 5 mL), sat. aq. NaHCO₃ (20 mL), dried over Na₂SO₄ and concentrated under reduced pressure to give the title compound (2.40 g, 100 %) as a red liquid. ¹H NMR (CD₂Cl₂): 1.48 (9H, s), 1.60 - 1.70 (1H, m), 1.93 - 1.99 (1H, m), 2.39 - 2.53 (1H, m), 2.82 (1H, br s), 3.02 (1H, br s), 4.11 - 4.32 (1H, m), 4.39 (1H, br s), 4.54 (1H, dd), 4.86 (1H, dd).

Intermediate 58c:

tert-Butyl 4-[[9-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl]methyl]-3,3-difluoro-piperidine-1-carboxylate



[1572] Intermediate 58b (750 mg, 1.96 mmol), Intermediate 58a (619 mg, 1.57 mmol), DIPEA (820 µl, 4.70 mmol), and 1,4-dioxane (7.0 ml) were stirred at 65 °C for 16 h. The reaction mixture was concentrated under reduced pressure. Purification by FSC (0 - 20% MeOH in DCM) gave the title compound (891 mg, 91 %) as a solid. m/z ES⁺ [M+H]⁺ = 629.4.

Intermediate 58d:

tert-Butyl *rel*-(4*R**)-4-[[9-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl]methyl]-3,3-difluoro-piperidine-1-carboxylate

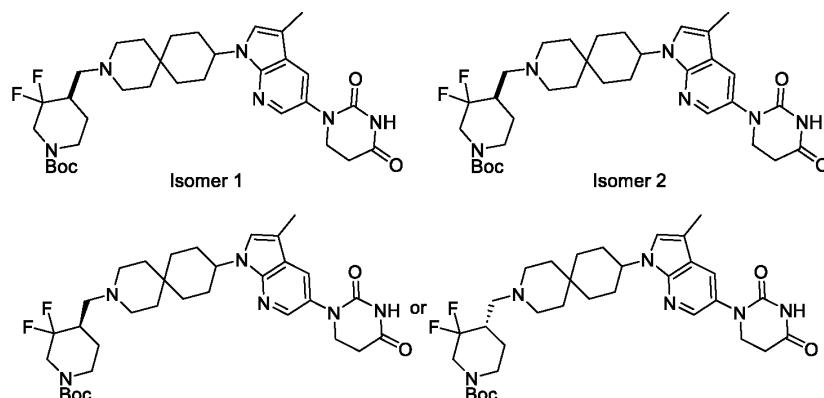
[*absolute configuration not yet confirmed]

tert-Butyl (4*R*)-4-[[9-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl]methyl]-3,3-difluoro-piperidine-1-carboxylate

or

246

tert-Butyl (4*S*)-4-[[9-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl]methyl]-3,3-difluoro-piperidine-1-carboxylate



[1573] Intermediate 58c (racemic) (664 mg) was purified by chiral SFC (Column: OJ-H 30mm × 250 5μm, MeOH/0.2% NH₄OH) to give the title compound, Isomer 1, that eluted first from the column (180 mg) as a solid and Isomer 2 (193 mg) that eluted second from the column as a solid. Isomer 1: *m/z* ES⁺ [M+H]⁺ = 629.5. Isomer 2: *m/z* ES⁺ [M+H]⁺ = 629.5.

Intermediate 58e:

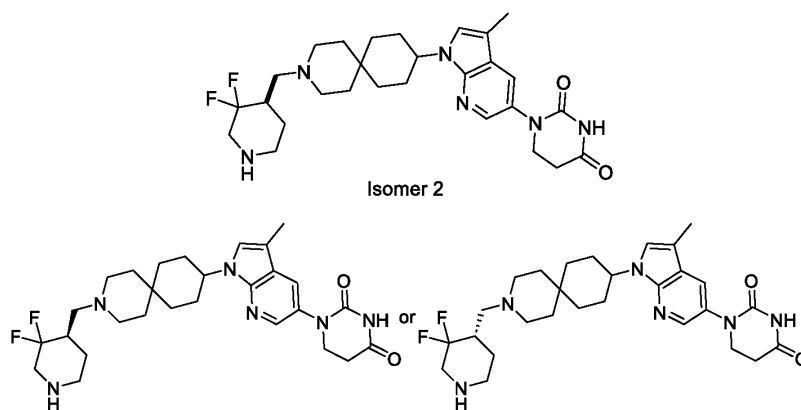
1-[3-Methyl-1-[3-[[*rel*-(4*R**)-3,3-difluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione (Isomer 2)

[*absolute configuration not yet confirmed]

1-[3-Methyl-1-[3-[[4*R*)-3,3-difluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

or

1-[3-Methyl-1-[3-[[4*S*)-3,3-difluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1574] Prepared from an analogous method to Intermediate 2c starting from Intermediate 58d, Isomer 2 (193 mg, 0.31 mmol). Purification by ion exchange chromatography (PoraPak Rxn CX cartridge) eluting with 2.9 N NH₃ in MeOH and 2.9 N NH₃ in MeOH/DCM gave the title compound (155 mg, 96 %) as a white solid. m/z ES⁺ [M+H]⁺ = 529.4.

Intermediate 58f:

tert-Butyl *N*-*tert*-butoxycarbonyl-*N*-[4-[8-[4-fluoro-3-[(*rel*-(4*R**)-4-[[9-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl)methyl]-3,3-difluoro-1-piperidyl]phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]-6-[2-(methoxymethoxy)phenyl]pyridazin-3-yl]carbamate

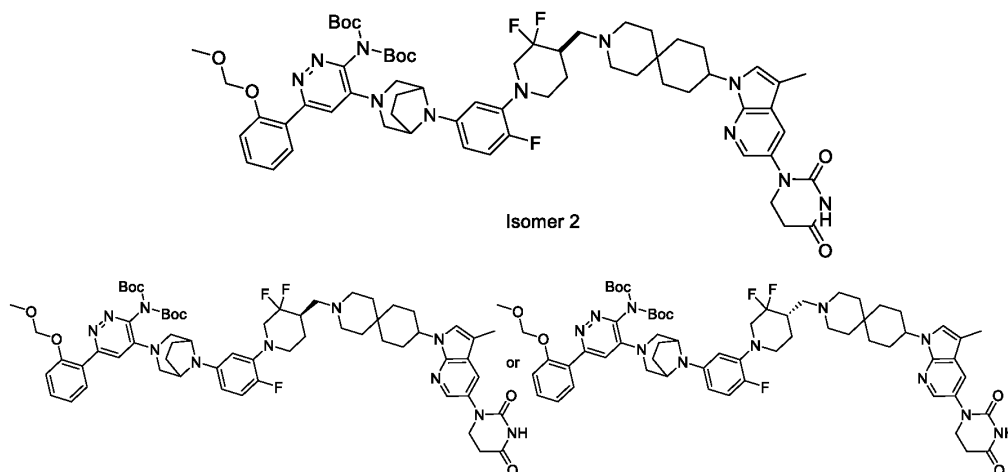
(Isomer 2)

[*absolute configuration not yet confirmed]

tert-Butyl *N*-*tert*-butoxycarbonyl-*N*-[4-[8-[4-fluoro-3-[(4*R*)-4-[[9-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl)methyl]-3,3-difluoro-1-piperidyl]phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]-6-[2-(methoxymethoxy)phenyl]pyridazin-3-yl]carbamate

or

tert-Butyl *N*-*tert*-butoxycarbonyl-*N*-[4-[8-[4-fluoro-3-[(4*S*)-4-[[9-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl)methyl]-3,3-difluoro-1-piperidyl]phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]-6-[2-(methoxymethoxy)phenyl]pyridazin-3-yl]carbamate



[1575] Prepared from an analogous method to Intermediate 56f starting with Intermediate 57a (114 mg, 0.17 mmol) and Intermediate 58e, Isomer 2 (75 mg, 0.14 mmol). Purification by FSC (elution gradient: 50-100% EtOAc in hexanes and then 0 - 20% MeOH in EtOAc) gave the title compound (57 mg, 34.6 %) as a tan solid. m/z ES⁺ [M+H]⁺ = 1162.7.

1-[3-Methyl-1-[3-[[*rel*-(4*R**)-1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3-difluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

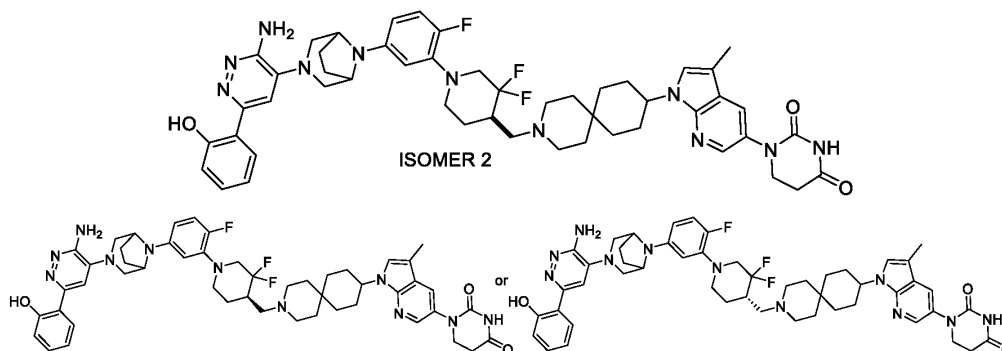
(ISOMER 2)

[*absolute configuration not yet confirmed]

1-[3-Methyl-1-[3-[[4*R*]-1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3-difluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

or

1-[3-Methyl-1-[3-[[4*S*]-1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3-difluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

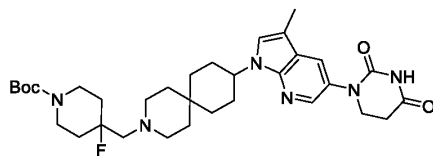


[1576] Prepared with an analogous method to Example 56 starting with Intermediate 58f (56 mg, 0.05 mmol). Purification by RP-HPLC (Xselect CSH C18 OBD, 5 μ m, 50-95% ACN/0.2% NH₄OH) and lyophilization gave the title compound (22.00 mg, 49.7 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.23 - 1.35 (2H, m), 1.39 (2H, br s), 1.53 (1H, q), 1.61 - 1.74 (4H, m), 1.80 (2H, br s), 1.89 - 2.07 (5H, m), 2.11 - 2.23 (3H, m), 2.23 - 2.33 (5H, m), 2.38 (2H, br t), 2.44 - 2.52 (1H, m, overlaps with residual solvent), 2.52 - 2.59 (1H, m), 2.72 - 2.85 (3H, m), 3.02 - 3.16 (3H, m), 3.22 - 3.29 (2H, m), 3.35 - 3.44 (1H, m, overlaps with residual water), 3.50 - 3.62 (1H, m), 3.81 (2H, t), 4.39 (2H, br s), 4.60 (1H, br t), 5.96 (2H, s), 6.45 - 6.55 (2H, m), 6.84 - 6.91 (2H, m), 6.97 (1H, dd), 7.23 (1H, t), 7.47 (1H, s), 7.55 (1H, s), 7.87 (1H, d), 7.91 (1H, d), 8.17 (1H, d), 10.40 (1H, s), 14.19 (1H, br s); ¹⁹F NMR (DMSO-*d*₆): δ -136.73 (1F, s), -113.73 (1F, br d), -103.22 (1F, br d); *m/z* ES⁺ [M+H]⁺ = 918.6.

Example 59:

Intermediate 59a:

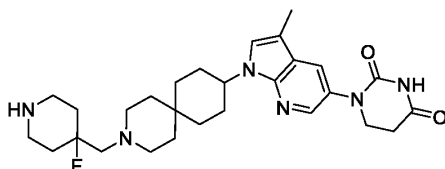
tert-Butyl 4-[[9-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl]methyl]-4-fluoro-piperidine-1-carboxylate



[1577] Prepared with analogous method to Intermediate 56d starting with Intermediate 54a (440 mg, 1.11 mmol) and Intermediate 25e (569 mg, 1.56 mmol). Purification by FSC (elution gradient: 0-20% MeOH in EtOAc with 10% DCM modifier) gave the title compound (721 mg, 106 %) as a solid. m/z ES⁺ [M+H]⁺ = 611.6.

Intermediate 59b:

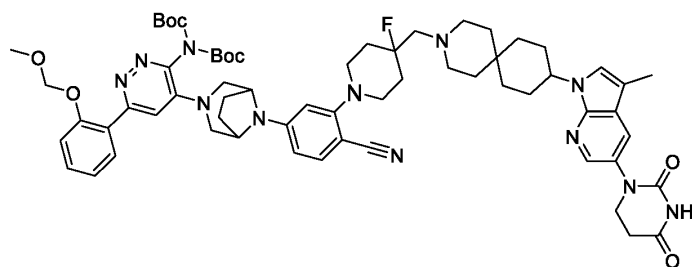
1-[1-[3-[(4-Fluoro-4-piperidyl)methyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1578] Prepared with an analogous method to Intermediate 2c starting with Intermediate 59a (177 mg, 0.29 mmol) in DCM (937 μ l). Purification by ion exchange chromatography (PoraPak Rxn CX cartridge) eluting with 2.9 N NH₃ in MeOH and 2.9 N NH₃ in MeOH/DCM gave the title compound (123 mg, 83 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.23 - 1.34 (2H, m), 1.34 - 1.41 (2H, m), 1.49 - 1.63 (2H, m), 1.64 - 1.74 (6H, m), 1.80 (2H, br d), 1.92 - 2.04 (2H, m), 2.25 (3H, s), 2.42 - 2.50 (6H, m), 2.64 - 2.73 (4H, m), 2.76 (2H, t), 3.81 (2H, t), 4.55 - 4.64 (1H, m), 7.54 (1H, s), 7.87 (1H, d), 8.16 (1H, d), 10.37 (1H, br s) (piperidine NH not observed); m/z ES⁺ [M+H]⁺ = 511.4.

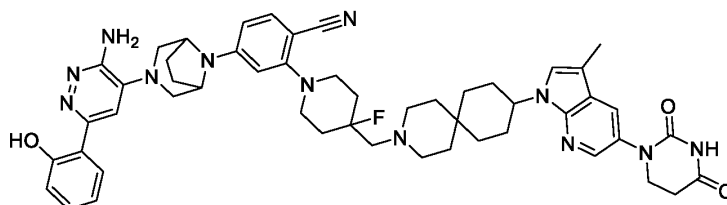
Intermediate 59c:

tert-Butyl *N*-*tert*-butoxycarbonyl-*N*-[4-[8-[4-cyano-3-[4-[9-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl]methyl]-4-fluoro-1-piperidyl]phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]-6-[2-(methoxymethoxy)phenyl]pyridazin-3-yl]carbamate



[1579] Prepared from an analogous method to Intermediate 56g starting with Intermediate 56f (103 mg, 0.15 mmol) and Intermediate 59c (65 mg, 0.13 mmol). Purification by FSC (elution gradient: 50-100% EtOAc in hexanes and then 0-20% MeOH in EtOAc) gave the title compound (67.6 mg, 46.1 %) as a tan solid. m/z ES⁺ [M+H]⁺ = 1151.8.

4-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-[4-[[9-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl)methyl]-4-fluoro-1-piperidyl]benzonitrile



[1580] Prepared from an analogous method to Example 56 starting with Intermediate 59c (67 mg, 0.06 mmol). Purification by FSC (elution gradient: 25-100% EtOAc in hexanes and then 0-20% MeOH in EtOAc) and lyophilization gave the title compound (27.8 mg, 52.7 %) as an off-white solid. ¹H NMR (DMSO-*d*₆): δ 1.21 - 1.34 (2H, m), 1.39 (2H, br s), 1.69 (4H, br s), 1.75 - 1.91 (4H, m), 1.93 - 2.04 (6H, m), 2.21 (2H, br d), 2.25 (3H, s), 2.47 - 2.62 (6H, m, overlaps with residual solvent), 2.76 (2H, t), 2.99 - 3.09 (4H, m), 3.23 - 3.43 (4H, m, overlaps with residual water), 3.81 (2H, t), 4.59 (3H, br s), 5.98 (2H, br s), 6.51 (1H, s), 6.58 (1H, br d), 6.83 - 6.91 (2H, m), 7.23 (1H, br t), 7.43 (1H, d), 7.50 (1H, s), 7.54 (1H, s), 7.84 - 7.88 (1H, m), 7.90 (1H, br d), 8.12 - 8.19 (1H, m), 10.37 (1H, s), 14.13 (1H, br s); ¹⁹F NMR (DMSO-*d*₆): δ -155.90 (1F, br s); *m/z* ES+ [M+H]⁺ = 907.7.

Example 60:

Intermediate 60a:

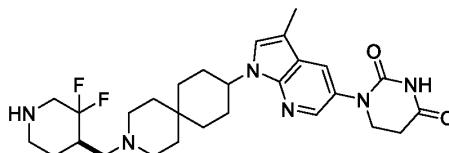
1-[3-Methyl-1-[3-[[*rel*-(4*R**)-3,3-difluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione (ISOMER 1)

[*absolute configuration not yet confirmed]

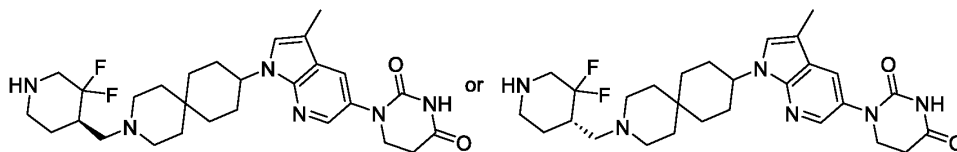
1-[3-Methyl-1-[3-[[4*R*)-3,3-difluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

or

1-[3-Methyl-1-[3-[[4*S*)-3,3-difluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



Isomer 1



[1581] Prepared from an analogous method to Intermediate 2c starting from Intermediate 58d, Isomer 1 (129 mg, 0.21 mmol). Purification by ion exchange chromatography (PoraPak Rxn CX cartridge) eluting with 2.9 N NH₃ in MeOH and 2.9 N NH₃ in MeOH/DCM gave the title compound (109 mg, 100 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.19 - 1.44 (5H, m), 1.62 - 1.74 (4H, m), 1.75 - 1.84 (2H, m), 1.87 (1H, br d), 1.92 - 2.04 (2H, m), 2.04 - 2.18 (1H, m), 2.20 - 2.33 (6H, m), 2.41 - 2.57 (4H, m), 2.63 - 2.80 (3H, m), 2.85 (1H, br dd), 2.95 - 3.04 (1H, m), 3.81 (2H, t), 4.55 - 4.63 (1H, m), 7.54 (1H, s), 7.87 (1H, d), 8.16 (1H, d), 10.37 (1H, s); ¹⁹F NMR (DMSO-*d*₆): δ -116.39 (1F, br dd), -104.75 (1F, br d); *m/z* ES⁺ [M+H]⁺ = 529.5.

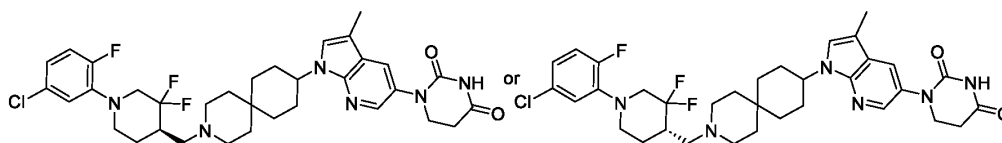
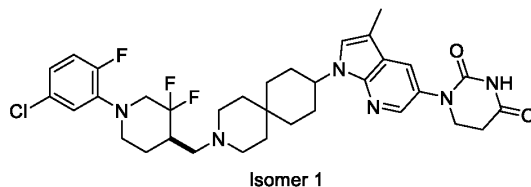
Intermediate 60b:

1-[3-Methyl-1-[3-[[*rel*-(4*R**)-1-(5-chloro-2-fluoro-phenyl)-3,3-difluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione
(ISOMER 1)

[*absolute configuration not yet confirmed]

1-[3-Methyl-1-[3-[(4*R*)-1-(5-chloro-2-fluoro-phenyl)-3,3-difluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione
or

1-[3-Methyl-1-[3-[(4*S*)-1-(5-chloro-2-fluoro-phenyl)-3,3-difluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1582] Pd(dba)₂ (23.49 mg, 0.04 mmol), *t*BuPhCphos (24.79 mg, 0.06 mmol), Intermediate 60a (Isomer 1) (108 mg, 0.20 mmol), and K₂CO₃ (85 mg, 0.61 mmol) were sealed in a vial and then evacuated and backfilled with nitrogen three times. 2-Bromo-4-chloro-1-fluorobenzene (49.8 μL, 0.41 mmol) and 1,4-dioxane (1943 μL) were added. The mixture was stirred at 100 °C for 15 h and cooled to r.t. Another portion of Pd(dba)₂ (11.75 mg, 0.02 mmol) and *t*BuPhCphos (12.40 mg, 0.03 mmol) were added, the reaction was

sparged with nitrogen, continued to stir at 100 °C for 7 h, and cooled to r.t.. An additional portion of Pd(dba)₂ (11.75 mg, 0.02 mmol), tBuPhCPhos (12.40 mg, 0.03 mmol), and 2-bromo-4-chloro-1-fluorobenzene (50 µL, 0.41 mmol) were added; the reaction was sparged with nitrogen; stirred at 100 °C for another 16 h; and cooled to r.t. The reaction was concentrated under reduced pressure to dryness and the crude material was triturated with Et₂O and filtered. The resulting solids were suspended in MeOH/DCM and filtered. The resulting solution was mixed with Celite® and concentrated under vacuum. Purification by FSC (elution gradient: 0 - 20% MeOH in DCM) gave the title compound (54.1 mg, 40.3 %) as a solid. ¹H NMR (DMSO-*d*₆): δ 1.23 - 1.36 (3H, m), 1.40 (2H, br s), 1.46 - 1.60 (1H, m), 1.66 - 1.75 (4H, m), 1.81 (2H, br s), 1.94 - 2.08 (3H, m), 2.21 - 2.33 (5H, m), 2.38 (1H, br t), 2.45 - 2.53 (2H, m, overlaps with residual solvent), 2.56 (1H, br d), 2.76 (2H, t), 2.88 (1H, br t), 3.09 - 3.20 (1H, m), 3.37 - 3.45 (1H, m), 3.54 - 3.65 (1H, m), 3.81 (2H, t), 4.55 - 4.66 (1H, m), 7.03 (1H, dt), 7.10 (1H, dd), 7.20 (1H, dd), 7.55 (1H, s), 7.87 (1H, d), 8.17 (1H, d), 10.37 (1H, s); ¹⁹F NMR (DMSO-*d*₆): δ -124.53 (1F, s), -113.98 (1F, br d), -103.65 (1F, br d); *m/z* ES⁺ [M+H]⁺ = 657.5.

Intermediate 60c:

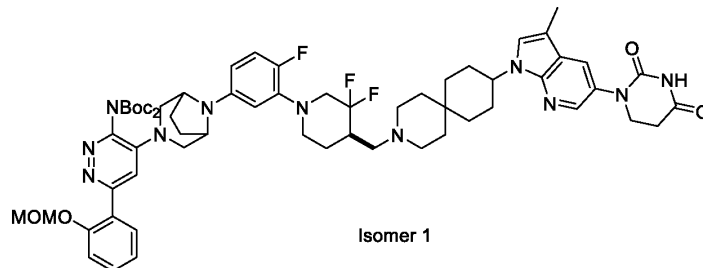
tert-Butyl *N*-*tert*-butoxycarbonyl-*N*-[4-[8-[4-fluoro-3-[(*rel*-(4*R**)-4-[[9-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl)methyl]-3,3-difluoro-1-piperidyl]phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]-6-[2-(methoxymethoxy)phenyl]pyridazin-3-yl]carbamate
(Isomer 1)

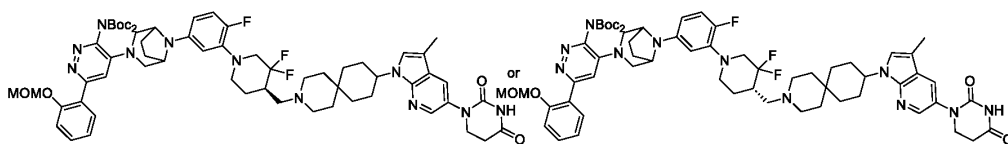
[*absolute configuration not yet confirmed]

tert-Butyl *N*-*tert*-butoxycarbonyl-*N*-[4-[8-[4-fluoro-3-[(4*R*)-4-[[9-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl)methyl]-3,3-difluoro-1-piperidyl]phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]-6-[2-(methoxymethoxy)phenyl]pyridazin-3-yl]carbamate

or

tert-Butyl *N*-*tert*-butoxycarbonyl-*N*-[4-[8-[4-fluoro-3-[(4*S*)-4-[[9-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl)methyl]-3,3-difluoro-1-piperidyl]phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]-6-[2-(methoxymethoxy)phenyl]pyridazin-3-yl]carbamate





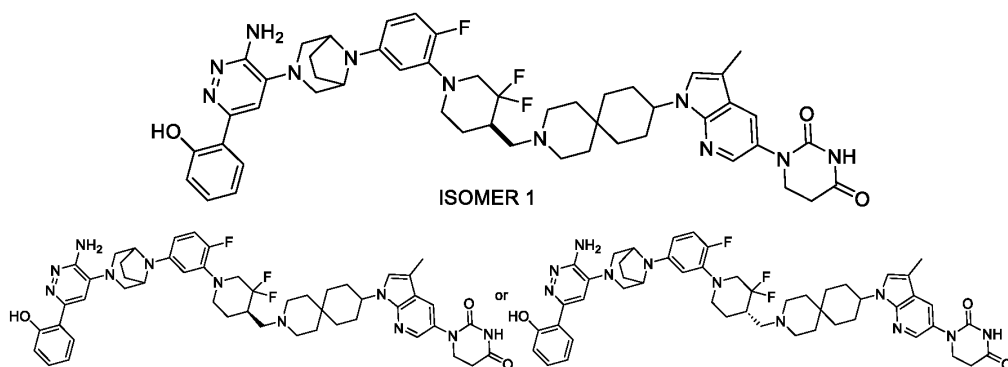
[1583] Intermediate 25d (49.5 mg, 0.09 mmol), Intermediate 60b, Isomer 1 (50 mg, 0.08 mmol), Cs_2CO_3 (18.26 μl , 0.23 mmol) and Pd-PEPPSI-IPentCl 2-methylpyridine (12.78 mg, 0.02 mmol) were sealed into a vial with stir bar. The vial was evacuated and backfilled with nitrogen three times. 1,4-Dioxane (743 μl) was added and the reaction was stirred at 100 °C for 16 h and cooled to r.t. The crude reaction mixture was diluted with DCM/MeOH, filtered through Celite®, and concentrated under reduced pressure. Purification by FSC (elution gradient: 75 to 100% EtOAc and then 20% MeOH in EtOAc) gave the title compound (26.8 mg, 30.3 %) as a white solid. m/z ES^+ $[\text{M}+\text{H}]^+ = 1162.8$.

1-[3-Methyl-1-[3-[[*rel*-(4*R**)-1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3-difluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione
(ISOMER 1)

[*absolute configuration not yet confirmed]

1-[3-Methyl-1-[3-[(4*R*)-1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3-difluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione
or

1-[3-Methyl-1-[3-[(4*S*)-1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3-difluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



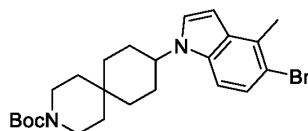
[1584] Prepared with an analogous method to Example 56 starting from Intermediate 60c (27 mg, 0.02 mmol). Purification by RP-HPLC (Xselect CSH C18 OBD, 5 μm , 25-50% ACN/0.1% FA) and lyophilization gave the title compound (5.50 mg, 25.8 %) as a solid. ^1H NMR ($\text{DMSO}-d_6$): δ 1.25 - 1.34

(2H, m), 1.35 - 1.45 (2H, m), 1.49 - 1.58 (1H, m), 1.65 - 1.74 (4H, m), 1.80 (2H, br s), 1.91 - 2.07 (5H, m), 2.13 (2H, br d), 2.16 - 2.34 (6H, m), 2.35 - 2.42 (1H, m), 2.46 - 2.53 (1H, m, overlaps with residual solvent), 2.54 - 2.60 (1H, m), 2.72 - 2.85 (3H, m), 3.03 - 3.15 (3H, m), 3.22 - 3.29 (2H, m), 3.49 - 3.62 (1H, m, overlaps with water), 3.80 (2H, t), 4.38 (2H, br s), 4.54 - 4.63 (1H, m), 5.93 (2H, s), 6.47 - 6.52 (2H, m), 6.84 - 6.89 (2H, m), 6.97 (1H, dd), 7.23 (1H, t), 7.46 (1H, s), 7.54 (1H, s), 7.87 (1H, d), 7.89 (1H, dd), 8.16 (1H, d), 10.38 (1H, s), 13.22 - 15.00 (1H, m) (two unassigned H's broadened beyond detection around residual water signal); ^{19}F NMR (DMSO-*d*₆): δ -194.42 (1F, s), -190.03 (1F, s), -136.71 (1F, br s), -113.71 (1F, br d), -103.20 (1F, br d); m/z ES⁺ [M+H]⁺ = 918.6.

Example 61:

Intermediate 61a:

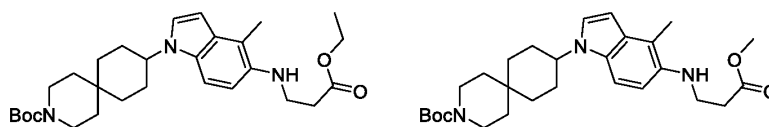
tert-Butyl 9-(5-bromo-4-methyl-indol-1-yl)-3-azaspiro[5.5]undecane-3-carboxylate



[1585] Prepared with an analogous method to Intermediate 4a starting from *tert*-butyl 9-hydroxy-3-azaspiro[5.5]undecane-3-carboxylate (0.914 g, 3.39 mmol), 5-bromo-4-methyl-1*H*-indole (0.475 g, 2.26 mmol) and 2-(tributyl-*l*-phosphaneylidene)acetonitrile (0.889 ml, 3.39 mmol). Purification by FSC (elution gradient: 0 - 12% EtOAc in hexanes) gave the title compound (478 mg, 45.8 %) as a white solid. ^1H NMR (CD₂Cl₂): δ 1.36 - 1.46 (4H, m), 1.48 (9H, s), 1.63 - 1.69 (2H, m), 1.87 - 2.01 (6H, m), 2.60 (3H, s), 3.40 - 3.46 (4H, m), 4.22 (1H, tt), 6.56 (1H, d), 7.15 (1H, d), 7.29 (1H, d), 7.34 (1H, d); m/z (ES⁺), [M+H]⁺ = 461.4.

Intermediate 61b:

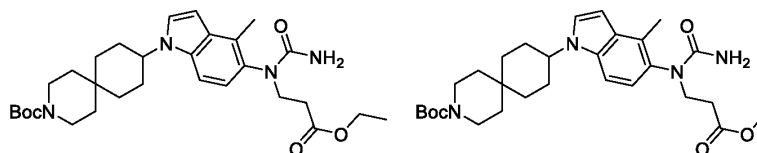
tert-Butyl 9-[5-[(3-ethoxy-3-oxo-propyl)amino]-4-methyl-indol-1-yl]-3-azaspiro[5.5]undecane-3-carboxylate and *tert*-butyl 9-[5-[(3-methoxy-3-oxo-propyl)amino]-4-methyl-indol-1-yl]-3-azaspiro[5.5]undecane-3-carboxylate



[1586] Prepared with an analogous method to Intermediate 14b with the addition of *t*BuBrettPhos (26.3 mg, 0.05 mmol) starting from Intermediate 61a (250 mg, 0.54 mmol). The reaction was diluted with EtOAc and MeOH, filtered through Celite®, and concentrated under reduced pressure adsorbing to Celite®. Purification by FSC (elution gradient: 0-25% EtOAc in hexanes) gave the title compound as an inseparable mixture of ethyl and methyl esters (165 mg, 61.2 %) as a yellow solid. Ethyl ester: m/z (ES⁺) [M+H]⁺ = 498.6; methyl ester: m/z (ES⁺) [M+H]⁺ = 484.6.

Intermediate 61c:

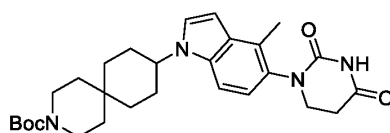
tert-Butyl 9-[5-[carbamoyl-(3-ethoxy-3-oxo-propyl)amino]-4-methyl-indol-1-yl]-3-azaspiro[5.5]undecane-3-carboxylate and *tert*-Butyl 9-[5-[carbamoyl-(3-methoxy-3-oxo-propyl)amino]-4-methyl-indol-1-yl]-3-azaspiro[5.5]undecane-3-carboxylate



[1587] Prepared with an analogous method to Intermediate 14c starting from Intermediate 61b (159 mg, 0.32 mmol) to give the title compound as a mixture of ethyl and methyl esters. Material taken to the next step without purification, quantitative yield assumed. Ethyl ester: m/z (ES^+) $[M+H]^+ = 541.6$; methyl ester: m/z (ES^+) $[M+H]^+ = 527.6$.

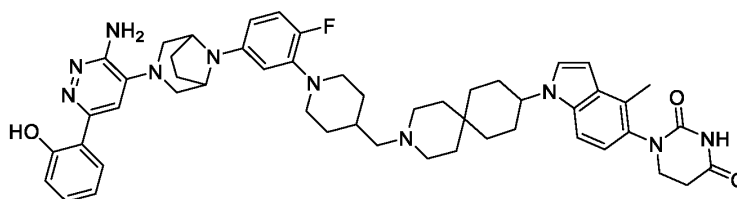
Intermediate 61d:

tert-butyl 9-[5-(2,4-dioxohexahydropyrimidin-1-yl)-4-methyl-indol-1-yl]-3-azaspiro[5.5]undecane-3-carboxylate



[1588] Prepared with an analogous method to Intermediate 14d starting from Intermediate 61c (169 mg, 0.32 mmol). Purification by FSC (elution gradient: 0 - 10% MeOH in DCM) gave the title compound (125 mg, 79 %) as an off-white solid. 1H NMR (CD_2Cl_2): δ 1.39 - 1.47 (4H, m), 1.48 (9H, s), 1.67 (2H, br t), 1.88 - 2.04 (6H, m), 2.45 (3H, s), 2.81 - 2.93 (2H, m), 3.41 - 3.48 (4H, m), 3.66 - 3.74 (1H, m), 3.81 - 3.88 (1H, m), 4.20 - 4.32 (1H, m), 6.61 (1H, d), 7.04 (1H, d), 7.31 (1H, d), 7.35 (1H, d), 7.54 (1H, s); m/z ES^+ $[M+H]^+ = 495.5$.

1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl)methyl]-3-azaspiro[5.5]undecan-9-yl]-4-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione



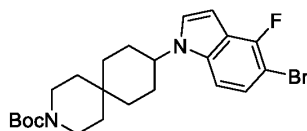
[1589] Prepared with an analogous method to Example 51 starting from Intermediate 61d (28.8 mg, 0.06 mmol) and Intermediate 11g (30.7 mg, 0.05 mmol). Purification by FSC (elution gradient: 0 - 20% MeOH in DCM) and lyophilization gave the title compound (25.07 mg, 58.6 %) as a white solid. 1H NMR ($DMSO-d_6$): δ 1.10 - 1.53 (7H, m), 1.60 - 1.83 (8H, m), 1.84 - 2.01 (5H, m), 2.14 (2H, br d), 2.18 - 2.49 (8H, m), 2.61 - 2.83 (4H, m), 3.11 (2H, br d), 3.23 - 3.29 (2H, m), 3.30 - 3.40 (2H, m, overlaps with residual

water), 3.49 - 3.58 (1H, m), 3.74 (1H, ddd), 4.26 - 4.41 (3H, m), 5.94 (2H, s), 6.39 - 6.50 (2H, m), 6.52 (1H, d), 6.84 - 6.90 (2H, m), 6.93 (1H, dd), 7.00 (1H, d), 7.23 (1H, t), 7.37 (1H, d), 7.47 (1H, s), 7.57 (1H, d), 7.91 (1H, d), 10.24 (1H, s), 14.16 (1H, br s). ^{19}F NMR (DMSO-*d*6): -136.38 (1F, s); m/z (ES⁺) [M+H]⁺ = 881.7.

Example 62:

Intermediate 62a:

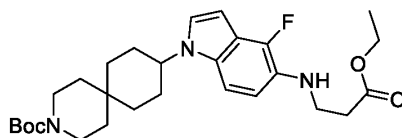
tert-Butyl 9-(5-bromo-4-fluoro-indol-1-yl)-3-azaspiro[5.5]undecane-3-carboxylate



[1590] Prepared with an analogous method to Intermediate 4a starting from *tert*-butyl 9-hydroxy-3-azaspiro[5.5]undecane-3-carboxylate (1.05 g, 3.90 mmol), 5-bromo-4-fluoro-1*H*-indole (0.556 g, 2.60 mmol) and 2-(tributyl-*l*5-phosphaneylidene)acetonitrile (1.090 ml, 4.16 mmol). Purification by FSC (elution gradient: 0-25% EtOAc in hexanes) gave the title compound (285 mg, 23.57 %) as a white solid. ^1H NMR (CD₂Cl₂): δ 1.37 - 1.46 (4H, m), 1.46 - 1.51 (9H, m), 1.63 - 1.68 (2H, m), 1.87 - 2.03 (6H, m), 3.41 - 3.47 (4H, m), 4.18 - 4.27 (1H, m), 6.61 (1H, d), 7.13 (1H, d), 7.27 - 7.33 (2H, m); ^{19}F NMR (CD₂Cl₂): δ -116.87 (1F, s); m/z (ES⁺), [M+H]⁺ = 465.1.

Intermediate 62b:

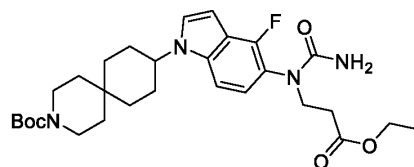
tert-Butyl 9-[5-[(3-ethoxy-3-oxo-propyl)amino]-4-fluoro-indol-1-yl]-3-azaspiro[5.5]undecane-3-carboxylate



[1591] Prepared with an analogous method to Intermediate 14b with the addition of *t*BuBrettPhos (26.0 mg, 0.05 mmol) starting from Intermediate 62a (250 mg, 0.54 mmol). Purification by FSC (elution gradient: 0-50% EtOAc in hexanes) gave the title compound (211 mg, 78 %) as a yellow solid. ^1H NMR (CD₂Cl₂): δ 1.29 (3H, t), 1.37 - 1.46 (4H, m), 1.48 (9H, s), 1.65 (2H, br s), 1.87 - 2.02 (6H, m), 2.63 (2H, t), 3.40 - 3.46 (4H, m), 3.52 (2H, t), 4.02 (1H, br d), 4.13 - 4.21 (3H, m), 6.45 (1H, d), 6.83 (1H, t), 7.09 (1H, d), 7.20 (1H, d); ^{19}F NMR (CD₂Cl₂): δ -145.81 (1F, s); m/z (ES⁺) [M+H]⁺ = 502.6.

Intermediate 62c:

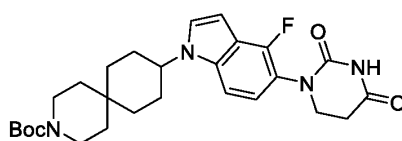
tert-Butyl 9-[5-[carbamoyl-(3-ethoxy-3-oxo-propyl)amino]-4-fluoro-indol-1-yl]-3-azaspiro[5.5]undecane-3-carboxylate



[1592] Prepared with an analogous method to Intermediate 14c starting from Intermediate 62b (210 mg, 0.42 mmol) to give the title compound. Material was taken to the next step without purification, quantitative yield assumed. m/z (ES^+) $[M+H]^+ = 545.6$.

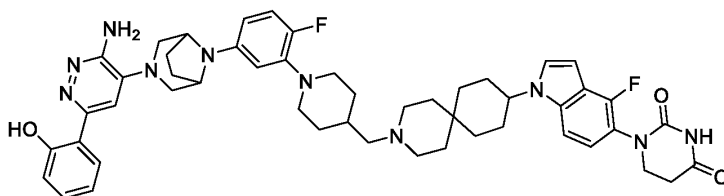
Intermediate 62d:

tert-Butyl 9-[5-(2,4-dioxohexahydropyrimidin-1-yl)-4-fluoro-indol-1-yl]-3-azaspiro[5.5]undecane-3-carboxylate



[1593] Prepared with an analogous method to Intermediate 14d starting from Intermediate 62c (229 mg, 0.42 mmol). Purification by FSC (elution gradient: 0 - 10% MeOH in DCM) and concentration afforded the title compound (184 mg, 88 %). 1H NMR (CD_2Cl_2): δ 1.39 - 1.46 (4H, m), 1.48 (9H, s), 1.64 - 1.69 (2H, m), 1.90 - 2.03 (6H, m), 2.87 (2H, t), 3.41 - 3.47 (4H, m), 3.84 (2H, t), 4.21 - 4.31 (1H, m), 6.66 (1H, d), 7.11 (1H, dd), 7.25 (1H, d), 7.33 (1H, d), 7.61 (1H, s); ^{19}F NMR (CD_2Cl_2): δ -130.40 (1F, s). m/z (ES^+) $[M+H]^+ = 499.5$.

1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-4-fluoro-indol-5-yl]hexahydropyrimidine-2,4-dione

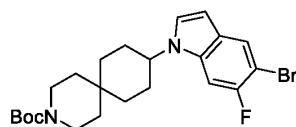


[1594] Prepared in an analogous method to Example 51 starting from Intermediate 62d (28.4 mg, 0.06 mmol) and Intermediate 11g (30 mg, 0.05 mmol). Purification by FSC (elution gradient: 0-20% MeOH in DCM) and lyophilization gave the title compound (22.6 mg, 53.9%) as a white solid. 1H NMR ($DMSO-d_6$): δ 1.20 - 1.49 (6H, m), 1.57 - 1.73 (3H, m), 1.78 (6H, br s), 1.87 - 2.04 (5H, m), 2.06 - 2.27 (4H, m), 2.28 - 2.47 (3H, m), 2.65 (2H, br t), 2.74 (2H, t), 3.11 (2H, br d), 3.24 - 3.30 (2H, m), 3.30 - 3.41 (2H, m, overlaps with residual water), 3.72 (2H, t), 4.30 - 4.41 (3H, m), 5.94 (2H, s), 6.39 - 6.51 (2H, m), 6.55 (1H, d), 6.83 - 6.97 (3H, m), 7.11 (1H, t), 7.23 (1H, t), 7.40 (1H, d), 7.47 (1H, s), 7.66 (1H, d), 7.91 (1H, d), 10.39 (1H, s), 14.16 (1H, br s); ^{19}F NMR ($DMSO-d_6$): δ -136.37 (1F, s), -130.31 (1F, s); m/z (ES^+) $[M+H]^+ = 885.7$.

Example 63:

Intermediate 63a:

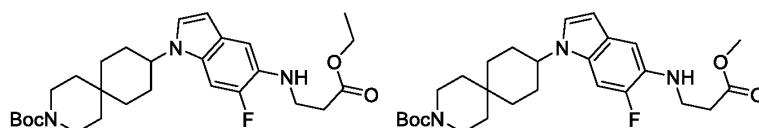
tert-Bbutyl 9-(5-bromo-6-fluoro-indol-1-yl)-3-azaspiro[5.5]undecane-3-carboxylate



[1595] Prepared in an analogous method to Intermediate 4a starting from *tert*-butyl 9-hydroxy-3-azaspiro[5.5]undecane-3-carboxylate (0.959 g, 3.56 mmol) and 5-bromo-6-fluoro-1*H*-indole (0.610 g, 2.85 mmol). Purification by FSC (elution gradient: 0-20% EtOAc in hexanes) gave the title compound (380.2 mg, 0.817 mmol, 28.7 %) as a white solid. ¹H NMR (CD₂Cl₂): δ 1.36 - 1.46 (4H, m), 1.48 (9H, s), 1.62 - 1.69 (2H, m), 1.88 - 2.01 (6H, m), 3.40 - 3.47 (4H, m), 4.09 - 4.18 (1H, m), 6.49 (1H, d), 7.21 (1H, d), 7.30 (1H, d), 7.78 (1H, d); *m/z* (ES⁺) [M+2H]⁺ = 467.3.

Intermediate 63b:

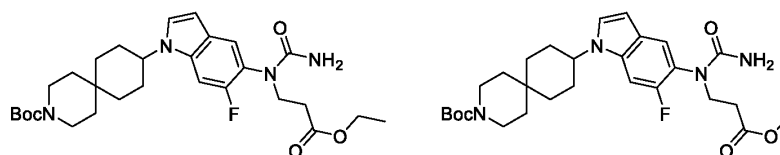
tert-Butyl 9-[5-[(3-ethoxy-3-oxo-propyl)amino]-6-fluoro-indol-1-yl]-3-azaspiro[5.5]undecane-3-carboxylate and *tert*-butyl 9-[6-fluoro-5-[(3-methoxy-3-oxo-propyl)amino]indol-1-yl]-3-azaspiro[5.5]undecane-3-carboxylate



[1596] Prepared in an analogous method to Intermediate 14b with the addition of *t*BuBrettPhos (20.83 mg, 0.04 mmol) starting from Intermediate 63a (200 mg, 0.43 mmol). The reaction mixture was diluted with EtOAc/MeOH, filtered through Celite®, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 - 25% EtOAc in hexanes) gave the title compound as an inseparable mixture of ethyl and methyl esters (185 mg, 86 %) as a solid. Ethyl ester: *m/z* (ES⁺) [M+H]⁺ = 502.5; methyl ester: *m/z* (ES⁺) [M+H]⁺ = 488.5.

Intermediate 63c:

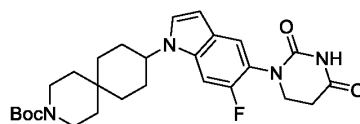
tert-Butyl 9-[5-[carbamoyl-(3-ethoxy-3-oxo-propyl)amino]-6-fluoro-indol-1-yl]-3-azaspiro[5.5]undecane-3-carboxylate and *tert*-butyl 9-[5-[carbamoyl-(3-methoxy-3-oxo-propyl)amino]-6-fluoro-indol-1-yl]-3-azaspiro[5.5]undecane-3-carboxylate



[1597] Prepared with an analogous method to Intermediate 14c starting from Intermediate 63b (185 mg, 0.37 mmol) to give a mixture of the title compounds. Carried onto the next step without purification, quantitative yield assumed. Ethyl ester: *m/z* (ES⁺) [M+H]⁺ = 545.5; methyl ester: *m/z* (ES⁺) [M+H]⁺ = 531.5.

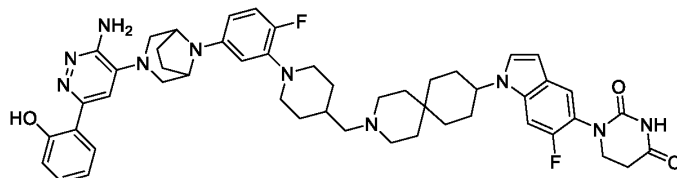
Intermediate 63d:

tert-Butyl 9-[5-(2,4-dioxohexahydropyrimidin-1-yl)-6-fluoro-indol-1-yl]-3-azaspiro[5.5]undecane-3-carboxylate



[1598] Prepared in an analogous method to Intermediate 14d starting from Intermediate 63c (0.37 mmol). Purification by FSC (elution gradient: 0-17% MeOH in DCM) gave the title compound (134 mg, 72.6 %) as an off-white solid. ¹H NMR (CD₂Cl₂): δ 1.38 - 1.46 (4H, m), 1.48 (9H, s), 1.63 - 1.69 (2H, m), 1.88 - 2.03 (6H, m), 2.87 (2H, t), 3.39 - 3.48 (4H, m), 3.83 (2H, t), 4.11 - 4.22 (1H, m), 6.56 (1H, d), 7.22 (1H, d), 7.33 (1H, d), 7.50 - 7.62 (2H, m); *m/z* (ES⁺) [M+Na]⁺ = 521.2.

1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-6-fluoro-indol-5-yl]hexahydropyrimidine-2,4-dione

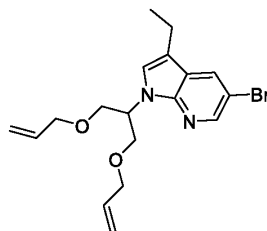


[1599] Prepared in an analogous method to Example 51 starting from Intermediate 63d (42.5 mg, 0.09 mmol) and Intermediate 11g (45 mg, 0.07 mmol). Purification by FSC (elution gradient: 0-20% MeOH in DCM) and lyophilization gave the title compound (34.5 mg, 54.8 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.13 - 1.53 (7H, m), 1.54 - 2.05 (13H, m), 2.10 - 2.27 (4H, m), 2.37 (3H, br s), 2.61 - 2.69 (2H, m), 2.74 (2H, br t), 3.11 (2H, br d), 3.24 - 3.29 (2H, m), 3.30 - 3.39 (2H, m), 3.71 (2H, br t), 4.26 - 4.39 (3H, m), 5.94 (2H, s), 6.39 - 6.52 (3H, m), 6.82 - 6.97 (3H, m), 7.23 (1H, t), 7.47 (1H, s), 7.51 - 7.57 (2H, m), 7.61 (1H, d), 7.91 (1H, br d), 10.38 (1H, s), 14.17 (1H, br s). ¹⁹F NMR (DMSO-*d*₆): -136.38 (1F, s), -129.61 (1F, s); *m/z* (ES⁺) [M+H]⁺ = 885.7.

Example 64:

Intermediate 64a:

1-[2-Allyloxy-1-(allyloxymethyl)ethyl]-5-bromo-3-ethyl-pyrrolo[2,3-*b*]pyridine

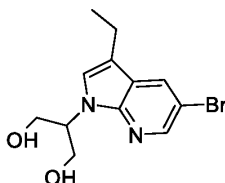


[1600] A flask was charged with 5-bromo-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridine (2.70 g, 12 mmol, prepared according to literature procedure: WO2022087634 A1), 1,3-bis(allyloxy)propan-2-ol (3.16 ml,

18.00 mmol) and toluene (48 ml). 2-(tributyl-*l*-5-phosphaneylidene)acetonitrile (4.72 ml, 18.00 mmol) was added. The flask was fitted with a reflux condenser and the mixture was stirred at 100 °C for 2 h, cooled to r.t. and concentrated *in vacuo*. Purification by FSC (0-20% EtOAc in hexanes) gave the title compound (3.42 g, 75 %) as a colorless oil. ¹H NMR (DMSO-*d*₆): δ 1.24 (3H, t), 2.69 (2H, q), 3.74 - 3.81 (2H, m), 3.82 - 3.88 (2H, m), 3.89 - 3.95 (4H, m), 5.06 - 5.18 (5H, m), 5.78 (2H, ddt), 7.49 (1H, s), 8.18 (1H, d), 8.27 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 379.3.

Intermediate 64b:

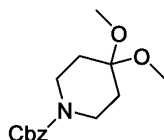
2-(5-Bromo-3-ethyl-pyrrolo[2,3-*b*]pyridin-1-yl)propane-1,3-diol



[1601] A flask was charged with Intermediate 64a (3.4234 g, 9.03 mmol), 1,3-dimethylbarbituric acid (2.82 g, 18.05 mmol) and MeOH (90 ml). The solution was sparged with N₂ for 5 mins, then Pd(PPh₃)₄ (0.521 g, 0.45 mmol) was added. The solution was sparged with N₂ for 5 mins and stirred at r.t. for 22 h then concentrated *in vacuo*. The crude residue was purified by FSC (0-100% EtOAc in hexanes). The residue was triturated with (5:1) hexanes to DCM and collected by vacuum filtration to give the title compound (2.60 g, 96 %) as a red solid. ¹H NMR (DMSO-*d*₆): δ 1.25 (3H, t), 2.69 (2H, q), 3.79 (4H, d), 4.79 (1H, quin), 4.90 (2H, br s), 7.46 (1H, s), 8.18 (1H, d), 8.25 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 299.2.

Intermediate 64c:

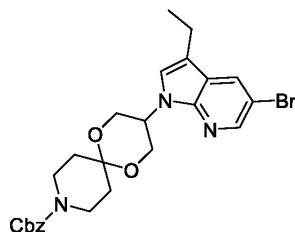
Benzyl 4,4-dimethoxypiperidine-1-carboxylate



[1602] A flask fitted with a reflux condenser was charged with benzyl 4-oxopiperidine-1-carboxylate (5.83 g, 25 mmol), PPTS (0.314 g, 1.25 mmol) and MeOH (100 mL). The reaction was stirred at 70 °C for 16 h. After cooling to r.t., the reaction was diluted with DCM (200 mL), washed with sat. aq. NaHCO₃ (2 x 200 mL), brine (200 mL), dried with Na₂SO₄ and concentrated *in vacuo*. The title compound (6.68 g, 96 %) was obtained as a pale-yellow oil. ¹H NMR (CDCl₃): δ 1.75 (4H, br s), 3.22 (6H, s), 3.50 - 3.55 (4H, m), 5.15 (2H, s), 7.32 - 7.43 (5H, m).

Intermediate 64d:

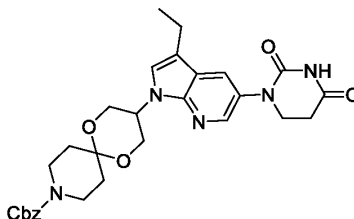
Benzyl 3-(5-bromo-3-ethyl-pyrrolo[2,3-*b*]pyridin-1-yl)-1,5-dioxo-9-azaspiro[5.5]undecane-9-carboxylate



[1000] A flask fitted with a reflux condenser was charged with Intermediate 64b (1.3733 g, 4.59 mmol), Intermediate 64c (1.966 g, 7.04 mmol), PPTS (0.058 g, 0.23 mmol) and toluene (25 mL). The reaction was stirred at 110 °C for 2 h then cooled to r.t. and concentrated *in vacuo*. Purification by FSC (0-75% EtOAc in hexanes, then 0-40% acetone in hexanes) gave the title compound (1.505 g, 63.7 %) as a colorless dry film. ¹H NMR (DMSO-*d*₆): δ 1.26 (3H, t), 1.89 (2H, br d), 1.97 - 2.03 (2H, m), 2.72 (2H, q), 3.47 (4H, br d), 4.04 (2H, dd), 4.33 (2H, br d), 4.79 - 4.84 (1H, m), 5.10 (2H, s), 7.30 - 7.35 (1H, m), 7.36 - 7.42 (4H, m), 7.74 (1H, s), 8.23 (1H, d), 8.29 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 513.9.

Intermediate 64e:

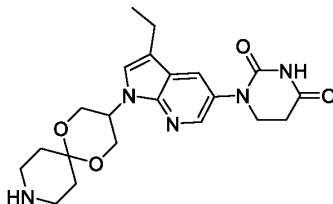
Benzyl 3-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-ethyl-pyrrolo[2,3-*b*]pyridin-1-yl]-1,5-dioxo-9-azaspiro[5.5]undecane-9-carboxylate



[1604] Prepared in an analogous manner to Intermediate 2b starting from Intermediate 64d (1.505 g, 2.93 mmol). The crude material was purified by FSC (elution gradient: 0-100% EtOAc in hexanes then 0-20% MeOH in EtOAc). This material was titrated with water to give the title compound (0.664 g, 41.4 %) as a brown solid. ¹H NMR (DMSO-*d*₆): δ 1.28 (3H, t), 1.89 - 2.02 (4H, m), 2.69 - 2.79 (4H, m), 3.43 - 3.53 (4H, m), 3.82 (2H, t), 4.08 (2H, br dd), 4.32 (2H, br d), 4.87 (1H, quin), 5.10 (2H, s), 7.31 - 7.36 (1H, m), 7.36 - 7.41 (4H, m), 7.72 (1H, s), 7.96 (1H, d), 8.20 (1H, d), 10.38 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 548.1.

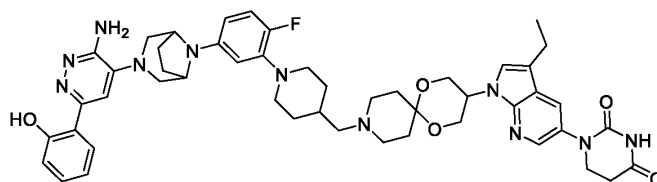
Intermediate 64f:

1-[1-(1,5-Dioxo-9-azaspiro[5.5]undecan-3-yl)-3-ethyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1605] A vial was charged with Intermediate 64e (664 mg, 1.21 mmol), DMF (6 mL) and Pd/C (129 mg, 0.12 mmol). H₂ was bubbled through the mixture for 10 mins and the resulting mixture was stirred under an atmosphere of H₂ for 4 h. The mixture was sparged with N₂, filtered through a pad of celite®, washing with DCM (50 mL) and concentrated *in vacuo*. Crude residue was dissolved in DCM (3 mL) and hexanes (50 mL) was added, precipitating a solid. This solid was collected by vacuum filtration, washed with Et₂O, and dried to give the title compound (380 mg, 76 %) as a grey solid. ¹H NMR (DMSO-*d*₆): δ 1.28 (3H, t), 1.78 - 1.92 (4H, m), 2.66 - 2.81 (8H, m), 3.82 (2H, t), 4.04 (2H, dd), 4.29 (2H, dd), 4.83 (1H, quin), 7.74 (1H, s), 7.96 (1H, d), 8.19 (1H, d), 10.38 (1H, br s) (N-H not observed); *m/z* (ES⁺) [M+H]⁺ = 414.1.

1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-ethyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

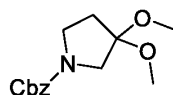


[1606] A vial was charged with Intermediate 13d (50.3 mg, 0.1 mmol), Intermediate 64f (45.5 mg, 0.11 mmol), DCM (1 mL) and MeOH (0.2 mL). The mixture was stirred at r.t. for 20 mins then Na(OAc)₃BH (42.4 mg, 0.20 mmol) was added. The reaction was stirred at r.t. for 10 mins then concentrated *in vacuo*. Purification by RPC (elution gradient: 0-50% MeCN in water with 0.1% HCOOH) gave the title compound (45.4 mg, 49.2 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.18 - 1.33 (5H, m), 1.56 - 1.70 (1H, m), 1.80 (2H, br d), 1.89 - 2.05 (6H, m), 2.10 - 2.18 (2H, m), 2.22 (2H, br d), 2.35 - 2.49 (4H, m), 2.65 (2H, br t), 2.69 - 2.81 (4H, m), 3.11 (2H, br d), 3.26 (2H, br d), 3.36 (2H, br d), 3.82 (2H, t), 4.04 (2H, br dd), 4.25 - 4.44 (4H, m), 4.80 - 4.88 (1H, m), 5.94 (2H, s), 6.43 (1H, dt), 6.47 - 6.51 (1H, m), 6.84 - 6.90 (2H, m), 6.93 (1H, dd), 7.21 - 7.26 (1H, m), 7.47 (1H, s), 7.74 (1H, s), 7.91 (1H, dd), 7.96 (1H, d), 8.20 (1H, d), 10.39 (1H, s), 13.13 - 14.96 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 900.5.

Example 65:

Intermediate 65a:

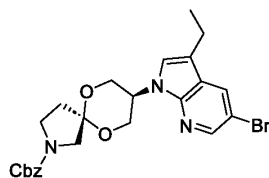
Benzyl 3,3-dimethoxypyrrolidine-1-carboxylate



[1607] Prepared in an analogous manner to Intermediate 64c starting from benzyl 3-oxopyrrolidine-1-carboxylate (2.192 g, 10 mmol). The title compound (2.476 g, 93 %) was obtained as a pale-yellow oil. ¹H NMR (CDCl₃) δ 2.07 (2H, q), 3.27 (6H, d), 3.48 - 3.57 (4H, m), 5.15 (2H, s), 7.31 - 7.41 (5H, m); *m/z* (ES⁺) [M+Na]⁺ = 288.2.

Intermediate 65b:

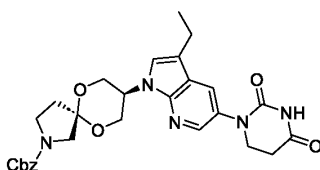
Benzyl (5*s*,8*s*)-8-(5-bromo-3-ethyl-pyrrolo[2,3-*b*]pyridin-1-yl)-6,10-dioxo-2-azaspiro[4.5]decane-2-carboxylate



[1608] Prepared in an analogous manner to Intermediate 64d starting from Intermediate 64b (1047 mg, 3.5 mmol) and Intermediate 65a (1857 mg, 7.00 mmol). Purification by FCS (0-75% EtOAc in hexanes) separated the desired diastereomer which eluted second off the column. This material was subsequently purified by RPC (elution gradient: 50-100% MeCN in water with 0.1% HCOOH) to give the title compound (467 mg, 26.7 %) as a colorless dry film. ¹H NMR (DMSO-*d*₆): δ 1.18 - 1.35 (3H, m), 2.28 - 2.40 (2H, m), 2.71 (2H, q), 3.39 - 3.55 (2H, m), 3.65 (2H, br d), 4.10 (2H, dd), 4.27 - 4.40 (2H, m), 4.85 (1H, br dd), 5.10 (2H, d), 7.28 - 7.48 (5H, m), 7.74 (1H, br d), 8.23 (1H, d), 8.28 (1H, br d); *m/z* (ES⁺) [M+H]⁺ = 500.

Intermediate 65c:

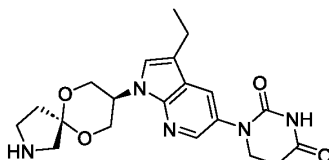
Benzyl (5*s*,8*s*)-8-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-ethyl-pyrrolo[2,3-*b*]pyridin-1-yl]-6,10-dioxo-2-azaspiro[4.5]decane-2-carboxylate



[1609] Prepared in an analogous manner to Intermediate 2b starting from Intermediate 65b (467 mg, 0.93 mmol). Purification by FSC (elution gradient: 0-100% EtOAc in hexanes then 0-20% MeOH in EtOAc) followed by trituration with water gave the title compound (224 mg, 44.9 %) as a beige solid. ¹H NMR (DMSO-*d*₆): δ 1.28 (3H, q), 2.27 - 2.38 (2H, m), 2.68 - 2.83 (4H, m), 3.41 - 3.52 (2H, m), 3.68 (2H, br d), 3.82 (2H, t), 4.13 (2H, dd), 4.28 - 4.38 (2H, m), 4.84 - 4.96 (1H, m), 5.11 (2H, br d), 7.28 - 7.35 (1H, m), 7.35 - 7.45 (4H, m), 7.72 (1H, br d), 7.97 (1H, d), 8.20 (1H, br d), 10.39 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 534.7.

Intermediate 65d:

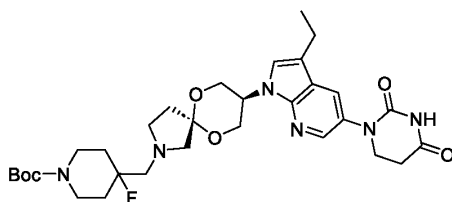
1-[1-((5*s*,8*s*)-6,10-Dioxo-2-azaspiro[4.5]decan-8-yl)-3-ethyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1610] Prepared in an analogous manner to Intermediate 64f starting from Intermediate 65c (223 mg, 0.42 mmol). The title compound (119 mg, 71.2 %) was obtained as an off-white solid. ¹H NMR (DMSO-*d*₆): δ 1.28 (3H, t), 2.05 (2H, t), 2.68 - 2.81 (4H, m), 2.90 (2H, t), 2.98 (2H, s), 3.82 (2H, t), 4.06 (2H, dd), 4.30 (2H, dd), 4.81 - 4.88 (1H, m), 7.70 (1H, s), 7.97 (1H, d), 8.20 (1H, d), 10.39 (1H, br s) (N-H not observed); *m/z* (ES⁺) [M+H]⁺ = 400.6.

Intermediate 65e:

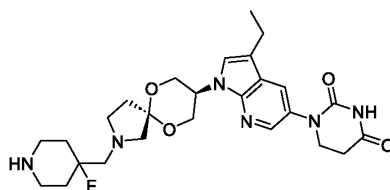
tert-Butyl 4-[[[(5*s*,8*s*)-8-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-ethyl-pyrrolo[2,3-*b*]pyridin-1-yl]-6,10-dioxo-2-azaspiro[4.5]decan-2-yl]methyl]-4-fluoro-piperidine-1-carboxylate



[1611] Prepared in an analogous manner to Intermediate 25f starting from Intermediate 65d (96 mg, 0.24 mmol) and Intermediate 25e (105 mg, 0.29 mmol). Purification by FSC (elution gradient: 0-100% EtOAc in hexanes the 0-30% MeOH in EtOAc) gave the title compound (115 mg, 78 %) as a beige solid. ¹H NMR (DMSO-*d*₆): δ 1.27 (3H, t), 1.40 (9H, s), 1.49 - 1.67 (2H, m), 1.75 - 1.88 (2H, m), 2.13 (2H, br t), 2.60 - 2.68 (2H, m), 2.69 - 2.81 (6H, m), 2.90 (2H, s), 2.97 - 3.10 (2H, m), 3.71 (2H, br d), 3.82 (2H, t), 4.04 (2H, dd), 4.32 (2H, dd), 4.78 - 4.85 (1H, m), 7.67 (1H, s), 7.97 (1H, d), 8.19 (1H, d), 10.38 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 615.3.

Intermediate 65f:

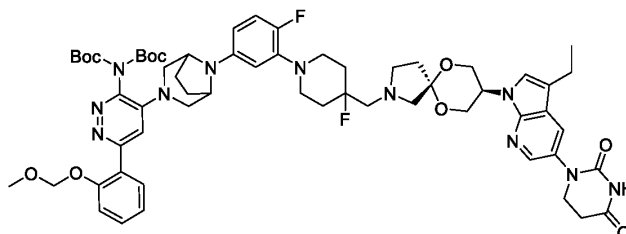
1-[3-Ethyl-1-[(5*s*,8*s*)-2-[(4-fluoro-4-piperidyl)methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1612] Prepared in an analogous manner to Intermediate 2c starting from Intermediate 65e (114.4 mg, 0.19 mmol). Purification by ion exchange chromatography (Porapak Rxn CX 2g cartridge) eluting with 2N NH₃ in MeOH gave the title compound (83 mg, 86 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.28 (3H, t), 1.49 - 1.65 (2H, m), 1.66 - 1.77 (2H, m), 2.13 (2H, br t), 2.56 - 2.64 (2H, m), 2.68 - 2.79 (11H, m), 2.89 (2H, s), 3.82 (2H, t), 4.04 (2H, dd), 4.31 (2H, dd), 4.79 - 4.85 (1H, m), 7.68 (1H, s), 7.96 (1H, d), 8.19 (1H, d), 10.38 (1H, br s); *m/z* (ES⁺) [M+H]⁺ = 515.1.

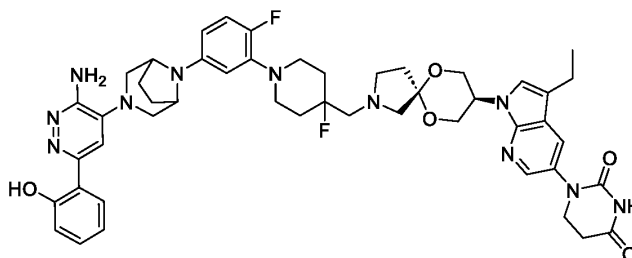
Intermediate 65g:

tert-Butyl *N*-*tert*-butoxycarbonyl-*N*-[4-[8-[3-[4-[[*(5s,8s)*-8-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-ethyl-pyrrolo[2,3-*b*]pyridin-1-yl]-6,10-dioxo-2-azaspiro[4.5]decan-2-yl]methyl]-4-fluoro-1-piperidyl]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]-6-[2-(methoxymethoxy)phenyl]pyridazin-3-yl]carbamate



[1613] A vial was charged with Intermediate 65f (0.083 g, 0.16 mmol), Intermediate 57a (0.108 g, 0.16 mmol), K₂CO₃ (0.067 g, 0.48 mmol), Pd-PEPPSI-IPentCl 2-methylpyridine (0.027 g, 0.03 mmol) and dioxane (1.6 mL). The vial was sparged with N₂ and was heated at 100 °C for 22 h. Reaction was cooled to r.t., filtered through celite® eluting with EtOAc/DCM and concentrated. Purification by FSC (elution gradient: 0-100% EtOAc in hexanes then 0-30% MeOH in EtOAc) gave the title compound (0.069 g, 37.0 %) as a brown dry film. *m/z* (ES⁺) [M+H]⁺ = 1148.7.

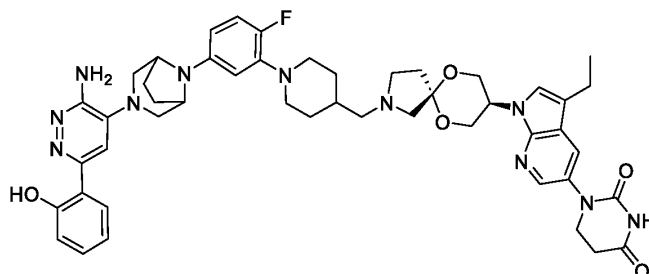
1-[1-[(*5s,8s*)-2-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-fluoro-4-piperidyl]methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]-3-ethyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1614] In a vial Intermediate 65g (68.5 mg, 0.06 mmol) was dissolved in DCM (2 mL) and TFA (0.4 mL). The reaction was stirred at r.t. for 2 h then concentrated under reduced pressure. The residue was dissolved in DCM and quenched with sat. aq. NaHCO₃ solution. The aq. layer was extracted with DCM, dried Na₂SO₄ and concentrated. The resulting residue was suspended in ACN/H₂O, frozen, and dried by lyophilization. Purification by RPC (elution gradient: 0-50% MeCN in water with 0.1% HCOOH) gave the title compound (12.50 mg, 22.89 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.27 (3H, t), 1.73 - 2.02 (6H, m), 2.10 - 2.19 (4H, m), 2.66 - 2.81 (8H, m), 2.89 - 3.00 (4H, m), 3.10 (2H, br d), 3.16 - 3.21 (2H, m), 3.26 (2H, br d), 3.82 (2H, t), 4.05 (2H, dd), 4.28 - 4.43 (4H, m), 4.82 (1H, t), 5.93 (2H, s), 6.45 (1H, dt), 6.53 (1H, dd), 6.83 - 6.90 (2H, m), 6.95 (1H, dd), 7.20 - 7.25 (1H, m), 7.47 (1H, s), 7.68 (1H, s), 7.91 (1H, dd), 7.96 (1H, d), 8.20 (1H, d), 10.38 (1H, s), 13.65 - 14.53 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 904.5

Example 66:

1-[1-[(5*s*,8*s*)-2-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl)methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]-3-ethyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

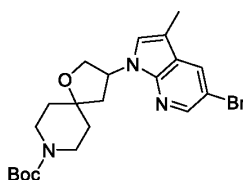


[1615] Prepared in an analogous manner to Example 64 starting from Intermediate 13d (25.1 mg, 0.05 mmol) and Intermediate 65d (19.97 mg, 0.05 mmol). Purification by RPC (elution gradient: 0-50% MeCN in water with 0.1% HCOOH) gave the title compound (23.0 mg, 50.3 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.23 - 1.32 (5H, m), 1.53 - 1.66 (1H, m), 1.82 (2H, br d), 1.91 - 1.98 (2H, m), 2.10 - 2.18 (4H, m), 2.32 (2H, br d), 2.59 - 2.67 (4H, m), 2.68 - 2.79 (5H, m), 2.83 (2H, s), 3.11 (2H, br d), 3.23 - 3.28 (3H, m), 3.82 (2H, t), 4.05 (2H, br dd), 4.30 (2H, br dd), 4.35 (2H, br s), 4.77 - 4.92 (1H, m), 5.94 (2H, s), 6.44 (1H, dt), 6.47 - 6.52 (1H, m), 6.83 - 6.89 (2H, m), 6.93 (1H, dd), 7.21 - 7.26 (1H, m), 7.47 (1H, s), 7.69 (1H, s), 7.91 (1H, d), 7.97 (1H, d), 8.20 (1H, d), 10.38 (1H, s), 13.67 - 14.81 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 886.5.

Example 67:

Intermediate 67a:

tert-Butyl 3-(5-bromo-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl)-1-oxa-8-azaspiro[4.5]decane-8-carboxylate



[1616] Prepared in an analogous manner to Intermediate 4a starting from 5-bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (422 mg, 2 mmol) and *tert*-butyl-3-hydroxy-1-oxa-8-azaspiro[4.5]decane-8-carboxylate (566 mg, 2.20 mmol). Purification by FSC (elution gradient: 0-25% acetone in hexanes) gave the title compound (341 mg, 37.9 %) as a colorless dry film. ¹H NMR (CDCl₃): δ 1.47 (9H, s), 1.55 - 1.64 (1H, m), 1.67 - 1.75 (1H, m), 1.75 - 1.85 (2H, m), 1.96 (1H, dd), 2.28 (3H, d), 2.43 (1H, dd), 3.34 - 3.45 (2H, m), 3.57 - 3.69 (2H, m), 4.08 (1H, dd), 4.24 (1H, dd), 5.52 - 5.59 (1H, m), 7.19 (1H, d), 7.96 (1H, s), 8.30 (1H, d); *m/z* (ES⁺) [M-tBu+2H]⁺ = 394.0.

Intermediate 67b:

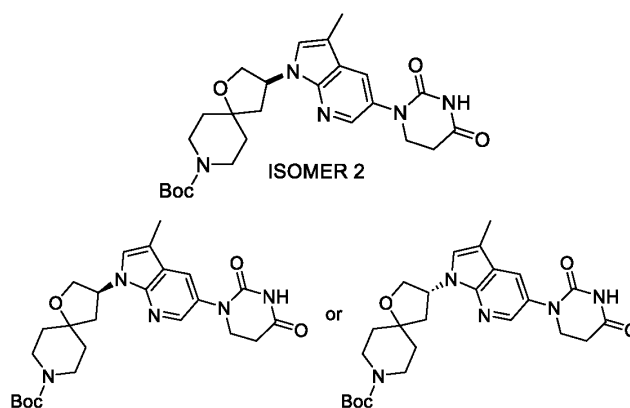
tert-Butyl *rel*-(3*S**)-3-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-1-oxa-8-azaspiro[4.5]decane-8-carboxylate (ISOMER 2)

[*absolute configuration not yet confirmed]

tert-Butyl (3*S*)-3-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-1-oxa-8-azaspiro[4.5]decane-8-carboxylate

or

tert-Butyl (3*R*)-3-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-1-oxa-8-azaspiro[4.5]decane-8-carboxylate



[1617] Prepared in an analogous manner to Intermediate 2b starting from Intermediate 67a (0.341 g, 0.76 mmol). Purification by FSC (elution gradient: 0-100% EtOAc in hexanes then 0-100%) gave racemic material. This material was purified by chiral SFC (column: Chiralpak IH 21 x 250 mm, 5 μ m, mobile phase: 80% CO₂, 20% MeOH w/ 0.2% NH₄OH, flow rate: 75 mL/min, BPR: 120 bar, column temp: 40 °C) to afford the title compound (102 mg, 28%) that eluted second off the column. ¹H NMR (DMSO-*d*₆): δ 1.41 (9H, s), 1.52 - 1.62 (1H, m), 1.63 - 1.77 (3H, m), 2.03 (1H, dd), 2.27 (3H, s), 2.41 (1H, dd), 2.76 (2H, t), 3.26 - 3.31 (1H, m), 3.32 - 3.37 (1H, m), 3.42 - 3.50 (2H, m), 3.81 (2H, t), 3.99 (1H, dd), 4.18 (1H, dd), 5.45 - 5.52 (1H, m), 7.48 (1H, s), 7.91 (1H, d), 8.20 (1H, d), 10.39 (1H, s); *m/z* (ES⁺) [M+Na]⁺ = 506.1.

Intermediate 67c:

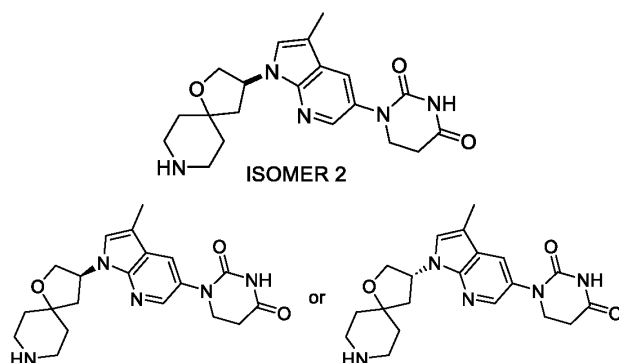
1-[3-Methyl-1-[(*rel*-(3*S**)-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione (ISOMER 2)

[*absolute configuration not yet confirmed]

1-[3-Methyl-1-[(3*S*)-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

or

1-[3-Methyl-1-[(3*R*)-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



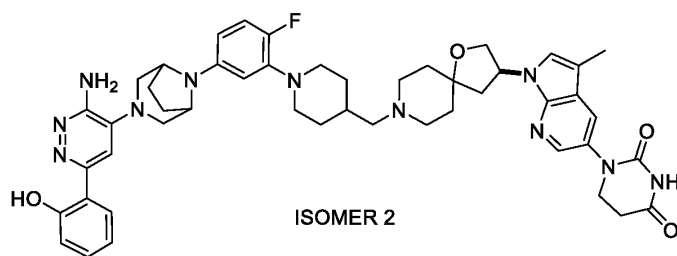
[1618] Prepared in an analogous manner to Intermediate 2c starting from Intermediate 67b (102 mg, 0.21 mmol). Purification by ion exchange chromatography (Porapak Rxn CX 2g cartridge) eluting with 2N NH₃ in MeOH gave the title compound (75 mg, 93 %) as an off-white solid. ¹H NMR (DMSO-*d*₆): δ 1.54 - 1.61 (2H, m), 1.66 (2H, t), 1.96 (1H, dd), 2.27 (3H, s), 2.32 - 2.45 (1H, m), 2.52 - 2.63 (2H, m), 2.76 (2H, t), 2.85 (2H, dq), 3.21 - 3.46 (1H, m), 3.81 (2H, t), 3.94 (1H, dd), 4.14 (1H, dd), 5.43 - 5.48 (1H, m), 7.47 (1H, s), 7.90 (1H, d), 8.20 (1H, d), 10.08 - 10.76 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 384.6.

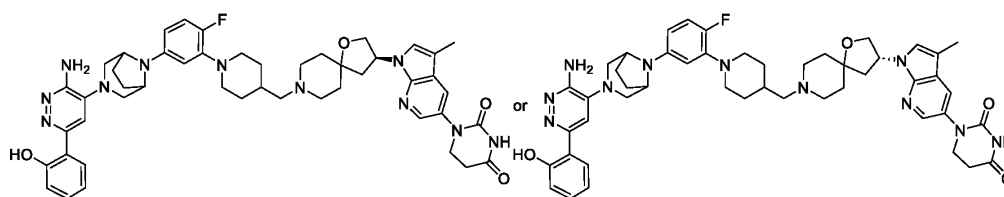
1-[3-Methyl-1-*rel*-(3*S**)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione
(ISOMER 2)

[*absolute configuration not yet confirmed]

1-[3-Methyl-1-[(3*S*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione
or

1-[3-Methyl-1-[(3*R*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione





[1619] Prepared in an analogous manner to Example 64 starting from Intermediate 13d (99 mg, 0.20 mmol) and Intermediate 67c (75.2 mg, 0.20 mmol). Purification by RPC (elution gradient: 0-50% MeCN in water with 0.1% HCOOH) gave the title compound (81 mg, 45.5 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.20 - 1.31 (2H, m), 1.59 - 1.84 (7H, m), 1.91 - 2.02 (3H, m), 2.10 - 2.16 (2H, m), 2.23 (2H, br d), 2.27 (3H, s), 2.34 - 2.45 (3H, m), 2.47 - 2.50 (1H, m), 2.53 - 2.57 (1H, m), 2.60 - 2.69 (2H, m), 2.77 (2H, t), 3.10 (2H, br d), 3.20 - 3.30 (1H, m), 3.22 - 3.30 (1H, m), 3.35 (2H, br d), 3.81 (2H, t), 3.96 (1H, dd), 4.15 (1H, dd), 4.34 (2H, br s), 5.46 (1H, quin), 5.94 (2H, s), 6.43 (1H, dt), 6.48 (1H, br dd), 6.82 - 6.99 (3H, m), 7.19 - 7.28 (1H, m), 7.47 (2H, s), 7.86 - 7.94 (2H, m), 8.20 (1H, d), 10.39 (1H, s) (phenol O-H not observed); *m/z* (ES⁺) [M+H]⁺ = 870.5.

Example 68:

Intermediate 68a:

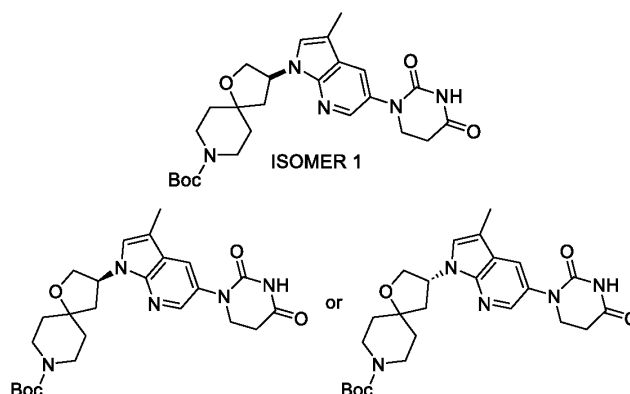
tert-Butyl *rel*-(3*S**)-3-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-1-oxa-8-azaspiro[4.5]decane-8-carboxylate (ISOMER 1)

[*absolute configuration not yet confirmed]

tert-Butyl (3*S*)-3-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-1-oxa-8-azaspiro[4.5]decane-8-carboxylate

or

tert-Butyl (3*R*)-3-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-1-oxa-8-azaspiro[4.5]decane-8-carboxylate



[1620] Prepared in an analogous manner to Intermediate 2b starting from Intermediate 67a (0.341 g, 0.76 mmol). Purification by FCS (0-100% EtOAc in hexanes then 0-100% MeOH in EtOAc) gave racemic material. This material was purified by chiral SFC (column: Chiralpak IH 21 x 250 mm, 5μm, mobile phase:

80% CO₂, 20% MeOH w/ 0.2% NH₄OH, flow rate: 75 mL/min, BPR: 120 bar, column temp: 40 °C) to afford the title compound (97 mg, 26%) that eluted first off of the column. ¹H NMR (DMSO-*d*₆): δ 1.41 (9H, s), 1.52 - 1.62 (1H, m), 1.63 - 1.77 (3H, m), 2.03 (1H, dd), 2.27 (3H, s), 2.41 (1H, dd), 2.76 (2H, t), 3.26 - 3.31 (1H, m), 3.32 - 3.37 (1H, m), 3.42 - 3.50 (2H, m), 3.81 (2H, t), 3.99 (1H, dd), 4.18 (1H, dd), 5.45 - 5.52 (1H, m), 7.48 (1H, s), 7.91 (1H, d), 8.20 (1H, d), 10.39 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 484.1.

Intermediate 68b:

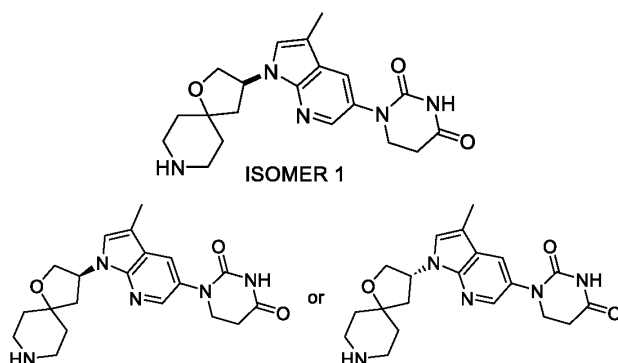
1-[3-Methyl-1-*rel*-(3*S**)-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione (ISOMER 1)

[*absolute configuration not yet confirmed]

1-[3-Methyl-1-[(3*S*)-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

or

1-[3-Methyl-1-[(3*R*)-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1621] Prepared in an analogous manner to Intermediate 2c starting from Intermediate 68a. Purification by ion exchange chromatography (Porapak Rxn CX 2g cartridge) eluting with 2N NH₃ in MeOH gave the title compound (72.5 mg, 95 %) as an off white solid. ¹H NMR (DMSO-*d*₆): δ 1.52 - 1.64 (2H, m), 1.66 (2H, t), 1.96 (1H, dd), 2.25 - 2.28 (3H, m), 2.39 (1H, dd), 2.52 - 2.63 (2H, m), 2.72 - 2.81 (2H, m), 2.85 (2H, dq), 3.23 - 3.40 (1H, m), 3.81 (2H, t), 3.95 (1H, dd), 4.14 (1H, dd), 5.42 - 5.49 (1H, m), 7.47 (1H, s), 7.90 (1H, d), 8.20 (1H, d), 10.15 - 10.56 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 384.6.

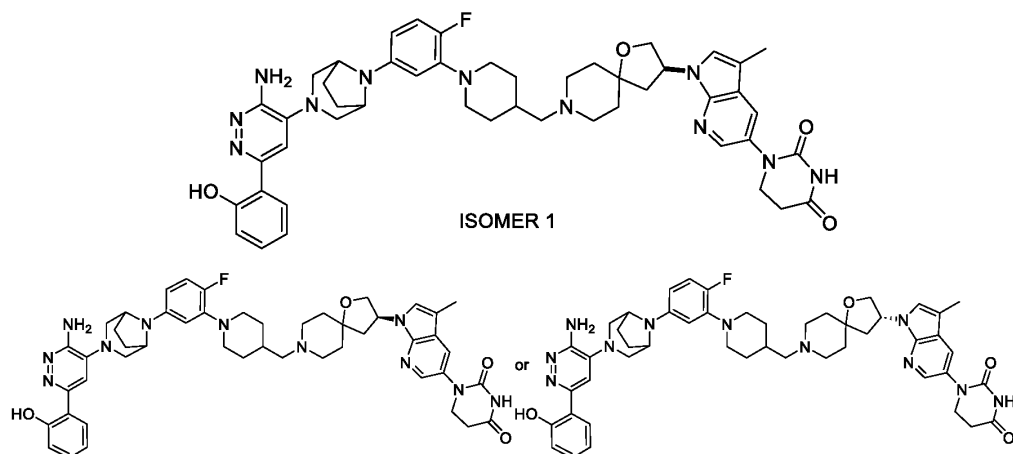
1-[3-Methyl-1-*rel*-(3*R**)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione (ISOMER 1)

[*absolute configuration not yet confirmed]

1-[3-Methyl-1-[(3*S*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

or

1-[3-Methyl-1-[(3*R*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

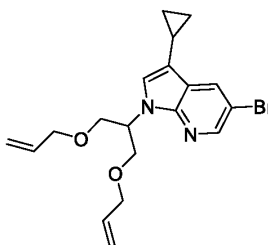


[1622] Prepared in an analogous manner to Example 64 starting from Intermediate 13d (95 mg, 0.19 mmol) and Intermediate 68b (72.5 mg, 0.19 mmol). Purification by RPC (elution gradient: 0-50% MeCN in water with 0.1% HCOOH) gave the title compound (102 mg, 59.5 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.19 - 1.33 (2H, m), 1.59 - 1.84 (7H, m), 1.91 - 2.03 (3H, m), 2.10 - 2.16 (2H, m), 2.22 (2H, br d), 2.27 (3H, s), 2.32 - 2.43 (3H, m), 2.48 - 2.50 (1H, m), 2.52 - 2.57 (1H, m), 2.64 (2H, br t), 2.76 (2H, t), 3.10 (2H, br d), 3.26 (2H, br d), 3.35 (2H, br d), 3.81 (2H, t), 3.96 (1H, dd), 4.15 (1H, dd), 4.35 (2H, br s), 5.46 (1H, quin), 5.94 (2H, s), 6.40 - 6.45 (1H, m), 6.46 - 6.51 (1H, m), 6.83 - 6.89 (2H, m), 6.92 (1H, dd), 7.20 - 7.27 (1H, m), 7.45 - 7.48 (2H, m), 7.89 - 7.93 (2H, m), 8.20 (1H, d), 10.39 (1H, s), 12.21 - 14.91 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 870.6.

Example 69

Intermediate 69a:

1-[2-Allyloxy-1-(allyloxymethyl)ethyl]-5-bromo-3-cyclopropyl-pyrrolo[2,3-*b*]pyridine

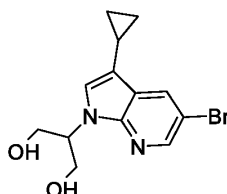


[1623] Prepared in an analogous manner to Intermediate 64a starting from bromo-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridine (3 g, 12.65 mmol) and 1,3-bis(allyloxy)propan-2-ol (3.34 ml, 18.98 mmol). Purification by FSC (elution gradient: 0-20% EtOAc in hexanes) gave the title compound (4.34 g, 88 %)

as a yellow oil. ^1H NMR (DMSO-*d*₆): δ 0.59 - 0.64 (2H, m), 0.84 - 0.91 (2H, m), 1.91 - 1.99 (1H, m), 3.73 - 3.78 (2H, m), 3.80 - 3.85 (2H, m), 3.88 - 3.92 (4H, m), 5.04 - 5.17 (5H, m), 5.70 - 5.85 (2H, m), 7.42 (1H, s), 8.20 (1H, d), 8.27 (1H, d); m/z (ES⁺) [M+H]⁺ = 391.3.

Intermediate 69b:

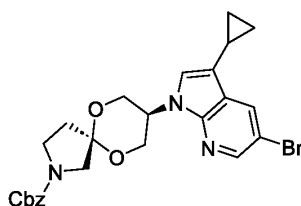
2-(5-Bromo-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-1-yl)propane-1,3-diol



[1624] Prepared in an analogous manner to Intermediate 64b starting from Intermediate 69a (4.34 g, 11.09 mmol). Purification by FSC (elution gradient: 0-100% EtOAc in hexanes) gave the title compound (3.02 g, 87 %) as a red solid. ^1H NMR (DMSO-*d*₆): δ 0.58 - 0.69 (2H, m), 0.81 - 0.92 (2H, m), 1.87 - 1.98 (1H, m), 3.77 (4H, d), 4.78 (1H, quin), 4.88 (2H, br s), 7.39 (1H, s), 8.18 (1H, d), 8.26 (1H, d); m/z (ES⁺) [M+H]⁺ = 311.2.

Intermediate 69c:

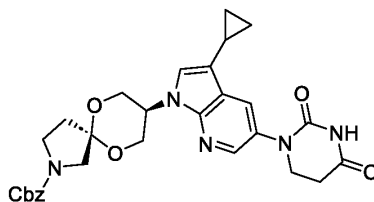
Benzyl (5*s*,8*s*)-8-(5-bromo-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-1-yl)-6,10-dioxo-2-azaspiro[4.5]decane-2-carboxylate



[1625] Prepared in an analogous manner to Intermediate 64d starting from Intermediate 69b (480 mg, 1.54 mmol). The material was purified by FSC (elution gradient: 0-75% EtOAc in hexanes) to give the desired isomer, which eluted off the column second. The title compound (0.314 g, 39.7 %) was obtained as a brown solid. ^1H NMR (DMSO-*d*₆): δ 0.64 (2H, br s), 0.88 (2H, br d), 1.91 - 1.99 (1H, m), 2.30 (2H, br d), 3.40 - 3.52 (2H, m), 3.66 (2H, br d), 4.09 (2H, br dd), 4.23 - 4.37 (2H, m), 4.84 (1H, br dd), 5.10 (2H, br d), 7.28 - 7.43 (5H, m), 7.64 (1H, br d), 8.24 (1H, br s), 8.29 (1H, br d); m/z (ES⁺) [M+H]⁺ = 512.3.

Intermediate 69d:

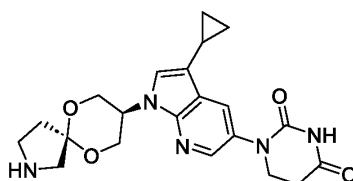
Benzyl (5*s*,8*s*)-8-[3-cyclopropyl-5-(2,4-dioxohexahydropyrimidin-1-yl)pyrrolo[2,3-*b*]pyridin-1-yl]-6,10-dioxo-2-azaspiro[4.5]decane-2-carboxylate



[1626] Prepared in an analogous manner to Intermediate 2b starting from Intermediate 69c (293 mg, 0.57 mmol). Purification by FSC (elution gradient: 0-100% EtOAc in hexanes then 0-20% MeOH in EtOAc) followed by trituration with water gave the title compound (151 mg, 48.4 %) as a brown solid. ¹H NMR (DMSO-*d*₆): δ 0.60 - 0.69 (2H, m), 0.83 - 0.95 (2H, m), 1.91 - 1.99 (1H, m), 2.26 - 2.34 (2H, m), 2.77 (2H, t), 3.40 - 3.52 (2H, m), 3.68 (2H, br d), 3.83 (2H, t), 4.12 (2H, br dd), 4.22 - 4.36 (2H, m), 4.83 - 4.98 (1H, m), 5.11 (2H, br d), 7.29 - 7.35 (1H, m), 7.39 (4H, br d), 7.62 (1H, br d), 7.99 (1H, br s), 8.20 (1H, br d), 10.39 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 546.1

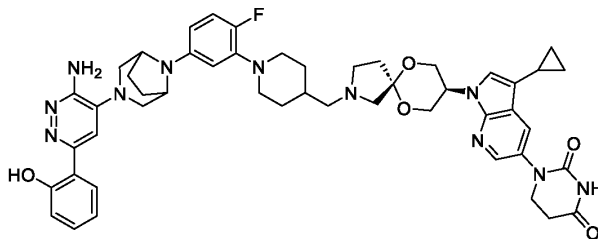
Intermediate 69e:

1-[3-Cyclopropyl-1-((5*s*,8*s*)-6,10-dioxo-2-azaspiro[4.5]decan-8-yl)pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1627] Prepared in an analogous manner to Intermediate 64f starting from Intermediate 69d (151 mg, 0.28 mmol). The title compound (90 mg, 79 %) was obtained as an off white solid. ¹H NMR (DMSO-*d*₆): δ 0.59 - 0.70 (2H, m), 0.85 - 0.92 (2H, m), 1.92 - 1.99 (1H, m), 2.04 (2H, t), 2.77 (2H, t), 2.87 - 2.92 (2H, m), 2.99 (2H, s), 3.83 (2H, t), 4.05 (2H, dd), 4.26 (2H, dd), 4.82 (1H, quin), 7.61 (1H, s), 7.99 (1H, d), 8.20 (1H, d), 10.38 (1H, br s) (N-H not observed); *m/z* (ES⁺) [M+H]⁺ = 412.1.

1-[1-[(5*s*,8*s*)-2-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]-3-cyclopropylpyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



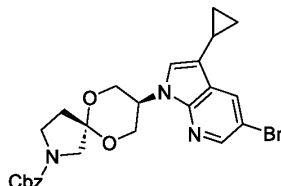
[1628] Prepared in an analogous manner to Example 64 starting from Intermediate 13d (25.1 mg, 0.05 mmol) and Intermediate 69e (20.6 mg, 0.05 mmol). Purification by RPC (0-50% MeCN in water with 0.1% HCOOH) gave the title compound (31.3 mg, 68.7 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 0.62 - 0.69 (2H, m), 0.83 - 0.93 (2H, m), 1.21 - 1.35 (2H, m), 1.53 - 1.66 (1H, m), 1.82 (2H, br d), 1.90 - 2.00 (3H, m), 2.09 - 2.17 (4H, m), 2.32 (2H, br d), 2.57 - 2.70 (4H, m), 2.77 (2H, t), 2.83 (2H, s), 3.11 (2H, br d), 3.23 - 3.30 (4H, m), 3.83 (2H, t), 4.04 (2H, br dd), 4.26 (2H, br dd), 4.35 (2H, br s), 4.79 - 4.85 (1H, m), 5.94 (2H, s), 6.44 (1H, dt), 6.49 (1H, dd), 6.84 - 6.89 (2H, m), 6.93 (1H, dd), 7.21 - 7.25 (1H, m), 7.47 (1H, s), 7.60

(1H, s), 7.91 (1H, d), 7.99 (1H, d), 8.21 (1H, s), 10.39 (1H, s), 13.83 - 14.53 (1H, m); m/z (ES⁺) [M+H]⁺ = 898.5.

Example 70

Intermediate 70a:

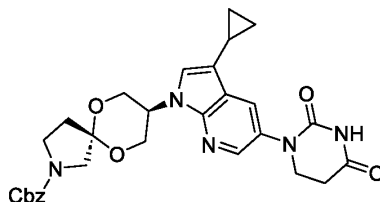
Benzyl (5*r*,8*r*)-8-(5-bromo-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-1-yl)-6,10-dioxo-2-azaspiro[4.5]decane-2-carboxylate



[1629] Prepared in an analogous manner to Intermediate 64d starting from Intermediate 69b (480 mg, 1.54 mmol). Purification by FSC (elution gradient: 0-75% EtOAc in hexanes) gave desired isomer which eluted off the column first. Subsequent purification by RPC (elution gradient: 0-50% MeCN in water with 0.1% HCOOH) gave the title compound (0.243 g, 30.8 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 0.61 - 0.67 (2H, m), 0.87 - 0.92 (2H, m), 1.94 - 2.02 (1H, m), 2.22 - 2.32 (2H, m), 3.39 - 3.50 (2H, m), 3.70 (2H, br d), 4.10 (2H, dd), 4.26 - 4.34 (2H, m), 4.77 - 4.85 (1H, m), 5.10 (2H, d), 7.30 - 7.42 (5H, m), 7.62 (1H, s), 8.25 (1H, d), 8.30 (1H, d); m/z (ES⁺) [M+H]⁺ = 512.0.

Intermediate 70b:

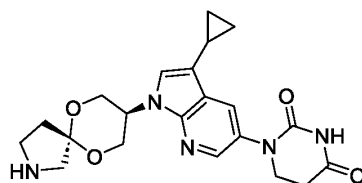
Benzyl (5*r*,8*r*)-8-[3-cyclopropyl-5-(2,4-dioxohexahydropyrimidin-1-yl)pyrrolo[2,3-*b*]pyridin-1-yl]-6,10-dioxo-2-azaspiro[4.5]decane-2-carboxylate



[1630] Prepared in an analogous manner to Intermediate 2b starting from Intermediate 70a (223 mg, 0.44 mmol). Purification by FSC (elution gradient: 0-100% EtOAc in hexanes then 0-20% MeOH in EtOAc) gave the title compound (149 mg, 62.8 %) as a brown solid. ¹H NMR (DMSO-*d*₆): δ 0.62 - 0.69 (2H, m), 0.85 - 0.95 (2H, m), 1.91 - 1.99 (1H, m), 2.26 - 2.34 (2H, m), 2.77 (2H, t), 3.39 - 3.53 (2H, m), 3.70 (2H, br d), 3.83 (2H, t), 4.13 (2H, dd), 4.25 - 4.34 (2H, m), 4.86 (1H, br d), 5.11 (2H, br d), 7.31 - 7.36 (1H, m), 7.39 (4H, br t), 7.62 (1H, s), 7.99 (1H, d), 8.21 (1H, d), 10.39 (1H, s); m/z (ES⁺) [M+H]⁺ = 546.1.

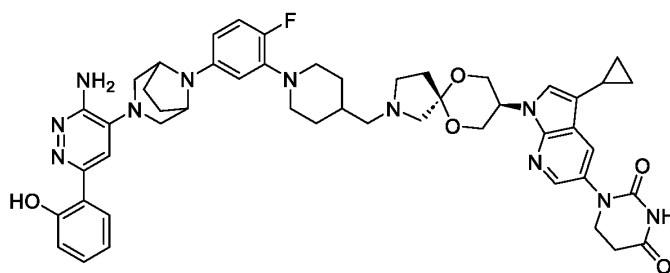
Intermediate 70c:

1-[3-Cyclopropyl-1-((5*r*,8*r*)-6,10-dioxo-2-azaspiro[4.5]decane-8-yl)pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1631] Prepared in an analogous manner to Intermediate 64f starting from Intermediate 70b (149 mg, 0.27 mmol). The title compound (108 mg, 96 %) was obtained as a grey solid. ¹H NMR (DMSO-*d*₆): δ 0.62 - 0.69 (2H, m), 0.86 - 0.94 (2H, m), 1.90 - 1.99 (1H, m), 2.05 (2H, t), 2.77 (2H, t), 2.85 - 2.92 (2H, m), 3.00 (2H, s), 3.83 (2H, t), 4.09 (2H, dd), 4.16 - 4.24 (2H, m), 4.78 - 4.89 (1H, m), 7.60 (1H, s), 7.99 (1H, d), 8.21 (1H, d), 10.38 (1H, br s); *m/z* (ES⁺) [M+H]⁺ = 412.1.

1-[1-[(5*r*,8*r*)-2-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

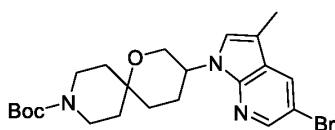


[1632] Prepared in an analogous manner to Example 64 starting from Intermediate 13d (25.1 mg, 0.05 mmol) and Intermediate 70c (20.6 mg, 0.05 mmol). Purification by RPC (elution gradient: 0-50% MeCN in water with 0.1% HCOOH) gave the title compound (28.2 mg, 61.5 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 0.62 - 0.69 (2H, m), 0.86 - 0.94 (2H, m), 1.22 - 1.35 (2H, m), 1.53 - 1.64 (1H, m), 1.82 (2H, br d), 1.91 - 2.01 (3H, m), 2.09 - 2.19 (4H, m), 2.32 (2H, br d), 2.56 - 2.71 (4H, m), 2.77 (2H, t), 2.84 (2H, s), 3.11 (2H, br d), 3.25 - 3.31 (4H, m), 3.83 (2H, t), 4.10 (2H, br dd), 4.17 - 4.24 (2H, m), 4.35 (2H, br s), 4.79 - 4.87 (1H, m), 5.94 (2H, s), 6.44 (1H, dt), 6.46 - 6.52 (1H, m), 6.84 - 6.90 (2H, m), 6.93 (1H, dd), 7.21 - 7.26 (1H, m), 7.47 (1H, s), 7.60 (1H, s), 7.89 - 7.93 (1H, m), 7.99 (1H, d), 8.21 (1H, d), 10.39 (1H, s), 13.59 - 14.61 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 898.5.

Example 71

Intermediate 71a:

tert-Butyl 3-(5-bromo-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl)-1-oxa-9-azaspiro[5.5]undecane-9-carboxylate



[1633] Prepared in an analogous manner to Intermediate 4a starting from 5-bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (366 mg, 1.73 mmol), *tert*-butyl-3-hydroxy-1-oxa-9-azaspiro[5.5]undecane-9-carboxylate (470 mg, 1.73 mmol). Purification by FSC (elution gradient: 0-25% acetone in hexanes) gave the title compound (241 mg, 30.0 %) as a colorless dry film. ¹H NMR (CDCl₃): δ 1.49 (9H, s), 1.51 - 1.60 (2H, m), 1.62 - 1.75 (2H, m), 1.84 (1H, br d), 2.01 - 2.13 (1H, m), 2.13 - 2.28 (2H, m), 2.29 (2H, d), 2.31 - 2.33 (1H, m), 3.12 - 3.27 (2H, m), 3.73 - 4.00 (4H, m), 4.75 - 4.86 (1H, m), 7.25 (1H, s), 7.97 (1H, d), 8.31 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 464.2.

Intermediate 71b:

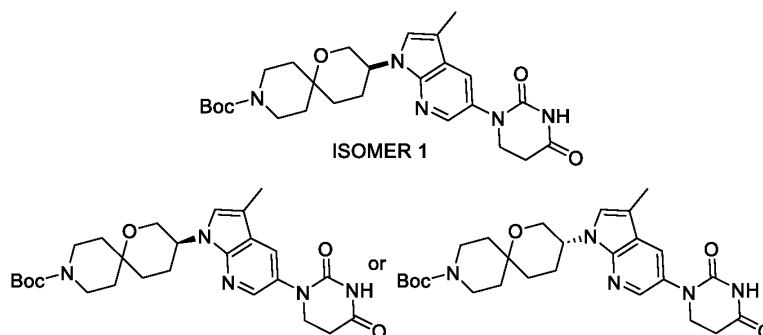
tert-Butyl *rel*-(3*S**)-3-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-1-oxa-9-azaspiro[5.5]undecane-9-carboxylate (ISOMER 1)

[*absolute configuration not yet confirmed]

tert-Butyl (3*S*)-3-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-1-oxa-9-azaspiro[5.5]undecane-9-carboxylate

or

tert-Butyl (3*R*)-3-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-1-oxa-9-azaspiro[5.5]undecane-9-carboxylate



[1634] Prepared in an analogous manner to Intermediate 2b starting from Intermediate 71a (0.216 g, 0.47 mmol). Purification by FSC (elution gradient: 0-100% EtOAc in hexanes then 0-30% MeOH in EtOAc) gave racemic material. This material was purified by chiral SFC (column: ChiralPAK IH 4.6x150mm, 5 μm, mobile phase: Phase A: 100% CO₂, Phase B methanol with 0.2% NH₄OH, gradient: Phase B, 10% to 60% from 0 to 5.0 mins with 60% hold until 5.90 mins and 60% to 10% from 5.90 mins to 6.00 mins, flow rate: 4.0 mL/min, diluent: DCM) to give the title compound which eluted first from the column (48 mg, 20%) as brown dry film. ¹H NMR (DMSO-*d*₆): δ 1.41 (9H, s), 1.43 - 1.57 (2H, m), 1.58 - 1.68 (2H, m), 1.75 (1H, dt), 1.86 - 1.94 (1H, m), 2.26 (3H, d), 2.27 - 2.33 (2H, m), 2.76 (2H, t), 2.96 - 3.16 (2H, m), 3.59 - 3.70 (2H, m), 3.74 - 3.89 (4H, m), 4.71 - 4.79 (1H, m), 7.60 (1H, s), 7.90 (1H, d), 8.19 (1H, d), 10.38 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 498.5.

Intermediate 71c:

1-[3-Methyl-1-[*rel*-(3*S**)-1-oxa-9-azaspiro[5.5]undecan-3-yl]pyrrolo[2,3-*b*]pyridin-5-

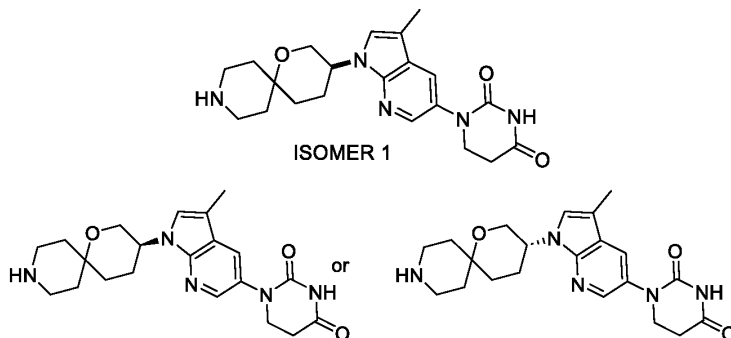
yl]hexahydropyrimidine-2,4-dione (ISOMER 1)

[*absolute configuration not yet confirmed]

1-[3-Methyl-1-[(3*S*)-1-oxa-9-azaspiro[5.5]undecan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

or

1-[3-Methyl-1-[(3*R*)-1-oxa-9-azaspiro[5.5]undecan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1635] Prepared in an analogous manner to Intermediate 2c starting from Intermediate 71b (48 mg, 0.10 mmol). Purification by ion exchange chromatography (Porapak Rxn CX 2g cartridge) eluting with 2N NH₃ in MeOH gave the title compound (30 mg, 78 %) as an off white solid. *m/z* (ES⁺) [M+H]⁺ = 398.1.

1-[3-Methyl-1-*rel*-(3*S*^{*})-9-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-9-azaspiro[5.5]undecan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

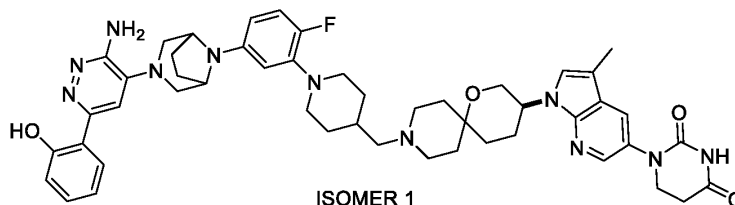
(ISOMER 1)

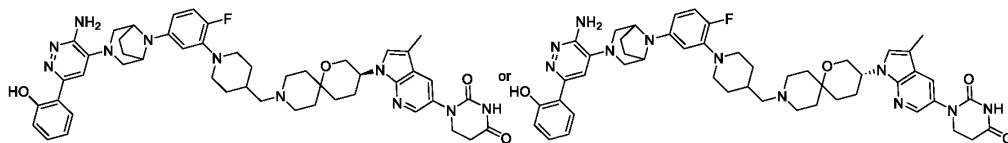
[*absolute configuration not yet confirmed]

1-[3-Methyl-1-[(3*S*)-9-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-9-azaspiro[5.5]undecan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

or

1-[3-Methyl-1-[(3*R*)-9-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-9-azaspiro[5.5]undecan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione





[1636] Prepared in an analogous manner to Example 64 starting from Intermediate 13d (37.7 mg, 0.075 mmol) and Intermediate 71c (29.8 mg, 0.08 mmol). Purification by RPC (elution gradient: 0-50% MeCN in water with 0.1% HCOOH) gave the title compound (44.4 mg, 64.9 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.21 - 1.32 (2H, m), 1.54 - 1.85 (8H, m), 1.87 - 2.00 (3H, m), 2.13 (2H, br d), 2.20 - 2.39 (8H, m), 2.65 (2H, br t), 2.76 (2H, t), 3.11 (2H, br d), 3.24 - 3.38 (6H, m), 3.71 - 3.89 (5H, m), 4.35 (2H, br s), 4.73 (1H, dt), 5.94 (2H, s), 6.40 - 6.52 (2H, m), 6.83 - 6.96 (3H, m), 7.20 - 7.27 (1H, m), 7.47 (1H, s), 7.60 (1H, s), 7.88 - 7.94 (2H, m), 8.19 (1H, s), 10.38 (1H, s), 13.36 - 14.81 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 884.6.

Example 72

Intermediate 72a:

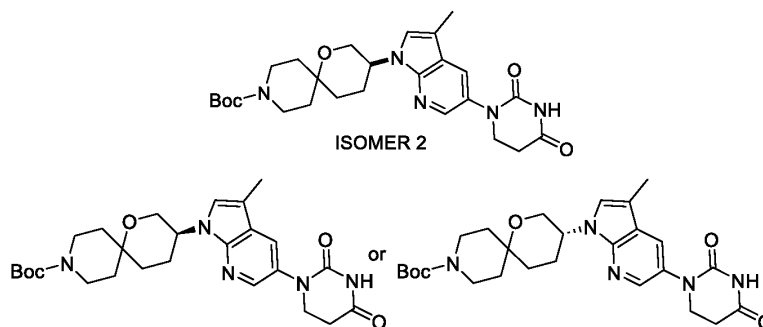
tert-Butyl *rel*-(3*S**)-3-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-1-oxa-9-azaspiro[5.5]undecane-9-carboxylate (ISOMER 2)

[*absolute configuration not yet confirmed]

tert-Butyl (3*S*)-3-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-1-oxa-9-azaspiro[5.5]undecane-9-carboxylate

or

tert-Butyl (3*R*)-3-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-1-oxa-9-azaspiro[5.5]undecane-9-carboxylate



[1637] Prepared in an analogous manner to Intermediate 2b starting from Intermediate 71a (0.216 g, 0.47 mmol). Purification by FSC (elution gradient: 0-100% EtOAc in hexanes then 0-30% MeOH in EtOAc) gave racemic material. This material was purified by chiral SFC (column: ChiralPAK IH 4.6x150mm, 5 μm, mobile phase: Phase A: 100% CO₂, Phase B methanol with 0.2% NH₄OH, gradient: Phase B, 10% to 60% from 0 to 5.0 mins with 60% hold until 5.90 mins and 60% to 10% from 5.90 mins to 6.00 mins, flow rate: 4.0 mL/min, diluent: DCM) to give the title compound which eluted second from the column (48 mg, 20%) as brown dry film. ¹H NMR (DMSO-*d*₆): δ 1.41 (9H, s), 1.43 - 1.57 (2H, m), 1.58 - 1.68 (2H, m), 1.75 (1H, dt), 1.86 - 1.94 (1H, m), 2.26 (3H, d), 2.27 - 2.33 (2H, m), 2.76 (2H, t), 2.96 - 3.16 (2H, m), 3.59

- 3.70 (2H, m), 3.74 - 3.89 (4H, m), 4.71 - 4.79 (1H, m), 7.60 (1H, s), 7.90 (1H, d), 8.19 (1H, d), 10.38 (1H, s; m/z (ES⁺) [M+H]⁺ = 498.5.

Intermediate 72b:

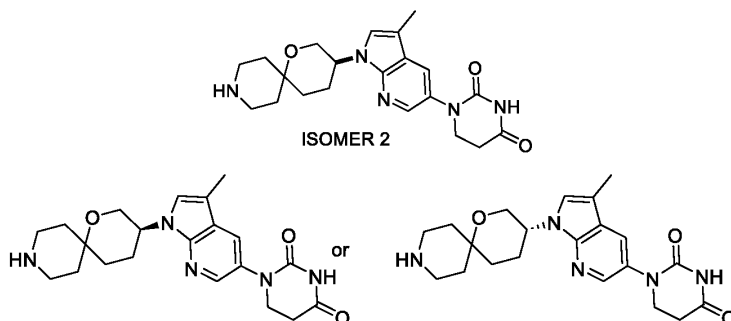
1-[3-Methyl-1-*rel*-(3*S**)-1-oxa-9-azaspiro[5.5]undecan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione (ISOMER 1)

[*absolute configuration not yet confirmed]

1-[3-Methyl-1-[(3*S*)-1-oxa-9-azaspiro[5.5]undecan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

or

1-[3-Methyl-1-[(3*R*)-1-oxa-9-azaspiro[5.5]undecan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1638] Prepared in an analogous manner to Intermediate 2c starting from Intermediate 72a (48 mg, 0.10 mmol). Purification by ion exchange chromatography (Porapak Rxn CX 2g cartridge) eluting with 2N NH₃ in MeOH gave the title compound (38 mg, 99%) as an off-white solid. m/z (ES⁺) [M+H]⁺ = 398.1

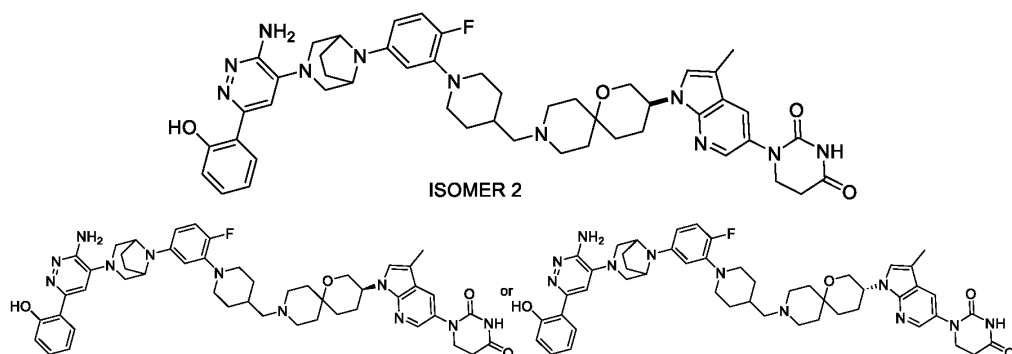
1-[3-Methyl-1-*rel*-(3*R**)-9-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-9-azaspiro[5.5]undecan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione (ISOMER 2)

[*absolute configuration not yet confirmed]

1-[3-Methyl-1-[(3*S*)-9-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-9-azaspiro[5.5]undecan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

or

1-[3-Methyl-1-[(3*R*)-9-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-9-azaspiro[5.5]undecan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

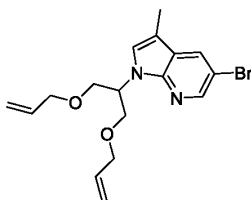


[1639] Prepared in an analogous manner to Example 64 starting from Intermediate 13d (50.3 mg, 0.1 mmol) and Intermediate 72b (39.7 mg, 0.10 mmol). Purification by RPC (elution gradient: 0-50% MeCN in water with 0.1% HCOOH) gave the title compound (56.0 mg, 61.4 %) as a white solid. ^1H NMR (DMSO-*d*₆): δ 1.20 - 1.32 (2H, m), 1.53 - 1.81 (8H, m), 1.85 - 2.00 (3H, m), 2.11 - 2.16 (2H, m), 2.21 - 2.39 (9H, m), 2.65 (2H, br t), 2.76 (2H, t), 3.11 (2H, br d), 3.26 - 3.34 (6H, m), 3.74 (1H, br dd), 3.79 - 3.86 (3H, m), 4.35 (2H, br s), 4.73 (1H, tt), 5.94 (2H, s), 6.41 - 6.51 (2H, m), 6.84 - 6.95 (3H, m), 7.23 (1H, t), 7.47 (1H, s), 7.60 (1H, s), 7.88 - 7.92 (2H, m), 8.19 (1H, s), 10.38 (1H, s), 13.01 - 15.01 (1H, m); m/z (ES⁺) [M+H]⁺ = 884.6.

Example 73

Intermediate 73a:

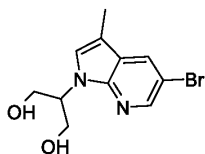
1-[2-Allyloxy-1-(allyloxymethyl)ethyl]-5-bromo-3-methyl-pyrrolo[2,3-*b*]pyridine



[1640] Prepared in an analogous manner to Intermediate 64a starting from 5-bromo-3-methyl-1H-pyrrolo[2,3-*b*]pyridine (5 g, 23.69 mmol) and 1,3-bis(allyloxy)propan-2-ol (6.24 ml, 35.53 mmol). Purification by FSC (elution gradient: 0-20% acetone in hexanes) gave the title compound (7.458g, 86%) as a yellow oil. ^1H NMR (DMSO-*d*₆): δ 2.23 (3H, d), 3.73 - 3.77 (2H, m), 3.79 - 3.84 (2H, m), 3.86 - 3.94 (4H, m), 5.05 - 5.15 (5H, m), 5.77 (2H, ddt), 7.46 (1H, s), 8.15 (1H, d), 8.25 (1H, d); m/z (ES⁺) [M+H]⁺ = 365.3.

Intermediate 73b:

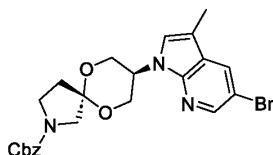
2-(5-Bromo-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl)propane-1,3-diol



[1641] Prepared in an analogous manner to Intermediate 64b starting from Intermediate 73a (2.775 g, 7.60 mmol). Trituration with (2:1) DCM/hexanes then trituration with Et₂O gave the title compound (1.734g, 80%) as an off-white solid. ¹H NMR (DMSO-*d*₆): δ 2.23 (3H, s), 3.76 (4H, t), 4.76 (1H, quin), 4.85 (2H, t), 7.43 (1H, s), 8.13 (1H, d), 8.23 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 285.0.

Intermediate 73c:

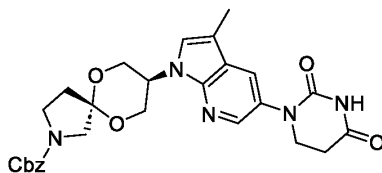
Benzyl (5*r*,8*r*)-8-(5-bromo-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl)-6,10-dioxo-2-azaspiro[4.5]decane-2-carboxylate



[1642] A vial was charged with to Intermediate 73b (0.635 g, 2.23 mmol), benzyl 3-oxopyrrolidine-1-carboxylate (0.976 g, 4.45 mmol), TsOH·H₂O (0.127 g, 0.67 mmol) and toluene (12 mL). The reaction was heated at 120 °C for 22 h. An additional portion of benzyl 3-oxopyrrolidine-1-carboxylate (0.976 g, 4.45 mmol) and TsOH·H₂O (0.127 g, 0.67 mmol) were added, and the reaction was stirred at 110 °C for 6h. The reaction was cooled to r.t., quenched with sat. aq. NaHCO₃, extracted with DCM, washed with brine, dried with Na₂SO₄, and concentrated. Purification by FSC (elution gradient: 0-100% EtOAc in hexanes then 0-30% MeOH) gave the title compound which eluted first off of the column (107 mg, 10 %) as a brown film. ¹H NMR (DMSO-*d*₆): δ 2.21 - 2.31 (5H, m), 3.37 - 3.52 (2H, m), 3.73 (2H, br d), 4.08 (2H, dd), 4.30 - 4.39 (2H, m), 4.82 (1H, br s), 5.11 (2H, d), 7.30 - 7.36 (1H, m), 7.37 - 7.43 (4H, m), 7.73 (1H, s), 8.22 (1H, d), 8.29 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 486.0.

Intermediate 73d:

Benzyl (5*r*,8*r*)-8-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-6,10-dioxo-2-azaspiro[4.5]decane-2-carboxylate

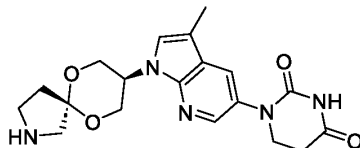


[1643] Prepared in an analogous manner to Intermediate 2b starting from Intermediate 73c (107 mg, 0.22 mmol). Purification by RPC (elution gradient: 0-50% MeCN in water with 0.1% HCOOH) gave the title compound (71.8 mg, 62.8 %) as a brown solid. ¹H NMR (CDCl₃): δ 2.29 (2H, t), 2.33 (3H, s), 2.90

(2H, t), 3.59 (2H, dt), 3.78 (1H, s), 3.86 (1H, s), 3.91 (2H, t), 4.15 - 4.24 (2H, m), 4.25 - 4.38 (2H, m), 4.91 (1H, br s), 5.17 (2H, s), 7.30 - 7.43 (5H, m), 7.58 - 7.70 (1H, m), 7.71 - 7.84 (2H, m), 8.20 (1H, d); m/z (ES^+) $[M+H]^+ = 520.1$.

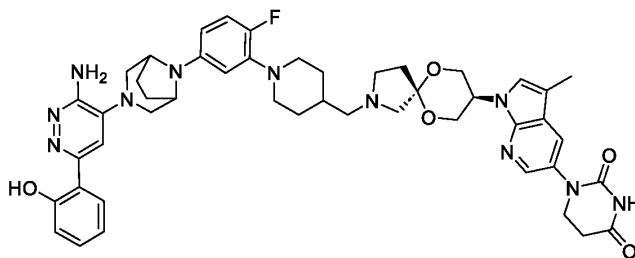
Intermediate 73e:

1-[1-((5*r*,8*r*)-6,10-Dioxo-2-azaspiro[4.5]decan-8-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1644] Prepared in an analogous manner to Intermediate 64f starting from Intermediate 73d (72 mg, 0.14 mmol). The title compound (52 mg, 98%) was obtained as a grey solid. m/z (ES^+) $[M+H]^+ = 386.1$.

1-[1-[1-((5*r*,8*r*)-2-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

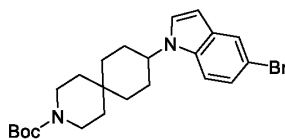


[1645] Prepared in an analogous manner to Example 64 starting from Intermediate 13d (60.3 mg, 0.12 mmol) and Intermediate 73e (54.0 mg, 0.14 mmol). Purification by RPC (elution gradient: 0-50% MeCN in water with 0.1% HCOOH) gave the title compound (41.8 mg, 39.0 %) as a white solid. 1H NMR (DMSO-*d*₆): δ 1.22 - 1.34 (2H, m), 1.55 - 1.66 (1H, m), 1.82 (2H, br d), 1.91 - 2.00 (2H, m), 2.10 - 2.17 (4H, m), 2.28 (3H, d), 2.33 (2H, br d), 2.60 (2H, br t), 2.66 (2H, br t), 2.77 (2H, t), 2.86 (2H, s), 3.11 (2H, br d), 3.27 (2H, br d), 3.36 (2H, br d), 3.82 (2H, t), 4.08 (2H, br dd), 4.25 (2H, br dd), 4.35 (2H, br s), 4.83 (1H, quin), 5.94 (2H, s), 6.43 (1H, dt), 6.49 (1H, dd), 6.84 - 6.90 (2H, m), 6.93 (1H, dd), 7.21 - 7.26 (1H, m), 7.47 (1H, s), 7.68 (1H, s), 7.89 - 7.95 (2H, m), 8.20 (1H, d), 10.39 (1H, s), 13.19 - 14.98 (1H, m); m/z (ES^+) $[M+H]^+ = 872.5$.

Example 74

Intermediate 74a:

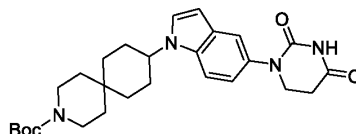
tert-Butyl 9-(5-bromoindol-1-yl)-3-azaspiro[5.5]undecane-3-carboxylate



[1646] Prepared in an analogous manner to Intermediate 2a starting from 5-bromo-1*H*-indole (0.588 g, 3 mmol) and *tert*-butyl 9-hydroxy-3-azaspiro[5.5]undecane-3-carboxylate (1.616 g, 6.00 mmol). Purification by FSC (elution gradient: 0-50% EtOAc in hexanes) gave the title compound (1.282 g, 95 %) as a colorless dry film. ¹H NMR (DMSO-*d*₆): δ 1.26 - 1.32 (2H, m), 1.33 - 1.39 (2H, m), 1.41 (9H, s), 1.57 - 1.62 (2H, m), 1.71 - 1.84 (4H, m), 1.85 - 1.96 (2H, m), 3.31 - 3.37 (4H, m), 4.34 (1H, tt), 6.44 (1H, d), 7.22 (1H, dd), 7.51 (1H, d), 7.60 (1H, d), 7.72 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 447.1.

Intermediate 74b:

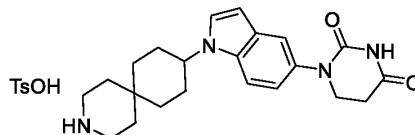
tert-Butyl 9-[5-(2,4-dioxohexahydropyrimidin-1-yl)indol-1-yl]-3-azaspiro[5.5]undecane-3-carboxylate



[1647] Prepared in an analogous manner to Intermediate 2b starting from Intermediate 74a (1.002 g, 2.24 mmol). Trituration with EtOAc/hexanes (1:1) followed by trituration with water gave the title compound (0.881 g, 82 %) as a brown solid. ¹H NMR (DMSO-*d*₆): δ 1.29 - 1.40 (4H, m), 1.41 (9H, s), 1.58 - 1.64 (2H, m), 1.73 - 1.88 (4H, m), 1.89 - 1.99 (2H, m), 2.73 (2H, t), 3.33 - 3.37 (4H, m), 3.77 (2H, t), 4.35 (1H, br t), 6.45 (1H, d), 7.07 (1H, dd), 7.45 (1H, d), 7.52 (1H, d), 7.59 (1H, br d), 10.25 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 481.3.

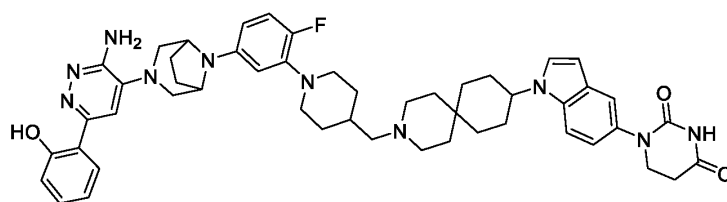
Intermediate 74c:

1-[1-(3-Azaspiro[5.5]undecan-9-yl)indol-5-yl]hexahydropyrimidine-2,4-dione



[1648] A vial was charged with Intermediate 74b (240 mg, 0.5 mmol) and TsOH·H₂O (105 mg, 0.55 mmol) and MeCN (2.5 mL). The suspension was stirred at 70 °C for 19.5 h. After cooling to r.t., the reaction was diluted with Et₂O. The solid was collected by vacuum filtration, washed with Et₂O and dried to give the title compound (208 mg, 73.0 %) as a grey solid in the form of the TsOH salt. ¹H NMR (DMSO-*d*₆): δ 1.38 - 1.48 (2H, m), 1.50 - 1.60 (2H, m), 1.77 - 1.97 (8H, m), 2.30 (3H, s), 2.73 (2H, t), 3.09 (4H, br s), 3.77 (2H, t), 4.31 - 4.43 (1H, m), 7.07 (1H, dd), 7.13 (2H, d), 7.46 (1H, d), 7.49 - 7.55 (3H, m), 7.59 (1H, d), 8.33 (2H, br s), 10.26 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 381.4.

1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]indol-5-yl]hexahydropyrimidine-2,4-dione

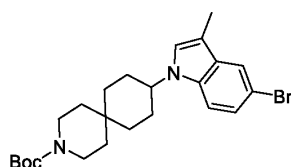


[1649] Prepared in an analogous manner to Example 64 starting from Intermediate 13d (50.3 mg, 0.1 mmol) and Intermediate 74c (62.7 mg, 0.11 mmol). Purification by RPC (elution gradient: 50-100% MeCN in water with 0.1% NH_4OH) gave the title compound (49.2 mg, 56.7 %) as a white solid. ^1H NMR ($\text{DMSO-}d_6$): δ 1.25 - 1.30 (2H, m), 1.31 - 1.45 (4H, m), 1.58 - 1.71 (3H, m), 1.73 - 1.85 (6H, m), 1.87 - 1.99 (4H, m), 2.11 - 2.17 (2H, m), 2.20 (2H, br d), 2.30 - 2.40 (4H, m), 2.65 (2H, br t), 2.73 (2H, t), 3.11 (2H, br d), 3.23 - 3.29 (2H, m), 3.34 - 3.39 (2H, m), 3.77 (2H, t), 4.28 - 4.40 (3H, m), 5.94 (2H, s), 6.39 - 6.52 (3H, m), 6.83 - 6.96 (3H, m), 7.07 (1H, dd), 7.20 - 7.27 (1H, m), 7.42 - 7.48 (2H, m), 7.51 (1H, d), 7.59 (1H, d), 7.89 - 7.93 (1H, m), 10.25 (1H, s), 14.17 (1H, br s; m/z (ES^+) $[\text{M}+\text{H}]^+ = 867.6$.

Example 75

Intermediate 75a:

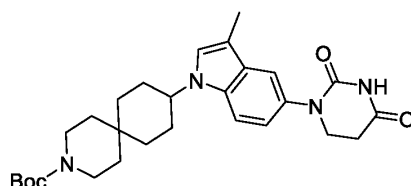
tert-Butyl 9-(5-bromo-3-methyl-indol-1-yl)-3-azaspiro[5.5]undecane-3-carboxylate



[1650] Prepared in an analogous manner to Intermediate 2a starting 5-bromo-3-methyl-1H-indole (630 mg, 3 mmol) and *tert*-butyl 9-hydroxy-3-azaspiro[5.5]undecane-3-carboxylate (1616 mg, 6.00 mmol). Purification by FSC (elution gradient: 0-30% EtOAc in hexanes) gave the title compound (846 mg, 61.1 %) as a colorless dry film. ^1H NMR (CDCl_3): δ 1.33 - 1.44 (4H, m), 1.48 (9H, s), 1.59 - 1.68 (2H, m), 1.83 - 1.95 (6H, m), 2.24 - 2.32 (3H, m), 3.38 - 3.47 (4H, m), 4.09 - 4.16 (1H, m), 6.99 (1H, s), 7.18 (1H, d), 7.24 - 7.27 (1H, m), 7.68 (1H, d); m/z (ES^+) $[\text{M}+\text{H}]^+ = 461.1$.

Intermediate 75b:

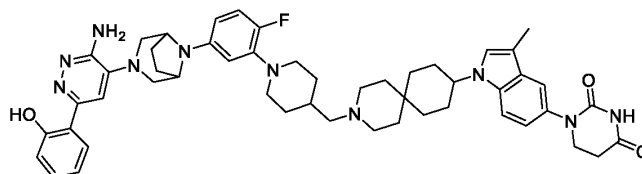
tert-Butyl 9-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-indol-1-yl]-3-azaspiro[5.5]undecane-3-carboxylate



[1651] Prepared in an analogous manner to Intermediate 2b starting from Intermediate 75a (0.846 g, 1.83 mmol). Trituration with EtOAc/hexanes (1:1) followed by trituration with water gave the title compound (0.711 g, 78 %) as a brown solid. ^1H NMR ($\text{DMSO-}d_6$): δ 1.24 - 1.40 (4H, m), 1.41 (9H, s), 1.56

- 1.64 (2H, m), 1.74 (2H, br d), 1.79 - 1.97 (4H, m), 2.24 (3H, s), 2.73 (2H, t), 3.32 - 3.37 (4H, m), 3.77 (2H, t), 4.28 (1H, tt), 7.05 (1H, dd), 7.32 - 7.41 (2H, m), 7.45 (1H, d), 10.24 (1H, br s); m/z (ES⁺) [M+H]⁺ = 495.4.

1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione

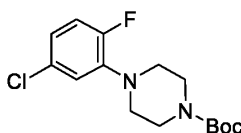


[1652] Prepared in an analogous manner to Example 39 starting from Intermediate 11g (63.3 mg, 0.1 mmol) and Intermediate 75b (59.4 mg, 0.12 mmol). Purification by RPC (elution gradient 0-50% MeCN in water with 0.1% HCOOH) gave the title compound (26.6 mg, 30.0 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.20 - 1.29 (2H, m), 1.30 - 1.41 (4H, m), 1.59 - 1.70 (3H, m), 1.70 - 1.83 (6H, m), 1.83 - 1.91 (2H, m), 1.91 - 1.98 (2H, m), 2.11 - 2.16 (2H, m), 2.20 (2H, br d), 2.24 (3H, s), 2.31 - 2.42 (4H, m), 2.64 (2H, br t), 2.73 (2H, t), 3.11 (2H, br d), 3.26 (2H, br d), 3.37 - 3.41 (2H, m), 3.77 (2H, t), 4.26 (1H, br t), 4.35 (2H, br s), 5.94 (2H, s), 6.41 - 6.50 (2H, m), 6.84 - 6.96 (3H, m), 7.04 (1H, dd), 7.19 - 7.27 (1H, m), 7.35 - 7.40 (2H, m), 7.41 - 7.50 (2H, m), 7.91 (1H, dd), 10.24 (1H, s), 13.75 - 14.57 (1H, m); m/z (ES⁺) [M+H]⁺ = 881.6.

Example 76

Intermediate 76a:

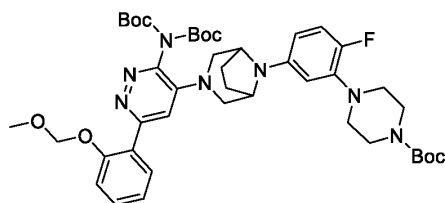
tert-Butyl 4-(5-chloro-2-fluoro-phenyl)piperazine-1-carboxylate



[1653] A vial was charged with Pd₂(dba)₃ (0.229 g, 0.25 mmol), *tert*-butyl piperazine-1-carboxylate (0.931 g, 5 mmol), Cs₂CO₃ (4.89 g, 15.00 mmol), 2-bromo-4-chloro-1-fluorobenzene (0.609 mL, 5.00 mmol), BINAP (0.311 g, 0.50 mmol) and 1,4-dioxane (24 mL). The reaction was sparged with N₂ and heated to 100 °C for 19 h. After cooling to r.t. the reaction was filtered through celite®, eluting with DCM and EtOAc and concentrated. Purification by FSC (elution gradient: 0-30% EtOAc in hexanes) gave the title compound (1.429 g, 91 %) as a yellow oil. ¹H NMR (DMSO-*d*₆): δ 1.41 (9H, s), 2.93 - 3.00 (4H, m), 3.39 - 3.49 (4H, m), 6.99 - 7.05 (2H, m), 7.17 (1H, dd); m/z (ES⁺) [M-*t*Bu+2H]⁺ = 259.2.

Intermediate 76b:

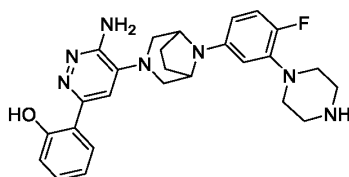
tert-Butyl 4-[5-[3-[3-[bis(*tert*-butoxycarbonyl)amino]-6-[2-(methoxymethoxy)phenyl]pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]piperazine-1-carboxylate



[1654] A vial was charged with Intermediate 25d (2.383 g, 4.4 mmol), Intermediate 76a (1.385 g, 4.40 mmol), Cs₂CO₃ (4.30 g, 13.20 mmol), RuPhos Pd G3 (368 mg, 0.44 mmol), and 1,4-dioxane (20 mL). The reaction was sparged with N₂ and heated to 100 °C for 1.5 h. A second portion of RuPhos Pd G3 (368 mg, 0.44 mmol) was added, and the reaction was stirred at 100 °C for an additional 2.5 h. After cooling to r.t. the reaction was filtered through celite®, eluting with DCM and EtOAc and concentrated. Purification by FSC (elution gradient: 0-80% EtOAc in hexanes) gave the title compound (714 mg, 19.79 %) as a brown dry film. ¹H NMR (DMSO-*d*₆): δ 1.35 - 1.46 (27H, m), 1.80 - 1.89 (2H, m), 1.90 - 1.99 (2H, m), 2.90 - 2.97 (3H, m), 3.22 - 3.34 (8H, m), 3.37 - 3.51 (4H, m), 4.41 (2H, br s), 5.22 (2H, s), 6.49 - 6.55 (2H, m), 6.96 (1H, dd), 7.12 - 7.19 (1H, m), 7.23 - 7.29 (1H, m), 7.46 (1H, t), 7.51 (1H, s), 7.70 - 7.76 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 820.9.

Intermediate 76c:

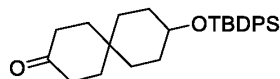
2-[6-Amino-5-[8-(4-fluoro-3-piperazin-1-yl-phenyl)-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-yl]phenol



[1655] A flask was charged with Intermediate 76b (0.613g, 0.75 mmol), DCM (6 mL) and TFA (1.5 mL). The mixture was stirred at r.t. 3 h on the rotovap pulling a slight vacuum of 750 mbar to remove formaldehyde generated during the reaction. The reaction was then fully concentrated *in vacuo*. Purification by RPC (elution gradient: 40-100% MeCN in water with 0.1% NH₄OH) gave the title compound (42 mg, 11.8 %) as an off white dry film. ¹H NMR (CDCl₃): δ 2.03 - 2.10 (2H, m), 2.16 - 2.23 (2H, m), 3.10 (8H, s), 3.23 - 3.34 (4H, m), 4.31 (2H, br s), 4.90 (2H, s), 6.36 - 6.48 (2H, m), 6.87 - 6.99 (2H, m), 7.02 - 7.08 (1H, m), 7.26 - 7.29 (2H, m), 7.53 - 7.59 (1H, m) (N-H and O-H not observed); *m/z* (ES⁺) [M+H]⁺ = 476.2.

Intermediate 76d:

9-[*tert*-Butyl(diphenyl)silyl]oxyspiro[5.5]undecan-3-one

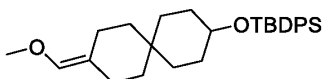


[1656] A vial was charged with 9-hydroxyspiro[5.5]undecan-3-one (963 mg, 5.28 mmol), imidazole (540 mg, 7.93 mmol) and DCM (20 mL). The reaction was cooled to 0 °C and *tert*-butylchlorodiphenylsilane (1.511 mL, 5.81 mmol) was added. The reaction was stirred at 0 °C for 10 mins

then warmed to r.t. After 2.5 h, the reaction was diluted with DCM and washed with 1M HCl. The aqueous was extracted with DCM and the combined organic extracts were washed with sat. aq. NaHCO₃ solution, brine, dried with Na₂SO₄ and concentrated. Purification by FCS (0-15% EtOAc in hexanes) gave the title compound (2142 mg, 96 %) as a colorless viscous oil. ¹H NMR (CDCl₃): δ 1.10 (9H, s), 1.19 - 1.27 (2H, m), 1.53 - 1.69 (6H, m), 1.71 - 1.78 (2H, m), 1.80 (2H, t), 2.32 (4H, dt), 3.75 - 3.83 (1H, m), 7.36 - 7.43 (4H, m), 7.42 - 7.48 (2H, m), 7.65 - 7.75 (4H, m).; *m/z* (ES⁺) [M+H]⁺ = 421.3.

Intermediate 76e:

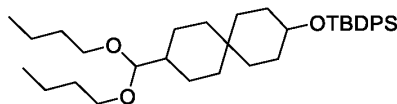
tert-Butyl-[3-(methoxymethylene)spiro[5.5]undecan-9-yl]oxy-diphenyl-silane



[1657] A flask was charged with (methoxymethyl)triphenylphosphonium chloride (4.96 g, 14.46 mmol). The flask was backfilled with N₂, THF (15 mL) was added, and the reaction was cooled to -78 °C. KO^tBu solution (14.46 mL, 14.46 mmol, 1M in THF) was added dropwise over 5 mins. The solution was stirred at -78 °C for 5 mins then r.t. for 10 mins. A second flask was charged with Intermediate 76d (2.028 g, 4.82 mmol) and THF (10 mL) under N₂. The mixture was cooled to -78 °C the solution of Wittig reagent was added dropwise over 15 mins. The reaction was warmed to r.t. and stirred for 1h the cooled back to -78 °C. A second batch of Wittig reagent was prepared from (methoxymethyl)triphenylphosphonium chloride (4.96 g, 14.46 mmol), KO^tBu solution (14.46 mL, 14.46 mmol, 1M in THF) and THF (15 mL) following the same procedure as above. The second batch of Wittig reagent was added dropwise over 15 mins and the reaction was stirred at -78 °C to 10 mins, warmed to r.t. and stirred for 2 h. The reaction was quenched with NH₄Cl, extracted with DCM, washed with brine, dried with Na₂SO₄, and concentrated. Purification by FSC (elution gradient: 0-15% EtOAc in hexanes) gave the title compound (1.998 g, 92 %) as a colorless liquid. ¹H NMR (CDCl₃): δ 1.01 - 1.08 (2H, m), 1.09 (9H, s), 1.25 (2H, td), 1.43 - 1.47 (2H, m), 1.50 - 1.59 (4H, m), 1.61 - 1.67 (2H, m), 1.90 - 1.97 (2H, m), 2.13 - 2.21 (2H, m), 3.54 (3H, d), 3.68 - 3.75 (1H, m), 5.76 (1H, d), 7.36 - 7.46 (6H, m), 7.69 - 7.73 (4H, m).

Intermediate 76f:

tert-Butyl-[9-(dibutoxymethyl)spiro[5.5]undecan-3-yl]oxy-diphenyl-silane

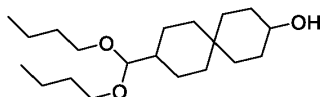


[1658] A vial was charged with Intermediate 76e (1.9984 g, 4.45 mmol), TsOH·H₂O (0.085 g, 0.45 mmol) and butan-1-ol (20 mL). The reaction was stirred at 70 °C for 17 h and the reaction was concentrated *in vacuo*. Purification by FSC (elution gradient: 0-12% EtOAc in hexanes) gave the title compound (2.077 g, 83 %) as a colorless oil. ¹H NMR (CDCl₃): δ 0.92 - 0.96 (6H, m), 0.99 - 1.05 (2H, m), 1.08 (9H, s), 1.12 - 1.20 (2H, m), 1.36 - 1.44 (6H, m), 1.50 - 1.65 (12H, m), 1.67 - 1.83 (2H, m), 1.85 - 1.93 (1H, m), 3.42

(2H, dtd), 3.60 (2H, dq), 3.69 - 3.76 (1H, m), 4.14 (1H, d), 7.36 - 7.40 (4H, m), 7.42 - 7.46 (2H, m), 7.66 - 7.71 (4H, m).

Intermediate 76g:

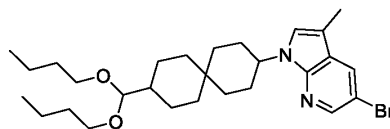
9-(Dibutoxymethyl)spiro[5.5]undecan-3-ol



[1659] A vial was charged with Intermediate 76f (1.8381 g, 3.25 mmol) and THF (5 mL). TBAF solution (16.27 mL, 16.27 mmol, 1M in THF) was added and the reaction was stirred at 60 °C for 1.5 h then cooled to r.t. and concentrated. Purification by FSC (elution gradient: 0-30% EtOAc in hexanes) gave the title compound (0.948 g, 89 %) as a colorless oil. ¹H NMR (DMSO-*d*₆): δ 0.94 (6H, td), 0.89 - 0.90 (1H, m), 0.97 - 1.08 (1H, m), 1.09 - 1.26 (5H, m), 1.33 - 1.66 (17H, m), 1.68 - 1.78 (1H, m), 1.79 - 1.97 (1H, m), 3.42 (2H, dt), 3.55 - 3.69 (2H, m), 4.11 - 4.19 (1H, m) (O-H not observed).

Intermediate 76h:

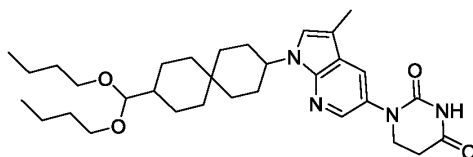
5-Bromo-1-[9-(dibutoxymethyl)spiro[5.5]undecan-3-yl]-3-methyl-pyrrolo[2,3-*b*]pyridine



[1660] Prepared in an analogous manner to Intermediate 4a starting from Intermediate 76g (0.807 g, 2.47 mmol), 5-bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (0.522 g, 2.47 mmol). Purification by FSC (elution gradient: 0-25% EtOAc in hexanes) gave the title compound (0.380 g, 29.6 %) as a colorless oil. *m/z* (ES⁺) [M+H]⁺ = 519.3.

Intermediate 76i:

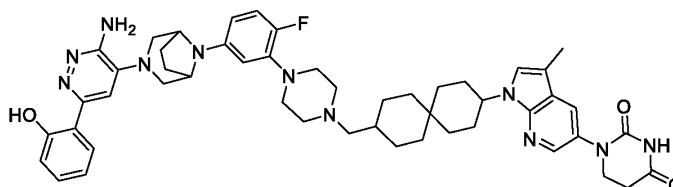
1-[1-[9-(Dibutoxymethyl)spiro[5.5]undecan-3-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1661] Prepared in an analogous manner to Intermediate 2b starting from Intermediate 76h (353 mg, 0.68 mmol). Purification by FSC (elution gradient: 0-100% EtOAc in hexanes then 0-30% MeOH in EtOAc) gave the title compound (225 mg, 59.8 %) as a brown solid. ¹H NMR (DMSO-*d*₆): δ 0.89 (6H, td), 1.08 - 1.18 (3H, m), 1.18 - 1.26 (2H, m), 1.31 - 1.38 (5H, m), 1.41 - 1.62 (10H, m), 1.69 (2H, br d), 1.87 - 1.98 (1H, m), 1.99 - 2.11 (2H, m), 2.25 (3H, s), 2.76 (2H, t), 3.35 - 3.41 (2H, m), 3.50 - 3.58 (2H, m), 3.81 (2H,

t), 4.17 (1H, d), 4.54 - 4.63 (1H, m), 7.55 (1H, s), 7.87 (1H, d), 8.16 (1H, d), 10.37 (1H, s); m/z (ES⁺) [M+H]⁺ = 553.5.

1-[1-[9-[[4-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]piperazin-1-yl]methyl]spiro[5.5]undecan-3-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

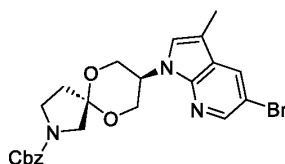


[1662] A vial was charged with Intermediate 76i (27.6 mg, 0.05 mmol), DCM (1 mL) and TFA (0.2 mL). The reaction was stirred at r.t. for 30 mins then concentrated. The crude residue was suspended in Et₂O, sonicated, and concentrated. To this residue was added Intermediate 76c (23.78 mg, 0.05 mmol) in DCM (1 mL) and MeOH (0.2 mL) immediately followed by Na(OAc)₃BH (21.19 mg, 0.10 mmol). The reaction was stirred at r.t. for 15 mins. The reaction was then diluted with DMSO then concentrated to remove the volatiles. Purification by RPC (elution gradient: 0-50% MeCN in water with 0.1% HCOOH) gave the title compound (22.0 mg, 49.2 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 0.96 - 1.18 (4H, m), 1.22 - 1.31 (1H, m), 1.32 - 1.38 (1H, m), 1.42 - 1.56 (3H, m), 1.58 - 1.75 (4H, m), 1.86 - 1.99 (3H, m), 2.00 - 2.24 (7H, m), 2.25 (3H, s), 2.46 - 2.50 (4H, m), 2.76 (2H, t), 2.97 - 3.07 (4H, m), 3.11 (2H, br d), 3.24 - 3.27 (2H, m), 3.81 (2H, t), 4.37 (2H, br s), 4.53 - 4.66 (1H, m), 5.94 (2H, s), 6.42 - 6.51 (2H, m), 6.83 - 6.90 (2H, m), 6.94 (1H, dd), 7.21 - 7.26 (1H, m), 7.47 (1H, s), 7.54 (1H, s), 7.87 (1H, d), 7.89 - 7.95 (1H, m), 8.17 (1H, d), 10.37 (1H, s), 13.87 - 14.47 (1H, m); m/z (ES⁺) [M+H]⁺ = 882.6.

Example 77

Intermediate 77a:

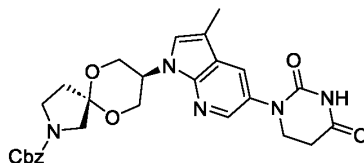
Benzyl (5*s*,8*s*)-8-(5-bromo-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl)-6,10-dioxaspiro[4.5]decane-2-carboxylate



[1663] Prepared in an analogous manner to Intermediate 73c starting from Intermediate 73b (0.635 g, 2.23 mmol). Purification by FSC (elution gradient: 0-100% EtOAc in hexanes then 0-30% MeOH) gave the title compound which eluted second off the column (77 mg, 7 %) as a brown film. ¹H NMR (DMSO-*d*₆): δ 2.27 (3H, d), 2.31 - 2.39 (2H, m), 3.40 - 3.52 (2H, m), 3.64 (2H, br d), 4.07 (2H, dd), 4.30 - 4.41 (2H, m), 4.80 - 4.87 (1H, m), 5.10 (2H, s), 7.30 - 7.35 (1H, m), 7.36 - 7.41 (4H, m), 7.75 (1H, br d), 8.21 (1H, d), 8.28 (1H, br d); m/z (ES⁺) [M+H]⁺ = 486.0.

Intermediate 77b:

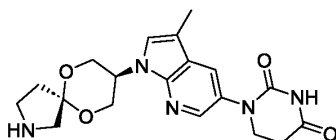
Benzyl (5*s*,8*s*)-8-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-6,10-dioxo-2-azaspiro[4.5]decane-2-carboxylate



[1664] Prepared in an analogous manner to Intermediate 2b starting from Intermediate 77a (77 mg, 0.16 mmol). Purification by RPC (elution gradient: 0-80% MeCN in water with 0.1% HCOOH) gave the title compound (31.0 mg, 37.7 %) as a brown solid. ¹H NMR (CDCl₃): δ 2.29 - 2.42 (5H, m), 2.92 (2H, t), 3.57 - 3.69 (2H, m), 3.74 (1H, s), 3.81 (1H, s), 3.93 (2H, t), 4.13 - 4.24 (2H, m), 4.29 - 4.44 (2H, m), 4.89 - 5.03 (1H, m), 5.18 (2H, s), 7.32 - 7.45 (5H, m), 7.51 - 7.61 (2H, m), 7.81 (1H, d), 8.21 (1H, br d); *m/z* (ES⁺) [M+H]⁺ = 520.2.

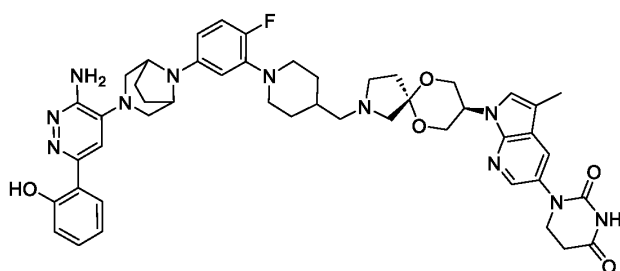
Intermediate 77c:

1-[1-((5*s*,8*s*)-6,10-Dioxo-2-azaspiro[4.5]decan-8-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1665] Prepared in an analogous manner to Intermediate 64f starting from Intermediate 77b (31 mg, 0.06 mmol). The title compound (22 mg, 96%) was obtained as a grey solid. *m/z* (ES⁺) [M+H]⁺ = 386.1.

1-[1-[1-[(5*s*,8*s*)-2-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



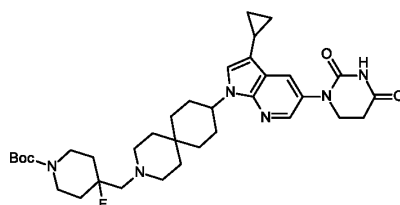
[1666] Prepared in an analogous manner to Example 64 starting from Intermediate 13d (30.2 mg, 0.06 mmol) and Intermediate 77c (23 mg, 0.06 mmol). Purification by RPC (elution gradient: 0-50% MeCN in water with 0.1% HCOOH) gave the title compound (24.2 mg, 45.5 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.21 - 1.36 (2H, m), 1.54 - 1.64 (1H, m), 1.82 (2H, br d), 1.90 - 1.98 (2H, m), 2.10 - 2.18 (4H, m), 2.28 (3H, s), 2.31 (2H, br d), 2.58 - 2.73 (4H, m), 2.74 - 2.79 (2H, m), 2.82 (2H, s), 3.11 (2H, br d), 3.24 -

3.29 (4H, m), 3.82 (2H, t), 4.03 (2H, br dd), 4.26 - 4.44 (4H, m), 4.83 (1H, br t), 5.94 (2H, s), 6.44 (1H, dt), 6.46 - 6.52 (1H, m), 6.82 - 6.90 (2H, m), 6.93 (1H, dd), 7.21 - 7.25 (1H, m), 7.47 (1H, s), 7.70 (1H, s), 7.90 - 7.95 (2H, m), 8.20 (1H, d), 10.39 (1H, s), 13.96 - 14.41 (1H, m); m/z (ES^+) $[M+H]^+ = 872.5$.

EXAMPLE 78

Intermediate 78a:

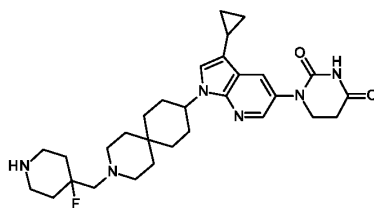
tert-Butyl 4-[[9-[3-cyclopropyl-5-(2,4-dioxohexahydropyrimidin-1-yl)pyrrolo[2,3-*b*]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl]methyl]-4-fluoro-piperidine-1-carboxylate



[1667] Prepared in an analogous manner to Intermediate 25f starting from Intermediate 25e (535 mg, 1.20 mmol) and Intermediate 36a (422 mg, 1 mmol). Purification by FSC (elution gradient: 0-100% EtOAc in hexanes then 0-30% MeOH in EtOAc) gave the title compound (392 mg, 61.6 %) as a beige solid. 1H NMR (CD_2Cl_2): δ 0.59 - 0.65 (2H, m), 0.86 - 0.91 (2H, m), 1.32 - 1.38 (2H, m), 1.39 - 1.43 (2H, m), 1.43 - 1.47 (9H, m), 1.55 - 1.65 (2H, m), 1.67 - 1.73 (2H, m), 1.78 - 1.94 (10H, m), 2.48 - 2.55 (5H, m), 2.83 - 2.88 (2H, m), 3.02 - 3.17 (2H, m), 3.79 - 3.90 (4H, m), 4.65 (1H, br d), 7.09 (1H, s), 7.52 (1H, s), 7.86 (1H, d), 8.17 (1H, d); m/z (ES^+) $[M+H]^+ = 637.8$.

Intermediate 78b:

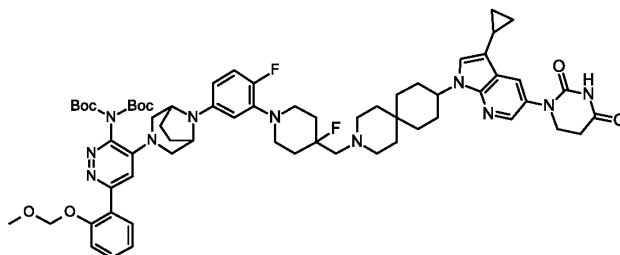
1-[3-Cyclopropyl-1-[3-[(4-fluoro-4-piperidyl)methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1668] Prepared in an analogous manner to Intermediate 2c starting from Intermediate 78a (401 mg, 0.63 mmol). Purification by ion exchange chromatography (Porapak Rxn CX 2g cartridge) eluting with 2N NH_3 in MeOH gave the title compound (309 mg, 91%) as an off white solid. m/z (ES^+) $[M+H]^+ = 537.6$

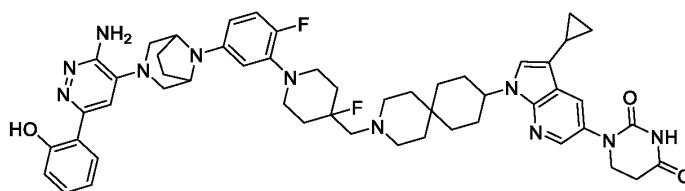
Intermediate 78c:

tert-Butyl *N*-*tert*-butoxycarbonyl-*N*-[4-[8-[3-[4-[[9-[3-cyclopropyl-5-(2,4-dioxohexahydropyrimidin-1-yl)pyrrolo[2,3-*b*]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl]methyl]-4-fluoro-1-piperidyl]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]-6-[2-(methoxymethoxy)phenyl]pyridazin-3-yl]carbamate



[1669] A vial was charged with Intermediate 78c (0.081 g, 0.15 mmol), Intermediate 57a (0.101 g, 0.15mmol), K_2CO_3 (0.062 g, 0.45 mmol), Pd-PEPPSI-IPentCl 2-methylpyridine (0.025 g, 0.03 mmol) and dioxane (1.5 ml). The vial was sparged with N_2 and was heated at 100 °C for 22 h. Reaction was cooled to r.t., filtered through celite® eluting with EtOAc/DCM and concentrated. Purification by FSC (elution gradient: 0-100% EtOAc in hexanes then 0-30% MeOH in EtOAc) gave the title compound (0.054 g, 31.0 %) as a brown dry film. m/z (ES^+) $[M+H]^+ = 1171.1$.

1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-fluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

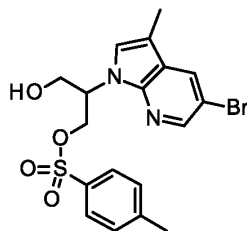


[1670] A vial was charged with Intermediate 78c (54 mg, 0.05 mmol) and CH_2Cl_2 (1 mL) was added HCl (4N in dioxane, 1ml, 4.00 mmol). The reaction was stirred at r.t. for 2h. Solvent was removed under reduced pressure. Purification by RPC (elution gradient: 50-100% CH_3CN in H_2O with 0.1% NH_4OH) gave the title compound (22.0 mg, 51.5 %) as a white solid. 1H NMR ($DMSO-d_6$): δ 0.60 - 0.68 (2H, m), 0.79 - 0.89 (2H, m), 1.22 - 1.31 (2H, m), 1.37 (2H, br s), 1.57 - 1.73 (4H, m), 1.72 - 1.83 (3H, m), 1.84 - 2.03 (8H, m), 2.12 (2H, br d), 2.51 - 2.71 (3H, m), 2.75 (2H, t), 2.86 - 2.99 (2H, m), 3.06 - 3.13 (2H, m), 3.16 (2H, br d), 3.25 (2H, br d), 3.80 (2H, t), 4.36 (2H, br s), 4.57 (1H, br t), 5.92 (2H, s), 6.44 (1H, dt), 6.48 - 6.59 (1H, m), 6.78 - 6.88 (2H, m), 6.93 (1H, dd), 7.17 - 7.25 (1H, m), 7.47 (2H, d), 7.85 - 7.97 (2H, m), 8.14 (1H, d), 10.35 (1H, s), 14.15 (1H, br s), 3 protons merged under DMSO; m/z (ES^+) $[M+H]^+ = 926.9$.

Example 79

Intermediate 79a:

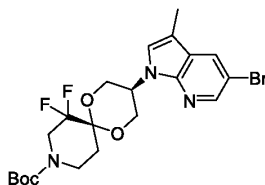
[2-(5-Bromo-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl)-3-hydroxy-propyl] 4-methylbenzenesulfonate



[1671] A mixture of Intermediate 73b (1.29 g, 4.52 mmol), 4-methylbenzenesulfonyl chloride (1.294 g, 6.79 mmol), 4,4,4-trifluoro-1-phenylbutane-1,3-dione (0.196 g, 0.90 mmol), iron(III) chloride (73 mg, 0.45 mmol) and hunig's base (1.5 ml, 8.60 mmol) in acetonitrile (10 mL) was stirred at r.t. for 2h. Solvent was removed under reduced pressure. Purification by FSC (elution gradient: 10-50 % EtOAc in Hexane) gave the title compound (1.610 g, 81 %) as an light grey solid. ¹H NMR (CD₂Cl₂) δ 2.24 (3H, d), 2.37 (3H, s), 4.03 - 4.05 (1H, m), 4.05 - 4.07 (1H, m), 4.42 - 4.47 (1H, m), 4.47 - 4.53 (1H, m), 4.55 - 4.61 (1H, m), 4.91 (1H, dd), 6.98 (1H, s), 7.05 (2H, d), 7.39 (2H, d), 7.94 (1H, d), 8.08 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 439.2.

Intermediate 79b:

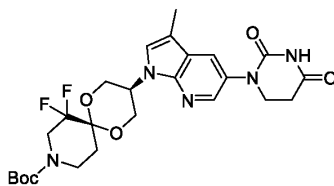
tert-Butyl (3*s*,6*s*)-3-(5-bromo-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl)-11,11-difluoro-1,5-dioxo-9-azaspiro[5.5]undecane-9-carboxylate



[1672] KO^tBu (1M in THF, 9 mL, 9.00 mmol) was added to a stirred solution of Intermediate 79a (1.47 g, 3.35 mmol) and *tert*-butyl 3,3-difluoro-4-oxopiperidine-1-carboxylate (2.361 g, 10.04 mmol) in DMF (12 mL) at 0°C. The reaction was allowed to warm to r.t. and was stirred for 1 h. LCMS showed both *cis* and *trans* isomers. The reaction was diluted with EtOAc and washed with NH₄Cl solution. Organic phase was dried over MgSO₄, filtered, and concentrated. Purification by FSC (elution gradient: 10-40% EtOAc in Hexane) gave the title compound (0.584 g, 34.7 %) which eluted second from the column. ¹H NMR (CD₂Cl₂): δ 1.45 - 1.47 (9H, m), 2.20 (2H, br s), 2.29 (3H, s), 3.48 - 3.56 (2H, m), 3.79 (2H, br t), 4.14 (3H, br d), 4.44 (2H, br d), 5.00 (1H, br s), 7.74 (1H, s), 8.24 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 502.3.

Intermediate 79c:

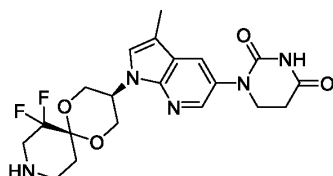
tert-Butyl (3*s*,6*s*)-3-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-11,11-difluoro-1,5-dioxo-9-azaspiro[5.5]undecane-9-carboxylate



[1673] Prepared in an analogous manner to Intermediate 2b starting from Intermediate 79b (0.485 g, 0.97 mmol). Purification FSC (elution gradient: 0-100% EtOAc in hexanes then 0-20% MeOH in EtOAc) gave title compound (0.220 g, 42.5 %) as a brown solid. ¹H NMR (CD₂Cl₂): δ 1.45 - 1.48 (9H, m), 2.20 (2H, br s), 2.32 (3H, s), 2.85 (2H, t), 3.53 (2H, br t), 3.73 - 3.86 (2H, m), 3.88 (2H, t), 4.16 (2H, br d), 4.45 (2H, br d), 5.07 (1H, br s), 7.50 (1H, s), 7.77 - 7.81 (2H, m), 8.17 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 536.7.

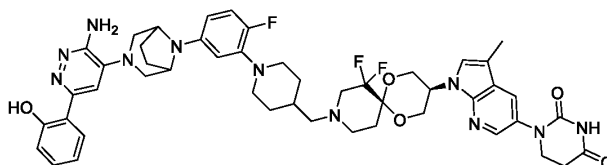
Intermediate 79d:

1-[1-((3*s*,6*s*)-11,11-Difluoro-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1674] Prepared in an analogous manner to Intermediate 2c starting from Intermediate 79c (220 mg, 0.41 mmol). Purification by ion exchange chromatography (Porapak Rxn CX 2g cartridge) eluting with 2N NH₃ in MeOH gave the title compound (175 mg, 98 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 2.08 - 2.24 (2H, m), 2.39 - 2.46 (1H, m), 2.65 - 2.73 (2H, m), 2.73 - 2.79 (2H, m), 2.94 (2H, td), 3.27 - 3.33 (3H, m), 3.80 (2H, t), 3.96 (2H, br d), 4.52 - 4.60 (2H, m), 4.87 (1H, br s), 7.81 (1H, s), 7.92 (1H, d), 8.17 (1H, d), 10.37 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 436.6.

1-[1-[(3*s*,6*s*)-9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-11,11-difluoro-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

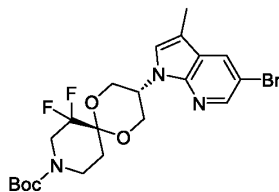


[1675] Prepared in an analogous manner to Example 64 starting from Intermediate 13d (12.5 mg, 0.025 mmol) and Intermediate 79d (10.9 mg, 0.03 mmol). Purification by RPC (elution gradient: 0-50% MeCN in water with 0.1% HCOOH) gave the title compound (10.0 mg, 43.4 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.22 - 1.30 (2H, m), 1.58 - 1.70 (1H, m), 1.77 (2H, br d), 1.91 - 1.97 (2H, m), 2.09 - 2.16 (2H, m), 2.26 - 2.28 (3H, m), 2.28 - 2.33 (2H, m), 2.63 - 2.68 (2H, m), 2.70 - 2.80 (4H, m), 3.09 (2H, br d), 3.18 - 3.28 (4H, m), 3.32 - 3.41 (4H, m), 3.80 (2H, t), 3.98 (2H, br d), 4.34 (2H, br s), 4.57 (2H, br d), 4.88 (1H, br s), 5.92 (2H, s), 6.40 - 6.49 (2H, m), 6.84 - 6.98 (3H, m), 7.22 (1H, t), 7.45 (1H, s), 7.80 (1H, s), 7.88 - 7.94 (2H, m), 8.18 (1H, d), 10.37 (1H, s), 14.15 (1H, br s); *m/z* (ES⁺) [M+H]⁺ = 923.0.

Example 80

Intermediate 80a:

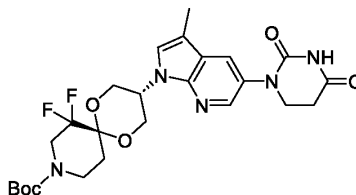
tert-Butyl (3*r*,6*r*)-3-(5-Bromo-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl)-11,11-difluoro-1,5-dioxo-9-azaspiro[5.5]undecane-9-carboxylate



[1676] Prepared in analogous manner as Intermediate 79b starting from Intermediate 79a (1.47 g, 3.35 mmol). Purification by FSC (elution gradient: 10-40% EtOAc in hexane) gave the title compound (0.825 g, 49.1 %) which eluted first from the column. ¹H NMR (CD₂Cl₂): δ 1.45 (9H, s), 2.04 (2H, br s), 2.29 (3H, d), 3.49 - 3.56 (2H, m), 3.77 (2H, t), 4.27 (2H, dd), 4.56 (2H, br d), 4.95 (1H, t), 7.42 (1H, s), 8.00 (1H, d), 8.26 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 502.3.

Intermediate 80b:

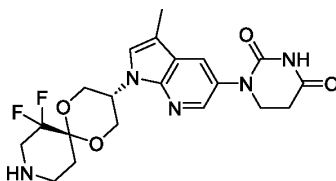
tert-Butyl (3*r*,6*r*)-3-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-11,11-difluoro-1,5-dioxo-9-azaspiro[5.5]undecane-9-carboxylate



[1677] Prepared in an analogous manner to Intermediate 2b starting from Intermediate 80a (0.485 g, 0.97 mmol). Purification by FSC (elution gradient: 0-100% EtOAc in hexanes then 0-20% MeOH in EtOAc) gave title compound (0.425 g, 48.3 %) as an off-white solid. ¹H NMR (CD₂Cl₂): δ 1.45 - 1.47 (9H, m), 2.07 (2H, br s), 2.32 (3H, s), 2.85 (2H, t), 3.47 - 3.59 (2H, m), 3.71 - 3.84 (2H, m), 3.87 (2H, t), 4.32 (2H, dd), 4.55 (2H, br d), 5.00 (1H, br t), 7.45 (1H, s), 7.61 (1H, s), 7.79 (1H, d), 8.19 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 536.6.

Intermediate 80c:

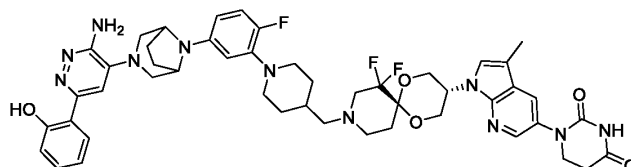
1-[1-((3*r*,6*r*)-11,11-Difluoro-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1678] Prepared in an analogous manner to Intermediate 2c starting from Intermediate 80b (425 mg, 0.79 mmol). Purification by ion exchange chromatography (Porapak Rxn CX 2g cartridge) eluting with 2N NH₃ in MeOH gave the title compound (321 mg, 93 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 2.10 -

2.22 (2H, m), 2.25 (3H, s), 2.36 - 2.43 (1H, m), 2.69 - 2.80 (4H, m), 2.85 - 3.01 (2H, m), 3.80 (2H, t), 4.22 (2H, dd), 4.29 - 4.35 (2H, m), 4.96 - 5.02 (1H, m), 7.59 (1H, s), 7.92 (1H, d), 8.21 (1H, d), 10.38 (1H, s); m/z (ES^+) $[M+H]^+ = 436.6$.

1-[1-[(3*r*,6*r*)-9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-11,11-difluoro-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

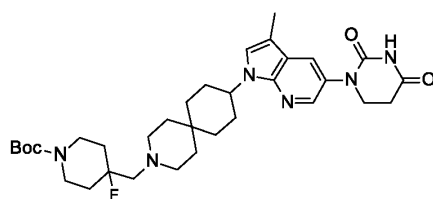


[1679] Prepared in an analogous manner to Example 64 starting from Intermediate 13d (25.1 mg, 0.05 mmol) and Intermediate 80c (28.3 mg, 0.07 mmol). Purification by RPC (elution gradient: 0-50% MeCN in water with 0.1% HCOOH) gave the title compound (21 mg, 45.6 %) as a white solid. 1H NMR (DMSO-*d*₆): δ 1.21 - 1.28 (2H, m), 1.58 - 1.69 (1H, m), 1.70 - 1.80 (2H, m), 1.91 - 1.97 (2H, m), 2.09 - 2.16 (2H, m), 2.22 - 2.27 (4H, m), 2.28 - 2.33 (2H, m), 2.60 - 2.69 (2H, m), 2.71 - 2.84 (4H, m), 3.06 - 3.12 (2H, m), 3.16 - 3.26 (3H, m), 3.31 - 3.39 (4H, m), 3.80 (2H, t), 4.25 (2H, br s), 4.29 - 4.38 (4H, m), 4.97 - 5.03 (1H, m), 5.92 (2H, s), 6.42 (1H, br dd), 6.46 - 6.51 (1H, m), 6.77 - 6.88 (2H, m), 6.88 - 6.95 (1H, m), 7.16 - 7.27 (1H, m), 7.45 (1H, s), 7.61 (1H, s), 7.85 - 7.96 (2H, m), 8.21 (1H, d), 10.38 (1H, s), 14.18 (1H, br d); m/z (ES^+) $[M+H]^+ = 923.0$.

Example 81

Intermediate 81a:

tert-Butyl 4-[[9-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl]methyl]-4-fluoro-piperidine-1-carboxylate

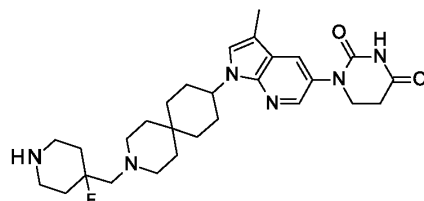


[1680] A mixture of Intermediate 54a (1317 mg, 3.33 mmol), *tert*-butyl 4-fluoro-4-formylpiperidine-1-carboxylate (1925 mg, 8.33 mmol), titanium(IV) isopropoxide (2 mL, 6.66 mmol) in THF (20 mL) was stirred overnight. Na(OAc)₃BH (2117 mg, 9.99 mmol) was added and the reaction was stirred for 2 h. The reaction was quenched with NH₄OH (2M, 50 mL), and was extracted with CHCl₃/IPA (3:1), dried over MgSO₄, filtered, and concentrated. Purification by FSC (elution gradient: 15-50% solvent B in CH₂Cl₂, solvent B 10% MeOH in CH₂Cl₂ with 1% NH₄OH) gave the title compound (501 mg, 24.63 %) as an off-white solid. 1H NMR (DMSO-*d*₆): δ 1.24 - 1.33 (2H, m), 1.33 - 1.37 (2H, m), 1.38 - 1.43 (9H, m), 1.49 -

1.63 (2H, m), 1.63 - 1.73 (4H, m), 1.73 - 1.83 (4H, m), 1.94 - 2.05 (2H, m), 2.21 - 2.28 (3H, m), 2.28 - 2.47 (6H, m), 2.69 - 2.77 (2H, m), 2.93 - 3.10 (2H, m), 3.62 - 3.74 (2H, m), 3.79 (2H, s), 4.48 - 4.65 (1H, m), 7.52 (1H, s), 7.85 (1H, d), 8.14 (1H, d), 10.35 (1H, s); m/z (ES⁺) [M+H]⁺ = 611.3.

Intermediate 81b:

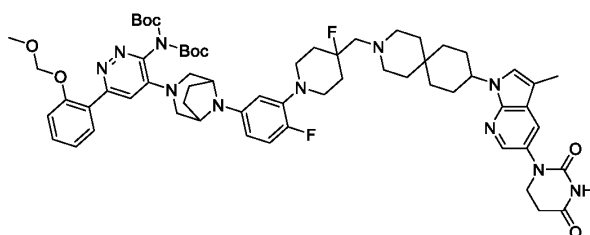
1-[1-[3-[(4-Fluoro-4-piperidyl)methyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1681] Prepared in an analogous manner to Intermediate 2c starting from Intermediate 81a (500 mg, 0.82 mmol). Purification by ion exchange chromatography (Porapak Rxn CX 2g cartridge) eluting with 2N NH₃ in MeOH gave the title compound (391 mg, 94 %) as a white solid. m/z (ES⁺) [M+H]⁺ = 511.5.

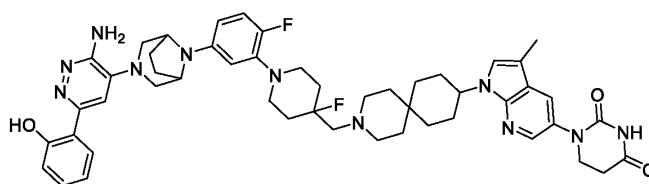
Intermediate 81c:

tert-Butyl *N*-*tert*-butoxycarbonyl-*N*-[4-[8-[3-[4-[9-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl]methyl]-4-fluoro-1-piperidyl]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]-6-[2-(methoxymethoxy)phenyl]pyridazin-3-yl]carbamate



[1682] Prepared in an analogous manner to Intermediate 78c starting from Intermediate 81b (0.184 g, 0.36 mmol), Intermediate 57a (0.201 g, 0.3 mmol. Purification by FSC (elution gradient: 0-100% EtOAc in hexanes then 0-30% MeOH in EtOAc) gave the title compound (0.14 g, 40.8 %) as a white solid. ¹H NMR (CD₂Cl₂): δ 1.35 - 1.39 (1H, m), 1.43 - 1.47 (18H, m), 1.53 - 1.62 (2H, m), 1.68 - 1.74 (2H, m), 1.82 - 2.08 (14H, m), 2.28 - 2.32 (3H, m), 2.47 - 2.58 (6H, m), 2.81 - 2.87 (2H, m), 2.92 - 3.00 (2H, m), 3.17 - 3.24 (2H, m), 3.33 - 3.35 (3H, m), 3.36 - 3.37 (2H, m), 3.83 - 3.89 (2H, m), 4.16 - 4.25 (2H, m), 4.62 - 4.72 (1H, m), 5.15 - 5.19 (2H, m), 5.30 - 5.31 (3H, m), 6.35 (1H, br d), 6.43 - 6.47 (1H, m), 6.88 (1H, dd), 7.12 - 7.23 (3H, m), 7.34 - 7.43 (2H, m), 7.63 (1H, s), 7.73 (1H, d), 7.85 (1H, dd), 8.16 (1H, d); m/z (ES⁺) [M+H]⁺ = 1144.8.

1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-fluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

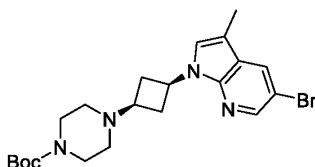


[1683] Prepared in an analogous manner to Example 78 starting from Intermediate 81c (135 mg, 0.12 mmol). Purification by RPC (elution gradient: 50-100% CH₃CN in water with 0.1% NH₄OH) gave the title compound (55.0 mg, 51.8 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.22 - 1.32 (10H, m), 1.36 - 1.41 (2H, m), 1.66 - 1.73 (4H, m), 1.78 - 1.83 (2H, m), 1.88 - 2.01 (6H, m), 2.08 - 2.16 (2H, m), 2.24 (3H, s), 2.73 - 2.78 (2H, m), 2.89 - 2.96 (2H, m), 3.04 - 3.12 (2H, m), 3.12 - 3.19 (2H, m), 3.20 - 3.26 (2H, m), 3.79 (2H, t), 4.36 (2H, br s), 4.54 - 4.63 (1H, m), 5.88 - 5.97 (2H, m), 6.40 - 6.48 (1H, m), 6.48 - 6.54 (1H, m), 6.80 - 6.90 (2H, m), 6.90 - 6.97 (1H, m), 7.19 - 7.24 (1H, m), 7.45 (1H, s), 7.52 (1H, s), 7.84 - 7.86 (1H, m), 7.86 - 7.93 (1H, m), 8.15 (1H, d), 10.35 (1H, s), 13.98 - 14.28 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 900.8.

Example 82

Intermediate 82a:

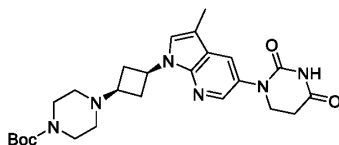
tert-Butyl 4-[3-(5-bromo-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl)cyclobutyl]piperazine-1-carboxylate



[1684] *tert*-Butyl piperazine-1-carboxylate (2.92 g, 15.7 mmol) and MgSO₄ (1.89 g, 15.7 mmol) were added to a solution of 3-hydroxycyclobutan-1-ol (1.35 g, 15.7 mmol) in DCM (35 mL). The resulting mixture was stirred at r.t. for 30 mins. Na(OAc)₃BH (4.99 g, 23.5 mmol) was added. The resulting mixture was stirred at r.t. for 200 min. Sat. aq. K₂CO₃ (30 mL) and water (100 mL) were added, and the phases were separated. The aqueous layer was extracted with DCM (2 x 50 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. To the residue was added 5-bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (3.31 g, 15.7 mmol) and 2-(tributyl-*l*5-phosphaneylidene)acetonitrile (4.11 mL, 15.7 mmol) and toluene (78 mL). The resulting mixture was stirred at 100 °C for 18 h. After cooling to r.t. the mixture was concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes then 0 to 60% acetone in hexanes) gave the title compound (443 mg, 6%). ¹H NMR (DMSO-*d*₆): δ 1.39 (9H, s), 2.18 - 2.30 (9H, m), 2.54 - 2.67 (3H, m), 3.32 (4H, br s), 4.87 - 4.98 (1H, m), 7.56 (1H, s), 8.14 (1H, d), 8.25 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 449.3.

Intermediate 82b:

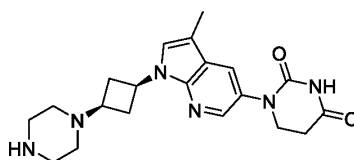
tert-Butyl 4-[3-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]cyclobutyl]piperazine-1-carboxylate



[1685] Prepared in an analogous manner to Intermediate 2b starting from Intermediate 82a (402 mg, 0.89 mmol). Purification by FSC (elution gradient : 0 to 100% [3:1 EtOAc/EtOH] in hexanes then 0 to 20% MeOH in DCM) gave the title compound (219 mg, 51%) as a brown solid. ^1H NMR ($\text{DMSO}-d_6$): δ 1.41 (9H, s), 2.22 - 2.33 (9H, m), 2.57 - 2.70 (3H, m), 2.76 (2H, t), 3.35 (4H, br s), 3.81 (2H, t), 4.92 - 5.05 (1H, m), 7.55 (1H, s), 7.89 (1H, d), 8.18 (1H, d), 10.38 (1H, s); m/z (ES^+) $[\text{M}+\text{H}]^+ = 483.5$.

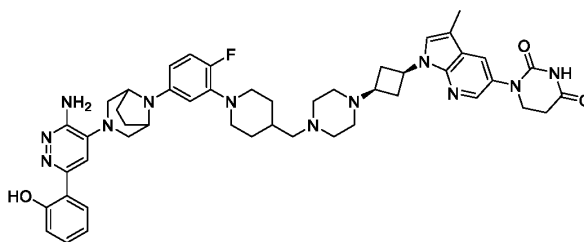
Intermediate 82c:

1-[3-Methyl-1-(3-piperazin-1-ylcyclobutyl)pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1686] 2 M aq. H_2SO_4 (3.00 mL, 6.00 mmol) was added to a solution of Intermediate 82b (212 mg, 0.44 mmol) in THF (3 mL). The resulting mixture was stirred at 50 °C for 1 h. The mixture was diluted with DCM-IPA (3:1, 20 mL). Sat. aq. K_2CO_3 (20 mL) was added, and the phases were separated. The aqueous layer was extracted with DCM-IPA (3:1, 2 x 20 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to give the title compound (162 mg, 96%) as a beige solid. ^1H NMR ($\text{DMSO}-d_6$): δ 1.81 - 2.09 (1H, m), 2.12 - 2.40 (9H, m), 2.53 - 2.61 (3H, m), 2.69 (4H, t), 2.74 (2H, t), 3.79 (2H, t), 4.90 - 5.03 (1H, m), 7.54 (1H, s), 7.87 (1H, d), 8.16 (1H, d), 10.37 (1H, br s); m/z (ES^+) $[\text{M}+\text{H}]^+ = 383.4$.

1-[1-[3-[4-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]piperazin-1-yl]cyclobutyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



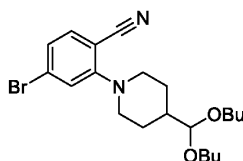
[1687] NMP (1 mL) was added to a mixture of Intermediate 82c (30 mg, 0.08 mmol) and Intermediate 13d (30 mg, 0.06 mmol). The resulting mixture was stirred at r.t. for 3 min. then $\text{Na}(\text{OAc})_3\text{BH}$ (25 mg, 0.12 mmol) was added. The resulting mixture was stirred at r.t. for 30 min. Purification by RPC (elution gradient: 0 to 60% MeCN in water with 0.1% formic acid) gave the title compound (21.1 mg, 41%) as a white solid.

^1H NMR (DMSO- d_6): δ 1.19 - 1.30 (2H, m), 1.61 (1H, td), 1.76 (2H, br d), 1.86 - 1.96 (2H, m), 2.07 - 2.46 (16H, m), 2.50 - 2.68 (6H, m), 2.74 (2H, t), 3.09 (2H, br d), 3.24 (2H, br d), 3.34 (2H, br d), 3.79 (2H, t), 4.33 (2H, br s), 4.96 (1H, br t), 5.92 (2H, s), 6.37 - 6.49 (2H, m), 6.81 - 6.95 (3H, m), 7.18 - 7.24 (1H, m), 7.45 (1H, s), 7.53 (1H, s), 7.84 - 7.92 (2H, m), 8.16 (1H, d), 10.36 (1H, s), 14.15 (1H, br s); m/z (ES $^+$) $[M+H]^+ = 869.5$.

Example 83

Intermediate 83a:

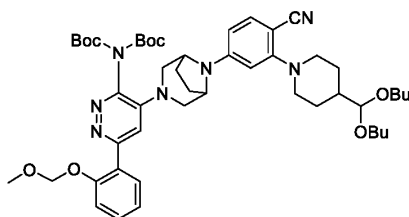
4-Bromo-2-(4-(dibutoxymethyl)piperidin-1-yl)benzonitrile



[1688] 4-(Dibutoxymethyl)piperidine (0.730 g, 3.00 mmol) was added to 4-bromo-2-fluorobenzonitrile (0.5 g, 2.50 mmol) in DMSO (3.91 ml) and DIPEA (1.092 ml, 6.25 mmol). The reaction mixture was heated to 120 °C for 3 h. The crude reaction mixture was cooled and diluted with 25 mL EtOAc and 25 mL water. The aqueous layer was extracted with EtOAc (3 x 25 mL). The combined organic layers were then washed with brine (25 mL). The organic layer was dried over Na₂SO₄, concentrated *in vacuo*, and the crude mixture purified by FSC (gradient 0-100% EtOAc/Hexanes) to yield the title compound (0.475 g, 44.9 %) as a yellow oil. ^1H NMR (DMSO- d_6): δ 0.83 - 0.92 (6H, m), 1.29 - 1.43 (6H, m), 1.44 - 1.53 (4H, m), 1.63 - 1.71 (1H, m), 1.75 (2H, br d), 2.73 - 2.82 (2H, m), 3.36 - 3.43 (2H, m), 3.53 - 3.58 (3H, m), 4.19 - 4.25 (1H, m), 7.20 - 7.23 (1H, m), 7.26 (1H, d), 7.54 - 7.65 (1H, m), 7.58 - 7.59 (1H, m); m/z (ES $^+$) $[M+H]^+ = 423.4$.

Intermediate 83b:

tert-Butyl *N*-*tert*-butoxycarbonyl-*N*-[4-[8-[4-cyano-3-[4-(dibutoxymethyl)-1-piperidyl]phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]-6-[2-(methoxymethoxy)phenyl]pyridazin-3-yl]carbamate

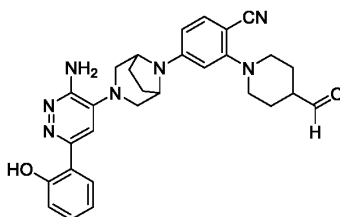


[1689] Intermediate 25d (400 mg, 0.74 mmol), Intermediate 83a (375 mg, 0.89 mmol), Cs₂CO₃ (722 mg, 2.22 mmol), RuPhos Pd G3 (61.8 mg, 0.07 mmol), and 1,4-dioxane (7385 μL) were added. The reaction was degassed, bubbling nitrogen through for 10 mins. The reaction was heated to 100 °C overnight. Reaction was cooled to r.t., filtered through celite® and concentrated. Purification by FSC (gradient: 0-100% EtOAc/Hexanes) gave the title compound (435 mg, 66.6 %). ^1H NMR (DMSO- d_6): δ 0.86 - 0.90

(6H, m), 1.32 - 1.37 (6H, m), 1.38 (17H, s), 1.44 - 1.53 (6H, m), 1.63 - 1.70 (1H, m), 1.74 (2H, br d), 1.85 - 1.91 (2H, m), 1.99 (1H, br d), 2.41 - 2.47 (1H, m), 2.53 - 2.61 (1H, m), 2.65 - 2.71 (2H, m), 3.15 - 3.20 (2H, m), 3.39 (3H, dt), 3.44 - 3.50 (3H, m), 3.51 - 3.58 (3H, m), 4.21 - 4.25 (1H, m), 4.56 - 4.61 (2H, m), 5.20 (2H, s), 6.42 - 6.46 (1H, m), 6.56 - 6.60 (1H, m), 7.12 - 7.17 (1H, m), 7.22 - 7.25 (1H, m), 7.40 (1H, d), 7.42 - 7.47 (1H, m), 7.50 - 7.53 (1H, m), 7.67 - 7.71 (1H, m); m/z (ES⁺) [M+H]⁺ = 884.3.

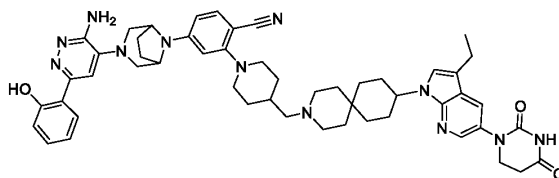
Intermediate 83c:

4-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-(4-formyl-1-piperidyl)benzonitrile



[1690] H₂SO₄ 2M aq. (1.131 mL, 2.26 mmol) was added to Intermediate 83b (100 mg, 0.11 mmol) in THF (1 mL) and the reaction mixture was heated to 60 °C for 1 h. The mixture was cooled in an ice-bath and quenched with sat. aq. NaHCO₃ (25 mL). The aqueous layer was extracted with DCM (3 x 25 mL) and the combined organic layers dried over Na₂SO₄ and filtered. The filtrate was concentrated to give the crude material which was used in the next step without further purification. m/z (ES⁺) [M+H]⁺ = 510.4.

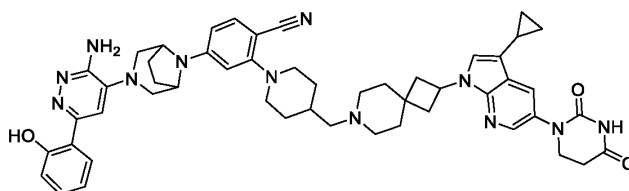
4-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-[4-[9-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-ethyl-pyrrolo[2,3-*b*]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl]methyl]-1-piperidyl]benzonitrile



[1691] Prepared in an analogous method to Example 11 starting from Intermediate 83c (28.3 mg, 0.06 mmol) and Intermediate 56c (25 mg, 0.06 mmol). Purification by RPC (elution gradient: 0-100% MeCN in water with 0.1% FA) gave the title compound (18.00 mg, 35.9 %) as an amorphous solid. ¹H NMR (DMSO-*d*₆): δ 1.24 - 1.30 (5H, m), 1.35 - 1.43 (2H, m), 1.71 (5H, br s), 1.81 (4H, br s), 1.94 - 2.04 (4H, m), 2.22 (4H, br t), 2.37 (4H, br s), 2.53 - 2.64 (1H, m), 2.70 (3H, q), 2.74 - 2.79 (3H, m), 3.02 - 3.09 (1H, m), 3.05 (1H, br d), 3.25 - 3.31 (2H, m), 3.31 - 3.43 (2H, m), 3.46 - 3.54 (1H, m), 3.49 - 3.65 (3H, m), 3.81 (2H, br t), 4.56 - 4.66 (2H, m), 5.95 - 6.02 (1H, m), 6.39 - 6.47 (1H, m), 6.52 - 6.60 (1H, m), 6.82 - 6.92 (2H, m), 7.20 - 7.27 (1H, m), 7.35 - 7.44 (1H, m), 7.47 - 7.53 (1H, m), 7.53 - 7.57 (1H, m), 7.89 - 7.93 (2H, m), 8.13 - 8.18 (1H, m), 10.23 - 10.45 (1H, m); m/z (ES⁺) [M+H]⁺ = 903.6.

Example 84

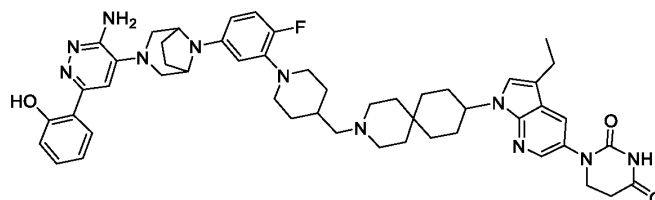
4-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-[4-[[2-[3-cyclopropyl-5-(2,4-dioxohexahydropyrimidin-1-yl)pyrrolo[2,3-*b*]pyridin-1-yl]-7-azaspiro[3.5]nonan-7-yl]methyl]-1-piperidyl]benzonitrile



[1692] Prepared in an analogous method to Example 11 starting from Intermediate 83c (57 mg, 0.11 mmol) and Intermediate 2c (52.8 mg, 0.13 mmol). Purification by RPC (elution gradient: 0-100% MeCN in water with 0.1% FA) gave the title compound (50.0 mg, 50.4 %) as an amorphous white solid. ¹H NMR (DMSO-*d*₆): δ 0.61 - 0.74 (2H, m), 0.78 - 0.97 (2H, m), 1.10 - 1.28 (2H, m), 1.64 - 1.76 (5H, m), 1.81 (1H, br s), 1.89 - 2.02 (3H, m), 2.15 - 2.27 (6H, m), 2.29 - 2.43 (5H, m), 2.69 - 2.79 (4H, m), 2.95 - 3.09 (2H, m), 3.27 (2H, br d), 3.49 (3H, br d), 3.80 (3H, br t), 4.46 - 4.66 (2H, m), 5.20 - 5.32 (1H, m), 5.96 (1H, s), 6.42 (1H, s), 6.49 - 6.60 (1H, m), 6.76 - 6.92 (2H, m), 7.16 - 7.25 (1H, m), 7.39 (1H, d), 7.45 - 7.51 (1H, m), 7.53 (1H, s), 7.83 - 7.97 (2H, m), 8.09 - 8.24 (2H, m), 10.22 - 10.44 (1H, m), 10.32 - 10.49 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 887.5.

Example 85

1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-ethyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



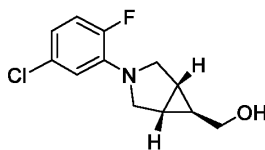
[1693] Prepared in an analogous method to Example 11 starting from Intermediate 11g (395 mg, 0.62 mmol) Intermediate 56c (281 mg, 0.69 mmol). Purification by RPC (elution gradient: 0-100% MeCN in water with 0.1% FA) gave the title compound (354 mg, 63.3 %) as an amorphous solid. ¹H NMR (DMSO-*d*₆): δ 1.20 - 1.32 (7H, m), 1.35 - 1.41 (2H, m), 1.57 - 1.64 (1H, m), 1.65 - 1.72 (4H, m), 1.74 - 1.82 (4H, m), 1.90 - 2.04 (4H, m), 2.08 - 2.15 (2H, m), 2.17 - 2.22 (2H, m), 2.30 - 2.39 (4H, m), 2.61 - 2.70 (4H, m), 2.72 - 2.77 (2H, m), 3.06 - 3.12 (2H, m), 3.21 - 3.27 (1H, m), 3.25 (3H, br d), 3.26 - 3.28 (1H, m), 3.75 - 3.82 (2H, m), 4.26 - 4.41 (2H, m), 4.52 - 4.68 (1H, m), 5.80 - 6.01 (2H, m), 6.37 - 6.52 (2H, m), 6.80 - 6.96 (3H, m), 7.16 - 7.27 (1H, m), 7.38 - 7.58 (2H, m), 7.80 - 7.93 (2H, m), 8.11 - 8.22 (1H, m), 10.35 (1H, s); *m/z* (ES⁺) [M+Na]⁺ = 918.49.

Example 86

Intermediate 86a:

303

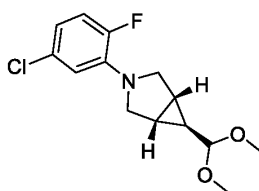
[(1*R*,5*S*,6*r*)-3-(5-Chloro-2-fluoro-phenyl)-3-azabicyclo[3.1.0]hexan-6-yl]methanol



[1694] BINAP (0.595 g, 0.95 mmol) was added to 2-bromo-4-chloro-1-fluorobenzene (2 g, 9.55 mmol), ((1*R*,5*S*,6*r*)-3-azabicyclo[3.1.0]hexan-6-yl)methanol (1.189 g, 10.50 mmol), Pd₂(dba)₃ (0.874 g, 0.95 mmol), and NaOtBu (2.75 g, 28.65 mmol) in toluene (20 mL) under nitrogen. The resulting mixture was stirred at 50 °C for 18 h. The reaction mixture was filtered and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 100% EtOAc in petroleum ether) gave the title compound (0.970 g, 42.0 %) as a yellow gum. ¹H NMR (DMSO-*d*₆): δ 0.92 – 0.97 (1H, m), 1.51 – 1.57 (2H, m), 3.25 – 3.28 (2H, m), 3.30 – 3.33 (2H, m), 3.57 – 3.62 (2H, m), 4.52 (1H, t), 6.67 – 6.70 (2H, m), 7.02 – 7.09 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 241.95.

Intermediate 86b:

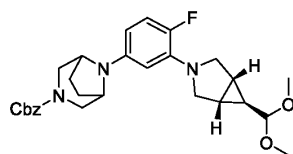
(1*R*,5*S*,6*r*)-3-(5-Chloro-2-fluoro-phenyl)-6-(dimethoxymethyl)-3-azabicyclo[3.1.0]hexane



[1695] Methyl *N*-(triethylammoniosulfonyl)carbamate (8.87 g, 37.24 mmol) was added to Intermediate 86a (1.5 g, 6.21 mmol) in DMSO (20.0 mL). The resulting mixture was stirred at r.t. for 2 h. The reaction mixture was diluted with DCM (125 mL) and washed sequentially with water (3 x 50 mL). The organic layer was dried over Na₂SO₄ and evaporated. To the crude product *p*TsOH • H₂O (0.214 g, 1.24 mmol), trimethoxymethane (1.976 g, 18.62 mmol), and MeOH (7 mL) were added. The resulting mixture was stirred at r.t. for 2 h. The reaction mixture was diluted with EtOAc (100 mL) and washed with sat. aq. NaHCO₃ (3 x 50 mL). The organic layer was dried over Na₂SO₄, filtered, and evaporated. Purification by RPC (elution gradient: 5 to 100% MeCN in water (0.1% NH₄HCO₃)) gave the title compound (0.790 g, 44.5 %) as a yellow solid. ¹H NMR (DMSO-*d*₆): δ 0.99 – 1.04 (1H, m), 1.67 – 1.71 (2H, m), 3.25 (6H, s), 3.26 – 3.29 (2H, m), 3.59 – 3.64 (2H, m), 4.18 (1H, d), 6.66 – 6.71 (2H, m), 7.02 – 7.09 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 286.1.

Intermediate 86c:

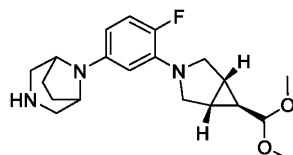
Benzyl 8-[3-[(1*R*,5*S*,6*r*)-6-(dimethoxymethyl)-3-azabicyclo[3.1.0]hexan-3-yl]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



[1696] Prepared in an analogous method to Intermediate 42c starting from Intermediate 86b (1g, 3.50 mmol) and benzyl (1*R*,5*S*)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate, HCl (0.990 g, 3.50 mmol). Purification by RPC (elution gradient: 5 to 100% MeCN in water (0.1% NH₄HCO₃)) gave the title compound (0.860 g, 49.6 %) as a yellow gum. ¹H NMR (DMSO-*d*₆): δ 1.04 – 1.10 (1H, m), 1.61 – 1.67 (4H, m), 1.85 – 1.90 (2H, m), 3.12 (1H, d), 3.16 – 3.27 (9H, m), 3.55 – 3.64 (4H, m), 4.14 – 4.23 (3H, m), 5.07 (2H, d), 6.10 – 6.19 (2H, m), 6.82 – 6.88 (1H, m), 7.29 – 7.40 (5H, m); *m/z* (ES⁺) [M+H]⁺ = 496.2.

Intermediate 86d:

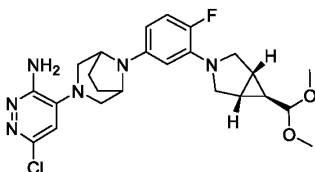
8-[3-[(1*R*,5*S*,6*r*)-6-(dimethoxymethyl)-3-azabicyclo[3.1.0]hexan-3-yl]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octane



[1697] Palladium hydroxide on carbon powder (244 mg, 0.174 mmol) was added to Intermediate 86c (860 mg, 1.74 mmol) in MeOH (10 mL) under hydrogen. The resulting mixture was stirred at r.t. for 2 h. The mixture was filtered through a pad of Celite®, and the filtrate was concentrated to afford the title compound (290 mg, 46.2 %) as a yellow solid, which was used without further purification. ¹H NMR (DMSO-*d*₆): δ 0.80 – 0.87 (1H, m), 1.04 – 1.10 (1H, m), 1.19 – 1.29 (1H, m), 1.64 – 1.68 (2H, m), 1.77 – 1.89 (5H, m), 2.34 – 2.38 (1H, m), 2.93 (1H, d), 3.16 – 3.20 (2H, m), 3.22 – 3.26 (7H, m), 3.57 – 3.62 (2H, m), 3.94 – 3.97 (1H, m), 4.17 (1H, d), 6.01 – 6.12 (2H, m), 6.77 – 6.85 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 362.3.

Intermediate 86e:

6-chloro-4-[8-[3-[(1*R*,5*S*,6*r*)-6-(dimethoxymethyl)-3-azabicyclo[3.1.0]hexan-3-yl]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-amine

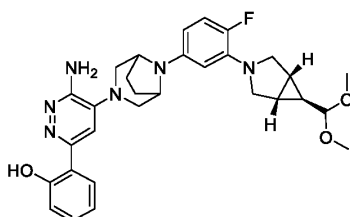


[1698] Prepared in an analogous method to Intermediate 49e starting from Intermediate 86d (200 mg, 0.55 mmol). Purification by RPC (elution gradient: 5 to 100% MeCN in water (0.1% NH₄HCO₃)) gave the title compound (100 mg, 37.0 %) as a yellow solid. ¹H NMR (DMSO-*d*₆): δ 1.03 – 1.09 (1H, m), 1.66 (2H, d), 1.90 (2H, d), 2.08 (2H, d), 2.95 (2H, d), 3.11 – 3.20 (3H, m), 3.21 – 3.25 (7H, m), (7H, s), 3.59 – 3.66

(2H, m), 4.18 (1H, d), 4.26 – 4.29 (2H, m), 5.80 (2H, s), 6.10 – 6.23 (2H, m), 6.81 – 6.90 (2H, m); m/z (ES⁻) $[M-H]^- = 487.4$.

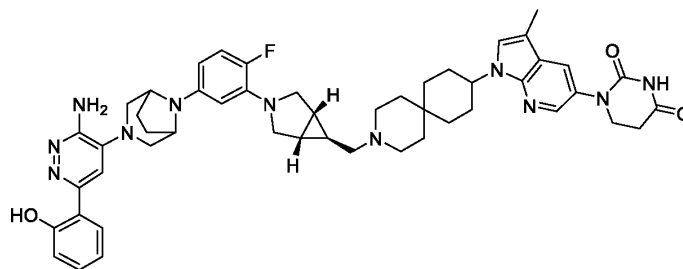
Intermediate 86f:

2-[6-Amino-5-[8-[3-[(1*R*,5*S*,6*r*)-6-(dimethoxymethyl)-3-azabicyclo[3.1.0]hexan-3-yl]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-yl]phenol



[1699] Pd(dppf)Cl₂ (29.9 mg, 0.04 mmol) was added to (2-hydroxyphenyl)boronic acid (85 mg, 0.61 mmol), Cs₂CO₃ (400 mg, 1.23 mmol), and Intermediate 86e (200 mg, 0.41 mmol) in 1,4-dioxane (3.0 mL) and water (0.6 mL) under nitrogen. The resulting mixture was stirred at 80 °C for 20 h. The solvent was removed under reduced pressure. Purification by FSC (elution gradient 0 to 100% EtOAc in petroleum ether) gave the title compound (110 mg, 49.2 %) as a yellow solid. ¹H NMR (DMSO-*d*₆): δ 1.00 – 1.09 (1H, m), 1.64 (2H, d), 1.90 – 1.95 (2H, m), 2.10 (2H, d), 3.08 (2H, d), 3.20 – 3.25 (10H, m), 3.57 – 3.66 (2H, m), 4.16 (1H, d), 4.23 – 4.37 (2H, m), 5.93 (2H, s), 6.10 – 6.23 (2H, m), 6.79 – 6.89 (3H, m), 7.21 (1H, t), 7.44 (1H, s), 7.90 (1H, d), 14.18 (1H, s); m/z (ES⁺) $[M+H]^+ = 547.3$.

1-[1-[3-[(1*R*,5*S*,6*s*)-3-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3-azabicyclo[3.1.0]hexan-6-yl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



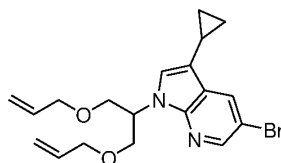
[1700] *p*TsOH·H₂O (30.6 mg, 0.16 mmol) was added to Intermediate 13b (80 mg, 0.16 mmol) in MeCN (1.5 mL). The resulting mixture was stirred at 80 °C for 16 h. The reaction mixture was evaporated to afford the crude amine. In a second vial, Intermediate 86f (142 mg, 0.23 mmol) was added to formic acid (3 mL) and stirred at 40 °C for 20 min. The reaction mixture was evaporated. The residue quenched with saturated Na₂CO₃ (10 mL), extracted with EtOAc (3 x 5 mL), the organic layer was dried over Na₂SO₄, filtered, and evaporated. The crude aldehyde residue was combined with crude amine in DCE (1.0 mL) and

NMP (1.0 mL). The resulting mixture was stirred at 40 °C for 2 h. Then Na(OAc)₃BH (136 mg, 0.64 mmol) was added and stirred at r.t. for 2 h. The solvent was removed under reduced pressure. The reaction mixture was diluted with DCM/*i*PrOH (1:1) (10 mL) and washed with sat. aq. NaHCO₃ (2 x 10 mL). The organic layer was dried over Na₂SO₄, filtered, and evaporated. Purification by RPC (elution gradient: 0-35% MeCN in water with 0.1% formic acid) gave the title compound (11.80 mg, 11.78 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.22 – 1.37 (3H, m), 1.38 – 1.45 (2H, m), 1.44 – 1.52 (2H, m), 1.75 (6H, d), 1.89 – 2.05 (4H, m), 2.12 (2H, d), 2.25 (3H, s), 2.33 (2H, d), 2.70 – 2.80 (2H, m), 3.09 (2H, d), 3.23 (5H, d), 3.42 – 3.56 (3H, m), 3.61 – 3.70 (2H, m), 3.76 – 3.85 (2H, m), 4.33 (2H, s), 4.54 – 4.66 (1H, m), 5.95 (2H, s), 6.12 – 6.24 (2H, m), 6.79 – 6.91 (3H, m), 7.16 – 7.28 (1H, m), 7.46 (1H, s), 7.54 (1H, s), 7.87 (1H, d), 7.90 – 7.94 (1H, m), 8.16 (1H, d), 10.40 (1H, s), 13.87 – 14.47 (1H, m); ¹⁹F NMR (DMSO-*d*₆): δ -138.29; *m/z* (ES⁺), [M+2H]^{+/2} = 440.9.

Example 87

Intermediate 87a:

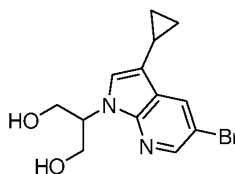
1-[2-Allyloxy-1-(allyloxymethyl)ethyl]-5-bromo-3-cyclopropyl-pyrrolo[2,3-*b*]pyridine



[1701] Prepared in an analogous manner to Intermediate 4a from 5-bromo-3-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridine (2g, 8.44 mmol). Purification by FSC (elution gradient: 0 to 50% EtOAc in petroleum ether) gave the title compound (3.10 g, 94 %) as a yellow liquid. ¹H NMR (DMSO-*d*₆): δ 0.56–0.68 (2H, m), 0.78–0.95 (2H, m), 1.9–1.99 (1H, m), 3.73–3.78 (2H, m), 3.8–3.85 (2H, m), 3.88–3.92 (4H, m), 3.99–4.01 (1H, m), 5.08–5.15 (4H, m), 5.71–5.81 (2H, m), 7.42 (1H, s), 8.20 (1H, d), 8.27 (1H, d); *m/z* (ES⁺), [M+H]⁺ = 391.1.

Intermediate 87b:

2-(5-Bromo-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-1-yl)propane-1,3-diol

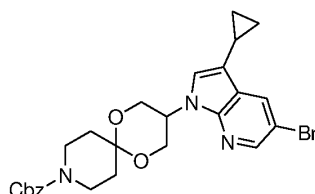


[1702] Pd(PPh₃)₄ (0.443 g, 0.38 mmol) was added to Intermediate 87a (3 g, 7.67 mmol) and 1,3-dimethylbarbituric acid (2.394 g, 15.33 mmol) in MeOH (45mL) over a period of 5 min. under nitrogen. The resulting mixture was stirred at r.t. for 16 h. The reaction mixture was poured into water (200 mL), extracted with DCM (3 x 200 mL), the organic layer was dried over Na₂SO₄, filtered, and evaporated. Purification by FSC (elution gradient: 0 to 70% EtOAc in petroleum ether) gave the title compound (2.1 g, 88 %) as a yellow liquid. ¹H NMR (DMSO-*d*₆): δ 0.6–0.67 (2H, m), 0.81–0.9 (2H, m), 1.15–1.21 (1H, m),

3.76 (4H, d), 4.73–4.82 (1H, m), 4.86 (2H, s), 7.38 (1H, s), 8.18 (1H, d), 8.25 (1H, d); m/z (ES^+), $[M+H]^+ = 311.1$.

Intermediate 87c:

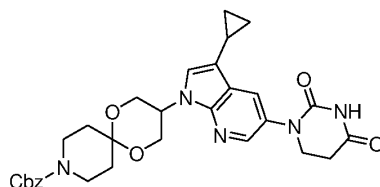
Benzyl 3-(5-bromo-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-1-yl)-1,5-dioxo-9-azaspiro[5.5]undecane-9-carboxylate



[1703] *para*-Toluenesulfonic acid (0.221 g, 1.29 mmol) was added to Intermediate 87b (2 g, 6.43 mmol) and benzyl 4-oxopiperidine-1-carboxylate (3.00 g, 12.85 mmol) in toluene (30 mL). The resulting mixture was stirred at 100 °C for 20 h. After cooling to r.t. the mixture was filtered, and filter-cake was washed with EtOAc. The combined filtrates were concentrated under reduced pressure. The residue was dissolved in EtOAc (100 mL), washed with sat. aq. $NaHCO_3$ (2 x 100 mL), dried over Na_2SO_4 , filtered, and concentrated. Purification by FSC (elution gradient: 0 to 100% EtOAc in petroleum ether) gave the title compound (3.20 g, 95 %) as a yellow liquid. 1H NMR ($DMSO-d_6$): δ 0.59–0.67 (2H, m), 0.86–0.91 (2H, m), 1.90 (2H, d), 1.94–1.97 (2H, m), 1.98 (1H, d), 3.44–3.48 (4H, m), 3.99–4.09 (2H, m), 4.28 (2H, d), 4.78–4.83 (1H, m), 5.10 (2H, s), 7.3–7.35 (5H, m), 7.65 (1H, s), 8.24 (1H, d), 8.30 (1H, d); m/z (ES^+) $[M+H]^+ = 526.2$.

Intermediate 87d:

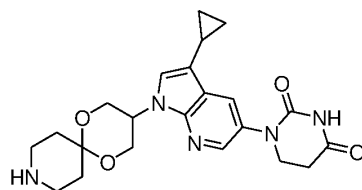
Benzyl 3-[3-cyclopropyl-5-(2,4-dioxohexahydropyrimidin-1-yl)pyrrolo[2,3-*b*]pyridin-1-yl]-1,5-dioxo-9-azaspiro[5.5]undecane-9-carboxylate



[1704] Prepared in an analogous method to Intermediate 6b starting Intermediate 87c (3g, 5.70 mmol). Purification by FSC (elution gradient 0 to 5% MeOH in DCM) gave the title compound (1.0 g, 31.4 %) as a light brown solid. 1H NMR ($DMSO-d_6$): δ 0.58–0.68 (2H, m), 0.87–0.95 (2H, m), 1.24 (1H, s), 1.91–2 (5H, m), 2.74–2.8 (2H, m), 3.45–3.49 (4H, m), 3.79–3.86 (2H, m), 4.04–4.11 (2H, m), 4.25 (1H, d), 4.81–4.89 (1H, m), 5.10 (2H, s), 7.31–7.43 (5H, m), 7.63 (1H, s), 7.99 (1H, d), 8.20 (1H, d), 10.40 (1H, s); m/z (ES^+) $[M+H]^+ = 560.1$.

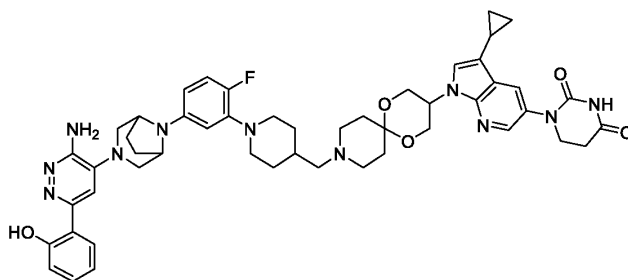
Intermediate 87e:

1-[3-Cyclopropyl-1-(1,5-dioxo-9-azaspiro[5.5]undecan-3-yl)pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1705] Pd-C (60 mg, 0.56 mmol) was added to Intermediate 87d (350 mg, 0.63 mmol) in DMF (10 mL) under nitrogen. The resulting mixture was stirred at r.t. under hydrogen atmosphere for 16 h. The catalyst was filtered off through celite® and filtrate was evaporated to afford the title compound (250 mg, 94 %) as a light grey solid. The crude product was used in the next step directly without further purification. ¹H NMR (DMSO-*d*₆): δ 0.60–0.67 (2H, m), 0.86–0.91 (2H, m), 1.16 (1H, d), 1.8–1.89 (4H, m), 1.92–2 (1H, m), 2.68–2.75 (4H, m), 2.75–2.8 (2H, m), 3.79–3.86 (2H, m), 4–4.11 (2H, m), 4.2–4.33 (2H, m), 4.78–4.88 (1H, m), 7.64 (1H, s), 7.94–8.04 (1H, m), 8.20 (1H, d), 10.40 (1H, s); *m/z* (ES⁺), [M+H]⁺ = 426.2.

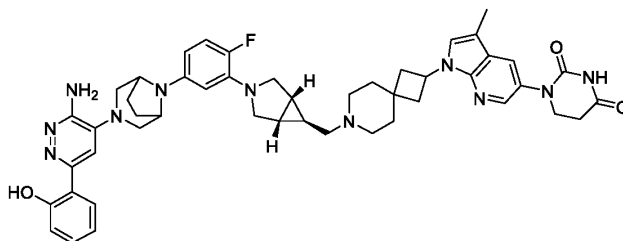
1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1706] Prepared in an analogous method to Example 40 starting Intermediate 11g (65 mg, 0.10 mmol) and Intermediate 87e (43.7 mg, 0.10 mmol). Purification by RPC (elution gradient: 0-72% MeCN in water with NH₄HCO₃+0.05% NH₃H₂O) gave the title compound (18.30 mg, 19.53 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 0.61–0.67 (2H, m), 0.86–0.92 (2H, m), 1.26 (3H, d), 1.63 (1H, s), 1.80 (2H, d), 1.86–1.99 (6H, m), 2.08 (1H, s), 2.1–2.17 (2H, m), 2.21 (2H, s), 2.32 (1H, s), 2.43 (4H, s), 2.62–2.67 (2H, m), 2.74–2.81 (2H, m), 3.11 (2H, d), 3.26 (2H, d), 3.78–3.86 (2H, m), 4–4.09 (2H, m), 4.2–4.3 (2H, m), 4.35 (2H, s), 4.78–4.87 (1H, m), 5.95 (2H, s), 6.41–6.46 (1H, m), 6.46–6.52 (1H, m), 6.83–6.9 (2H, m), 6.9–6.96 (1H, m), 7.19–7.27 (1H, m), 7.47 (1H, s), 7.65 (1H, s), 7.9–8 (2H, m), 8.20 (1H, d), 10.40 (1H, s), 14.18 (1H, s). ¹⁹F NMR (DMSO-*d*₆): δ -136.401; *m/z* (ES⁺) [M+H]⁺ = 912.5.

Example 88

1-[1-[7-[[1-(1*R*,5*S*,6*S*)-3-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3-azabicyclo[3.1.0]hexan-6-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

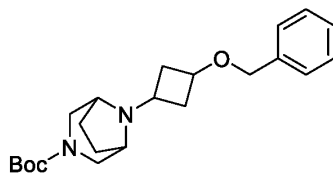


[1707] Prepared in an analogous method to Example 41 starting from Intermediate 86f (40 mg, 0.07 mmol) and Intermediate 42f (32.3 mg, 0.09 mmol). Purification by RPC (elution gradient; 50 to 63% MeCN in water with 10mmol/L NH_4HCO_3 + 0.05% $\text{NH}_3\text{H}_2\text{O}$) gave the title compound (7.94 mg, 12.74 %) as a white solid. ^1H NMR (DMSO-*d*6): δ 0.88 (2H, d), 1.24 (1H, s), 1.48 (2H, s), 1.71 (2H, s), 1.75 (2H, d), 1.95 (2H, d), 2.13 (2H, d), 2.22 (3H, t), 2.27 (4H, s), 2.37 (4H, s), 2.76 (2H, t), 3.10 (2H, d), 3.24 (4H, d), 3.64 – 3.69 (2H, m), 3.81 (2H, t), 4.33 (2H, s), 5.24 – 5.29 (1H, m), 5.94 (2H, s), 6.15 – 6.24 (2H, m), 6.83 – 6.89 (3H, m), 7.19 – 7.24 (1H, m), 7.47 (1H, s), 7.62 (1H, s), 7.89 (1H, d), 7.90 – 7.93 (1H, m), 8.17 (1H, d), 10.39 (1H, s), 14.19 (1H, s); ^{19}F NMR (DMSO): δ -138.32; m/z (ES^+) $[\text{M}+\text{H}]^+ = 852.4$.

Example 89

Intermediate 89a:

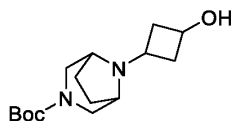
tert-Butyl 8-(3-benzyloxycyclobutyl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



[1708] Prepared in an analogous method to Intermediate 41a starting from 3-(benzyloxy)cyclobutan-1-one (8 g, 45.40 mmol) and *tert*-butyl (1*R*,5*S*)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (11.57 g, 54.48 mmol). Purification by RPC (elution gradient: 0 to 80% MeCN in water with 0.1% NH_4HCO_3) gave the title compound (11.79 g, 69.7 %) as a yellow gum. ^1H NMR (DMSO *d*6): δ 1.39 (9H, d), 1.42 (2H, d), 1.61–1.68 (2H, m), 1.71–1.78 (2H, m), 1.98–2.06 (1H, m), 2.35–2.41 (1H, m), 2.43–2.49 (1H, m), 2.78 (1H, d), 2.88–2.97 (1H, m), 3–3.17 (2H, m), 3.49–3.64 (2H, m), 3.69–3.76 (1H, m), 4.36 (2H, d), 7.26–7.37 (5H, m); m/z (ES^+) $[\text{M}+\text{H}]^+ = 373.3$.

Intermediate 89b:

tert-Butyl 8-(3-hydroxycyclobutyl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate

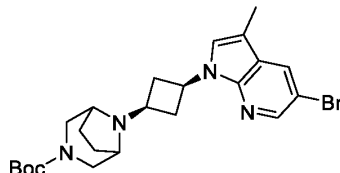


[1709] Prepared in an analogous method to Intermediate 41b starting from Intermediate 89a (11 g, 29.53 mmol). The precipitate was filtered through celite®, washed with MeOH (50 mL) and dried under vacuum to afford the title compound (8.00 g, 96 %) as a brown gum, which was used without further

purification. ^1H NMR ($\text{DMSO-}d_6$): δ 1.36 (9H, s), 1.52 – 1.60 (1H, m), 1.66 – 1.76 (2H, m), 1.78 – 2.04 (1H, m), 2.25 – 2.39 (2H, m), 2.75 (1H, d), 2.82 – 2.94 (1H, m), 3.03 (2H, d), 3.16 (2H, s), 3.45 – 3.65 (2H, m), 3.73 (1H, d), 4.06 – 4.26 (1H, m), 4.93 (1H, d); m/z (ES^+) $[\text{M}+\text{H}]^+ = 283.3$.

Intermediate 89c:

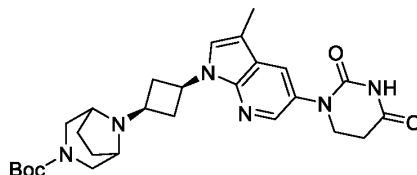
tert-Butyl 8-[(1*s*,3*s*)-3-(5-bromo-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl)cyclobutyl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



[1710] Prepared in an analogous method to Intermediate 41c starting from Intermediate 89a (5 g, 17.71 mmol) and 5-bromo-3-methyl-1H-pyrrolo[2,3-*b*]pyridine (3.74 g, 17.71 mmol). Purification by RPC (elution gradient: 0 to 100% MeCN in water with 0.1% NH_4HCO_3) gave the title compound (0.600 g, 7.13 %) as a brown solid. ^1H NMR (CDCl_3): δ 1.46 (9H, s), 1.60 – 1.71 (3H, m), 1.82 – 1.93 (2H, m), 2.28 (3H, s), 2.67 – 2.77 (2H, m), 2.79 – 2.90 (1H, m), 2.96 – 3.24 (5H, m), 3.63 (1H, d), 3.77 (1H, d), 4.98 – 5.11 (1H, m), 7.32 (1H, s), 7.93 (1H, d), 8.27 (1H, d); m/z (ES^+) $[\text{M}+\text{H}]^+ = 477.4$.

Intermediate 89d:

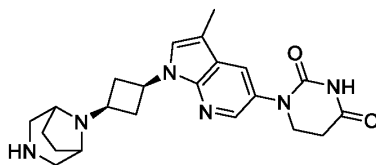
tert-Butyl 8-[(1*s*,3*s*)-3-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]cyclobutyl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



[1711] Prepared in an analogous method to Intermediate 41d starting from Intermediate 89c (250 mg, 0.53 mmol). Purification by RPC (elution gradient: 0 to 70% MeOH in water with 0.1% NH_4HCO_3) gave the title compound (45.0 mg, 16.83 %) as a white solid. ^1H NMR (CDCl_3): δ 1.48 (9H, s), 1.62 – 1.70 (2H, m), 1.86 – 1.94 (2H, m), 2.19 – 2.23 (2H, m), 2.33 (3H, s), 2.72 – 2.79 (2H, m), 2.83 – 2.88 (1H, m), 2.92 (2H, t), 2.99 – 3.12 (2H, m), 3.14 – 3.26 (2H, m), 3.65 (1H, d), 3.79 (1H, d), 3.92 (2H, t), 5.06 – 5.16 (1H, m), 7.39 (1H, s), 7.55 (1H, s), 7.78 (1H, d), 8.22 (1H, d); m/z (ES^+) $[\text{M}+\text{H}]^+ = 509.3$.

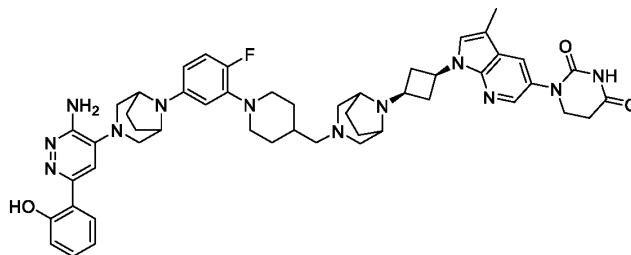
Intermediate 89e:

1-[1-[(1*s*,3*s*)-3-(3,8-Diazabicyclo[3.2.1]octan-8-yl)cyclobutyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1712] Prepared in an analogous manner to Intermediate 1i from Intermediate 89d (40 mg, 0.08 mmol). The crude product was evaporated to dryness to afford the title compound (25.00 mg, 78 %) as a brown gum. The product was used in the next step directly without further purification. ¹H NMR (DMSO-*d*₆): δ 2.16 – 2.22 (2H, m), 2.27 (3H, s), 2.33 – 2.38 (2H, m), 2.74 – 2.81 (5H, m), 2.88 – 2.95 (2H, m), 3.47 – 3.56 (2H, m), 3.61 – 3.67 (2H, m), 3.70 – 3.84 (3H, m), 4.18 – 4.22 (2H, m), 5.10 – 5.18 (1H, m), 7.65 (1H, s), 7.94 (1H, d), 8.21 (1H, d), 10.41 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 409.1.

1-[1-[(1*s*,3*s*)-3-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]cyclobutyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

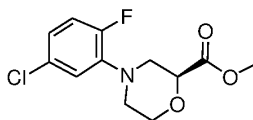


[1713] Prepared in an analogous manner to Example 41 from Intermediate 89e (25 mg, 0.06 mmol) and Intermediate 11g (40.3 mg, 0.07 mmol). Purification by RPC (elution gradient: 43% to 57% MeCN in water with 10 mmol/L NH₄HCO₃ + 0.05% NH₃H₂O) gave the title compound (8.0 mg, 14.6 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.20 – 1.27 (3H, m), 1.55 – 1.61 (1H, m), 1.65 – 1.72 (2H, m), 1.73 – 1.83 (4H, m), 1.90 – 1.98 (2H, m), 2.06 – 2.24 (8H, m), 2.28 (3H, s), 2.54 – 2.67 (7H, m), 2.76 (2H, t), 2.84 – 2.91 (1H, m), 3.10 (2H, d), 3.14 – 3.19 (2H, m), 3.26 (2H, d), 3.81 (2H, t), 4.35 (2H, d), 4.90 – 4.99 (1H, m), 5.95 (2H, s), 6.41 – 6.50 (2H, m), 6.84 – 6.96 (3H, m), 7.23 (1H, t), 7.53 (2H, d), 7.87 – 7.93 (2H, m), 8.18 (1H, t), 10.39 (1H, s), 14.18 (1H, s); ¹⁹F NMR (DMSO-*d*₆): δ -136.45; *m/z* (ES⁺) [M+H]⁺ = 895.7.

Example 90

Intermediate 90a:

Methyl (2*S*)-4-(5-chloro-2-fluoro-phenyl)morpholine-2-carboxylate

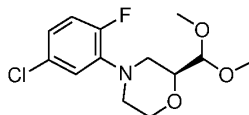


[1714] Prepared in an analogous manner to Intermediate 42a starting from methyl (*S*)-morpholine-2-carboxylate (2 g, 13.78 mmol) and 2-bromo-4-chloro-1-fluorobenzene (2.89 g, 13.78 mmol). Purification

by FSC (elution gradient: 0 to 30% EtOAc in petroleum ether) gave the title compound (1.470 g, 39.0 %) as a white liquid. ^1H NMR (DMSO- d_6): δ 2.92 – 2.99 (1H, m), 3.08 – 3.14 (2H, m), 3.33 – 3.37 (1H, m), 3.69 (3H, s), 3.71 – 3.76 (1H, m), 3.98 – 4.05 (1H, m), 4.40 – 4.44 (1H, m), 7.04 – 7.07 (1H, m), 7.07 – 7.10 (1H, m), 7.18 – 7.23 (1H, m); m/z (ES^+) $[\text{M}+\text{H}]^+ = 274.1$.

Intermediate 90b:

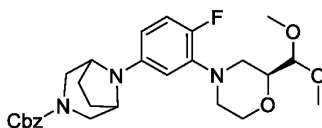
(2S)-4-(5-Chloro-2-fluoro-phenyl)-2-(dimethoxymethyl)morpholine



[1715] Prepared in an analogous manner to Intermediate 42b starting from Intermediate 90a (1.47g, 5.37 mmol). Purification by FSC (elution gradient: 0 to 50% EtOAc in petroleum ether) gave the title compound (0.810 g, 52.1 %) as a yellow liquid. ^1H NMR (DMSO- d_6): δ 2.60 – 2.66 (1H, m), 2.76 – 2.85 (1H, m), 3.14 – 3.19 (1H, m), 3.25 – 3.30 (1H, m), 3.33 (6H, d), 3.61 – 3.69 (2H, m), 3.89 – 3.95 (1H, m), 4.32 (1H, d), 6.99 – 7.06 (2H, m), 7.14 – 7.23 (1H, m); m/z (ES^+) $[\text{M}+\text{H}]^+ = 290.1$.

Intermediate 90c:

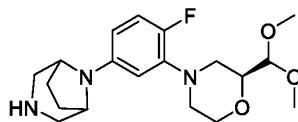
Benzyl 8-[3-[(2S)-2-(dimethoxymethyl)morpholin-4-yl]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



[1716] Prepared in an analogous manner to Intermediate 42c starting from Intermediate 90b (800 mg, 2.76 mmol) and benzyl (1R,5S)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (816 mg, 3.31 mmol). Purification by FSC (elution gradient: 0 to 30% EtOAc in petroleum ether) gave the title compound (1220 mg, 88 %) as a yellow oil. ^1H NMR (DMSO- d_6): δ 1.62 – 1.69 (2H, m), 1.86 – 1.93 (2H, m), 2.59 (1H, dd), 2.76 – 2.83 (1H, m), 3.07 – 3.15 (2H, m), 3.20 – 3.28 (2H, m), 3.33 (6H, s), 3.54 – 3.67 (4H, m), 3.88 – 3.93 (1H, m), 4.20 – 4.29 (2H, m), 4.31 (1H, d), 5.06 – 5.09 (2H, m), 6.40 – 6.46 (2H, m), 6.92 – 6.98 (1H, m), 7.16 – 7.63 (5H, m); m/z (ES^+) $[\text{M}+\text{H}]^+ = 500.4$.

Intermediate 90d:

(2S)-4-[5-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-2-fluoro-phenyl]-2-(dimethoxymethyl)morpholine

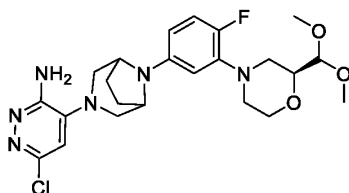


[1717] Prepared in an analogous manner to Intermediate 88d starting from Intermediate 90c (1.2g, 2.40 mmol). The reaction mixture was filtered through celite® the filtrate was collected and evaporated to afford the title compound (0.670 g, 76 %) as a yellow oil. ^1H NMR (DMSO- d_6): δ 1.73 – 1.95 (4H, m), 2.34 – 2.43 (2H, m), 2.5 – 2.60 (1H, m), 2.75 – 2.82 (1H, m), 2.94 (1H, d), 3.06 – 3.11 (1H, m), 3.23 – 3.27 (1H, m),

3.30(6H, s) 3.59 – 3.69 (2H, m), 3.91 (1H, d), 3.96 – 4.05 (1H, m), 4.15 – 4.18 (1H, m), 4.27 – 4.33 (1H, m), 6.30 – 6.42 (2H, m), 6.87 – 6.96 (1H, m); m/z (ES⁺) [M+H]⁺ = 366.3.

Intermediate 90e:

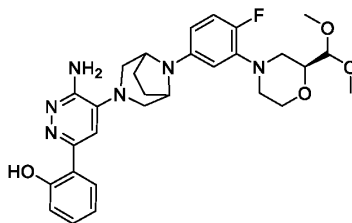
6-Chloro-4-[8-[3-[(2*S*)-2-(dimethoxymethyl)morpholin-4-yl]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-amine



[1718] Prepared in an analogous manner to Intermediate 49e starting from Intermediate 90d (670mg, 1.83 mmol) and 4-bromo-6-chloropyridazin-3-amine (420 mg, 2.02 mmol). Purification by FSC (elution gradient: 0 to 20% EtOAc in petroleum ether then 0 to 10% MeOH in DCM) gave the title compound (650 mg, 71.9 %) as a grey gum. ¹H NMR (DMSO-*d*₆): δ 1.92 – 1.96 (2H, m), 2.11 – 2.15 (2H, m), 2.59 (1H, t), 2.78 – 2.86 (1H, m), 3.08 – 3.14 (3H, m), 3.24 – 3.29 (3H, m), 3.62 – 3.68 (2H, m), 3.89 – 3.94 (1H, m), 4.31 (1H, d), 4.34 – 4.38 (2H, m), 5.95 (2H, s), 6.47 – 6.49 (2H, m), 6.87 – 6.88 (2H, m), 6.95 – 6.99 (1H, m), 7.20 – 7.25 (1H, m), 7.46 (1H, s), 7.88 – 7.93 (1H, m), 14.17 (1H, s); m/z (ES⁺) [M+H]⁺ = 493.3.

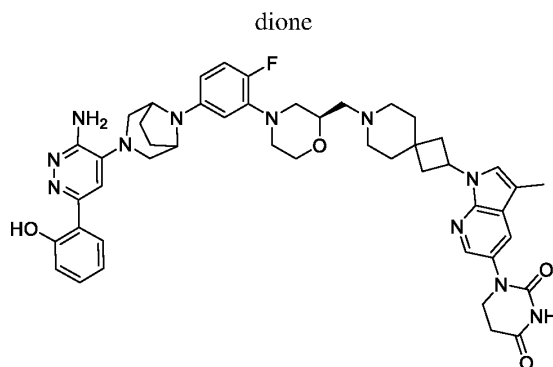
Intermediate 90f:

2-[6-Amino-5-[8-[3-[(2*S*)-2-(dimethoxymethyl)morpholin-4-yl]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-yl]phenol



[1719] Prepared in an analogous manner to Intermediate 2h starting from Intermediate 90e (640mg, 1.30 mmol) and (2-hydroxyphenyl)boronic acid (358 mg, 2.60 mmol). Purification by FSC (elution gradient: 0 to 30% EtOAc in petroleum ether, then 0 to 10% MeOH in DCM) gave the title compound (530 mg, 74.1 %) as a grey solid. ¹H NMR (DMSO-*d*₆) δ 0.81 – 0.89 (1H, m), 0.91 – 0.96 (1H, m), 1.07 – 1.12 (1H, m), 1.19 – 1.29 (1H, m), 1.89 – 2.17 (4H, m), 2.53 – 2.65 (2H, m), 2.80 – 2.87 (1H, m), 3.07 – 3.19 (2H, m), 3.22 – 3.32 (4H, m), 3.46 – 3.57 (1H, m), 3.61 – 3.70 (2H, m), 3.89 – 3.96 (1H, m), 4.32 (1H, d), 4.34 – 4.42 (2H, m), 6.13 – 6.23 (1H, m), 6.28 – 6.41 (1H, m), 6.46 – 6.53 (2H, m), 6.83 – 6.94 (2H, m), 6.94 – 7.06 (2H, m), 7.18 – 7.48 (2H, m), 8.00 – 8.18 (1H, m); m/z (ES⁺) [M+H]⁺ = 551.4.

1-[1-[7-[(2*R*)-4-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]morpholin-2-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-

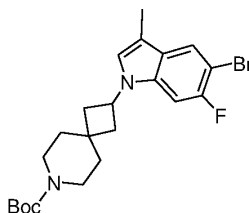


[1720] Prepared in an analogous manner to Example 42 starting from Intermediate 90f (40 mg, 0.07 mmol) and Intermediate 42f (26.7 mg, 0.07 mmol). Purification by RPC (elution gradient: 18% to 33% in MeCN in water with 0.1% formic acid) gave the title compound (4.48 mg, 6.79 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.65 – 1.73 (4H, m), 1.94 – 1.98 (2H, d), 2.14 – 2.17 (2H, d), 2.20 (2H, t), 2.25 – 2.29 (2H, m), 2.34 – 2.40 (5H, m), 2.45 – 2.48 (1H, m), 2.73 – 2.79 (3H, m), 3.10 (2H, t), 3.14 – 3.20 (2H, m), 3.25 – 3.30 (3H, m), 3.34 (2H, d), 3.63 – 3.70 (2H, m), 3.73 – 3.77 (1H, m), 3.80 (2H, t), 3.87 – 3.92 (1H, m), 4.34 – 4.40 (2H, m), 5.21 – 5.30 (1H, m), 5.98 (2H, s), 6.45 – 6.50 (2H, m), 6.87 (2H, t), 6.94 – 7.00 (1H, m), 7.21 – 7.26 (1H, m), 7.47 (1H, s), 7.61 (1H, s), 7.87 – 7.93 (2H, m), 8.17 (1H, d), 8.26 – 8.31 (1H, m), 10.39 (1H, s), 14.15 (1H, s); ¹⁹F NMR (DMSO): δ -136.815; *m/z* (ES⁺) [M+H]⁺ = 856.3.

Example 91

Intermediate 91a:

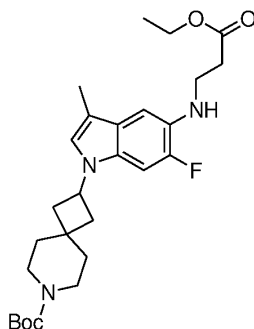
tert-Butyl 2-(5-bromo-6-fluoro-3-methyl-indol-1-yl)-7-azaspiro[3.5]nonane-7-carboxylate



[1721] Prepared in an analogous manner to Intermediate 4a starting from 5-bromo-6-fluoro-3-methyl-1*H*-indole (400 mg, 1.75 mmol) and *tert*-butyl 2-hydroxy-7-azaspiro[3.5]nonane-7-carboxylate (508 mg, 2.10 mmol). Purification by FSC (elution gradient: 0 to 30% EtOAc in petroleum ether) gave the title compound (560 mg, 70.7 %) as a yellow oil. ¹H NMR (CDCl₃): δ 1.47 (9 H, s), 1.57 – 1.64 (2 H, m), 1.69 – 1.76 (2 H, m), 2.12 – 2.21 (2 H, m), 2.27 (3 H, s), 2.49 – 2.58 (2 H, m), 3.31 – 3.38 (2 H, m), 3.41 – 3.48 (2 H, m), 4.65 – 4.76 (1 H, m), 6.98 – 7.00 (1 H, m), 7.02 (1 H, d), 7.66 (1 H, d); *m/z* (ES⁺) [M-*t*Bu+H]⁺ = 395.

Intermediate 91b:

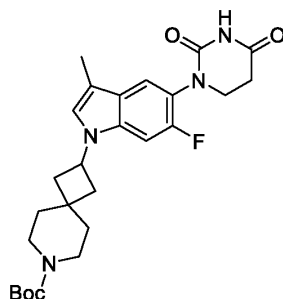
tert-Butyl 2-[5-[(3-ethoxy-3-oxo-propyl)amino]-6-fluoro-3-methyl-indol-1-yl]-7-azaspiro[3.5]nonane-7-carboxylate



[1722] $\text{Pd}_2(\text{dba})_3$ (46.7 mg, 0.05 mmol) was added to Intermediate 91a (230 mg, 0.51 mmol), ethyl 3-aminopropanoate (65.7 mg, 0.56 mmol), CPhos (22.25 mg, 0.05 mmol) and Cs_2CO_3 (664 mg, 2.04 mmol) in 1,4-dioxane (5 mL) under nitrogen. The resulting mixture was stirred at 100 °C for 16 h. The reaction mixture was poured into water (20 mL), extracted with EtOAc (3 x 20 mL), the organic layer was dried over Na_2SO_4 , filtered, and evaporated. Purification by FSC (elution gradient: 0 to 30% EtOAc in petroleum ether) gave the title compound (200 mg, 80 %) as a yellow oil. ^1H NMR ($\text{DMSO}-d_6$): δ 1.16 – 1.22 (3H, m), 1.40 (9H, s), 1.50 – 1.57 (2H, m), 1.62 – 1.69 (2H, m), 2.00 – 2.09 (2H, m), 2.19 (3H, s), 2.36 – 2.44 (2H, m), 2.60 – 2.68 (2H, m), 3.18 – 3.27 (2H, m), 3.32 – 3.41 (4H, m), 4.01 – 4.13 (2H, m), 4.72 – 4.89 (2H, m), 6.69 (1H, d), 7.16 – 7.26 (2H, m); m/z (ES^+) $[\text{M}+\text{H}]^+ = 488$.

Intermediate 91c:

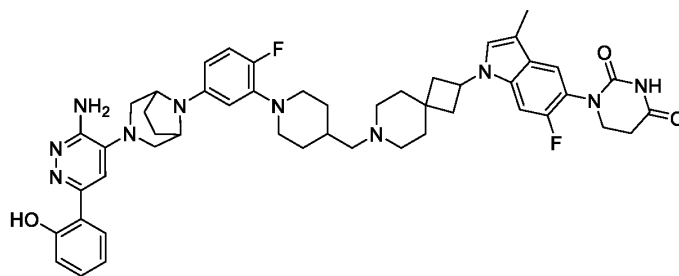
tert-Butyl 2-[5-(2,4-dioxohexahydropyrimidin-1-yl)-6-fluoro-3-methyl-indol-1-yl]-7-azaspiro[3.5]nonane-7-carboxylate



[1723] Potassium cyanate (59.9 mg, 0.74 mmol) was added to Intermediate 91b (180 mg, 0.37 mmol) in DCM (2 mL) and acetic acid (2 mL). The resulting mixture was stirred at r.t. for 2 h. The reaction mixture was poured into sat. aq. NH_4Cl (10 mL), extracted with DCM (3 x 5 mL), the organic layer was dried over Na_2SO_4 , filtered and evaporated. To the crude product was added NaOH (29.5 mg, 0.74 mmol) and EtOH (4 mL). The resulting mixture was stirred at r.t. for 2 h. The reaction mixture was poured into sat. aq. NH_4Cl (20 mL), extracted with EtOAc (3 x 20 mL), the organic layer was dried over Na_2SO_4 , filtered, and evaporated. Purification by FSC (elution gradient: 0 to 30% EtOAc in petroleum ether then 0 to 6% MeOH in DCM) gave the title compound (70.0 mg, 39.1 %) as a white solid. ^1H NMR ($\text{DMSO}-d_6$): δ 1.40 (9H, s), 1.51 – 1.60 (2H, m), 1.64 – 1.71 (2H, m), 2.05 – 2.14 (2H, m), 2.24 (3H, s), 2.40 – 2.48 (2H, m), 2.68 –

2.78 (2H, m), 3.20 – 3.27 (2H, m), 3.33 – 3.39 (2H, m), 3.65 – 3.74 (2H, m), 4.90 – 5.03 (1H, m), 7.40 – 7.46 (2H, m), 7.49 (1H, d), 10.39 (1H, s); m/z (ES^+); m/z (ES^+) $[M-tBu+H]^+ = 429$.

1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-6-fluoro-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione

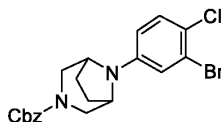


[1724] Prepared in an analogous manner to Example 86 starting from Intermediate 91c (60 mg, 0.12 mmol) and Intermediate 11g (90 mg, 0.16 mmol). Purification by RPC (elution gradient: 62% to 80% MeCN in water with 10 mmol/L NH_4HCO_3 + 0.1% NH_3H_2O) gave the title compound (25 mg, 25 %) as a white solid. 1H NMR ($DMSO-d_6$): δ 1.17 – 1.31 (3H, m), 1.62 (3H, s), 1.70 – 1.82 (4H, m), 1.89 – 1.99 (2H, m), 2.01 – 2.09 (2H, m), 2.09 – 2.17 (4H, m), 2.24 (4H, s), 2.31 – 2.45 (4H, m), 2.58 – 2.68 (2H, m), 2.70 – 2.78 (2H, m), 3.10 (2H, d), 3.25 (2H, d), 3.34 – 3.40 (2H, m), 3.65 – 3.75 (2H, m), 4.34 (2H, s), 4.86 – 5.00 (1H, m), 5.95 (2H, s), 6.38 – 6.51 (2H, m), 6.81 – 6.98 (3H, m), 7.18 – 7.26 (1H, m), 7.38 – 7.54 (4H, m), 7.88 – 7.93 (1H, m), 10.39 (1H, s), 14.18 (1H, s); ^{19}F NMR ($DMSO-d_6$): δ -129.64, -136.40; m/z (ES^+) $[M+H]^+ = 871$.

Example 92

Intermediate 92a:

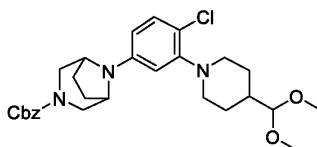
Benzyl 8-(3-bromo-4-chloro-phenyl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



[1725] A flask was charged with $NaOtBu$ (0.606 g, 6.30 mmol), *rac*-BINAP (0.785 g, 1.26 mmol), benzyl (1*R*,5*S*)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (1.552 g, 6.30 mmol), 2-bromo-1-chloro-4-iodobenzene (2 g, 6.30 mmol) and $Pd_2(dba)_3$ (0.577 g, 0.63 mmol) in toluene (20 mL) under nitrogen. The resulting mixture was stirred at 50 °C for 16 h. The reaction mixture was diluted with EtOAc (50 mL) and washed sequentially with sat. aq. $NaHCO_3$ (100 mL) and brine (100 mL). The organic layer was dried over Na_2SO_4 , filtered, and evaporated. Purified by FSC (elution gradient: 0 to 20% EtOAc in petroleum ether) gave the title compound (1.0g, 36.4 %) as a brown oil. 1H NMR ($DMSO-d_6$): δ 1.68 (2H, t), 1.91 (2H, td), 3.13 (2H, dd), 3.49 – 3.70 (2H, m), 4.25 – 4.42 (2H, m), 5.08 (2H, d), 6.90 (1H, dd), 7.23 (1H, d), 7.28 – 7.42 (6H, m); m/z (ES^+) $[M+H]^+ = 435$.

Intermediate 92b:

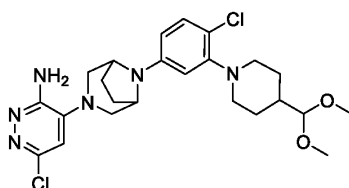
Benzyl 8-[4-chloro-3-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



[1726] A flask was charged with Cs_2CO_3 (2.243 g, 6.88 mmol), 4-(dimethoxymethyl)piperidine (0.365 g, 2.29 mmol), Intermediate 92a, (1 g, 2.29 mmol), Ruphos (0.107 g, 0.23 mmol), and RuphosPd G3 (0.192 g, 0.23 mmol) in 1,4-dioxane (10 mL) under nitrogen. The resulting mixture was stirred at 80 °C for 16 h. The reaction mixture was diluted with EtOAc and the solvent was removed under reduced pressure. Purification by RPC (elution gradient: 0 to 60% MeCN in water with 0.04% NH_4HCO_3) gave the title compound (0.500 g, 42.4 %) as a brown solid. ^1H NMR ($\text{DMSO}-d_6$): δ 1.38 (2H, qd), 1.61 – 1.76 (6H, m), 1.85 – 1.94 (2H, m), 3.11 (1H, d), 3.28 (10H, s), 3.59 (2H, d), 4.12 (1H, d), 4.28 (2H, d), 5.07 (2H, d), 6.46 – 6.57 (2H, m), 7.14 (1H, d), 7.28 – 7.42 (5H, m); m/z (ES^+) $[\text{M}+\text{H}]^+ = 514$.

Intermediate 92c:

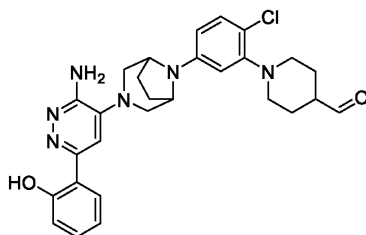
6-Chloro-4-[8-[4-chloro-3-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-amine



[1727] A vial was charged with Intermediate 92b (0.5 g, 0.97 mmol) and 10% Pd/C (0.058 g, 0.49 mmol) in DCM (10 mL) under hydrogen. The resulting mixture was stirred at r.t for 16 h. The reaction mixture was filtered through celite®, and filtrate was concentrated. The white solid (0.30 g) was dissolved in DMSO (3 mL) and then DIPEA (0.510 mL, 2.92 mmol) and 4-bromo-6-chloropyridazin-3-amine (223 mg, 107 mmol) were added under nitrogen. The resulting mixture was stirred at 100 °C for 16 h. The reaction mixture was diluted with DCM (50 mL) and washed sequentially with water (10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 , filtered, and evaporated. Purification by FSC (elution gradient: 0 to 10% MeOH in DCM) gave the title compound (0.170 g, 42.4 %) as a white solid. ^1H NMR ($\text{DMSO}-d_6$): δ 1.18 (1H, t), 1.24 (1H, s), 1.39 (2H, qd), 1.64 – 1.76 (3H, m), 1.88 – 1.96 (2H, m), 2.11 (2H, q), 2.58 (2H, td), 2.94 (2H, d), 3.12 – 3.20 (2H, m), 3.27 – 3.38 (6H, m), 4.13 (1H, d), 4.36 (2H, t), 5.82 (2H, s), 6.50 – 6.57 (2H, m), 6.88 (1H, s), 7.14 (1H, d); m/z (ES^+) $[\text{M}+\text{H}]^+ = 507$.

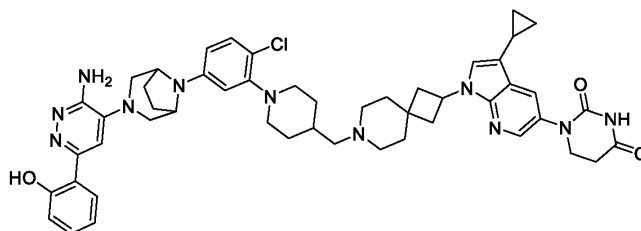
Intermediate 92d:

1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-chlorophenyl]piperidine-4-carbaldehyde



[1728] A vial was charged with Pd(dppf)Cl² (0.029 g, 0.04 mmol) (2-hydroxyphenyl)boronic acid (0.065 g, 0.47 mmol), Cs₂CO₃ (0.385 g, 1.18 mmol) and Intermediate 92c (0.17 g, 0.39 mmol) in water (0.50 mL) and 1,4-dioxane (5 mL) under nitrogen. The resulting mixture was stirred at 80 °C for 4 h. The solvent was removed under reduced pressure. Purification by FSC (elution gradient: 0 to 80% EtOAc in petroleum ether) and concentration of the product containing fractions give a brown solid. The brown solid was dissolved in formic acid (0.5 mL). The resulting mixture was stirred at 40 °C for 1 h. The solvent was evaporated to dryness to afford the title compound (0.060 g, 34.5 %) as a white solid. The product was used in the next step directly without further purification. *m/z* (ES⁺) [M+H]⁺ = 519.

1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3-azabicyclo[3.2.1]octan-8-yl]-2-chloro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione

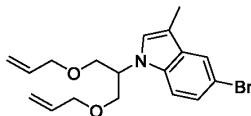


[1729] A vial was charged with Intermediate 92d (52.8 mg, 0.10 mmol) and Intermediate 2c (40 mg, 0.10 mmol), DCE (1 mL), and NMP (1.0 mL). The resulting solution was stirred at 40 °C for 0.5 h. Then, Na(OAc)₃BH (129 mg, 0.61 mmol) was added and stirred at r.t. for 1 h. The reaction mixture was diluted with DCE (20 mL) and washed sequentially with sat. aq. NaHCO₃ (5 mL), and brine (5 mL). The organic layer was separated, dried over Na₂SO₄, filtered and evaporated. Purification by preparative HPLC (Mobile Phase A: water with 10 mmol/L NH₄HCO₃ + 0.05% NH₃H₂O, Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 65% B to 90% B) gave the title compound (5.09 mg, 5.47 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 0.62 – 0.72 (2H, m), 0.81 – 0.91 (2H, m), 1.25 (3H, d), 1.71 (5H, s), 1.74 – 1.83 (2H, m), 1.88 – 2.01 (3H, m), 2.17 (4H, dd), 2.22 (2H, d), 2.28 – 2.40 (5H, m), 2.62 (2H, t), 2.76 (2H, t), 3.09 (2H, d), 3.28 (4H, d), 3.81 (2H, t), 4.41 (2H, s), 5.25 (1H, p), 5.97 (2H, s), 6.52 – 6.61 (2H, m), 6.81 – 6.90 (2H, m), 7.15 (1H, d), 7.23 (1H, td), 7.47 (1H, s), 7.56 (1H, s), 7.87 – 7.97 (2H, m), 8.17 (1H, d), 10.40 (1H, s), 14.20 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 896.

EXAMPLE 93

Intermediate 93a:

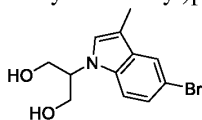
1-[2-Allyloxy-1-(allyloxymethyl)ethyl]-5-bromo-3-methyl-indole



[1730] Prepared in an analogous manner to Intermediate 64a using 5-bromo-3-methyl-1*H*-indole (15.0 g, 71.4 mmol) and 1,3-bis(allyloxy)propan-2-ol (18.5 g, 107.1 mmol), stirring at 100 °C or 16 h. Purification by FSC (elution gradient: 0 to 100% DCM in petroleum ether) gave the title compound (18.0 g, 69%) as a yellow liquid. ¹H NMR (DMSO-*d*₆): δ 2.22 (3H, d), 3.73 – 3.79 (4H, m), 3.88 – 3.93 (4H, m), 4.79 (1H, p), 5.08 – 5.12 (2H, m), 5.13 – 5.18 (2H, m), 5.73 – 5.84 (2H, m), 7.19 – 7.22 (1H, m), 7.30 (1H, d), 7.46 (1H, d), 7.65 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 363.9.

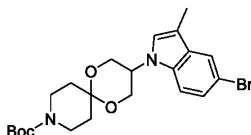
Intermediate 93b:

2-(5-Bromo-3-methyl-indol-1-yl)propane-1,3-diol



[1731] Tetrakis(triphenylphosphine)palladium(0) (2.86 g, 2.47 mmol) was added to Intermediate 93a (18.0 g, 49.4 mmol) and 1,3-dimethylbarbituric acid (15.4 g, 98.8 mmol) in MeOH (50 mL) under nitrogen. The resulting mixture was stirred at r.t. for 16 h and concentrated under reduced pressure. Purification by RPC (elution gradient: 5 to 100% MeCN in water with 0.1% NH₄HCO₃) gave the title compound (9.40 g, 66%) as a yellow gum. ¹H NMR (DMSO-*d*₆): δ 2.24 (3H, d), 3.69 – 3.83 (4H, m), 4.37 – 4.45 (1H, m), 4.88 (2H, t), 7.19 – 7.23 (1H, m), 7.30 (1H, d), 7.41 (1H, d), 7.65 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 283.9.

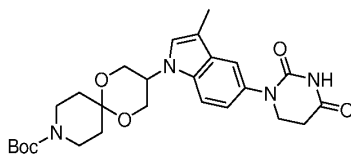
Intermediate 93c:

tert-Butyl 3-(5-bromo-3-methyl-indol-1-yl)-1,5-dioxo-9-azaspiro[5.5]undecane-9-carboxylate

[1732] Pyridinium *p*-toluenesulfonate (0.354 g, 1.41 mmol) was added to 93b (1 g, 3.52 mmol) and *tert*-butyl 4-oxopiperidine-1-carboxylate (2.104 g, 10.56 mmol) in toluene (10 mL) at 25 °C under nitrogen. The resulting mixture was stirred at 100 °C for 2 days. The solvent was removed under reduced pressure. Purification by RPC (elution gradient: 5 to 100% MeCN in water 0.1% NH₄HCO₃) gave the title compound (0.700 g, 42 %) as a yellow solid. ¹H NMR (DMSO-*d*₆): δ 1.41 (9H, s), 1.84 (2H, t), 1.93 (2H, t), 2.25 (3H, d), 3.34 – 3.41 (4H, m), 3.93 – 4.01 (2H, m), 4.24 – 4.31 (2H, m), 4.51 – 4.57 (1H, m), 7.21 – 7.25 (1H, m), 7.45 (1H, d), 7.59 – 7.61 (1H, m), 7.68 (1H, d); *m/z* (ES⁺) [M-*t*Bu+H]⁺ = 408.9.

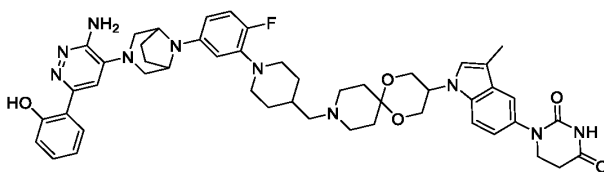
Intermediate 93d:

tert-Butyl 3-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-indol-1-yl]-1,5-dioxo-9-azaspiro[5.5]undecane-9-carboxylate



[1733] Prepared in an analogous manner to Intermediate 4b starting from Intermediate 93c (620 mg, 1.33 mmol). Purification by FSC (elution gradient: 0-10% MeOH in DCM) gave the title compound (488 mg, 73 %) as a yellow solid. ¹H NMR (DMSO-*d*₆): δ 1.42 (9H, s), 1.84-1.95 (4H, m), 2.26 (3H, s), 2.73 (2H, t), 3.34 – 3.42 (4H, m), 3.78 (2H, t), 3.96 – 4.03 (2H, m), 4.20 – 4.31 (2H, m), 4.50 – 4.60 (1H, m), 7.05 – 7.11 (1H, m), 7.39 – 7.50 (2H, m), 7.58 (1H, s), 10.27 (1H, s); *m/z* (ES⁺), [M-*t*Bu+H]⁺ = 443.1.

1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione

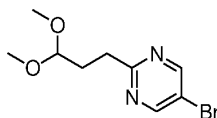


[1734] TFA (0.300 mL) was added to Intermediate 93d (100 mg, 0.20 mmol) in DCM (1.0 mL). The resulting mixture was stirred at r.t for 1 h. The solvent was removed under reduced pressure gave the intermediate deprotected amine. Formic acid (1.0 mL) was added to Intermediate 11g (127 mg, 0.20 mmol) at r.t. The resulting mixture was stirred at 40 °C for 20 min. The solvent was removed under reduced pressure. The reaction mixture was diluted with DCM (5 mL) and washed sequentially with sat. aq. NaHCO₃ (5 mL). The organic layer was separated, dried over Na₂SO₄, filtered and concentrated. To the residue was added intermediate deprotected amine arising from Intermediate 93d and DCE (0.50 mL) and NMP (0.50 mL). The resulting mixture was stirred at 40 °C for 40 min then sodium triacetoxyborohydride (170 mg, 0.80 mmol) was added. The resulting mixture was stirred at r.t. for 16 h. The reaction mixture was diluted with DCM and IPA (3:1, 15 mL), and washed with sat. aq. NaHCO₃ (10 mL). The organic layer was separated, dried over Na₂SO₄, filtered and concentrated. Purification by RPC (elution gradient: 5 to 100% MeCN in water (0.1% NH₄HCO₃)) and lyophilization gave the title compound (16.0 mg, 8.8 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.20 – 1.31 (2H, m), 1.54 – 1.67 (1H, m), 1.73 – 1.83 (2H, m), 1.85 – 2.05 (6H, m), 2.11 – 2.16 (2H, m), 2.21 (2H, d), 2.26 (3H, s), 2.41 (4H, s), 2.59 – 2.69 (2H, m), 2.69 – 2.77 (2H, m), 3.11 (2H, d), 3.26 (2H, d), 3.36 (2H, d), 3.73 – 3.82 (2H, m), 3.92 – 4.01 (2H, m), 4.18 – 4.30 (2H, m), 4.30 – 4.41 (2H, m), 4.47 – 4.57 (1H, m), 5.95 (2H, s), 6.39 – 6.51 (2H, m), 6.82 – 6.98 (3H, m), 7.05 – 7.10 (1H, m), 7.20 – 7.27 (1H, m), 7.40 – 7.50 (3H, m), 7.60 (1H, s), 7.91 (1H, d), 10.27 (1H, s), 14.20 (1H, s); ¹⁹F NMR (DMSO-*d*₆) δ-136.38; *m/z* (ES⁺) [M+H]⁺ = 885.4.

EXAMPLE 94

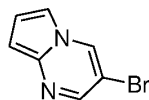
Intermediate 94a:

5-Bromo-2-(3,3-dimethoxypropyl)pyrimidine



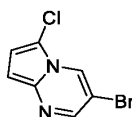
[1735] Iodine (5.55 g, 21.85 mmol) was added to zinc (14.29 g, 218.53 mmol) in DMF (30 mL) at r.t. under nitrogen. The resulting mixture was stirred at r.t. for 15 min, then 3-bromo-1,1-dimethoxypropane (20 g, 109.26 mmol) in DMF (70 mL) was added. The resulting mixture was stirred at 80 °C for 4 h. The reaction mixture was filtered and the filtrate was collected. To the filtrate was added 5-bromo-2-iodopyrimidine (34.2 g, 120.19 mmol) and tetrakis(triphenylphosphine)palladium(0) (12.63 g, 10.93 mmol). The resulting mixture was stirred at 80 °C for 12 h. The solvent was removed under reduced pressure. Purification by FSC (elution gradient: 0 to 100% EtOAc in petroleum ether) gave the title compound (10.90 g, 38%) as a colorless oil. ¹H NMR (CDCl₃): δ 2.05 – 2.24 (2H, m), 2.92 – 3.05 (2H, m), 3.32 (6H, s), 4.45 (1H, t), 8.69 (2H, s); *m/z* (ES⁺) [M+H]⁺ = 261.0.

Intermediate 94b:

3-Bromopyrrolo[1,2-*a*]pyrimidine

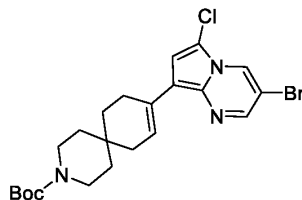
[1736] Formic acid (2 mL, 52.15 mmol) was added to Intermediate 94a (10 g, 38.30 mmol). The resulting mixture was stirred at r.t. for 30 min. The solvent was removed under reduced pressure. The residue was diluted with DCM (100 mL) and washed with sat. aq. NaHCO₃ (50 mL) and brine (50 mL). The organic layer was dried over Na₂SO₄, filtered, and evaporated. To the residue was added burgess reagent (36.5 g, 153.19 mmol) in THF (100 mL) under nitrogen. The resulting mixture was stirred at r.t. for 20 min. The solvent was removed under reduced pressure. Purification by FSC (elution gradient: 0 to 20% EtOAc in petroleum ether) gave the title compound (1.6 g, 21 %) as a yellow solid. ¹H NMR (CDCl₃): δ 6.61 – 6.73 (1H, m), 6.95 – 7.01 (1H, m), 7.16 – 7.23 (1H, m), 8.06 (1H, d), 8.31 – 8.36 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 197.0.

Intermediate 94c:

3-Bromo-6-chloro-pyrrolo[1,2-*a*]pyrimidine

[1737] NCS (1.084 g, 8.12 mmol) was added to Intermediate 94b (1.6 g, 8.12 mmol) in THF (10 mL). The resulting mixture was stirred at -10 °C for 20 min. The solvent was removed under reduced pressure. Purification by FSC (elution gradient: 0 to 30% EtOAc in petroleum ether) gave the title compound (0.430 g, 22.9 %) as a yellow solid. ¹H NMR (CDCl₃): δ 6.70 – 6.74 (1H, m), 6.92 (1H, d), 8.09 (1H, d), 8.33 – 8.38 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 230.9.

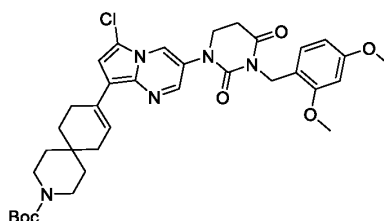
Intermediate 94d:

tert-Butyl 9-(3-bromo-6-chloro-pyrrolo[1,2-*a*]pyrimidin-8-yl)-3-azaspiro[5.5]undec-9-ene-3-carboxylate

[1738] POCl₃ (0.260 mL, 2.79 mmol) was added to a mixture of Intermediate 94c (430 mg, 1.86 mmol) and *tert*-butyl 9-oxo-3-azaspiro[5.5]undecane-3-carboxylate (993 mg, 3.72 mmol) in DCM (20 mL). The resulting mixture was stirred at r.t. for 16 h. The reaction mixture was diluted with DCM (25 mL) and washed with sat. aq. NaHCO₃ (20 mL) and brine (20 mL). The organic layer was separated, dried over Na₂SO₄, filtered, and evaporated. Purification by FSC (elution gradient: 0 to 30% DCM in petroleum ether) gave the title compound (250 mg, 28 %) as a yellow solid. ¹H NMR (CDCl₃): δ 1.35 – 1.40 (14H, m), 1.60 (2H, t), 2.07 – 2.13 (2H, m), 2.46 – 2.54 (2H, m), 3.22 – 3.33 (2H, m), 3.37 – 3.49 (2H, m), 6.40 – 6.46 (1H, m), 6.81 (1H, s), 7.92 (1H, d), 8.17 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 480.0.

Intermediate 94e:

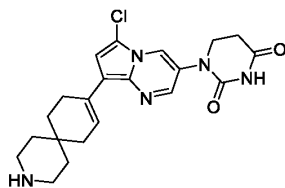
tert-Butyl 9-[6-chloro-3-[3-[(2,4-dimethoxyphenyl)methyl]-2,4-dioxo-hexahydropyrimidin-1-yl]pyrrolo[1,2-*a*]pyrimidin-8-yl]-3-azaspiro[5.5]undec-9-ene-3-carboxylate



[1739] 3-[(2,4-Dimethoxyphenyl)methyl]hexahydropyrimidine-2,4-dione (91 mg, 0.34 mmol) was added to (1*S*,2*S*)-cyclohexane-1,2-diamine (10.69 mg, 0.09 mmol), K₃PO₄ (199 mg, 0.94 mmol), copper(I) iodide (17.82 mg, 0.09 mmol) and Intermediate 94d (150 mg, 0.31 mmol) in dioxane (5 mL) under nitrogen. The resulting mixture was stirred at 90 °C for 16 h. Purification by FSC (elution gradient: 0 to 5% MeOH in DCM) gave the title compound (110 mg, 53 %) as a yellow solid. ¹H NMR (DMSO-*d*₆): δ 1.33 – 1.37 (3H, m), 1.40 (9H, s), 1.61 (2H, t), 2.07 – 2.15 (2H, m), 2.53 – 2.60 (2H, m), 3.26 – 3.31 (2H, m), 3.37 – 3.45 (2H, m), 3.75 (3H, s), 3.81 (3H, s), 3.93 (2H, t), 4.79 (2H, s), 6.43 – 6.52 (2H, m), 6.56 (1H, d), 6.93 (1H, d), 7.20 (1H, s), 8.14 (1H, d), 8.61 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 608.2.

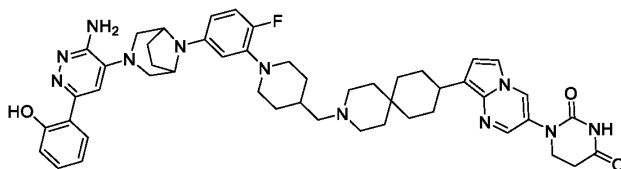
Intermediate 94f:

1-[8-(3-Azaspiro[5.5]undec-9-en-9-yl)-6-chloro-pyrrolo[1,2-*a*]pyrimidin-3-yl]hexahydropyrimidine-2,4-dione



[1740] Methanesulfonic acid (159 mg, 1.66 mmol) was added to Intermediate 94e (110 mg, 0.17 mmol) in TFA (1 mL). The resulting mixture was stirred at 80 °C for 1 h. The solvent was removed under reduced pressure. Purification by RPC (elution gradient: 0 to 50% MeCN in water) gave the title compound (40.0 mg, 58 %) as a yellow solid. ¹H NMR (DMSO-*d*₆): δ 1.37 – 1.44 (4H, m), 1.61 (2H, t), 2.08 – 2.15 (2H, m), 2.53 – 2.59 (2H, m), 2.73 – 2.72 (6H, m), 3.80 – 3.88 (2H, m), 6.44 – 6.49 (1H, m), 7.19 (1H, s), 8.14 (1H, d), 8.56 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 414.2.

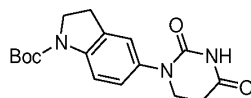
1-[8-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[1,2-*a*]pyrimidin-3-yl]hexahydropyrimidine-2,4-dione



[1741] Pd-C (5 mg, 0.05 mmol) was added to Intermediate 94f (35 mg, 0.08 mmol) in DMF (2.00 mL) under hydrogen. The resulting mixture was stirred at 40 °C for 10 h at r.t. The reaction mixture was filtered through celite®, filtrate was concentrated gave the free amine. Formic acid (1 mL, 26.07 mmol) was added to Intermediate 11g (53.5 mg, 0.08 mmol). The resulting mixture was stirred at 40 °C for 1 h. The solvent was removed under reduced pressure. The reaction mixture was diluted with DCM (5 mL) and washed with sat. aq. NaHCO₃ (2 mL) and brine (2 mL). The organic layer was dried over Na₂SO₄, filtered, and evaporated. To the crude aldehyde was added free amine in DMF (2.00 mL). Sodium triacetoxyborohydride (35.8 mg, 0.17 mmol) was added and the reaction was stirred for 2 h at r.t. The reaction mixture was diluted with DCM (5 mL) and washed with sat. aq. NaHCO₃ (2 mL) and brine (2 mL). The organic layer was dried over Na₂SO₄, filtered, and evaporated. Purification by RPC (elution gradient: 53-74% MeCN in water with 10mmol/L NH₄HCO₃ + 0.05%NH₃H₂O) gave the title compound (0.56 mg, 0.7 %) as a yellow solid. ¹H NMR (DMSO-*d*₆): δ 1.54 – 1.31(6H, m), 1.34 – 1.41 (2H, m), 1.50 – 1.83 (11H, m), 1.91 – 1.98 (2H, m), 2.10 – 2.22 (4H, m), 2.29 – 2.40 (3H, m), 2.64 (3H, t), 2.75 (2H, t), 2.90 – 2.98 (1H, m), 3.10 (2H, d), 3.23 – 3.29 (2H, m), 3.79 (2H, t), 4.31 – 4.38 (2H, m), 5.95 (2H, s), 6.38 – 6.52 (2H, m), 6.84 – 6.97 (4H, m), 7.21 – 7.27 (1H, m), 7.37 (1H, d), 7.47 (1H, s), 7.89 – 7.93 (1H, m), 7.97 (1H, d), 8.63 (1H, d), 10.51 (1H, s), 14.18 (1H, s); ¹⁹F NMR (DMSO-*d*₆): δ -136.38; *m/z* (ES⁺) [M+H]⁺ = 868.4.

EXAMPLE 95

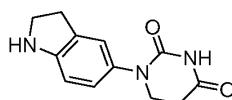
Intermediate 95a:

tert-Butyl 5-(2,4-dioxohexahydropyrimidin-1-yl)indoline-1-carboxylate

[1742] *tert*-Butyl 5-bromoindoline-1-carboxylate (3 g, 10.06 mmol) was added to hexahydropyrimidine-2,4-dione (2.296 g, 20.12 mmol), Cs₂CO₃ (9.83 g, 30.18 mmol), GPhos (0.378 g, 0.70 mmol) and GPhos Pd G6 (0.665 g, 0.70 mmol) in 1,4-dioxane (30 mL) under nitrogen. The resulting mixture was stirred at 100 °C for 2 h. The reaction mixture was concentrated. The residue was dissolved in DCM (100 mL), and washed with sat. aq. K₂CO₃ (75 mL). The organic layer was separated, dried over Na₂SO₄, filtered, and evaporated. Purification by FSC (elution gradient: 0 to 50% EtOAc in petroleum ether, then 0 to 5% MeOH in DCM) gave the title compound (1.8 g, 54 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.49 – 1.54 (9H, s), 2.67 – 2.71 (2H, t), 3.04 – 3.09 (2H, t), 3.69 – 3.73 (2H, t), 3.90 – 3.96 (2H, t), 7.06 – 7.09 (1H, m), 7.17 (1H, d), 7.47 – 7.69 (1H, m), 10.31 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 331.9.

Intermediate 95b:

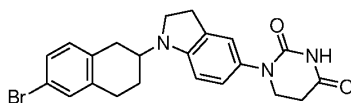
1-Indolin-5-ylhexahydropyrimidine-2,4-dione



[1743] *p*-Toluenesulfonic acid (1.122 g, 6.52 mmol) was added to Intermediate 95a (1.8 g, 5.43 mmol) in MeOH (15 mL). The resulting mixture was stirred at r.t. for 1 h. The solvent was removed under reduced pressure. Purification by FSC (elution gradient: 5 to 40% MeCN in water with 0.1% NH₄HCO₃) gave the title compound (800 mg, 63 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 2.64 – 2.68 (2H, t), 2.88 – 2.93 (2H, t), 3.41 – 3.45 (2H, t), 3.64 (2H, t), 5.53 (1H, s), 6.47 (1H, d), 6.80 – 6.83 (1H, m), 6.96 (1H, d), 10.20 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 232.1.

Intermediate 95c:

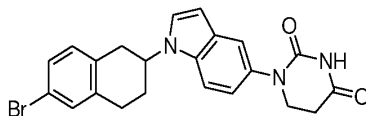
1-[1-(6-Bromotetralin-2-yl)indolin-5-yl]hexahydropyrimidine-2,4-dione



[1744] 6-Bromo-3,4-dihydronaphthalen-2(1*H*)-one (759 mg, 3.37 mmol) was added to Intermediate 95b (780 mg, 3.37 mmol) in acetic acid (7 mL). The resulting mixture was stirred at r.t. for 10 min. Then sodium triacetoxyborohydride (2145 mg, 10.12 mmol) was added and stirred for 30 min. The reaction mixture was evaporated. The residue was dissolved in DCM (75 mL) and washed with sat. aq. NaHCO₃ (50 mL). The organic layer was separated, dried over Na₂SO₄, filtered, and evaporated to afford the title compound (1.0 g mg, 67 %) as a brown solid. The product was used in the next step directly without further purification. *m/z* (ES⁺) [M+H]⁺ = 440.1.

Intermediate 95d:

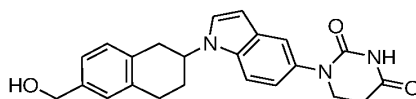
1-[1-(6-Bromotetralin-2-yl)indol-5-yl]hexahydropyrimidine-2,4-dione



[1745] Manganese(IV) oxide (1.974 g, 22.71 mmol) was added to a stirred solution of Intermediate 95c (1 g, 2.27 mmol) in DCM (10 mL). The resulting mixture was stirred at r.t. for 2 h. The reaction mixture was filtered, filtrate was concentrated to afford the title compound (0.830 g, 83 %) as a brown solid. m/z (ES^+) $[M+H]^+ = 438.0$.

Intermediate 95e:

1-[1-[6-(Hydroxymethyl)tetralin-2-yl]indol-5-yl]hexahydropyrimidine-2,4-dione

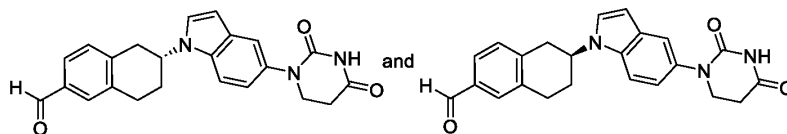


[1746] XPhos Pd G2 (0.090 g, 0.11 mmol) was added to Intermediate 95d (1g, 2.28 mmol) and (tributylstannyl)methanol (0.366 g, 1.14 mmol) in 1,4-dioxane (10 mL) under nitrogen. The resulting mixture was stirred at 80 °C for 16 h. The reaction was quenched with sat. aq. KF solution (20 mL). The mixture was extracted with EtOAc (3 x 20 mL), The organic layer was dried over Na_2SO_4 , filtered and concentrated. Purification by FSC (elution gradient: 0 to 50% EtOAc in petroleum ether, then 0 to 5% EtOH in DCM) gave the title compound (0.430 g, 48 %) as a white solid. 1H NMR (DMSO- d_6) δ 2.13 – 2.19 (1H, m), 2.22 – 2.30 (1H, m), 2.71 – 2.75 (2H, m), 2.85 – 2.91 (1H, m), 3.02 – 3.10 (1H, m), 3.19 (2H, d), 3.77 (2H, t), 4.48 (2H, d), 4.82 – 4.89 (1H, m), 5.13 (1H, t), 6.49 (1H, d), 7.08 – 7.13 (4H, m), 7.49 (1H, d), 7.52 (1H, d), 7.60 (1H, d), 10.29 (1H, s); m/z (ES^+) $[M+H]^+ = 390.0$.

Intermediate 95f and Intermediate 95g:

(2*R*)-2-[5-(2,4-Dioxohexahydropyrimidin-1-yl)indol-1-yl]tetralin-6-carbaldehyde

and

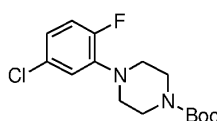
(2*S*)-2-[5-(2,4-Dioxohexahydropyrimidin-1-yl)indol-1-yl]tetralin-6-carbaldehyde

[1747] MnO_2 (938mg, 10.78 mmol) was added to Intermediate 95e (420 mg, 1.08 mmol) in DCM (5 mL) at r.t. The resulting mixture was stirred at r.t for 2 h. The mixture was filtered, and filtrate was concentrated. Purification by Prep-Chiral HPLC (Column: CHIRALPAK SB 2x25 cm, 5 μm ; Mobile Phase A: MTBE (0.5% 2M NH_3 -MeOH), Mobile Phase B: EtOH; Flow rate: 20 mL/min; Gradient: isocratic 30% Mobile Phase A and 70% Mobile Phase B; wavelength: 220/254 nm; RT1: 14.16 min; RT2: 18.935 min; Sample Solvent: EtOH) separated the enantiomers. Intermediate 95f, which eluted first off the column (40.0 mg, 9 %) was obtained as a grey solid (ee=100%, *absolute configuration not yet confirmed). 1H NMR

(DMSO-*d*₆): δ 2.18 – 2.22 (1H, m), 2.28 – 2.35 (1H, m), 2.74 (2H, t), 3.01 – 3.06 (1H, m), 3.12 – 3.20 (1H, m), 3.28 – 3.32 (2H, m), 3.79 (2H, t), 4.91 – 4.97 (1H, m), 6.51 (1H, d), 7.08 – 7.11 (1H, m), 7.39 (1H, d), 7.49 (1H, d), 7.55 (1H, d), 7.63 (1H, d), 7.69 – 7.72 (1H, m), 7.75 (1H, d), 9.98 (1H, s), 10.28 (1H, s); m/z (ES⁺) [M+H]⁺ = 388.1. Intermediate 95g, which eluted second off the column (60.0 mg, 14 %) was obtained as a grey solid (ee=97.5%, *absolute configuration not yet confirmed). ¹H NMR (DMSO-*d*₆): δ 2.17 – 2.24 (1H, m), 2.28 – 2.36 (1H, m), 2.70 – 2.76 (3H, m), 3.01 – 3.06 (1H, m), 3.13 – 3.20 (2H, m), 3.79 (2H, t), 4.91 – 4.97 (1H, m), 6.51 (1H, d), 7.09 (1H, d), 7.39 (1H, d), 7.49 (1H, s), 7.55 (1H, d), 7.63 (1H, d), 7.69 – 7.72 (1H, m), 7.75 (1H, s), 9.98 (1H, s), 10.28 (1H, s); m/z (ES⁺) [M+H]⁺ = 388.15.

Intermediate 95h:

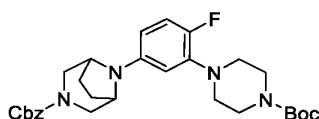
tert-Butyl 4-(5-chloro-2-fluoro-phenyl)piperazine-1-carboxylate



[1748] NaOtBu (5.51 g, 57.29 mmol) was added to *tert*-butyl 1-piperazinecarboxylate (3.56 g, 19.10 mmol), 2-bromo-4-chloro-1-fluorobenzene (4 g, 19.10 mmol), Pd₂dba₃ (0.874 g, 0.95 mmol) and BINAP (1.189 g, 1.91 mmol) in toluene (40 mL). The resulting mixture was stirred at 50 °C for 20 h under nitrogen. The reaction mixture was poured into water (250 mL), extracted with EtOAc (3 x 250 mL), the organic layer was dried over Na₂SO₄, filtered and evaporated. Purification by FSC (elution gradient: 0 to 40% EtOAc in petroleum ether) gave the title compound (5.30 g, 88 %) as a yellow solid. ¹H NMR (DMSO-*d*₆): δ 1.43 (9H, s), 2.96–3.01 (4H, m), 3.44–3.49 (4H, m), 7–7.08 (2H, m), 7.19–7.22 (1H, m); m/z (ES⁺) [M+H]⁺ = 315.2.

Intermediate 95i:

Benzyl 8-[3-(4-*tert*-butoxycarbonylpiperazin-1-yl)-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate

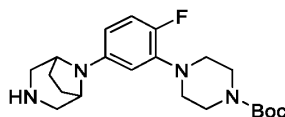


[1749] Benzyl 3,8-diazabicyclo[3.2.1]octane-3-carboxylate (0.939 g, 3.81 mmol) was added to Intermediate 95h (1 g, 3.18 mmol), Ruphos Pd G3 (0.266 g, 0.32 mmol), RuPhos (0.148 g, 0.32 mmol), and Cs₂CO₃ (3.11 g, 9.53 mmol) in 1,4-dioxane (20 mL) under nitrogen. The resulting mixture was stirred at 100 °C for 18 h. The reaction mixture was concentrated and diluted with EtOAc (150 mL) and washed with sat. aq. NH₄Cl (150 mL). The organic layer was dried over Na₂SO₄, filtered, and evaporated. Purification by FSC (elution gradient: 0 to 60% EtOAc in petroleum ether) gave the title compound (1.40 g, 84 %) as a yellow liquid. ¹H NMR (DMSO-*d*₆): δ 1.42 (9H, s), 1.63 – 1.68 (2H, m), 1.87 – 1.92 (2H, m), 2.92 – 2.95 (4H, m), 3.09 – 3.12 (1H, m), 3.22 – 3.25 (1H, m), 3.41 – 3.48 (4H, m), 3.55 – 3.60 (2H, m), 4.23 – 4.27

(2H, m), 5.05 – 5.09 (2H, m), 6.42–6.47 (2H, m), 6.93–6.98 (1H, m), 7.32–7.39 (5H, m); m/z (ES^+) $[M+H]^+ = 525.4$.

Intermediate 95j:

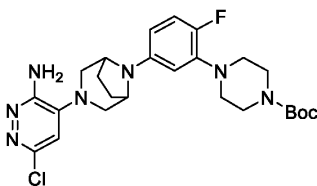
tert-Butyl 4-[5-(3,8-diazabicyclo[3.2.1]octan-8-yl)-2-fluoro-phenyl]piperazine-1-carboxylate



[1750] 10% Pd/C (200 mg, 0.19 mmol) was added to Intermediate 95i (1.3g, 2.48 mmol) in MeOH (50 mL) under hydrogen. The resulting mixture was stirred at r.t. for 18 h. The reaction mixture was filtered through celite®, filtrate was concentrated to give the title compound (0.870 g, 90 %) as a yellow liquid. 1H NMR ($DMSO-d_6$): δ 1.42 (9H, s), 1.78 – 1.95 (4H, m), 2.35 – 2.42 (2H, m), 2.89 – 2.99 (6H, m), 3.41 – 4.50 (4H, m), 3.98 – 4.07 (2H, m), 6.28–6.41 (2H, m), 6.87–6.96 (1H, m); m/z (ES^+) $[M+H]^+ = 391.1$.

Intermediate 95k:

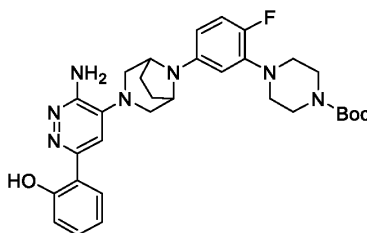
tert-Butyl 4-[5-[3-(3-amino-6-chloro-pyridazin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]piperazine-1-carboxylate



[1751] 4-bromo-6-chloropyridazin-3-amine (499 mg, 2.39 mmol) was added to Intermediate 95j (850 mg, 2.18 mmol) and DIPEA (1.141 mL, 6.53 mmol) in DMSO (10 mL) under nitrogen. The resulting mixture was stirred at 100 °C for 24 h. The reaction mixture was diluted with EtOAc (125 mL) and washed with sat. aq. NH_4Cl (125 mL), organic layer was dried over Na_2SO_4 , filtered, and evaporated. Purification by FSC (elution gradient: 0 to 20% EtOAc in petroleum ether, then 0 to 10% MeOH in DCM) gave the title compound (930 mg, 82 %) as a yellow solid. 1H NMR ($DMSO-d_6$): δ 1.40 (9H, s), 1.88 – 2.02 (2H, m), 2.07 – 2.11 (2H, m), 2.88 – 2.98 (6H, m), 3.11 – 3.16 (2H, m), 3.27 – 3.33 (4H, m), 4.29 – 4.34 (2H, m), 5.80 (2H, s), 6.4–6.49 (2H, m), 6.85 (1H, s), 6.88–7.0 (1H, m); m/z (ES^+) $[M+H]^+ = 518.3$.

Intermediate 95l:

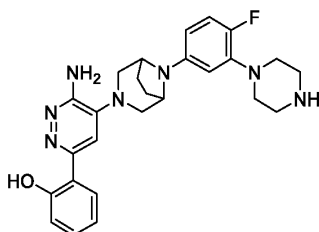
tert-Butyl 4-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]piperazine-1-carboxylate



[1752] Prepared in an analogous method to Intermediate 6f starting from Intermediate 95k (910 mg, 1.76 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in petroleum ether) gave the title compound (620 mg, 61%) as a yellow solid. ¹H NMR (DMSO-*d*₆): δ 1.42 (9H, s), 1.91 – 1.96 (2H, m), 2.11 – 2.17 (2H, m), 2.92–3.01 (4H, m), 3.09 – 3.12 (2H, m), 3.22 – 3.27 (2H, m), 3.43 – 3.51 (4H, m), 4.35 – 4.40 (2H, m), 5.96 (2H, s), 6.45–6.52 (2H, m), 6.82–6.9 (2H, m), 6.94–7.0 (1H, m), 7.19–7.26 (1H, m), 7.46 (1H, s), 7.87–7.93 (1H, m), 14.18 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 576.3.

Intermediate 95m:

2-[6-Amino-5-[8-(4-fluoro-3-piperazin-1-yl-phenyl)-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-yl]phenol

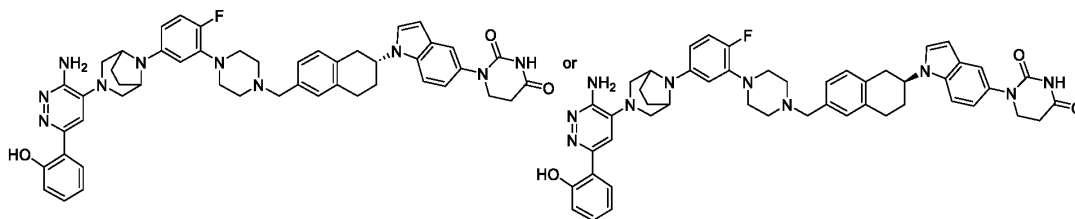


[1753] 4M HCl in 1,4-dioxane (20 mL, 80 mmol) was added to Intermediate 95l (600 mg, 1.04 mmol). The resulting mixture was stirred at r.t. for 1 h. The solvent was removed under reduced pressure. The reaction mixture was diluted with petroleum ether. The solid was collected and dried to afford the title compound (400 mg, 81 %) as a yellow solid. The product was used in the next step directly without further purification. ¹H NMR (DMSO-*d*₆): δ 1.90 – 2.08 (4H, m), 3.14 – 3.29 (8H, m), 3.31 – 3.40 (2H, m), 4.01 – 4.05 (2H, m), 4.39 – 4.45 (2H, m), 6.53 – 6.56 (2H, m), 6.94 – 7.07 (2H, m), 7.12 (1H, d), 7.34 – 7.48 (2H, m), 7.50 (1H, d), 9.38 (2H, s), 14.74 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 476.2.

1-[1-[(2*S*)-6-[4-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]piperazin-1-yl]methyl]tetralin-2-yl]indol-5-yl]hexahydropyrimidine-2,4-dione

or

1-[1-[(2*R*)-6-[4-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]piperazin-1-yl]methyl]tetralin-2-yl]indol-5-yl]hexahydropyrimidine-2,4-dione



[1754] Sodium triacetoxyborohydride (32.8 mg, 0.15 mmol) was added to a stirred solution of Intermediate 95f (20 mg, 0.05 mmol) and Intermediate 95m (49.1 mg, 0.10 mmol) in DMF (2 mL). The resulting mixture was stirred at r.t. for 5 h. The reaction mixture was diluted with DCM (10 mL) and washed with sat. aq. Na₂CO₃ (5 mL). The organic layer was dried over Na₂SO₄, filtered, and evaporated. Purification

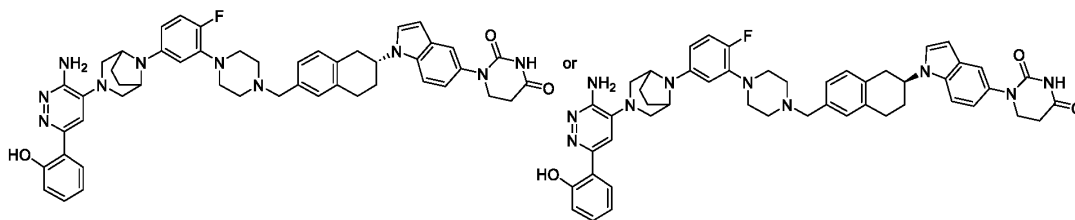
by preparative HPLC (Xbridge Prep Shield RP18 OBD, 30 x 150 mm, 5 μ m; Mobile Phase A: water (with 10 mmol/L NH_4HCO_3 + 0.05% $\text{NH}_3\text{H}_2\text{O}$); Mobile Phase B: ACN, gradient: 57% B to 70% B) gave the title compound (10.0 mg, 22 %) as a white solid. ^1H NMR ($\text{DMSO}-d_6$): δ 1.92 – 1.98 (2H, m), 2.11 – 2.20 (3H, m), 2.27 – 2.32 (1H, m), 2.52 – 2.56 (4H, m), 2.73 (2H, t), 2.89 – 2.95 (1H, m), 2.99 – 3.14 (7H, m), 3.18 – 3.28 (4H, m), 3.47 – 3.52 (2H, m), 3.78 (2H, t), 4.35 – 4.38 (2H, m), 4.85 – 4.90 (1H, m), 5.95 (2H, s), 6.43 – 6.51 (3H, m), 6.84 – 6.89 (2H, m), 6.91 – 6.97 (1H, m), 7.07 – 7.15 (4H, m), 7.21 – 7.26 (1H, m), 7.45 – 7.50 (2H, m), 7.54 (1H, d), 7.61 (1H, d), 7.91 (1H, d), 10.28 (1H, s), 14.19 (1H, s); ^{19}F NMR ($\text{DMSO}-d_6$): δ -136.59; m/z (ES^+) $[\text{M}+\text{H}]^+ = 847.3$.

EXAMPLE 96

1-[1-[(2*S*)-6-[[4-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]piperazin-1-yl]methyl]tetralin-2-yl]indol-5-yl]hexahydropyrimidine-2,4-dione

or

1-[1-[(2*R*)-6-[[4-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]piperazin-1-yl]methyl]tetralin-2-yl]indol-5-yl]hexahydropyrimidine-2,4-dione

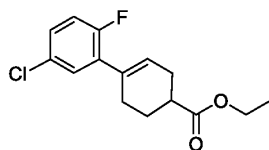


[1755] Intermediate 95g (30 mg, 0.08 mmol) was added to Intermediate 95m (73.6 mg, 0.15 mmol) in DCE (2 mL) and NMP (2 mL). The resulting mixture was stirred at 50°C for 4 h. Then sodium triacetoxyborohydride (49.2 mg, 0.23 mmol) was added and stirred for at r.t. for 1 h. The reaction mixture was evaporated to dryness and redissolved in DCM (5 mL), and washed sequentially with sat. aq. NaHCO_3 (2 x 2 mL). The organic layer was dried over Na_2SO_4 , filtered, and evaporated. Purification by preparative HPLC (Column: Xbridge Prep Shield RP18 OBD, Mobile Phase A: Water (with 10 mmol/L NH_4HCO_3 + 0.05% $\text{NH}_3\text{H}_2\text{O}$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 40% B to 58% B over 8 min) gave the title compound (15.0 mg, 22 %) as a white solid following lyophilization. ^1H NMR ($\text{DMSO}-d_6$): δ 1.90 – 1.98 (2H, m), 2.10 – 2.19 (3H, m), 2.22 – 2.30 (1H, m), 2.52 – 2.54 (1H, m), 2.73 (2H, t), 2.87 – 2.94 (1H, m), 2.99 – 3.13 (6H, m), 3.15 – 3.21 (5H, m), 3.22 – 3.26 (2H, d), 3.45 – 3.53 (2H, m), 3.78 (2H, t), 4.07 – 4.13 (1H, m), 4.32 – 4.39 (2H, m), 4.83 – 4.91 (1H, m), 5.95 (2H, s), 6.42 – 6.51 (3H, m), 6.82 – 6.89 (2H, m), 6.91 – 6.97 (1H, m), 7.03 – 7.15 (4H, m), 7.20 – 7.26 (1H, m), 7.43 – 7.50 (2H, m), 7.53 (1H, d), 7.61 (1H, d), 7.90 (1H, d), 10.27 (1H, s), 14.18 (1H, s); ^{19}F NMR ($\text{DMSO}-d_6$): δ -136.59; m/z (ES^+) $[\text{M}+\text{H}]^+ = 847.3$.

EXAMPLE 97 and EXAMPLE 98

Intermediate 97a:

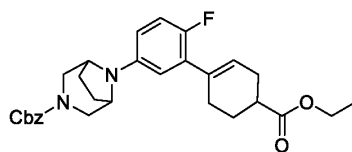
Ethyl 4-(5-chloro-2-fluoro-phenyl)cyclohex-3-ene-1-carboxylate



[1756] 1,1'-Bis(diphenylphosphino)ferrocenedichloropalladium (II) dichloromethane adduct (0.780 g, 0.95 mmol) was added to 2-bromo-4-chloro-1-fluorobenzene (4 g, 19.10 mmol), ethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-ene-1-carboxylate (5.35 g, 19.10 mmol) and Cs_2CO_3 (18.67 g, 57.29 mmol) in 1,4-dioxane (80 mL) under nitrogen. The resulting mixture was stirred at 50 °C for 16 h. The reaction mixture was poured into water (300 mL), extracted with EtOAc (3 x 50 mL), the organic layer was dried over Na_2SO_4 , filtered and evaporated. Purification by FSC (elution gradient: 0 to 70% EtOAc in petroleum ether) gave the title compound (4.0 g, 74 %) as a yellow oil. ^1H NMR ($\text{DMSO}-d_6$): δ 1.19 (3H, t), 1.62 – 1.75 (1H, m), 1.95 – 2.09 (1H, m), 2.22 – 2.46 (4H, m), 2.55 – 2.65 (1H, m), 4.06 – 4.15 (2H, m), 5.96 – 5.98 (1H, m), 7.14 – 7.25 (1H, m), 7.29 – 7.36 (2H, m).

Intermediate 97b:

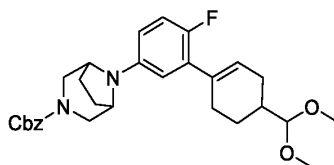
Benzyl 8-[3-(4-ethoxycarbonylcyclohexen-1-yl)-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



[1757] Prepared in an analogous method to Intermediate 6e starting from Intermediate 97a (2 g, 7.07 mmol), Purification by FSC (elution gradient: 0 to 40% EtOAc in petroleum ether, then 0 to 10% MeOH in DCM) gave the title compound (1.4 g, 40 %) as a yellow solid. ^1H NMR ($\text{DMSO}-d_6$): δ 1.17 – 1.22 (3H, m), 1.61 – 1.73 (3H, m), 1.85 – 1.91 (2H, m), 1.99 – 2.07 (1H, m), 2.28 – 2.46 (4H, m), 2.57 – 2.64 (1H, m), 3.08 – 3.12 (1H, m), 3.20 – 3.23 (1H, m), 3.59 (2H, d), 4.06 – 4.13 (2H, m), 4.25 (2H, d), 5.07 (2H, d), 5.88 (1H, s), 6.68 – 6.71 (1H, m), 6.72 – 6.77 (1H, m), 6.94 – 7.00 (1H, m), 7.29 – 7.39 (5H, m); m/z (ES^+) $[\text{M}+\text{H}]^+ = 493.4$.

Intermediate 97c:

Benzyl 8-[3-[4-(dimethoxymethyl)cyclohexen-1-yl]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



[1758] DIBAL-H (1M in DCM) (1.523 mL, 1.52 mmol) was added dropwise to a solution Intermediate 97b (500 mg, 1.02 mmol) in DCM (10 mL) at -60 °C under nitrogen. The resulting mixture was stirred at -

60 °C for 30 min. The reaction mixture was quenched with sat. aq. NH_4Cl (50 mL), extracted with DCM (3 x 50 mL), the organic layer was dried over Na_2SO_4 , filtered, and evaporated. To the crude residue was added Trimethyl orthoformate (323 mg, 3.05 mmol) and $p\text{TsOH}\cdot\text{H}_2\text{O}$ (19.31 mg, 0.10 mmol) in MeOH (10 mL). The resulting mixture was stirred at 40 °C for 2 h. The reaction mixture was concentrated. Purification by FSC (elution gradient: 0 to 40% EtOAc in petroleum ether then 0 to 10% MeOH in DCM) gave the title compound (300 mg, 59 %) as a yellow solid. ^1H NMR ($\text{DMSO}-d_6$): δ 1.29 – 1.40 (1H, m), 1.61 – 1.68 (2H, m), 1.81 – 1.99 (5H, m), 2.19 (1H, d), 2.25 – 2.42 (2H, m), 3.10 (1H, d), 3.22 (1H, d), 3.28 (6H, s), 3.58 (2H, d), 4.15 (1H, d), 4.20 – 4.32 (2H, m), 5.07 (2H, d), 5.84 – 5.87 (1H, m), 6.67 – 6.77 (2H, m), 6.93 – 7.00 (1H, m), 7.28 – 7.42 (5H, m); m/z (ES^+) $[\text{M}+\text{H}]^+ = 495.4$.

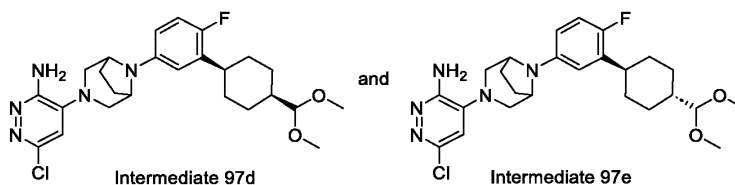
Intermediate 97d:

6-Chloro-4-[8-[3-[(1*s*,4*s*)-4-(dimethoxymethyl)cyclohexyl]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-amine

and

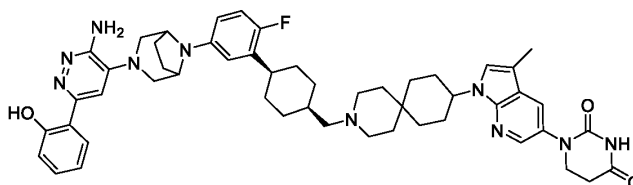
Intermediate 97e:

6-Chloro-4-[8-[3-[(1*r*,4*r*)-4-(dimethoxymethyl)cyclohexyl]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-amine



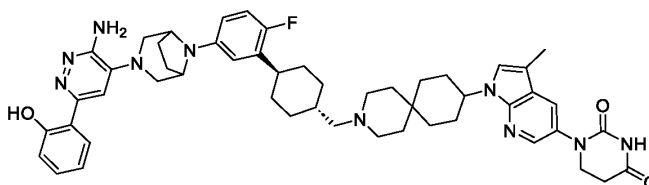
[1759] Pd/C (200 mg, 0.188 mmol) was added to Intermediate 97c (580 mg, 1.17 mmol) in DCM (50 mL) under hydrogen. The resulting mixture was stirred at r.t. for 5 days. The reaction mixture was filtered through celite® and the filtrate was concentrated to afford crude product. To this residue was added DIPEA (0.491 mL, 2.81 mmol), 4-bromo-6-chloropyridazin-3-amine (215 mg, 1.03 mmol) and DMSO (7 mL). The resulting mixture was stirred at 100 °C for 16 h. The reaction mixture was poured into water (50 mL), extracted with EtOAc (3 x 20 mL), the organic layer was dried over Na_2SO_4 , filtered, and evaporated. Purification by FSC (elution gradient: 0-30% EtOAc in petroleum ether, then 0 to 10% MeOH in DCM) gave the mixture of trans and cis isomers as a yellow gum. The mixture was purified by preparative chiral-HPLC on a Column: CHIRALPAK IF 2x25 cm, 5 μm ; Mobile Phase A: MTBE (with 0.5% NH_3 in MeOH), Mobile Phase B: EtOH; Flow rate: 11 mL/min; Gradient: isocratic 10% Mobile Phase B; Wavelength: 220/254 nm gave the cis isomer, Intermediate 97d (60.0 mg, 13.05 %) as a yellow solid. ^1H NMR ($\text{DMSO}-d_6$) δ 1.38 – 1.96 (13H, m), 2.05 – 2.10 (2H, m), 2.72 – 2.77 (1H, m), 2.91 – 2.95 (2H, m), 3.16 – 3.19 (2H, m), 3.26 (6H, s), 4.67 (1H, d), 5.78 (2H, s), 6.62 – 6.99 (4H, m); m/z (ES^+) $[\text{M}+\text{H}]^+ = 490.5$. And gave the trans isomer, Intermediate 97e (110 mg, 23.93 %) as a yellow solid. ^1H NMR ($\text{DMSO}-d_6$): δ 1.10 (1H, s), 1.11 – 1.26 (2H, m), 1.40 – 1.99 (10H, m), 2.08 (2H, d), 2.57 – 2.70 (1H, m), 2.93 (2H, d), 3.17 (2H, d), 3.25 (6H, s), 4.02 (1H, d), 5.80 (2H, s), 6.61 – 6.97 (4H, m); m/z (ES^+) $[\text{M}+\text{H}]^+ = 490.4$.

1-[1-[3-[[*(1s,4s)*-4-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]cyclohexyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione (EXAMPLE 97)



and

1-[1-[3-[[*(1r,4r)*-4-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]cyclohexyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione (EXAMPLE 98)



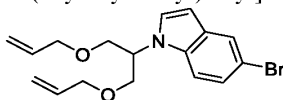
[1760] PdCl₂(dppf) (6.42 mg, 8.78 μmol) was added to Intermediate 97d (43 mg, 0.09 mmol), Cs₂CO₃ (86 mg, 0.26 mmol) and (2-hydroxyphenyl)boronic acid (24.21 mg, 0.18 mmol) in water (0.5 mL) and dioxane (5 mL) under nitrogen. The resulting mixture was stirred at 80 °C for 2 h. The crude product was purified by flash silica chromatography (elution gradient 0 to 5% MeOH) to afford 2-(6-amino-5-(8-(3-(4-(dimethoxymethyl)cyclohexyl)-4-fluorophenyl)-3,8-diaza-bicyclo[3.2.1]octan-3-yl)pyridazin-3-yl)phenol as a yellow solid. Due to the low yield the material was used directly for the next step. To the residue was added formic acid (1 mL, 26.07 mmol). The resulting mixture was stirred at r.t. for 1 h. The solvent was removed under reduced pressure. The reaction mixture was diluted with DCM (20 mL) and washed sequentially with sat. aq. Na₂CO₃ (2 x 10 mL). The organic layer was dried over Na₂SO₄, filtered, and evaporated. To the crude material was added Intermediate 58a (34.7 mg, 0.09 mmol), NMP (2.000 mL) and DCE (2.00 mL). The resulting mixture was stirred at 60 °C for 2 h. Then the sodium triacetoxyborohydride (55.8 mg, 0.26 mmol) was added. The resulting mixture was stirred at 40 °C for 1 h. During the reductive amination some of the cis isomer was epimerized to trans isomer. The reaction mixture was diluted with DCM (20 mL) and washed sequentially with saturated Na₂CO₃ (10 mL x 2). The organic layer was dried over Na₂SO₄, filtered, and evaporated. To separate the diastereomers, the crude product was purified by preparative HPLC (Column: Xselect CSH Prep C18 OBD, 30x150mm, 5μm; Mobile Phase A: Water(0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/min mL/min; Gradient: 29% B to 34% B over 10 min; Wave length: 254nm/220nm nm; RT1 8.57 min, RT2 9.23 min. Fractions containing the desired compound were evaporated to dryness to afford the cis isomer EXAMPLE 97 (4.10 mg, 5%). ¹H NMR (DMSO-*d*₆): δ 0.94 – 1.03 (2H, m), 1.26 – 1.35 (2H, m), 1.37 – 1.41 (2H, m), 1.51 – 1.63 (3H, m), 1.63 – 1.73 (4H, s), 1.73 –

1.83 (4H, m), 1.84 – 1.91 (2H, m), 1.91 – 2.04 (4H, m), 2.09 – 2.19 (4H, m), 2.25 (3H, s), 2.31 – 2.40 (4H, m), 2.67 – 2.72 (1H, m), 2.74 – 2.78 (2H, m), 3.06 – 3.11 (2H, m), 3.26 – 3.29 (2H, m), 3.81 (2H, t), 4.37 – 4.42 (2H, m), 4.57 – 4.63 (1H, m), 5.95 (2H, s), 6.70 – 6.75 (1H, m), 6.78 – 6.82 (1H, m), 6.85 – 6.90 (2H, m), 6.93 – 6.98 (1H, m), 7.21 – 7.25 (1H, m), 7.46 (1H, s), 7.55 (1H, s), 7.87 (1H, d), 7.89 – 7.92 (1H, m), 8.17 (1H, s), 10.39 (1H, s), 14.17 (1H, s); ^{19}F NMR (DMSO-*d*6): δ -133.61. m/z (ES^+) $[\text{M}+\text{H}]^+ = 881.7$. And the trans isomer EXAMPLE 98 (5.00 mg, 6 %) as a white solid. ^1H NMR (DMSO-*d*6): δ 1.29 – 1.35 (2H, m), 1.37 – 1.42 (2H, m), 1.53 – 1.68 (4H, m), 1.68 – 1.75 (8H, m), 1.78 – 1.84 (2H, m), 1.93 – 2.05 (5H, m), 2.11 – 2.18 (2H, m), 2.25 (3H, s), 2.40 – 2.43 (5H, m), 2.68 – 2.73 (1H, m), 2.73 – 2.79 (2H, m), 3.06 – 3.12 (2H, m), 3.28 (3H, m), 3.81 (2H, t), 4.39 – 4.43 (2H, m), 4.56 – 4.64 (1H, m), 5.95 (2H, s), 6.69 – 6.76 (1H, m), 6.77 – 6.83 (1H, m), 6.83 – 6.91 (2H, m), 6.92 – 6.99 (1H, m), 7.20 – 7.27 (1H, m), 7.47 (1H, s), 7.55 (1H, s), 7.87 (1H, d), 7.89 – 7.94 (1H, m), 8.17 (1H, d), 8.28 (1H, s), 10.39 (1H, s), 14.12 (1H, s). ^{19}F NMR (DMSO-*d*6): δ -133.23. m/z (ES^+) $[\text{M}+\text{H}]^+ = 881.4$.

EXAMPLE 99

Intermediate 99a:

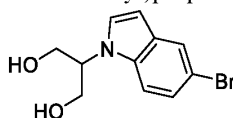
1-[2-Allyloxy-1-(allyloxymethyl)ethyl]-5-bromo-indole



[1761] 1,3-Bis(allyloxy)propan-2-ol (6.16 ml, 35.03 mmol) and 2-(tributyl-*l*-phosphaneylidene)acetonitrile (9.18 ml, 35.03 mmol) were added to a solution of 5-bromo-1*H*-indole (4.579 g, 23.36 mmol) in toluene (78 mL). The resulting mixture was stirred at 100 °C for 19 h. More 1,3-bis(allyloxy)propan-2-ol (6.16 ml, 35.03 mmol) and 2-(tributyl-*l*-phosphaneylidene)acetonitrile (9.18 ml, 35.03 mmol) were added and stirring was continued at 100 °C for 23 h. After cooling to r.t., the mixture was concentrated under reduced pressure. Purification by FSC (1st purification: elution gradient: 0 to 25% EtOAc in hexanes; 2nd purification: elution gradient: 10 to 100% DCM in hexanes) gave the title compound as a colorless oil. ^1H NMR (DMSO-*d*6): δ 3.72 – 3.84 (4H, m), 3.86 – 3.95 (4H, m), 4.87 (1H, quin), 5.03 – 5.19 (4H, m), 5.77 (2H, ddt), 6.45 (1H, d), 7.21 (1H, dd), 7.48 – 7.57 (2H, m), 7.71 (1H, d); m/z ES^+ $[\text{M}+\text{H}]^+ = 350.2$.

Intermediate 99b:

2-(5-Bromoindol-1-yl)propane-1,3-diol

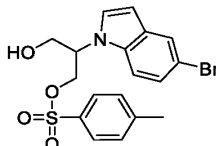


[1762] $\text{Pd}(\text{PPh}_3)_4$ (0.867 g, 0.75 mmol) was added to a suspension of Intermediate 99a (5.254 g, 15.00 mmol) and 1,3-dimethylbarbituric acid (4.68 g, 30.00 mmol) in MeOH (75 ml) under argon. The flask was evacuated and backfilled with argon (3x). The resulting mixture was stirred at 35 °C for 3.5 h and concentrated under reduced pressure. Purification by FSC (1st purification: elution gradient: 0 to 80% acetone in hexanes, 2nd purification: elution gradient: 0 to 60% acetone in hexanes) gave the title compound

(4.13 g, 102 %) as a red oil. Product contains ~37 mol%/11 wt% EtOAc and minor other impurities, the material was carried to the next step without further purification. ^1H NMR (DMSO-*d*₆): δ 3.69 - 3.87 (4H, m), 4.45 (1H, br t), 4.87 (2H, br t), 6.42 (1H, d), 7.16 - 7.24 (1H, m), 7.45 (1H, br d), 7.50 (1H, d), 7.65 - 7.77 (1H, m); m/z ES⁺ [M+H]⁺ = 270.1.

Intermediate 99c:

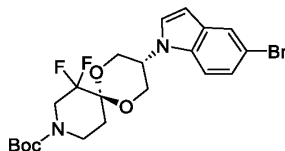
[2-(5-Bromoindol-1-yl)-3-hydroxy-propyl] 4-methylbenzenesulfonate



[1763] To a solution of Intermediate 99b (2.93 g, 10.85 mmol), 4-methylbenzenesulfonyl chloride (2.482 g, 13.02 mmol), 4,4,4-trifluoro-1-phenylbutane-1,3-dione (0.469 g, 2.17 mmol), and iron(III) chloride (0.063 mL, 1.09 mmol) in acetonitrile (25 mL) was added DIPEA (3.60 mL, 20.62 mmol). The reaction was stirred at r.t. for 2h. Solvent was removed. Purification by FSC (elution gradient: 10-50 % EtOAc in hexane) gave the title compound (4.32 g, 94 %) as a light orange solid. ^1H NMR (CD₂Cl₂): δ 1.81 - 1.92 (1H, m), 2.40 (3H, s), 3.98 - 4.06 (2H, m), 4.40 (2H, d), 4.66 (1H, quin), 6.45 (1H, d), 7.11 (1H, d), 7.17 - 7.26 (4H, m), 7.54 (2H, d), 7.70 (1H, d); m/z (ES⁺) [M+H]⁺ = 424.1.

Intermediate 99d:

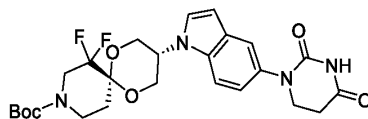
tert-Butyl (3*r*,6*r*)-3-(5-bromoindol-1-yl)-11,11-difluoro-1,5-dioxo-9-azaspiro[5.5]undecane-9-carboxylate



[1764] A solution of Intermediate 99c (2.12 g, 5 mmol) and *tert*-butyl 3,3-difluoro-4-oxopiperidine-1-carboxylate (3.52 g, 15.00 mmol) in DMF (5 mL) was stirred at 0 °C. Potassium *tert*-butoxide solution 1 M in THF (15 mL, 15.00 mmol) was added dropwise. The reaction was allowed to warm to r.t. and stirred for 1h. The reaction was diluted with EtOAc and was washed with sat. aq. NH₄Cl solution. The organic phase was dried over MgSO₄, filtered, and concentrated. Purification by FSC (elution gradient: 10-40% EtOAc in hexanes) gave the title compound (891 mg, 36.6 %) as a white solid. ^1H NMR (CD₂Cl₂): δ 1.44 - 1.48 (9H, m), 1.94 - 2.00 (2H, m), 3.49 - 3.55 (2H, m), 3.78 (2H, t), 4.18 (2H, br d), 4.60 (3H, br s), 6.52 (1H, d), 7.19 - 7.25 (1H, m), 7.30 (1H, d), 7.56 (1H, br s), 7.76 (1H, s); m/z (ES⁺) [M+H]⁺ = 487.1.

Intermediate 99e:

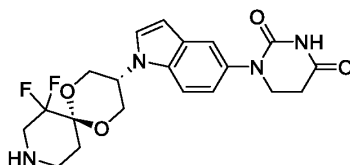
tert-Butyl (3*r*,6*r*)-3-[5-(2,4-dioxohexahydropyrimidin-1-yl)indol-1-yl]-11,11-difluoro-1,5-dioxo-9-azaspiro[5.5]undecane-9-carboxylate



[1765] A solution of Intermediate 99d (0.852 g, 1.75 mmol), hexahydropyrimidine-2,4-dione (0.399 g, 3.50 mmol), K_3PO_4 (0.742 g, 3.50 mmol) and *t*BuBrettPhos Pd G3 (0.299 g, 0.35 mmol) in dioxane (10 mL) was evacuated and backfilled with nitrogen. The reaction was stirred at 95 °C for 24 h. The reaction was cooled to r.t. diluted with DCM (30 mL), washed with water, dried over $MgSO_4$, filtered, and concentrated down. Purification by FSC (elution gradient: 20-100% EtOAc in hexanes, then 10% MeOH in EtOAc) gave the title compound (0.502 g, 55.2 %) as an off-white solid. 1H NMR (CD_2Cl_2): δ 1.45 (9H, s), 2.00 (2H, br s), 2.82 (2H, t), 3.49 - 3.55 (2H, m), 3.74 - 3.83 (2H, m), 3.86 (2H, t), 4.20 (2H, dd), 4.59 - 4.69 (3H, m), 6.58 (1H, d), 7.14 (1H, dd), 7.36 (1H, d), 7.49 - 7.56 (2H, m), 7.58 (1H, br s); m/z (ES^+) $[M+H]^+ = 521.3$.

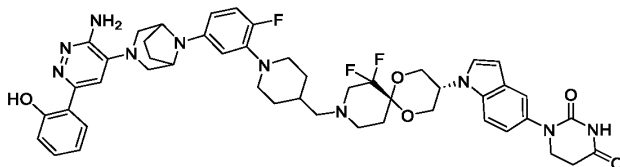
Intermediate 99f:

1-[1-((3*r*,6*r*)-11,11-Difluoro-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl)indol-5-yl]hexahydropyrimidine-2,4-dione



[1766] To a solution of intermediate 99e (505 mg, 0.97 mmol) in DCM (4 mL) was added TFA (1.5 mL, 19.40 mmol). The reaction was stirred at r.t. for 2h. The solvent was removed under reduced pressure and the residue was dissolved in MeOH (10 mL), and carbonate resin (1g, 2.5-3.5 mmol/g) was added. The reaction was stirred at r.t. for 1h and resin was filtered off and filtrate was concentrated to give the title compound (205 mg, 50.3 %) as a white solid. 1H NMR ($DMSO-d_6$): δ 2.38 - 2.47 (2H, m), 2.62 - 2.75 (2H, m), 3.12 - 3.20 (2H, m), 3.66 - 3.73 (2H, m), 3.74 - 3.79 (2H, m), 4.20 - 4.30 (2H, m), 4.30 - 4.43 (2H, m), 4.76 - 4.98 (1H, m), 6.53 (1H, d), 7.07 - 7.13 (1H, m), 7.46 - 7.49 (1H, m), 7.60 (1H, d), 7.67 (1H, d), 10.25 (1H, s), NH proton was not observed; m/z (ES^+) $[M+H]^+ = 421.1$.

1-[1-[1-((3*r*,6*r*)-9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-11,11-difluoro-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl)indol-5-yl]hexahydropyrimidine-2,4-dione

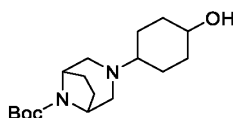


[1767] Prepared in an analogous manner to Example 64 starting from Intermediate 13d (25.1 mg, 0.05 mmol) and Intermediate 99f (21.02 mg, 0.05 mmol). Purification by RPC (elution gradient: 20 to 60% MeCN in water with 0.1% FA) gave the title compound, the trans isomer (30.0 mg, 66.2 %) as a white solid following lyophilization. 1H NMR ($DMSO-d_6$) δ 1.24 (2H, br d), 1.58 - 1.69 (1H, m), 1.72 - 1.83 (4H, m), 1.90 - 1.99 (2H, m), 2.06 - 2.21 (4H, m), 2.29 (2H, br d), 2.61 - 2.68 (2H, m), 2.68 - 2.83 (4H, m), 3.09 (2H,

br d), 3.20 - 3.26 (2H, m), 3.35 - 3.41 (2H, m), 3.75 (2H, t), 4.19 (2H, br dd), 4.33 (4H, br d), 4.83 (1H, br s), 5.92 (2H, s), 6.41 (1H, br d), 6.44 - 6.50 (1H, m), 6.51 (1H, d), 6.79 - 6.88 (2H, m), 6.91 (1H, dd), 7.09 (1H, dd), 7.19 - 7.24 (1H, m), 7.42 - 7.50 (2H, m), 7.57 (1H, d), 7.70 (1H, d), 7.89 (1H, d), 10.25 (1H, s), 14.03 - 14.23 (1H, m); m/z (ES⁺) [M+H]⁺ = 907.5.

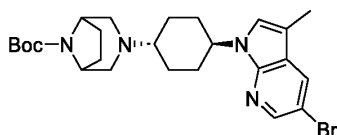
EXAMPLE 100

Intermediate 100a:

tert-Butyl 3-(4-hydroxycyclohexyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

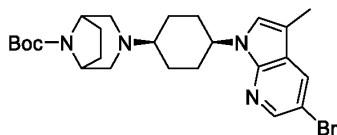
[1768] To a solution of 4-hydroxycyclohexan-1-one (1.14 g, 10 mmol) and *tert*-butyl 3,8-diazabicyclo[3.2.1]octane-8-carboxylate (2.12 g, 10.00 mmol) in THF (45 mL) was added DIPEA (5.2 mL, 30.00 mmol) and MgSO₄ (0.722 g, 6.00 mmol). The reaction was stirred at r.t. for 10 min. then sodium triacetoxyborohydride (4.24 g, 20.00 mmol) was added. The reaction was stirred at r.t. for overnight. Solvent was removed, and the residue was partitioned between NaHCO₃ solution (40 mL) and DCM (80 mL). The organic phase was separated and dried over MgSO₄, filtered, and concentrated. Purification by FSC (elution gradient: 20-100% EtOAc in hexane then 10% MeOH in EtOAc with 1% NH₄OH) gave the title compound (2.25 g, 72.5 %) as a colorless gum, a mixture of *cis* and *trans* isomers. (NMR showed a ratio of 39:61). ¹H NMR (DMSO-*d*₆): δ 1.04 - 1.16 (2H, m), 1.28 - 1.45 (11H, m), 1.51 - 1.84 (8H, m), 2.04 - 2.33 (3H, m), 2.51 - 2.68 (2H, m), 3.30 - 3.64 (1H, m), 3.95 - 4.01 (2H, m), 4.23 - 4.48 (1H, m). Desired mass was not detected.

Intermediate 100b:

tert-Butyl 3-[(1*r*,4*r*)-4-(5-bromo-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl)cyclohexyl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

and

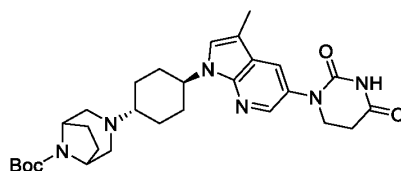
Intermediate 100c:

tert-Butyl 3-[(1*s*,4*s*)-4-(5-bromo-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl)cyclohexyl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

[1769] To a solution of Intermediate 100a (2.18 g, 7.02 mmol) and 5-bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (1.482 g, 7.02 mmol) in toluene (20 mL) was added 2-(tributyl-*l*-5-phosphaneylidene)acetonitrile (1.8 mL, 7.02 mmol). The reaction was stirred at 100 °C overnight. The reaction was concentrated under reduced pressure. Purification by FSC (elution gradient: 0-50% EtOAc in hexanes) gave the trans isomer, Intermediate 100b (0.302 g, 8.54 %) as a solid. ¹H NMR (DMSO-*d*₆): δ 1.45 - 1.47 (9H, m), 1.53 - 1.60 (2H, m), 1.72 (2H, br s), 1.84 - 1.90 (2H, m), 1.94 - 1.98 (2H, m), 2.07 - 2.17 (6H, m), 2.28 (4H, s), 2.82 - 2.86 (2H, m), 4.19 (2H, br s), 4.70 - 4.78 (1H, m), 7.11 (1H, s), 7.96 (1H, d), 8.24 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 503.3. And the cis isomer, Intermediate 100c (0.760 g, 21.50 %) as a solid. ¹H NMR (DMSO-*d*₆): δ 1.44 - 1.46 (9H, m), 1.52 - 1.57 (2H, m), 1.73 - 1.85 (6H, m), 1.96 (2H, br d), 2.08 (2H, br d), 2.26 (3H, s), 2.32 - 2.43 (1H, m), 2.52 (2H, br s), 2.58 - 2.64 (2H, m), 4.13 (2H, br s), 4.58 - 4.66 (1H, m), 7.09 (1H, s), 7.95 (1H, d), 8.24 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 503.3.

Intermediate 100d:

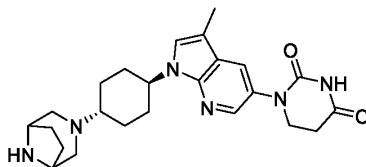
tert-Butyl 3-[(1*r*,4*r*)-4-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]cyclohexyl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[1770] Prepared in an analogous method to Intermediate 2b starting from Intermediate 100b (331 mg, 0.66 mmol) gave the title compound (225 mg, 63.8%) as an off white solid. ¹H NMR (CD₂Cl₂): δ 1.39 - 1.44 (10H, m), 1.43 - 1.55 (2H, m), 1.60 - 1.71 (2H, m), 1.75 - 1.86 (2H, m), 1.91 - 1.97 (2H, m), 1.97 - 2.05 (4H, m), 2.14 - 2.22 (2H, m), 2.24 - 2.30 (3H, m), 2.70 - 2.79 (2H, m), 2.80 - 2.88 (2H, m), 3.79 (2H, t), 4.04 - 4.12 (2H, m), 4.67 (1H, br s), 7.30 (1H, s), 7.86 (1H, d), 8.14 (1H, d), 10.35 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 537.6.

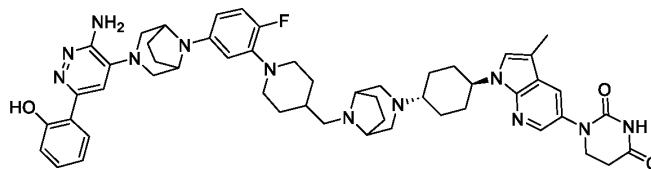
Intermediate 100e:

1-[1-[(1*r*,4*r*)-4-(3,8-Diazabicyclo[3.2.1]octan-3-yl)cyclohexyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1771] Prepared in an analogous method to Intermediate 1i starting from Intermediate 100d (220 mg, 0.41 mmol) gave the title compound (145 mg, 81%) as a white solid in the form of free base. *m/z* (ES⁺) [M+H]⁺ = 437.3.

1-[1-[(1*r*,4*r*)-4-[8-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl)methyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]cyclohexyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

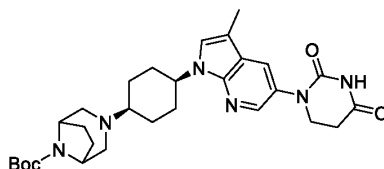


[1772] Prepared in an analogous method to EXAMPLE 64 starting from Intermediate 100e (32.7 mg, 0.08mmol) and Intermediate 13d (25.1 mg, 0.05 mmol). Purification by RPC (elution gradient: 45-100% MeCN in water with 0.1% NH₄OH) followed by FSC (20-100% Solvent B in DCM; solvent B: 10% MeOH in DCM with 1% NH₄OH) gave the title compound (18 mg, 39%) as a white solid following lyophilization. ¹H NMR (DMSO-*d*₆): δ 1.27 (2H, br d), 1.42 - 1.56 (3H, m), 1.56 - 1.68 (2H, m), 1.80 - 2.15 (16H, m), 2.15 - 2.25 (3H, m), 2.25 - 2.29 (3H, m), 2.57 - 2.69 (2H, m), 2.69 - 2.78 (4H, m), 2.98 - 3.19 (4H, m), 3.21 - 3.28 (2H, m), 3.33 - 3.40 (2H, m), 3.80 (2H, t), 4.33 (2H, br s), 4.60 - 4.75 (1H, m), 5.92 (2H, s), 6.38 - 6.50 (2H, m), 6.81 - 6.96 (3H, m), 7.19 - 7.23 (1H, m), 7.28 (1H, s), 7.45 (1H, s), 7.84 - 7.91 (2H, m), 8.15 (1H, d), 10.36 (1H, s), 14.15 (1H, br s); *m/z* (ES⁺) [M+H]⁺ = 923.8.

EXAMPLE 101

Intermediate 101a:

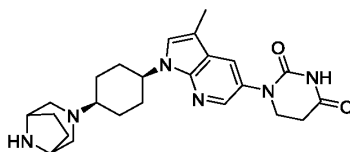
tert-Butyl 3-[(1*s*,4*s*)-4-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]cyclohexyl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[1773] Prepared in an analogous method to Intermediate 2b starting from Intermediate 100c (744 mg, 1.48 mmol) gave the title compound (451 mg, 56.9%) as an off-white solid. ¹H NMR (CD₂Cl₂): δ 1.39 - 1.42 (9H, m), 1.43 - 1.50 (2H, m), 1.68 - 1.77 (4H, m), 1.82 - 1.90 (4H, m), 1.91 - 1.98 (2H, m), 2.23 (3H, s), 2.34 - 2.38 (1H, m), 2.39 - 2.44 (2H, m), 2.61 (2H, br d), 2.74 (2H, t), 3.79 (2H, t), 3.99 - 4.06 (2H, m), 4.57 (1H, br s), 7.42 (1H, s), 7.85 (1H, d), 8.16 - 8.17 (1H, m), 10.35 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 537.6

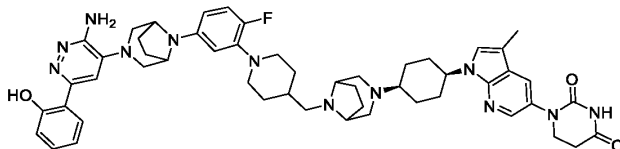
Intermediate 101b:

1-[1-[(1*s*,4*s*)-4-(3,8-Diazabicyclo[3.2.1]octan-3-yl)cyclohexyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1774] Prepared in an analogous method to Intermediate 1i starting from Intermediate 101a (450 mg, 0.84 mmol) gave the title compound (315 mg, 86%) as a white solid. m/z (ES⁺) [M+H]⁺ = 437.3.

1-[1-[(1*s*,4*s*)-4-[8-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl)methyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]cyclohexyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

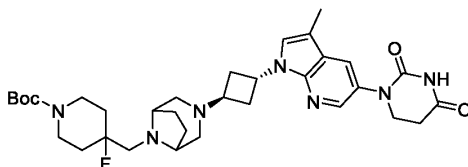


[1775] Prepared in an analogous method to EXAMPLE 64 starting from Intermediate 101b (22 mg, 0.05 mmol) and Intermediate 13d (25.1 mg, 0.05 mmol). Purification by RPC (gradient: 20 to 60% MeCN in water with 0.1% FA) gave the title compound (14.2 mg, 30.8%) a white solid. ¹H NMR (CD₂Cl₂): δ 1.18 - 1.34 (2H, m), 1.37 - 1.56 (3H, m), 1.59 - 1.69 (2H, m), 1.70 - 1.77 (2H, m), 1.77 - 2.01 (11H, m), 2.04 - 2.27 (8H, m), 2.28 - 2.36 (1H, m), 2.51 - 2.58 (2H, m), 2.59 - 2.68 (2H, m), 2.68 - 2.78 (2H, m), 3.00 - 3.16 (4H, m), 3.18 - 3.26 (2H, m), 3.32 - 3.35 (2H, m), 3.35 - 3.38 (1H, m), 3.79 (2H, t), 4.33 (2H, br s), 4.59 (1H, br s), 5.92 (2H, s), 6.31 - 6.48 (2H, m), 6.73 - 6.94 (3H, m), 7.17 - 7.25 (1H, m), 7.45 (1H, s), 7.83 - 7.90 (2H, m), 8.15 (1H, d), 10.36 (1H, s), 14.15 (1H, br s); m/z (ES⁺) [M+H]⁺ = 923.8.

EXAMPLE 102

Intermediate 102a:

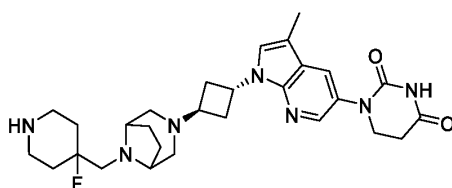
tert-Butyl 4-[[[(1*r*,3*r*)-3-[3-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]cyclobutyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]methyl]-4-fluoro-piperidine-1-carboxylate



[1776] Prepared in an analogous method to Intermediate 25f starting from Intermediate 41e (172 mg, 0.42 mmol) and Intermediate 25e (0.473 g, 1.29 mmol). Purification by SFC (elution gradient: 10-60% EtOAc in hexane, then 10% MeOH in EtOAc) gave the title compound (241 mg, 92 %) as an off-white solid. ¹H NMR (CD₂Cl₂): δ 1.42 - 1.48 (10H, m), 1.59 - 1.74 (2H, m), 1.78 - 1.90 (6H, m), 2.07 - 2.15 (2H, m), 2.30 - 2.35 (3H, m), 2.37 - 2.48 (4H, m), 2.51 - 2.58 (2H, m), 2.70 (2H, br d), 2.85 (2H, br t), 3.02 - 3.13 (4H, m), 3.13 - 3.18 (1H, m), 3.87 (4H, br t), 7.30 (1H, s), 7.45 (1H, br s), 7.75 (1H, s), 8.17 (1H, s); m/z (ES⁺) [M+H]⁺ = 624.6.

Intermediate 102b:

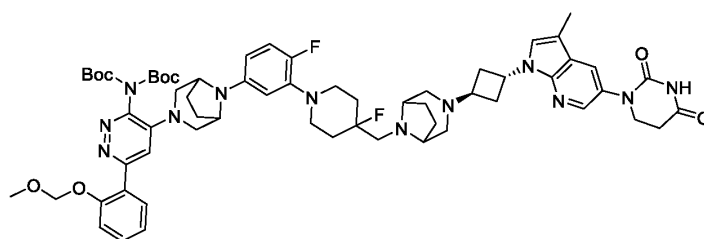
1-[1-[(1*r*,3*r*)-3-[8-[(4-Fluoro-4-piperidyl)methyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]cyclobutyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1777] Prepared in an analogous method to Intermediate 1i starting from Intermediate 102a (242 mg, 0.39 mmol). The reaction was basified with solid supported bicarbonate resin, the resin was filtered off, and the filtrate concentrated to give the title compound (195 mg, 96%) as a white solid in the form of free base m/z (ES^+) $[M+H]^+ = 524.4$.

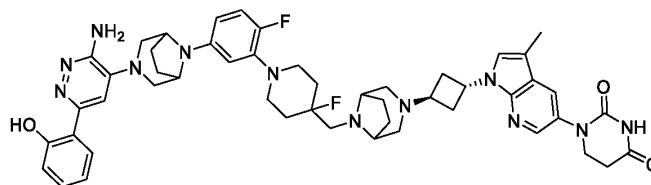
Intermediate 102c:

tert-Butyl *N*-*tert*-butoxycarbonyl-*N*-[4-[8-[3-[4-[[3-[3-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]cyclobutyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]methyl]-4-fluoro-1-piperidyl]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]-6-[2-(methoxymethoxy)phenyl]pyridazin-3-yl]carbamate



[1778] A solution of Intermediate 102b (79 mg, 0.15 mmol), Intermediate 57a (101 mg, 0.15 mmol), K_2CO_3 (62.2 mg, 0.45 mmol), and Pd-PEPPSI-IPentCl (25.2 mg, 0.03 mmol) in dioxane (1.5 mL) was degassed, for 5 min. and backfilled with N_2 . The reaction was heated at 100 °C overnight. The solvent was removed. Purification by FSC (elution gradient: 10-50% EtOAc in hexane then 10% MeOH in EtOAc) gave the title compound (41.0 mg, 23.62 %) as a white solid. m/z (ES^+) $[M+H]^+ = 1157.8$.

1-[1-[(1*r*,3*r*)-3-[8-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-fluoro-4-piperidyl]methyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]cyclobutyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



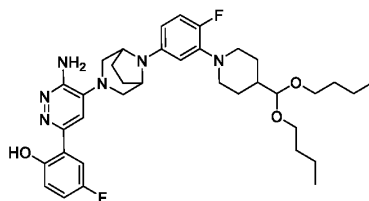
[1779] A solution of Intermediate 102c (41 mg, 0.04 mmol) in DCM (1 mL) was added HCl (4N in dioxane, 1 mL, 4 mmol). The reaction was stirred at r.t. for 4 h. The solvent was removed. Purification by RPC (elution gradient: 45-100% MeCN in water with 0.1% NH_4OH) gave the title compound (11.00 mg, 34.0 %) as a white solid. 1H NMR ($DMSO-d_6$): δ 1.18 - 1.22 (2H, m), 1.70 - 1.80 (4H, m), 1.80 - 1.90 (2H,

m), 1.90 - 2.00 (4H, m), 2.02 - 2.09 (2H, m), 2.09 - 2.17 (2H, m), 2.25 (3H, s), 2.36 - 2.46 (4H, m), 2.65 - 2.71 (2H, m), 2.74 (2H, t), 2.87 - 2.97 (2H, m), 3.01 - 3.06 (1H, m), 3.09 (2H, br d), 3.12 - 3.26 (6H, m), 3.79 (2H, t), 4.36 (2H, br s), 5.18 - 5.32 (1H, m), 5.92 (2H, s), 6.39 - 6.47 (1H, m), 6.47 - 6.55 (1H, m), 6.82 - 6.89 (2H, m), 6.93 (1H, dd), 7.17 - 7.25 (1H, m), 7.45 (1H, s), 7.61 (1H, s), 7.84 - 7.90 (2H, m), 8.16 (1H, d), 10.36 (1H, br s), 14.15 (1H, br s); m/z (ES^-) $[M-H]^- = 913.6$.

EXAMPLE 103

Intermediate 103a:

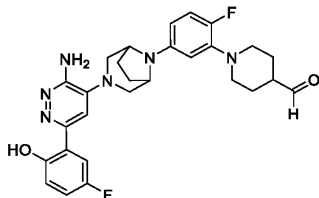
2-[6-Amino-5-[8-[3-[4-(dibutoxymethyl)-1-piperidyl]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-yl]-4-fluoro-phenol



[1780] Intermediate 11f (225 mg, 0.39 mmol) was added to a stirred solution of (5-fluoro-2-hydroxyphenyl)boronic acid (61.0 mg, 0.39 mmol), XPhos Pd G3 (33.1 mg, 0.04 mmol), and K_2CO_3 (162 mg, 1.17 mmol) in 1,4-dioxane (2.1 mL) and water (0.5 mL) under nitrogen atmosphere. The reaction was sparged with nitrogen for 5 minutes then heated at 105 °C for 2 h. The reaction mixture was cooled to r.t. Aqueous layer was removed, and the organic layer was concentrated. Purification FSC (elution gradient: 10-30% EtOAc in hexanes then 10% MeOH in EtOAc) gave the title compound (235 mg, 92 %) as a yellow solid. 1H NMR (CD_2Cl_2): δ 0.90 - 0.96 (6H, m), 1.32 - 1.41 (4H, m), 1.50 - 1.59 (6H, m), 1.65 - 1.75 (1H, m), 1.79 - 1.89 (2H, m), 2.01 - 2.08 (2H, m), 2.12 - 2.19 (2H, m), 2.57 - 2.69 (2H, m), 3.17 - 3.28 (4H, m), 3.40 - 3.50 (4H, m), 3.56 - 3.67 (2H, m), 4.14 - 4.22 (1H, m), 4.25 - 4.33 (2H, m), 4.76 - 4.92 (2H, m), 6.27 - 6.50 (2H, m), 6.86 - 7.01 (3H, m), 7.18 (1H, s), 7.30 (1H, dd), 13.40 - 13.69 (1H, m); m/z (ES^+) $[M+H]^+ = 651.3$.

Intermediate 103b:

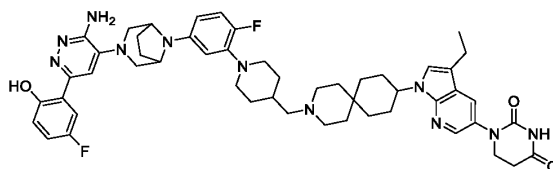
1-[5-[3-[3-Amino-6-(5-fluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]piperidine-4-carbaldehyde



[1781] A solution of Intermediate 103a (260 mg, 0.4 mmol) and *p*-toluenesulfonic acid monohydrate (76 mg, 0.40 mmol) in a mixture of acetone (1.8 mL) and water (0.2 mL) in a microwave tube was heated at 80 °C for 30 min. The solvent was removed, and the residue was partitioned between EtOAc and sat. aq.

NaHCO₃ solution, the organic phase was separated, dried over MgSO₄, filtered, and concentrated to afford the title compound (195 mg, 96%) as a yellow solid. m/z (ES⁺) [M+H]⁺ = 521.4.

1-[1-[3-[1-[5-[3-[3-Amino-6-(5-fluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-ethyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

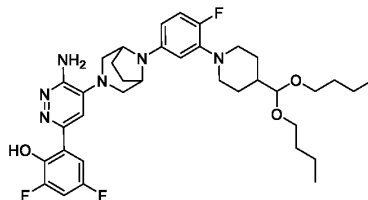


[1782] Prepared in an analogous method to EXAMPLE 64 starting from Intermediate 103b (36 mg, 0.07 mmol) and intermediate 56c (29 mg, 0.07 mmol). Purification by RPC (elution gradient: 50-100% MeCN in water with 0.1% FA) gave the title compound (31.0 mg, 48.4 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.20 - 1.30 (4H, m), 1.34 - 1.42 (2H, m), 1.44 - 1.61 (4H, m), 1.69 - 1.79 (3H, m), 1.80 - 1.89 (2H, m), 1.91 - 2.10 (7H, m), 2.21 - 2.32 (1H, m), 2.34 - 2.43 (1H, m), 2.65 - 2.72 (4H, m), 2.72 - 2.79 (2H, m), 3.02 - 3.12 (4H, m), 3.29 - 3.44 (6H, m), 3.47 - 3.58 (2H, m), 3.76 - 3.82 (2H, m), 4.34 - 4.40 (2H, m), 4.59 - 4.68 (1H, m), 6.48 (2H, br t), 6.97 - 7.08 (3H, m), 7.14 - 7.29 (2H, m), 7.46 (2H, br t), 7.56 (1H, s), 7.91 (1H, d), 8.15 (1H, d), 10.39 (1H, s) (OH proton was not observed); m/z (ES⁺) [M+H]⁺ = 914.5.

EXAMPLE 104

Intermediate 104a:

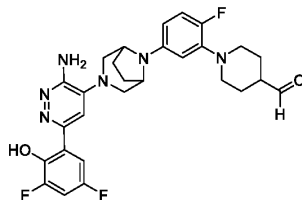
2-[6-Amino-5-[8-[3-[4-(dibutoxymethyl)-1-piperidyl]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-yl]-4,6-difluoro-phenol



[1783] Prepared in an analogous method to Intermediate 103a starting from Intermediate 11f (250 mg, 0.43 mmol) and (3,5-difluoro-2-hydroxyphenyl)boronic acid (76 mg, 0.43 mmol). Purification by FSC (elution gradient: 10-40% EtOAc in hexanes, then 10% MeOH in EtOAc) gave the title compound (241 mg, 83 %) as a yellow solid. ¹H NMR (CD₂Cl₂): δ 0.88 - 0.95 (6H, m), 1.37 - 1.43 (4H, m), 1.51 - 1.59 (10H, m), 1.64 - 1.77 (1H, m), 1.78 - 1.88 (2H, m), 2.02 - 2.08 (2H, m), 2.12 - 2.19 (2H, m), 2.58 - 2.65 (2H, m), 3.18 - 3.26 (4H, m), 3.59 - 3.64 (2H, m), 4.17 - 4.20 (1H, m), 4.29 (2H, br s), 4.83 - 4.91 (2H, m), 6.32 - 6.38 (1H, m), 6.43 (1H, dd), 6.85 - 6.94 (2H, m), 7.10 - 7.18 (2H, m), 13.89 - 14.10 (1H, m); m/z (ES⁺) [M+H]⁺ = 669.3.

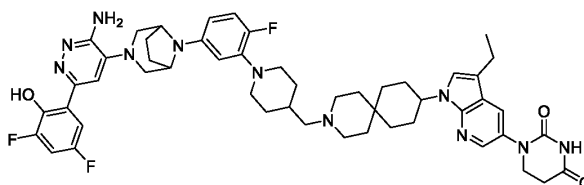
Intermediate 104b:

1-[5-[3-[3-Amino-6-(3,5-difluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]piperidine-4-carbaldehyde



[1784] Prepared in an analogous method to Intermediate 103b starting from Intermediate 104a (268 mg, 0.4 mmol) gave the title compound (192 mg, 89 %) as a yellow solid. m/z (ES^+) $[M+H]^+ = 539.6$.

1-[1-[3-[[1-[5-[3-[3-Amino-6-(3,5-difluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-ethyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

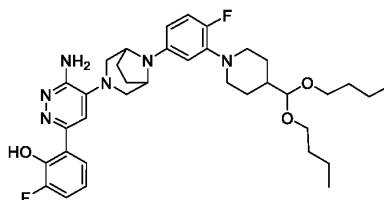


[1785] Prepared in an analogous method to EXAMPLE 64 starting from Intermediate 104b (38 mg, 0.07 mmol) and Intermediate 56c (29 mg, 0.07 mmol) gave the title compound (18 mg, 27.6 %) as a white solid following lyophilization. 1H NMR (DMSO- d_6): δ 1.24 - 1.31 (4H, m), 1.33 - 1.43 (2H, m), 1.44 - 1.62 (4H, m), 1.70 - 1.80 (3H, m), 1.81 - 1.88 (2H, m), 1.91 - 1.97 (3H, m), 1.97 - 2.05 (2H, m), 2.05 - 2.12 (2H, m), 2.22 - 2.29 (1H, m), 2.34 - 2.42 (1H, m), 2.66 - 2.73 (4H, m), 2.73 - 2.79 (2H, m), 3.01 - 3.14 (4H, m), 3.22 - 3.31 (2H, m), 3.34 - 3.45 (6H, m), 3.79 (2H, t), 4.36 (2H, br s), 4.63 (1H, br t), 6.43 - 6.52 (2H, m), 6.73 - 6.90 (2H, m), 6.94 - 7.00 (1H, m), 7.37 - 7.42 (1H, m), 7.46 - 7.52 (2H, m), 7.55 (1H, s), 7.90 (1H, d), 8.15 (1H, d), 10.36 (1H, s) (OH proton not observed); m/z (ES^+) $[M+H]^+ = 932.5$.

EXAMPLE 105

Intermediate 105a:

2-[6-Amino-5-[8-[3-[4-(dibutoxymethyl)-1-piperidyl]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-yl]-6-fluoro-phenol

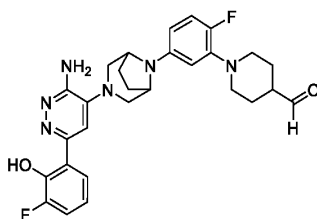


[1786] Prepared in an analogous method to Intermediate 103a starting from Intermediate 11f (230 mg, 0.4 mmol) and (3,5-difluoro-2-hydroxyphenyl)boronic acid (62 mg, 0.4 mmol). Purification by FSC (elution gradient: 10-30% EtOAc in hexane then 10% MeOH in EtOAc) gave the title compound (231 mg, 89 %)

as a yellow solid. ^1H NMR (CD_2Cl_2): δ 0.90 - 0.95 (6H, m), 1.33 - 1.43 (4H, m), 1.44 - 1.54 (6H, m), 1.64 - 1.77 (1H, m), 1.79 - 1.88 (2H, m), 1.98 - 2.08 (2H, m), 2.08 - 2.22 (2H, m), 2.61 (2H, br t), 3.17 - 3.33 (4H, m), 3.43 (4H, br d), 3.57 - 3.64 (2H, m), 4.18 (1H, br d), 4.29 (2H, br s), 4.77 - 4.90 (2H, m), 6.35 (1H, br d), 6.40 - 6.45 (1H, m), 6.72 - 6.85 (1H, m), 6.89 (1H, br dd), 7.09 (1H, br t), 7.27 (1H, s), 7.39 (1H, br d), 14.14 - 14.43 (1H, m); m/z (ES^+) $[\text{M}+\text{H}]^+ = 651.3$.

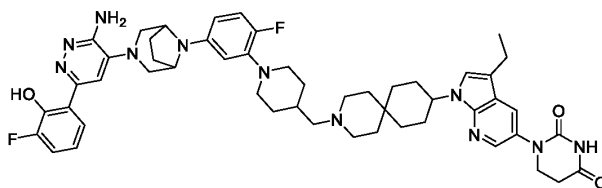
Intermediate 105b:

1-[5-[3-[3-Amino-6-(3-fluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]piperidine-4-carbaldehyde



[1787] Prepared in an analogous method to Intermediate 103b starting from Intermediate 105a (260 mg, 0.4 mmol) gave the title compound (185 mg, 89 %) as a yellow solid. m/z (ES^+) $[\text{M}+\text{H}]^+ = 521.5$.

1-[1-[3-[[1-[5-[3-[3-Amino-6-(3-fluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-ethyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

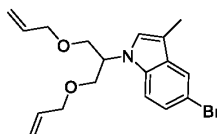


[1788] Prepared in an analogous method to EXAMPLE 64 starting from Intermediate 105b (31 mg, 0.06 mmol) and Intermediate 56c (25 mg, 0.06 mmol). Purification by RPC (elution gradient: 20 to 60% MeCN in water with 0.1% FA) gave the title compound (21 mg, 38.3 %) as a white solid. ^1H NMR ($\text{DMSO}-d_6$): δ 1.19 - 1.30 (4H, m), 1.34 - 1.44 (2H, m), 1.45 - 1.62 (4H, m), 1.70 - 1.79 (3H, m), 1.80 - 1.88 (2H, m), 1.90 - 2.09 (7H, m), 2.19 - 2.31 (1H, m), 2.31 - 2.43 (1H, m), 2.64 - 2.73 (4H, m), 2.73 - 2.79 (2H, m), 3.01 - 3.12 (4H, m), 3.24 - 3.32 (2H, m), 3.34 - 3.38 (2H, m), 3.43 - 3.51 (2H, m), 3.74 - 3.85 (2H, m), 4.32 - 4.39 (2H, m), 4.57 - 4.71 (1H, m), 6.41 - 6.52 (2H, m), 6.78 - 6.99 (4H, m), 7.30 - 7.37 (2H, m), 7.41 - 7.47 (3H, m), 7.55 (1H, s), 7.90 (1H, d), 8.16 (1H, d), 10.36 (1H, s) (OH proton not observed); m/z (ES^+) $[\text{M}+\text{H}]^+ = 914.6$.

EXAMPLE 106

Intermediate 106a:

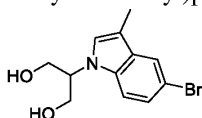
1-[2-Allyloxy-1-(allyloxymethyl)ethyl]-5-bromo-3-methyl-indole



[1789] 2-(Tributyl-15-phosphaneylidene)acetone nitrile (3.24 mL, 12.38 mmol) was added in dropwise to a stirred solution of 5-bromo-3-methyl-1H-indole (2 g, 9.52 mmol) and 1,3-bis(allyloxy)propan-2-ol (2.132 g, 12.38 mmol) in toluene (20 mL) under nitrogen atmosphere. The reaction mixture was heated to 100 °C for overnight. The reaction mixture was concentrated under reduced pressure and purified by FSC (elution gradient: 0-30% EtOAc in Hexanes) gave the title compound (1.800 g, 51.9 %) as an orange oil. ¹H NMR (CDCl₃): δ 2.30 (3H, s), 3.84 (4H, dd), 3.97 - 3.99 (4H, m), 4.59 - 4.67 (1H, m), 5.18 - 5.27 (4H, m), 5.79 - 5.91 (2H, m), 7.19 - 7.30 (3H, m), 7.64 - 7.71 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 364.1, 366.1.

Intermediate 106b:

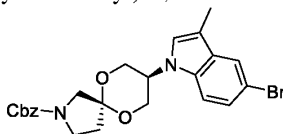
2-(5-Bromo-3-methyl-indol-1-yl)propane-1,3-diol



[1790] Pd(PPh₃)₄ (0.422 g, 0.37 mmol) and 1,3-dimethylbarbituric acid (1.629 g, 10.43 mmol) were added to a solution of Intermediate 106a (1.9g, 5.22 mmol) in methanol (20 mL). The flask was evacuated and backfilled with nitrogen (3x). The resulting mixture was stirred at r.t. for 24 h and concentrated under reduced pressure. Purification by FSC (elution gradient: 0-100% EtOAc in hexanes) gave the title compound (1.0 g, 67.5 %) as an orange gum. ¹H NMR (DMSO-*d*₆): δ 2.23 (3H, d), 3.69 - 3.80 (4H, m), 4.39 (1H, s), 4.55 - 5.00 (2H, br.s), 7.19 (1H, dd), 7.29 (1H, s), 7.40 (1H, d), 7.63 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 286.0.

Intermediate 106c:

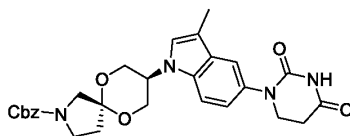
Benzyl (5*s*,8*s*)-8-(5-bromo-3-methyl-indol-1-yl)-6,10-dioxo-2-azaspiro[4.5]decane-2-carboxylate



[1791] Prepared in an analogous method to Intermediate 64d starting from Intermediate 106b (920 mg, 3.24 mmol) and Intermediate 65a (1288 mg, 4.86 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound, *cis* isomer that eluted second from the column (600 mg, 38.2 %) as an orange gum. ¹H NMR (DMSO-*d*₆): δ 2.24 (3H, s), 2.32 (2H, br t), 3.44 (1H, br t), 3.48 (1H, br t), 3.70 (2H, br s), 4.00 - 4.05 (2H, m), 4.30 (2H, br s), 4.56 - 4.63 (1H, m), 5.10 (2H, s), 7.22 - 7.25 (1H, m), 7.32 - 7.34 (1H, m), 7.38 (4H, br d), 7.46 (1H, br t), 7.57 - 7.63 (1H, m), 7.68 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 485.1, 487.0.

Intermediate 106d:

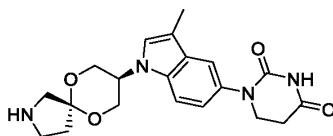
Benzyl (5*s*,8*s*)-8-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-indol-1-yl]-6,10-dioxo-2-azaspiro[4.5]decane-2-carboxylate



[1792] Prepared in an analogous method to Intermediate 2b using Intermediate 106c (650 mg, 1.34 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (470 mg, 67.7 %) as a yellow solid. ¹H NMR (DMSO-*d*₆): δ 2.26 (3H, s), 2.32 (2H, br t), 2.73 (2H, t), 3.44 (1H, br t), 3.49 (1H, br t), 3.66 (2H, s), 3.78 (2H, t), 4.01 - 4.08 (2H, m), 4.26 - 4.36 (2H, m), 4.58 - 4.64 (1H, m), 5.10 (2H, s), 7.08 (1H, dd), 7.33 (1H, br d), 7.39 (4H, br d), 7.43 (1H, d), 7.47 (1H, br t), 7.58 (1H, br d), 10.25 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 519.3.

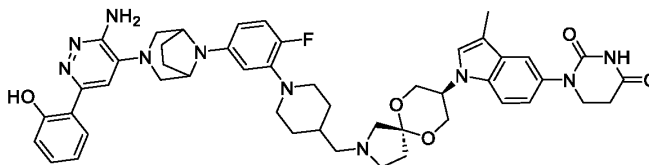
Intermediate 106e:

1-[1-((5s,8s)-6,10-Dioxo-2-azaspiro[4.5]decan-8-yl)-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione



[1793] Prepared in an analogous manner to Intermediate 64f starting from Intermediate 106d (500 mg, 0.96 mmol). Purification by FSC (elution gradient: 0 to 100% [0.5% NH₄OH in MeOH] in DCM) gave the title compound (240 mg, 64.7 %) as an off-white solid. ¹H NMR (DMSO-*d*₆): δ 2.05 (2H, t), 2.26 (3H, s), 2.74 (2H, t), 2.89 (2H, t), 2.98 (2H, s), 3.78 (2H, t), 4.00 (2H, dd), 4.26 (2H, dd), 4.55 (1H, br t), 7.08 (1H, dd), 7.43 (1H, d), 7.45 (1H, d), 7.55 (1H, s), 10.25 (1H, br s), NH proton not observed; *m/z* (ES⁺) [M+H]⁺ = 385.4.

1-[1-[(5s,8s)-2-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione



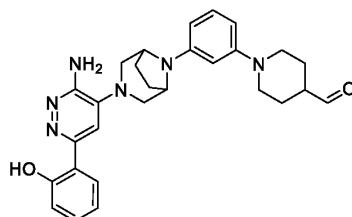
[1794] Prepared in an analogous manner to EXAMPLE 64 starting from Intermediate 13d (60 mg, 0.12 mmol) and Intermediate 106e (45.9 mg, 0.12 mmol). Purification by RPC (elution gradient: 0-80% MeCN in water with 0.1% HCOOH) gave the title compound (57.0 mg, 54.1 %) as a white solid following lyophilization. ¹H NMR (DMSO-*d*₆): δ 1.20 - 1.34 (2H, m), 1.56 - 1.67 (1H, m), 1.81 (2H, br d), 1.91 - 1.98 (2H, m), 2.10 - 2.16 (4H, m), 2.26 (3H, s), 2.31 (2H, br d), 2.59 - 2.70 (4H, m), 2.74 (2H, t), 2.82 (2H, s), 3.11 (2H, br d), 3.26 (2H, br d), 3.36 (2H, br d), 3.78 (2H, t), 3.98 (2H, br dd), 4.25 (2H, br dd), 4.35 (2H, br s), 4.52 - 4.59 (1H, m), 5.94 (2H, s), 6.43 (1H, br d), 6.49 (1H, dd), 6.84 - 6.96 (3H, m), 7.08 (1H, dd),

7.21 - 7.26 (1H, m), 7.43 (1H, d), 7.44 - 7.48 (2H, m), 7.55 (1H, s), 7.89 - 7.94 (1H, m), 10.26 (1H, s), 13.33 - 14.77 (1H, br s); m/z (ES^+) $[M+H]^+ = 871.8$.

EXAMPLE 107

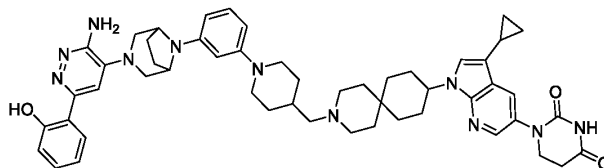
Intermediate 107a:

1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]piperidine-4-carbaldehyde



[1795] Prepared in an analogous method to Intermediate 83c starting from Intermediate 3e (150 mg, 0.24 mmol) gave the title compound (90 mg, 76 %) as an orange solid. The crude product was used for the next step. m/z (ES^+) $[M+H]^+ = 485.4$.

1-[1-[3-[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

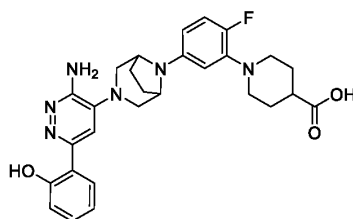


[1796] Prepared in an analogous method to EXAMPLE 64 starting from Intermediate 107a (25mg, 0.05 mmol) and Intermediate 36a (21.75 mg, 0.05 mmol). Purification by RPC (elution gradient: 0-60% MeCN in water with 0.1% formic acid) gave the title compound (12.00 mg, 26.1 %) as a white solid following lyophilization. 1H NMR ($DMSO-d_6$): δ 0.65 (2H, dd), 0.82 - 0.90 (2H, m), 1.12 - 1.33 (4H, m), 1.39 (2H, br s), 1.64 - 1.82 (8H, m), 1.88 - 2.03 (5H, m), 2.13 (2H, br d), 2.24 (2H, br d), 2.41 (4H, br s), 2.62 (2H, br t), 2.76 (2H, t), 3.09 (2H, br d), 3.25 (2H, br d), 3.64 (3H, br d), 3.81 (2H, t), 4.38 (2H, br s), 4.58 (1H, br s), 5.93 (2H, s), 6.28 (1H, br d), 6.34 (1H, br d), 6.42 (1H, s), 6.80 - 6.90 (2H, m), 7.01 (1H, t), 7.16 - 7.27 (1H, m), 7.47 (2H, d), 7.86 - 8.00 (2H, m), 8.13 - 8.24 (1H, m), 10.37 (1H, s), 15.43 (1H, br s); m/z (ES^+) $[M+H]^+ = 890.5$.

EXAMPLE 108

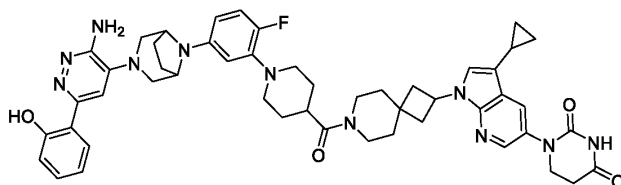
Intermediate 108a:

1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluorophenyl]piperidine-4-carboxylic acid



[1797] Potassium peroxomonosulfate (Oxone) (0.278 mL, 0.50 mmol) was added to stirred solution of Intermediate 13d (250 mg, 0.50 mmol) in DMF (4 mL). The resulting mixture was stirred for 3 h at r.t. The reaction mixture was filtered, and filtrate was concentrated. Purification by RPC (elution gradient: 25-50% MeCN in water with 0.1% formic acid) gave the title compound (50.0 mg, 19.38 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.70 (2H, br d), 1.87 - 1.99 (4H, m), 2.13 (2H, br d), 2.30 - 2.41 (1H, m), 2.72 (2H, br t), 3.10 (2H, br d), 3.26 (2H, br d), 3.32 (2H, br d), 4.36 (2H, br s), 5.93 (2H, s), 6.40 - 6.53 (2H, m), 6.80 - 7.01 (3H, m), 7.18 - 7.29 (1H, m), 7.47 (1H, s), 7.91 (1H, br d), 12.61 - 14.63 (1H, m), (COOH proton not observed); *m/z* (ES⁺) [M+H]⁺ = 519.3.

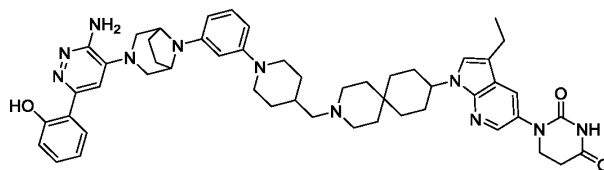
1-[1-[7-[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]piperidine-4-carbonyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1798] HATU (12.10 mg, 0.03 mmol) was added to a stirred solution of Intermediate 108a (15 mg, 0.03 mmol) Intermediate 2c (11.38 mg, 0.03 mmol) and DIPEA (10.10 μl, 0.06 mmol) in DMF (1 mL). The resulting mixture was stirred at r.t. for 1 h. The reaction mixture was directly purified by RPC (elution gradient: 0-80% MeCN in water with 0.1% NH₄OH) gave the title compound (10.0 mg, 38.7 %) as a white solid following lyophilization. ¹H NMR (DMSO-*d*₆): δ 0.70 (2H, br d), 0.88 (2H, br d), 1.60 - 1.81 (8H, m), 1.91 - 2.01 (3H, m), 2.14 (2H, br d), 2.29 (2H, br s), 2.41 (2H, br s), 2.77 (5H, br t), 3.11 (2H, br d), 3.26 (2H, br d), 3.40 (4H, br d), 3.53 (2H, br s), 3.82 (2H, br t), 4.36 (2H, br s), 5.24 - 5.37 (1H, m), 5.94 (2H, br s), 6.42 - 6.52 (2H, m), 6.83 - 6.90 (2H, m), 6.94 (1H, br dd), 7.23 (1H, br t), 7.47 (1H, s), 7.58 (1H, br s), 7.91 (1H, br d), 7.96 (1H, d), 8.18 (1H, d), 10.38 (1H, br s), 14.16 (1H, br s); *m/z* (ES⁺) [M+H]⁺ = 894.7.

EXAMPLE 109

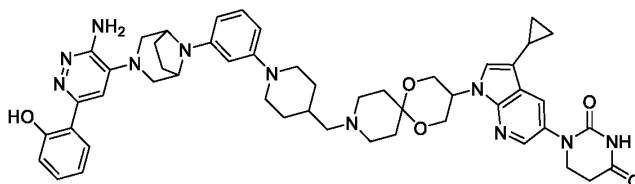
1-[1-[3-[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-ethyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1799] Prepared in an analogous method to EXAMPLE 64 starting from Intermediate 107a (25 mg, 0.05 mmol) and Intermediate 56c (21.13 mg, 0.05 mmol). Purification by RPC (elution gradient: 0-60% MeCN in water with 0.1% formic acid) gave the title compound (12.00 mg, 26.5 %) as a white solid following lyophilization. ¹H NMR (DMSO-*d*₆): δ 1.13 - 1.33 (7H, m), 1.38 (2H, br s), 1.59 - 1.83 (9H, m), 1.91 - 2.06 (4H, m), 2.08 - 2.24 (4H, m), 2.35 (4H, br s), 2.56 - 2.72 (4H, m), 2.75 (2H, t), 3.09 (2H, br d), 3.25 (2H, br d), 3.64 (2H, br d), 3.80 (2H, t), 4.39 (2H, br s), 4.54 - 4.65 (1H, m), 5.92 (2H, s), 6.24 - 6.29 (1H, m), 6.34 (1H, br d), 6.42 (1H, s), 6.81 - 6.89 (2H, m), 7.01 (1H, t), 7.18 - 7.27 (1H, m), 7.45 (1H, s), 7.54 (1H, s), 7.87 - 7.94 (2H, m), 8.15 (1H, d), 10.36 (1H, s), 13.85 - 14.76 (1H, br s); *m/z* (ES⁺) [M+H]⁺ = 878.7.

EXAMPLE 110

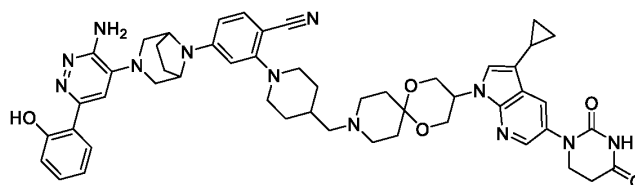
1-[1-[9-[[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1800] Prepared in an analogous method to EXAMPLE 64 starting from Intermediate 107a (25mg, 0.05 mmol) and Intermediate 87e (21.95 mg, 0.05 mmol). Purification by RPC (elution gradient: 0-60% MeCN in water with 0.1% formic acid) gave the title compound (14.00 mg, 30.4 %) as a white solid following lyophilization. ¹H NMR (DMSO-*d*₆): δ 0.58 - 0.68 (2H, m), 0.84 - 0.95 (2H, m), 1.11 - 1.28 (2H, m), 1.77 (2H, br d), 1.89 - 2.02 (7H, m), 2.09 - 2.23 (4H, m), 2.40 (4H, br s), 2.54 (1H, s), 2.61 (2H, br t), 2.76 (2H, t), 3.09 (2H, br d), 3.25 (2H, br d), 3.62 - 3.67 (2H, m), 3.81 (2H, t), 4.03 (2H, br dd), 4.23 (2H, br dd), 4.38 (2H, br s), 4.81 (1H, br t), 5.92 (2H, s), 6.28 (1H, br d), 6.33 (1H, br d), 6.42 (1H, s), 6.81 - 6.91 (2H, m), 7.01 (1H, t), 7.18 - 7.27 (1H, m), 7.45 (1H, s), 7.63 (1H, s), 7.91 (1H, dd), 7.97 (1H, d), 8.19 (1H, d), 10.38 (1H, s), 13.30 - 15.40 (1H, br s); *m/z* (ES⁺) [M+H]⁺ = 894.5.

EXAMPLE 111

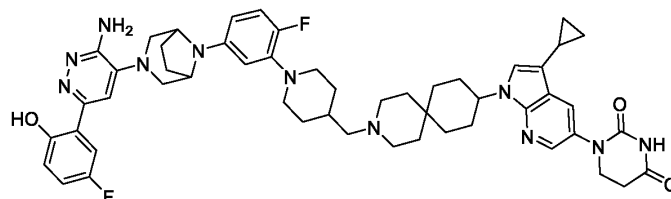
4-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-[4-[[3-[3-cyclopropyl-5-(2,4-dioxohexahydropyrimidin-1-yl)pyrrolo[2,3-*b*]pyridin-1-yl]-1,5-dioxo-9-azaspiro[5.5]undecan-9-yl]methyl]-1-piperidyl]benzonitrile



[1801] Prepared in an analogous method to EXAMPLE 64 starting from Intermediate 83c (20 mg, 0.04 mmol) and Intermediate 87c (20.04 mg, 0.05 mmol). Purification by RPC (elution gradient: 0-100% MeCN in water with 0.1% formic acid) gave the title compound (15.0 mg, 41.6 %) as a white solid following lyophilization. ^1H NMR (DMSO-*d*6): δ 0.62 - 0.68 (2H, m), 0.87 - 0.91 (2H, m), 1.21 - 1.32 (4H, m), 1.64 - 1.70 (1H, m), 1.81 - 1.84 (1H, m), 1.93 - 2.01 (5H, m), 2.18 - 2.25 (3H, m), 2.74 - 2.81 (6H, m), 3.05 (4H, br d), 3.56 (5H, br s), 3.83 (3H, br t), 4.05 (2H, br dd), 4.25 (2H, br d), 4.56 - 4.60 (2H, m), 4.80 - 4.85 (1H, m), 5.76 (2H, s), 5.97 - 6.01 (1H, m), 6.51 (2H, s), 6.54 - 6.60 (1H, m), 6.85 - 6.90 (1H, m), 7.19 - 7.26 (1H, m), 7.37 - 7.43 (1H, m), 7.48 - 7.53 (1H, m), 7.64 - 7.67 (1H, m), 7.99 (1H, d), 8.19 - 8.24 (1H, m), 10.34 - 10.43 (1H, m), 14.14 (1H, br s); m/z (ES^+) $[\text{M}+\text{H}]^+ = 919.8$.

EXAMPLE 112

1-[1-[3-[[1-[5-[3-[3-Amino-6-(5-fluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

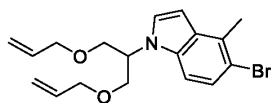


[1802] Prepared in an analogous method to EXAMPLE 64 starting from Intermediate 103b (21 mg, 0.04 mmol) and Intermediate 36a (20mg, 0.05 mmol). Purification by RPC (elution gradient: 0-60% MeCN in water with 0.1% FA) gave the title compound (22.0 mg, 59.4 %) as a white solid. ^1H NMR (DMSO-*d*6): δ 0.60 - 0.69 (2H, m), 0.80 - 0.89 (2H, m), 1.20 - 1.31 (4H, m), 1.33 - 1.40 (2H, m), 1.57 - 1.71 (5H, m), 1.73 - 1.84 (4H, m), 1.89 - 2.01 (5H, m), 2.08 - 2.14 (2H, m), 2.16 - 2.23 (2H, m), 2.33 (4H, br s), 2.62 (2H, br t), 2.75 (2H, br t), 3.07 - 3.13 (2H, m), 3.20 - 3.26 (2H, m), 3.27 - 3.33 (2H, m), 3.80 (2H, br t), 4.33 (2H, br s), 4.57 (1H, br t), 6.01 (2H, br s), 6.34 - 6.53 (2H, m), 6.82 - 6.95 (2H, m), 7.05 (1H, td), 7.48 (2H, d), 7.81 - 7.87 (1H, m), 7.92 (1H, d), 8.14 (1H, d), 10.39 (1H, s), 13.50 - 14.56 (1H, m); m/z (ES^+) $[\text{M}+\text{H}]^+ = 926.5$.

EXAMPLE 113

Intermediate 113a:

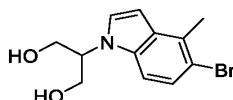
1-[2-Allyloxy-1-(allyloxymethyl)ethyl]-5-bromo-4-methyl-indole



[1803] A mixture of 5-bromo-4-methyl-1*H*-indole (0.61 g, 2.90 mmol), 1,3-bis(allyloxy)propan-2-ol (0.77 mL, 4.36 mmol) and 2-(tributyl-*l*5-phosphaneylidene)acetonitrile (1.14 mL, 4.36 mmol) in toluene (9.7 mL) was stirred at 70 °C for 16 h. After cooling to r.t., the mixture was concentrated under reduced pressure. Purification by FSC (1st purification: 0-10% acetone in hexanes; 2nd purification: 30-100% DCM in hexanes) gave the title compound (0.34 g, 33%) as a yellow oil. ¹H NMR (DMSO-*d*₆): δ 2.49 (3H, s), 3.72 - 3.83 (4H, m), 3.85 - 3.94 (4H, m), 4.79 - 4.89 (1H, m), 5.04 - 5.11 (2H, m), 5.11 - 5.18 (2H, m), 5.69 - 5.84 (2H, m), 6.55 (1H, d), 7.24 (1H, d), 7.34 (1H, d), 7.50 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 364.0.

Intermediate 113b:

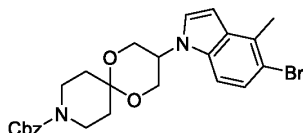
2-(5-Bromo-4-methyl-indol-1-yl)propane-1,3-diol



[1804] Prepared in an analogous method to Intermediate 64b using Intermediate 113a (338 mg, 0.93 mmol). Purification by FSC (elution gradient: 0-80% acetone in hexanes) and trituration with DCM-hexanes (1:1) gave the title compound (153 mg, 58%) as a red solid. ¹H NMR (DMSO-*d*₆) δ 2.49 (3H, s), 3.67 - 3.86 (4H, m), 4.34 - 4.51 (1H, m), 4.86 (2H, t), 6.51 (1H, d), 7.20 - 7.24 (1H, m), 7.25 - 7.29 (1H, m), 7.47 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 284.2.

Intermediate 113c:

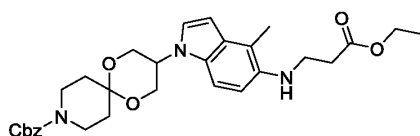
Benzyl 3-(5-bromo-4-methyl-indol-1-yl)-1,5-dioxo-9-azaspiro[5.5]undecane-9-carboxylate



[1805] Prepared in an analogous method to Intermediate 64d using Intermediate 113b (737 mg, 2.59 mmol). Purification by FSC (1st purification: 0-30% acetone in hexanes; 2nd purification: 0-15% EtOAc in DCM) gave the title compound (836 mg, 65%) as a white foam. ¹H NMR (DMSO-*d*₆): δ 1.83 (2H, br s), 1.98 (2H, br s), 2.43 - 2.55 (3H, m), 3.44 (4H, br s), 3.98 (2H, br dd), 4.31 (2H, br d), 4.56 (1H, br t), 5.08 (2H, s), 6.57 (1H, d), 7.23 - 7.41 (7H, m), 7.78 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 499.2.

Intermediate 113d:

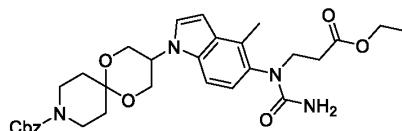
Benzyl 3-[5-[(3-ethoxy-3-oxo-propyl)amino]-4-methyl-indol-1-yl]-1,5-dioxo-9-azaspiro[5.5]undecane-9-carboxylate



[1806] A 40 mL vial was charged with Intermediate 113c (0.84 g, 1.67 mmol), ethyl 3-aminopropanoate hydrochloride (0.39 g, 2.51 mmol), Cs₂CO₃ (1.96 g, 6.03 mmol), Pd₂(dba)₃ (0.08 g, 0.08 mmol) and CPhos (0.09 g, 0.20 mmol). 1,4-dioxane (11 mL) was added. Argon was bubbled through the mixture for 5 min. The resulting mixture was stirred at 85 °C for 5 h. After cooling to r.t., the mixture was filtered through a pad of Celite® with DCM. The filtrate was concentrated under reduced pressure. Purification by FSC (1st purification: 0-40% acetone in hexanes; 2nd purification: 0-80% EtOAc in hexanes) gave the title compound (0.52 g, 57%) as an off-white solid. ¹H NMR (DMSO-*d*₆): δ 1.17 (3H, t), 1.85 (2H, br s), 1.93 (2H, br s), 2.20 (3H, s), 2.57 (2H, t), 3.31 - 3.36 (2H, m), 3.38 - 3.50 (4H, m), 3.98 (2H, br dd), 4.06 (2H, q), 4.17 - 4.34 (3H, m), 4.39 - 4.48 (1H, m), 5.08 (2H, s), 6.32 (1H, d), 6.63 (1H, d), 7.15 (1H, d), 7.26 - 7.42 (5H, m), 7.58 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 536.2.

Intermediate 113c:

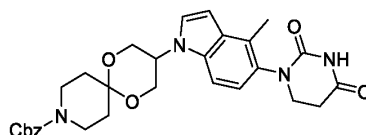
Benzyl 3-[5-[carbamoyl-(3-ethoxy-3-oxo-propyl)amino]-4-methyl-indol-1-yl]-1,5-dioxo-9-azaspiro[5.5]undecane-9-carboxylate



[1807] Potassium cyanate (382 mg, 4.71 mmol) was added to a solution of Intermediate 113d (505 mg, 0.94 mmol) in DCM (3.1 mL) and acetic acid (3.1 mL). The resulting mixture was stirred at r.t. for 25 min. The mixture was diluted with DCM (20 mL), washed with water (25 mL), sat. aq. NaHCO₃ (25 mL) and brine-sat. aq. NaHCO₃ (1:1, 25 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give the title compound as a yellowish foam which was used for the next step without further purification. Quantitative yield was assumed. *m/z* (ES⁺) [M+H]⁺ = 579.2.

Intermediate 113f:

Benzyl 3-[5-(2,4-dioxohexahydropyrimidin-1-yl)-4-methyl-indol-1-yl]-1,5-dioxo-9-azaspiro[5.5]undecane-9-carboxylate

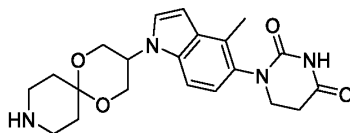


[1808] Sodium ethoxide, 21 wt% in EtOH (0.71 mL, 1.89 mmol) was added to a solution of Intermediate 113e (546 mg, 0.94 mmol) in EtOH (8.7 mL). The resulting mixture was stirred at r.t. for 60 min. Water (40 mL), sat. aq. NH₄Cl (40 mL) and DCM (30 mL) were added, and the phases were separated. The aqueous layer was extracted with DCM (2 x 30 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Trituration with Et₂O gave the title compound (405 mg, 81%) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.86 (2H, br s), 1.97 (2H, br s), 2.31 (3H, s), 2.65 - 2.84 (2H, m), 3.38 - 3.57 (5H, m), 3.68 - 3.78 (1H, m), 4.00 (2H, td), 4.30 (2H, br d), 4.51 - 4.67 (1H, m),

5.08 (2H, s), 6.56 (1H, d), 7.01 (1H, d), 7.26 - 7.46 (6H, m), 7.77 (1H, d), 10.23 (1H, s); m/z (ES^+) $[M+H]^+ = 533.2$.

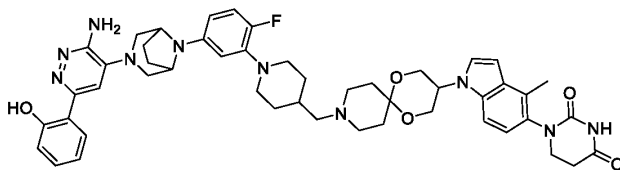
Intermediate 113g:

1-[1-(1,5-Dioxa-9-azaspiro[5.5]undecan-3-yl)-4-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione



[1809] Prepared in an analogous manner to Intermediate 64f starting from Intermediate 113f (400 mg, 0.75 mmol) gave the title compound (281 mg, 94%) as a white solid. 1H NMR ($DMSO-d_6$): δ 1.71 - 1.81 (2H, m), 1.82 - 1.93 (2H, m), 2.07 (1H, br s), 2.31 (3H, s), 2.61 - 2.83 (6H, m), 3.52 (1H, dt), 3.68 - 3.79 (1H, m), 3.96 (2H, td), 4.28 (2H, br dd), 4.50 - 4.60 (1H, m), 6.55 (1H, d), 7.01 (1H, d), 7.34 (1H, d), 7.78 (1H, d), 10.23 (1H, br s); m/z (ES^+) $[M+H]^+ = 399.1$.

1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxa-9-azaspiro[5.5]undecan-3-yl]-4-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione

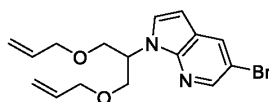


[1810] Prepared in an analogous manner to EXAMPLE 64 using Intermediate 113g (30 mg, 0.08 mmol) and Intermediate 13d (32 mg, 0.06 mmol). Purification by RPC (elution gradient: 20-45% MeCN in water with 0.1% HCOOH) gave the title compound (31.6 mg, 55%) as a white solid. 1H NMR ($DMSO-d_6$): δ 1.13 - 1.31 (2H, m), 1.54 - 1.67 (1H, m), 1.78 (2H, br d), 1.84 - 2.05 (6H, m), 2.08 - 2.16 (2H, m), 2.20 (2H, br d), 2.31 (3H, s), 2.41 (4H, br d), 2.57 - 2.82 (4H, m), 3.09 (2H, br d), 3.25 (2H, br d), 3.29 - 3.39 (2H, m), 3.52 (1H, dt), 3.73 (1H, ddd), 3.92 - 4.03 (2H, m), 4.24 - 4.39 (4H, m), 4.55 (1H, br t), 5.92 (2H, s), 6.41 (1H, dt), 6.47 (1H, dd), 6.55 (1H, d), 6.82 - 6.96 (3H, m), 7.01 (1H, d), 7.22 (1H, ddd), 7.34 (1H, d), 7.45 (1H, s), 7.79 (1H, d), 7.89 (1H, dd), 10.23 (1H, s), 12.03 - 15.85 (1H, m); m/z (ES^+) $[M+H]^+ = 885.5$.

EXAMPLE 114

Intermediate 114a:

1-[2-Allyloxy-1-(allyloxymethyl)ethyl]-5-bromo-pyrrolo[2,3-*b*]pyridine

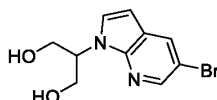


[1811] A mixture of 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (3.94 g, 20.0 mmol), 1,3-diallyloxypentan-2-ol (4.52 mL, 26.0 mmol) and 2-(tributyl-*i*-5-phosphaneylidene)acetonitrile (6.81 mL, 26.0 mmol) in

toluene (100 mL) was stirred at 100 °C for 20 h. After cooling to r.t., the mixture was concentrated under reduced pressure. Purification by FSC (elution gradient: 0-20% EtOAc in hexanes) gave the title compound (5.00 g, 71%) as a pale-yellow oil. ¹H NMR (DMSO-*d*₆): δ 3.85 - 3.96 (4H, m), 3.99 (4H, d), 5.14 - 5.29 (5H, m), 5.79 - 5.89 (2H, m), 6.42 (1H, d), 7.52 (1H, d), 8.03 (1H, d), 8.33 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 351.2.

Intermediate 114b:

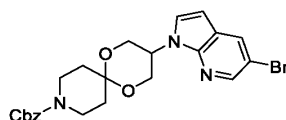
2-(5-Bromopyrrolo[2,3-*b*]pyridin-1-yl)propane-1,3-diol



[1812] Prepared in an analogous method to Intermediate 64b using Intermediate 114a (5.00 g, 14.2 mmol). Trituration with DCM–hexanes (1:1) gave the title compound (3.52 g, 91%) as a white solid. ¹H NMR (DMSO-*d*₆) δ 3.81 (4H, t), 4.84 (1H, quin), 4.90 (2H, t), 6.46 (1H, d), 7.68 (1H, d), 8.20 (1H, d), 8.28 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 270.9.

Intermediate 114c:

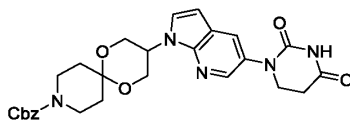
Benzyl 3-(5-bromopyrrolo[2,3-*b*]pyridin-1-yl)-1,5-dioxo-9-azaspiro[5.5]undecane-9-carboxylate



[1813] Prepared in an analogous method to Intermediate 64d using Intermediate 114b (4.00 g, 14.8 mmol), stirring at 110 °C for 4 h. After cooling to r.t., the mixture was diluted with EtOAc and washed with sat. aq. NaHCO₃ (2x) and brine. The combined aqueous layers were extracted with EtOAc. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Trituration with hexanes–acetone gave the title compound (5.72 g, 80%) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.85 (2H, br s), 2.03 (2H, br s), 3.40 - 3.53 (4H, m), 4.00 - 4.08 (2H, m), 4.39 (2H, br d), 4.85 (1H, br t), 5.10 (2H, s), 6.53 (1H, d), 7.32 - 7.41 (5H, m), 7.98 (1H, d), 8.24 - 8.28 (1H, m), 8.32 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 486.1.

Intermediate 114d:

Benzyl 3-[5-(2,4-dioxohexahydropyrimidin-1-yl)pyrrolo[2,3-*b*]pyridin-1-yl]-1,5-dioxo-9-azaspiro[5.5]undecane-9-carboxylate

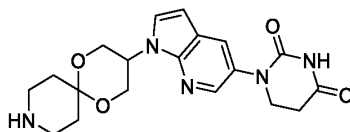


[1814] A 250 mL flask was charged with Intermediate 114c (7.30 g, 15.0 mmol), hexahydropyrimidine-2,4-dione (3.42 g, 30.0 mmol), *t*BuBrettPhos (0.72 g, 1.50 mmol), [Pd(cinnamyl)Cl]₂ (0.39 g, 0.75 mmol) and K₃PO₄ (6.37 g, 30.0 mmol). The flask was evacuated and backfilled with nitrogen (3x). The solids were suspended in 1,4-dioxane (85 mL). The flask was evacuated and backfilled with nitrogen (3x). The resulting mixture was stirred at 90 °C for 6 h. After cooling to r.t., the mixture was diluted

with EtOAc (85 mL) and filtered through a pad of Celite®. The filtrate was washed with sat. aq. NH₄Cl, water, and brine. The combined aqueous layers were back extracted with EtOAc. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Trituration with DCM–hexanes gave the title compound (5.50 g, 71%) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.89 (2H, br s), 1.97 - 2.06 (2H, m), 2.76 (2H, t), 3.48 (4H, br s), 3.82 (2H, t), 4.01 - 4.14 (2H, m), 4.38 (2H, br d), 4.90 (1H, br t), 5.10 (2H, s), 6.55 (1H, d), 7.31 - 7.36 (1H, m), 7.36 - 7.41 (4H, m), 7.93 - 7.99 (2H, m), 8.23 (1H, d), 10.39 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 520.3.

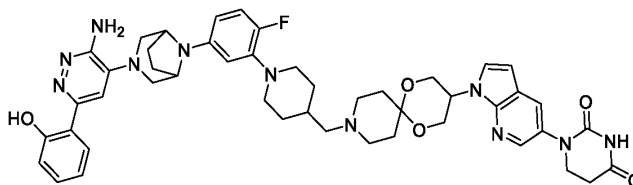
Intermediate 114e:

1-[1-(1,5-Dioxa-9-azaspiro[5.5]undecan-3-yl)pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1815] Prepared in an analogous manner to Intermediate 64f starting from Intermediate 114d (39 mg, 0.08 mmol). The residue was filtered through a pad of Celite® with DCM–*i*PrOH (3:1). The filtrate was concentrated under reduced pressure and lyophilized from water–MeCN to give the title compound as an off-white solid. ¹H NMR (DMSO-*d*₆): δ 1.74 - 1.86 (2H, m), 1.93 (2H, br s), 2.75 (6H, br t), 3.80 (2H, br t), 4.02 (2H, br dd), 4.34 (2H, br d), 4.80 - 4.93 (1H, m), 6.52 (1H, d), 7.88 - 7.98 (2H, m), 8.21 (1H, s), 10.38 (1H, br s), (one NH proton not observed); *m/z* (ES⁺) [M+H]⁺ = 386.1.

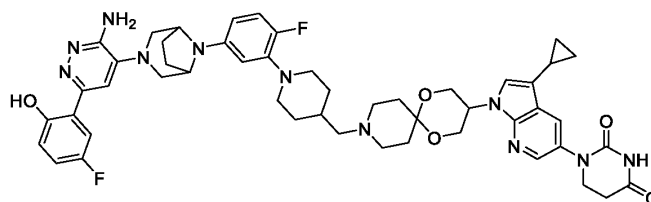
1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxa-9-azaspiro[5.5]undecan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1816] Prepared in an analogous manner to EXAMPLE 64 using Intermediate 114e (27 mg, 0.06 mmol) and Intermediate 13d (32 mg, 0.06 mmol). Purification by RPC (elution gradient: 20-45% MeCN in water with 0.1% HCOOH) gave the title compound (39.4 mg, 68%) as an off-white solid. ¹H NMR (DMSO-*d*₆): δ 1.17 - 1.34 (2H, m), 1.53 - 1.68 (1H, m), 1.78 (2H, br d), 1.86 - 1.96 (4H, m), 2.02 (2H, br s), 2.08 - 2.16 (2H, m), 2.21 (2H, br d), 2.35 - 2.48 (4H, m), 2.63 (2H, br t), 2.75 (2H, t), 3.09 (2H, br d), 3.25 (2H, br d), 3.34 (2H, br d), 3.80 (2H, t), 4.02 (2H, dd), 4.29 - 4.39 (4H, m), 4.79 - 4.96 (1H, m), 5.92 (2H, s), 6.41 (1H, dt), 6.47 (1H, dd), 6.52 (1H, d), 6.82 - 6.96 (3H, m), 7.16 - 7.26 (1H, m), 7.45 (1H, s), 7.89 (1H, dd), 7.92 - 7.98 (2H, m), 8.21 (1H, d), 10.38 (1H, s), 11.87 - 15.76 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 872.5.

EXAMPLE 115

1-[1-[9-[[1-[5-[3-[3-Amino-6-(5-fluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

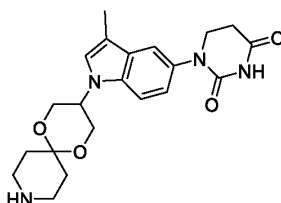


[1817] Prepared in an analogous method to EXAMPLE 64 starting from Intermediate 103b (21 mg, 0.04 mmol) and Intermediate 87e (20 mg, 0.05mmol). Purification by RPC (elution gradient: 0-60% MeCN in water with 0.1% FA) gave the title compound (21.0 mg, 56.4 %) as a white solid. ¹H NMR (DMSO-*d*6): δ 0.58 - 0.67 (2H, m), 0.81 - 0.93 (2H, m), 1.11 - 1.37 (2H, m), 1.54 - 1.66 (1H, m), 1.74 - 1.83 (2H, m), 1.86 - 2.01 (7H, m), 2.09 - 2.16 (2H, m), 2.16 - 2.24 (2H, m), 2.29 - 2.45 (4H, m), 2.57 - 2.68 (2H, m), 2.71 - 2.79 (2H, m), 3.04 - 3.12 (2H, m), 3.19 - 3.25 (2H, m), 3.27 - 3.34 (2H, m), 3.78 - 3.84 (2H, m), 4.02 (2H, br dd), 4.16 - 4.28 (2H, m), 4.33 (2H, br s), 4.74 - 4.87 (1H, m), 6.01 (2H, br s), 6.37 - 6.50 (2H, m), 6.82 - 6.94 (2H, m), 7.05 (1H, td), 7.47 (1H, s), 7.63 (1H, s), 7.84 (1H, dd), 7.97 (1H, d), 8.16 - 8.20 (1H, m), 10.40 (1H, s), 13.46 - 14.75 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 930.7.

EXAMPLE 116

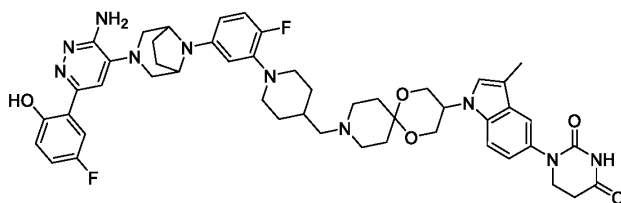
Intermediate 116a:

1-[1-(1,5-Dioxo-9-azaspiro[5.5]undecan-3-yl)-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione



[1818] TFA (2.0 mL) was added to a stirred solution of Intermediate 93d (300 mg, 0.60 mmol) in DCM (6 mL). The resulting mixture was stirred at r.t. for 2 h. The solvent was removed under reduced pressure. The reaction mixture was adjusted to pH 8 with DIPEA. The solvent was removed under reduced pressure. Purification by RPC (elution gradient: 5 to 100% MeCN in water with 0.5% NH₄HCO₃) gave the title compound (130 mg, 54.2 %) as a white solid. ¹H NMR (DMSO-*d*6): δ 1.73 - 1.94 (4H, m), 2.26 (3H, s), 2.62 - 2.80 (6H, m), 3.78 (2H, t), 3.91 - 4.02 (2H, m), 4.20 - 4.32 (2H, m), 4.46 - 4.59 (1H, m), 7.02 - 7.10 (1H, m), 7.38 - 7.49 (2H, m), 7.59 (1H, s), 10.27 (1H, s). *m/z* (ES⁺) [M+H]⁺ = 399.2.

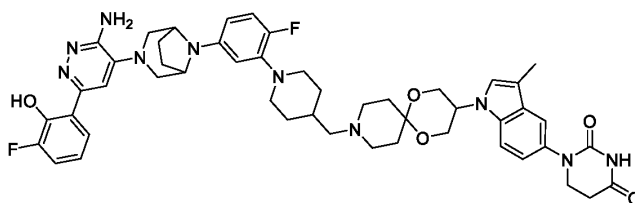
1-[1-[9-[[1-[5-[3-[3-Amino-6-(5-fluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione



[1819] Prepared in an analogous method to EXAMPLE 64 starting from Intermediate 103b (21 mg, 0.04 mmol) and intermediate 116a (19mg, 0.05 mmol). Purification by RPC (elution gradient: 0-60% MeCN in water with 0.1% FA) gave the title compound (19.2 mg, 53.2 %) as a white solid. ^1H NMR (DMSO-*d*6): δ 1.17 - 1.30 (2H, m), 1.54 - 1.67 (1H, m), 1.74 - 1.81 (2H, m), 1.88 - 2.00 (6H, m), 2.07 - 2.15 (2H, m), 2.18 - 2.22 (2H, m), 2.22 - 2.27 (3H, m), 2.30 - 2.45 (4H, m), 2.58 - 2.67 (2H, m), 2.68 - 2.75 (2H, m), 3.05 - 3.11 (2H, m), 3.17 - 3.25 (2H, m), 3.29 - 3.35 (2H, m), 3.74 - 3.80 (2H, m), 3.91 - 3.99 (2H, m), 4.15 - 4.29 (2H, m), 4.29 - 4.40 (2H, m), 4.51 (1H, br s), 6.01 (2H, br s), 6.37 - 6.50 (2H, m), 6.83 - 6.94 (2H, m), 7.02 - 7.08 (2H, m), 7.37 - 7.48 (3H, m), 7.58 (1H, s), 7.84 (1H, dd), 10.26 (1H, s), 13.13 - 14.84 (1H, m); m/z (ES^+) $[\text{M}+\text{H}]^+ = 903.5$.

EXAMPLE 117

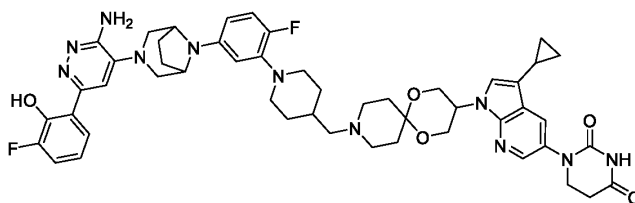
1-[1-[9-[[1-[5-[3-[3-Amino-6-(3-fluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione



Prepared in an analogous method to EXAMPLE 64 starting from Intermediate 105b (21 mg, 0.04 mmol) and Intermediate 116a (19mg, 0.05 mmol). Purification by RPC (gradient: 0-60% MeCN in water with 0.1% FA) gave the title compound (16.2 mg, 44.8 %) as a white solid. ^1H NMR (DMSO-*d*6): δ 1.16 - 1.31 (2H, m), 1.60 (1H, br s), 1.74 - 1.81 (2H, m), 1.89 - 2.01 (6H, m), 2.09 - 2.15 (2H, m), 2.15 - 2.20 (2H, m), 2.23 - 2.28 (3H, m), 2.30 - 2.44 (4H, m), 2.59 - 2.67 (2H, m), 2.70 - 2.74 (2H, m), 3.07 - 3.13 (2H, m), 3.23 - 3.27 (2H, m), 3.30 - 3.35 (2H, m), 3.74 - 3.79 (2H, m), 3.91 - 3.98 (2H, m), 4.19 - 4.29 (2H, m), 4.33 (2H, br s), 4.44 - 4.57 (1H, m), 6.05 (2H, br s), 6.38 - 6.51 (2H, m), 6.75 - 6.86 (1H, m), 6.91 (1H, dd), 7.05 (1H, dd), 7.18 (1H, dd), 7.38 - 7.45 (2H, m), 7.45 - 7.51 (1H, m), 7.58 (1H, s), 7.75 (1H, br d), 10.26 (1H, s), 14.29 - 15.83 (1H, m); m/z (ES^+) $[\text{M}+\text{H}]^+ = 903.6$.

EXAMPLE 118

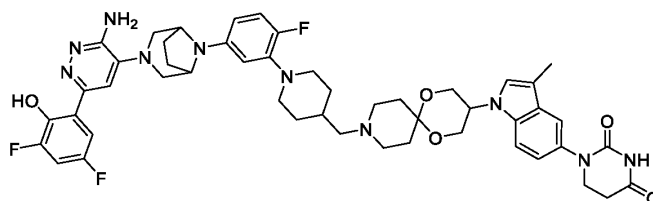
1-[1-[9-[[1-[5-[3-[3-Amino-6-(3-fluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1820] Prepared in an analogous method to EXAMPLE 64 starting from Intermediate 105b (21 mg, 0.04 mmol) and Intermediate 87e (20 mg, 0.05 mmol). Purification by RPC (elution gradient: 0-60% MeCN in water with 0.1% FA) gave the title compound (20.5 mg, 55.1 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 0.62 (2H, br d), 0.83 - 0.91 (2H, m), 1.14 - 1.30 (2H, m), 1.51 - 1.67 (1H, m), 1.74 - 1.82 (2H, m), 1.82 - 2.03 (7H, m), 2.03 - 2.16 (2H, m), 2.16 - 2.22 (2H, m), 2.28 - 2.47 (4H, m), 2.58 - 2.69 (2H, m), 2.71 - 2.81 (2H, m), 3.04 - 3.13 (2H, m), 3.18 - 3.26 (2H, m), 3.28 - 3.34 (2H, m), 3.78 - 3.86 (2H, m), 3.99 - 4.07 (2H, m), 4.16 - 4.29 (2H, m), 4.33 (2H, br s), 4.80 (1H, br s), 6.05 (2H, br s), 6.37 - 6.50 (2H, m), 6.74 - 6.87 (1H, m), 6.91 (1H, br dd), 7.14 - 7.21 (1H, m), 7.48 (1H, s), 7.63 (1H, s), 7.75 (1H, br d), 7.97 (1H, d), 8.15 - 8.22 (1H, m), 10.40 (1H, s), 14.29 - 15.71 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 930.7.

EXAMPLE 119

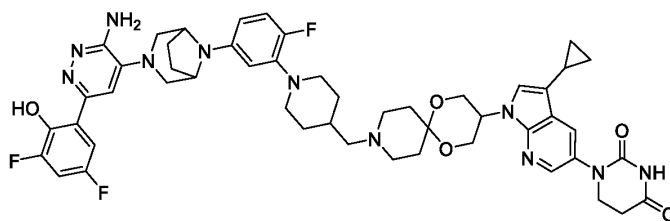
1-[1-[9-[[1-[5-[3-[3-Amino-6-(3,5-difluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxaspiro[5.5]undecan-3-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione



[1821] Prepared in an analogous method to EXAMPLE 64 starting from Intermediate 104b (22 mg, 0.04 mmol) and Intermediate 116a (19 mg, 0.05 mmol). Purification by RPC (gradient: 0-60% MeCN in water with 0.1% FA) gave the title compound (19.5 mg, 52.9 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.23 (2H, q), 1.60 (1H, br s), 1.73 - 1.81 (2H, m), 1.87 - 1.98 (6H, m), 2.07 - 2.16 (2H, m), 2.16 - 2.22 (2H, m), 2.23 - 2.27 (3H, m), 2.31 - 2.44 (4H, m), 2.62 (2H, br t), 2.72 (2H, br t), 3.08 - 3.14 (2H, m), 3.23 - 3.28 (2H, m), 3.33 - 3.37 (2H, m), 3.74 - 3.80 (2H, m), 3.92 - 3.99 (2H, m), 4.24 (2H, br d), 4.33 (2H, br s), 4.45 - 4.56 (1H, m), 6.12 (2H, br s), 6.37 - 6.50 (2H, m), 6.92 (1H, dd), 7.02 - 7.08 (1H, m), 7.21 - 7.28 (1H, m), 7.38 - 7.45 (2H, m), 7.49 (1H, s), 7.58 (1H, s), 7.77 (1H, br d), 10.26 (1H, s), 14.02 - 15.51 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 921.6.

EXAMPLE 120

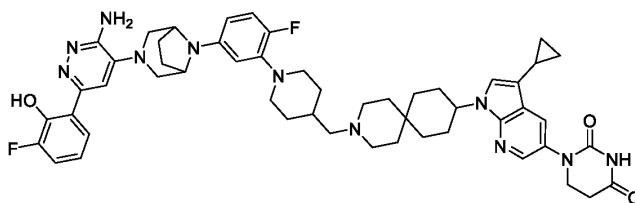
1-[1-[9-[[1-[5-[3-[3-Amino-6-(3,5-difluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxaspiro[5.5]undecan-3-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1822] Prepared in an analogous method to EXAMPLE 64 starting from Intermediate 104b (22 mg, 0.04 mmol) and Intermediate 87e (20 mg, 0.05 mmol). Purification by RPC (elution gradient: 0-60% MeCN in water with 0.1% FA) gave the title compound (19.5 mg, 51.4 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 0.58 - 0.67 (2H, m), 0.79 - 0.93 (2H, m), 1.19 - 1.28 (2H, m), 1.60 (1H, br s), 1.72 - 1.83 (2H, m), 1.85 - 2.05 (7H, m), 2.08 - 2.23 (4H, m), 2.29 - 2.46 (4H, m), 2.57 - 2.69 (2H, m), 2.71 - 2.80 (2H, m), 3.07 - 3.14 (2H, m), 3.21 - 3.26 (2H, m), 3.28 - 3.35 (2H, m), 3.79 - 3.85 (2H, m), 4.00 - 4.07 (2H, m), 4.16 - 4.28 (2H, m), 4.33 (2H, br s), 4.65 - 4.95 (1H, m), 6.12 (2H, br s), 6.38 - 6.49 (2H, m), 6.91 (1H, dd), 7.16 - 7.33 (1H, m), 7.49 (1H, s), 7.63 (1H, s), 7.77 (1H, br d), 7.97 (1H, d), 8.18 (1H, d), 10.40 (1H, s), 14.32 - 15.52 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 948.5.

EXAMPLE 121

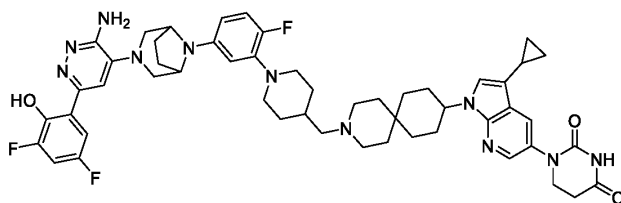
1-[1-[3-[[1-[5-[3-[3-Amino-6-(3-fluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1000] Prepared in an analogous method to EXAMPLE 64 starting from Intermediate 105b (36 mg, 0.07 mmol) and Intermediate 36a (35 mg, 0.08 mmol). Purification by RPC (elution gradient: 0-60% MeCN in water with 0.1% FA) gave the title compound (41 mg, 63.2 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 0.59 - 0.69 (2H, m), 0.79 - 0.88 (2H, m), 1.18 - 1.30 (4H, m), 1.32 - 1.42 (2H, m), 1.59 - 1.73 (5H, m), 1.74 - 1.84 (4H, m), 1.85 - 2.03 (6H, m), 2.12 (2H, br d), 2.24 (2H, br d), 2.31 - 2.47 (4H, m), 2.55 - 2.66 (2H, m), 2.75 (2H, t), 3.06 - 3.13 (2H, m), 3.23 - 3.29 (2H, m), 3.32 - 3.38 (2H, m), 3.77 - 3.83 (2H, m), 4.33 (2H, br s), 4.57 (1H, br t), 6.03 (2H, br s), 6.37 - 6.50 (2H, m), 6.91 (1H, dd), 7.17 (1H, dd), 7.48 (2H, d), 7.74 (1H, br d), 7.92 (1H, d), 8.12 - 8.17 (1H, m), 10.36 (1H, s), (OH proton not observed); *m/z* (ES⁺) [M+H]⁺ = 926.7.

EXAMPLE 122

1-[1-[3-[[1-[5-[3-[3-Amino-6-(3,5-difluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

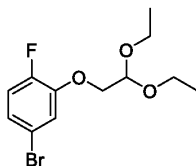


[1824] Prepared in an analogous method to example 64 starting from Intermediate 104b (38 mg, 0.07 mmol) and Intermediate 36a (35 mg, 0.08 mmol). Purification by RPC (elution gradient: 0-60% MeCN in water with 0.1% FA) gave the title compound (36 mg, 54.5 %) as a white solid. ^1H NMR (DMSO- d_6): δ 0.59 - 0.69 (2H, m), 0.78 - 0.90 (2H, m), 1.17 - 1.32 (4H, m), 1.35 - 1.45 (2H, m), 1.58 - 1.73 (5H, m), 1.73 - 1.85 (4H, m), 1.87 - 2.02 (5H, m), 2.11 (2H, br d), 2.16 - 2.29 (2H, m), 2.29 - 2.45 (4H, m), 2.63 (2H, br t), 2.75 (2H, t), 3.08 - 3.13 (2H, m), 3.23 - 3.27 (2H, m), 3.33 - 3.38 (2H, m), 3.77 - 3.86 (2H, m), 4.33 (2H, br s), 4.57 (1H, br t), 6.10 (2H, br s), 6.37 - 6.50 (2H, m), 6.91 (1H, dd), 7.19 - 7.29 (1H, m), 7.49 (2H, d), 7.76 (1H, br d), 7.92 (1H, d), 8.09 - 8.16 (1H, m), 10.36 (1H, s), 14.32 - 15.21 (1H, m); m/z (ES $^+$) $[\text{M}+\text{H}]^+ = 944.6$.

EXAMPLE 123

Intermediate 123a:

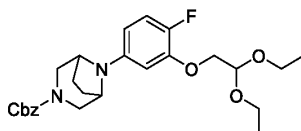
4-Bromo-2-(2,2-diethoxyethoxy)-1-fluorobenzene



[1825] A mixture of 5-bromo-2-fluorophenol (1.910 g, 10 mmol), 2-bromo-1,1-diethoxyethane (1.971 g, 10.00 mmol), K_2CO_3 (1.38 g, 10 mmol), and NaI (0.150 g, 1.00 mmol) in DMF (8 mL) was heated at 120 $^\circ\text{C}$ overnight. The reaction was cooled to r.t. The reaction mixture partitioned between water and EtOAc. The organic phase was washed with 10% LiCl solution, dried over MgSO_4 and concentrated. Purification by FSC (elution gradient: 0-10% EtOAc in hexane) gave the title compound (1.650 g, 53.7 %) as a colorless oil. ^1H NMR (CD_2Cl_2) δ 1.18 - 1.24 (6H, m), 3.58 - 3.64 (2H, m), 3.68 - 3.77 (2H, m), 4.01 (2H, d), 4.81 (1H, t), 6.97 (1H, dd), 7.02 - 7.06 (1H, m), 7.16 (1H, dd).

Intermediate 123b:

Benzyl 8-[3-(2,2-diethoxyethoxy)-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate

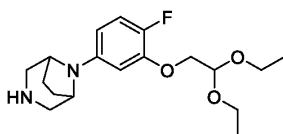


[1826] A mixture of Intermediate 123a (1.347g, 4.38 mmol), benzyl 3,8-diazabicyclo[3.2.1]octane-3-carboxylate (1.08 g, 4.38 mmol), RuPhosPdG3 (0.183 g, 0.22 mmol) and KO^tBu (0.738 g, 6.58 mmol) in toluene (20 mL) was degassed for 5 min. and backfilled with nitrogen. The mixture was stirred under

nitrogen at 105 °C for 2 h. The reaction was allowed to cool to r.t., filtered through Celite®. The filtrate was concentrated. Purification by FSC (elution gradient: 0-30% EtOAc in hexane) gave the title compound (1.60 g, 77 %) as colorless oil. ¹H NMR (CD₂Cl₂): δ 1.17 - 1.23 (6H, m), 1.74 - 1.86 (2H, m), 1.93 - 2.00 (2H, m), 3.21 - 3.28 (1H, m), 3.28 - 3.40 (1H, m), 3.57 - 3.65 (2H, m), 3.65 - 3.78 (4H, m), 4.00 (2H, d), 4.01 - 4.07 (1H, m), 4.09 - 4.14 (1H, m), 4.81 (1H, t), 5.10 (2H, s), 6.30 (1H, dt), 6.45 (1H, dd), 6.93 (1H, dd), 7.29 - 7.37 (5H, m); *m/z* (ES⁺) [M+H]⁺ = 473.6.

Intermediate 123c:

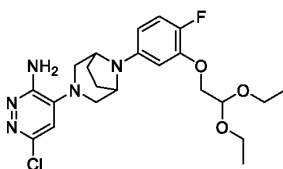
8-[3-(2,2-Diethoxyethoxy)-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octane



[1827] Intermediate 123b (1.6 g, 3.39 mmol) and Pd/C (50% wet base) (0.180 g, 0.17 mmol) in THF (40 mL) was degassed and flushed with hydrogen. The reaction was stirred at r.t. under hydrogen atmosphere for 2h. Catalyst was filtered off through celite® and filtrate was concentrated to give the title compound (1.10 g, 96 %) as a black gum. The crude material was used for the next step. ¹H NMR (CD₂Cl₂): δ 1.21 (6H, t), 1.89 - 2.05 (4H, m), 2.50 - 2.58 (2H, m), 3.14 (2H, d), 3.58 - 3.67 (2H, m), 3.74 (2H, dq), 3.95 - 4.03 (4H, m), 4.81 (1H, t), 6.26 (1H, dt), 6.41 (1H, dd), 6.91 (1H, dd); (NH proton not observed); *m/z* (ES⁺) [M+H]⁺ = 339.5.

Intermediate 123d:

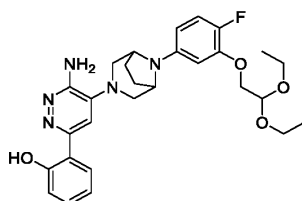
6-Chloro-4-[8-[3-(2,2-diethoxyethoxy)-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-amine



[1828] Prepared in an analogous method to Intermediate 3c starting from Intermediate 123c (1.147 g, 3.39 mmol) and 4-bromo-6-chloro-pyridazin-3-amine (0.707 g, 3.39 mmol). Purification by FSC (elution gradient: 10-80% EtOAc in hexane, then 10% MeOH in EtOAc) gave the title compound (1.180 g, 74.7 %) as a brown gum. ¹H NMR (CD₂Cl₂) δ 1.19 - 1.22 (6H, m), 2.00 - 2.04 (2H, m), 2.09 - 2.19 (2H, m), 3.06 - 3.12 (2H, m), 3.17 (2H, dd), 3.62 (2H, dq), 3.75 (2H, dq), 4.00 - 4.03 (2H, m), 4.23 (2H, br s), 4.68 (2H, s), 4.78 - 4.85 (1H, m), 6.33 (1H, dt), 6.49 (1H, dd), 6.70 (1H, s), 6.95 (1H, dd); *m/z* (ES⁺) [M+H]⁺ = 466.5.

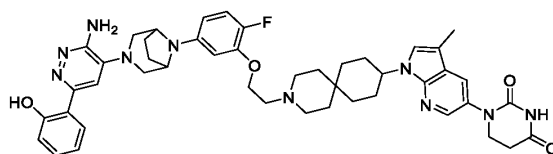
Intermediate 123e:

2-[6-Amino-5-[8-[3-(2,2-diethoxyethoxy)-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-yl]phenol



[1829] Prepared in an analogous manner to Intermediate 2h from Intermediate 123d (1.18g, 2.53 mmol). The reaction mixture was cooled to r.t. and partitioned between water (50 mL) and EtOAc (100 mL). The organic phase was separated, dried over MgSO_4 , filtered and concentrated. The residue was triturated in MeOH, product was precipitated out, solids were filtered and dried to give the title compound (0.820 g, 61.8 %) as a yellow solid. ^1H NMR (CD_2Cl_2): δ 1.20 - 1.24 (6H, m), 2.04 - 2.09 (2H, m), 2.12 - 2.19 (2H, m), 3.17 - 3.29 (5H, m), 3.58 - 3.63 (2H, m), 3.76 (3H, dq), 4.03 (2H, d), 4.28 (2H, br s), 4.78 - 4.85 (3H, m), 6.36 (1H, dt), 6.52 (1H, dd), 6.85 - 6.92 (1H, m), 6.92 - 7.01 (2H, m), 7.24 - 7.30 (2H, m), 7.60 (1H, d), 13.75 (1H, br s); m/z (ES^+) $[\text{M}+\text{H}]^+ = 524.6$.

1-[1-[3-[2-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenoxy]ethyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

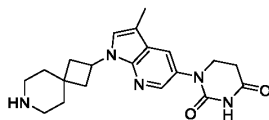


[1830] A mixture of Intermediate 123e (26.2 mg, 0.05 mmol) and *p*-toluenesulfonic acid monohydrate (9.5 mg, 0.05 mmol) in acetone (1mL) and water (0.1 mL) were heated at 60 °C overnight. Solvent was removed and the residue was partitioned between CH_2Cl_2 (20 mL) and sat. aq. NaHCO_3 (10 mL) solution. The organic phase separated, dried over MgSO_4 , filtered, and concentrated to give crude aldehyde. To the residue was added Intermediate 58a (24 mg, 0.06 mmol) in NMP (2.0 mL). The reaction was stirred at r.t. for 2 h, then sodium triacetoxyhydroborate (21 mg, 0.10 mmol) was added. The reaction was stirred at r.t. for 2 h. The reaction mixture was concentrated. Purification by RPC (elution gradient: 20-50% MeCN in water with 0.1% FA) gave the title compound (12.0 mg, 29.0 %) as a white solid. ^1H NMR ($\text{DMSO}-d_6$): δ 1.25 - 1.32 (2H, m), 1.35 - 1.42 (2H, m), 1.64 - 1.73 (4H, m), 1.76 - 1.85 (2H, m), 1.91 - 1.99 (4H, m), 2.09 - 2.15 (2H, m), 2.23 - 2.26 (3H, m), 2.31 - 2.43 (2H, m), 2.51 - 2.57 (2H, m), 2.69 - 2.80 (4H, m), 3.08 - 3.12 (2H, m), 3.18 - 3.24 (2H, m), 3.79 (2H, t), 4.17 (2H, br s), 4.39 (2H, br s), 4.54 - 4.63 (1H, m), 5.93 (2H, s), 6.37 - 6.43 (1H, m), 6.65 - 6.71 (1H, m), 6.82 - 6.89 (2H, m), 7.00 (1H, dd), 7.19 - 7.22 (1H, m), 7.45 (1H, s), 7.52 (1H, s), 7.80 - 7.92 (2H, m), 8.13 - 8.17 (1H, m), 10.35 (1H, s), 14.02 - 14.29 (1H, m); m/z (ES^+) $[\text{M}+\text{H}]^+ = 829.5$.

EXAMPLE 124

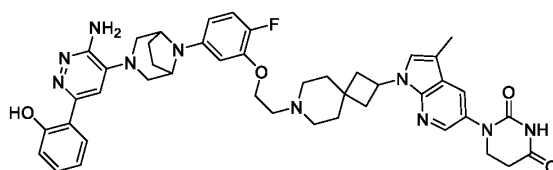
Intermediate 124a:

1-[1-(7-Azaspiro[3.5]nonan-2-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1831] Prepared from an analogous method to Intermediate 2c starting from Intermediate 15b (826 mg, 1.77 mmol). Purification by ion exchange chromatography (PoraPak Rxn CX cartridge) eluting with 1.5 N NH₃ in MeOH gave the title compound (631 mg, 97 %) as a white solid. *m/z* (ES⁺) [M+H]⁺ = 368.3.

1-[1-[7-[2-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenoxy]ethyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

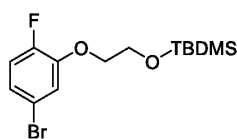


[1832] Prepared in an analogous method to EXAMPLE 123 starting from Intermediate 123e (26 mg, 0.05 mmol) and Intermediate 124a (22 mg, 0.06mmol). Purification by RPC (elution gradient: 0-60% MeCN in water with 0.1% FA) gave the title compound (4 mg, 10 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.67 (2H, br t), 1.71 (2H, br s), 1.91 - 1.98 (2H, m), 2.11 - 2.16 (2H, m), 2.16 - 2.23 (2H, m), 2.24 - 2.27 (3H, m), 2.30 - 2.47 (6H, m), 2.62 - 2.70 (2H, m), 2.74 (2H, t), 3.10 (2H, br d), 3.19 - 3.25 (2H, m), 3.79 (2H, t), 4.14 (2H, t), 4.39 (2H, br s), 5.24 (1H, quin), 5.93 (2H, s), 6.39 (1H, dt), 6.67 (1H, dd), 6.82 - 6.87 (2H, m), 6.99 (1H, dd), 7.19 - 7.23 (1H, m), 7.45 (1H, s), 7.58 (1H, s), 7.84 - 7.90 (2H, m), 8.15 (1H, d), 10.35 (1H, s), 14.05 - 14.20 (1H, m) ; *m/z* (ES⁺) [M+H]⁺ = 801.5.

EXAMPLE 125

Intermediate 125a:

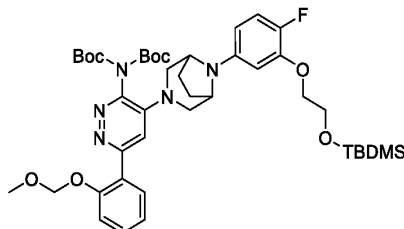
2-(5-Bromo-2-fluoro-phenoxy)ethoxy-*tert*-butyl-dimethyl-silane



[1833] A solution of di-*tert*-butyl azodicarboxylate (1.900 g, 8.25 mmol) in DCM (7 mL) was added dropwise to a solution of 5-bromo-2-fluorophenol (1.432 g, 7.5 mmol), 2-((*tert*-butyldimethylsilyl)oxy)ethan-1-ol (1.322 g, 7.50 mmol) and triphenylphosphine (2.361 g, 9.00 mmol) in DCM (30 mL) at r.t. The resulting solution was stirred at r.t. for 2 h. The solvent was removed under reduced pressure. Purification by FSC (elution gradient: 0-5% EtOAc in hexanes) gave the title compound (2.120 g, 81 %) as an colorless oil. ¹H NMR (CD₂Cl₂): δ 0.09 (6H, s), 0.90 (9H, s), 3.95 - 4.00 (2H, m), 4.07 - 4.11 (2H, m), 6.92 - 6.99 (1H, m), 6.99 - 7.07 (1H, m), 7.17 (1H, dd).

Intermediate 125b:

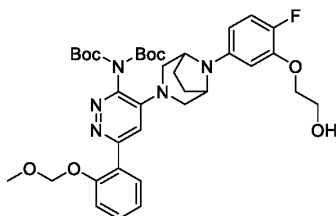
tert-Butyl *N*-*tert*-butoxycarbonyl-*N*-[4-[8-[3-[2-[*tert*-butyl(dimethyl)silyl]oxyethoxy]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]-6-[2-(methoxymethoxy)phenyl]pyridazin-3-yl]carbamate



[1834] Intermediate 125a (0.524g, 1.5 mmol), Intermediate 25d (0.813 g, 1.50 mmol), RuPhos Pd G3 (0.125 g, 0.15 mmol) and *KOt*Bu (0.252 g, 2.25 mmol) in toluene (7.50 mL) was degassed and backfilled with nitrogen. The mixture was stirred under nitrogen at 105 °C for 2 h. The reaction was cooled to r.t. filtered through Celite® and the filtrate was concentrated. Purification by FSC (elution gradient : 0-30 % EtOAc in hexanes) gave the title compound (0.516 g, 42.5 %) as colorless oil. ¹H NMR (CD₂Cl₂): δ 0.09 - 0.13 (6H, m), 0.90 - 0.92 (9H, m), 1.44 - 1.47 (18H, m), 1.94 - 1.99 (2H, m), 2.02 - 2.10 (2H, m), 3.35 - 3.36 (3H, m), 3.37 - 3.38 (3H, m), 3.92 - 4.01 (3H, m), 4.04 - 4.07 (2H, m), 4.21 (2H, br s), 5.18 (2H, s), 6.33 (1H, br d), 6.49 (1H, dd), 6.94 (1H, dd), 7.14 - 7.19 (1H, m), 7.19 - 7.24 (1H, m), 7.39 - 7.45 (2H, m), 7.85 (1H, dd); *m/z* (ES⁺) [M+H]⁺ = 811.0.

Intermediate 125c:

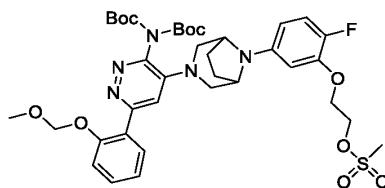
tert-Butyl *N*-*tert*-butoxycarbonyl-*N*-[4-[8-[4-fluoro-3-(2-hydroxyethoxy)phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]-6-[2-(methoxymethoxy)phenyl]pyridazin-3-yl]carbamate



[1835] Intermediate 125b (440 mg, 0.54 mmol) in THF (1 mL) was cooled to 0 °C. Then TBAF (0.6 mL, 0.6 mmol) was added slowly. The reaction was allowed to warm to r.t., and stirred for 30 min. The reaction was diluted with EtOAc and was washed with water. The organic phase was dried over MgSO₄, filtered and concentrated to give the title compound (369 mg, 98%) as a brown gum. *m/z* (ES⁺) [M+H]⁺ = 696.3.

Intermediate 125d:

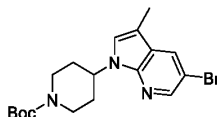
2-[5-[3-[3-[Bis(*tert*-butoxycarbonyl)amino]-6-[2-(methoxymethoxy)phenyl]pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenoxy]ethyl methanesulfonate



[1836] Intermediate 125c (376 mg, 0.54 mmol) and DIPEA (141 μ l, 0.81 mmol) in DCM (5 ml) were cooled to 0 °C and a solution of methane sulfonic anhydride (141 mg, 0.81 mmol) in DCM (1 ml) was added. The reaction was allowed to warm to r.t. and stirred for 30 min. The reaction was diluted with DCM, and was washed NaHCO₃ solution, followed by brine. The organic phase was dried over MgSO₄ and was concentrated. Purification by SFC (gradient, 15-90 % EtOAc in hexane) gave the title compound (270 mg, 64.6 %) as a white foam. ¹H NMR (CD₂Cl₂): δ 1.40 - 1.46 (18H, m), 1.94 - 2.00 (2H, m), 2.04 - 2.11 (2H, m), 3.08 (3H, s), 3.33 - 3.42 (7H, m), 4.19 - 4.25 (2H, m), 4.27 - 4.31 (2H, m), 4.52 - 4.57 (2H, m), 5.19 (2H, s), 6.40 (1H, br d), 6.50 (1H, dd), 6.98 (1H, dd), 7.13 - 7.24 (2H, m), 7.39 - 7.45 (2H, m), 7.86 (1H, dd); m/z (ES⁺) [M+H]⁺ = 774.8.

Intermediate 125e:

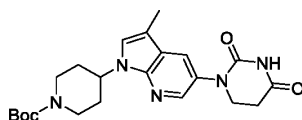
tert-Butyl 4-(5-bromo-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl)piperidine-1-carboxylate



[1837] *tert*-Butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (6.59 g, 23.59 mmol) and Cs₂CO₃ (11.5 g, 35.4 mmol) were added to a solution of 5-bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (4.98 g, 23.6 mmol) in DMF (79 mL) and the mixture was heated to 75 °C. More *tert*-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (6.59 g, 23.59 mmol) and Cs₂CO₃ (7.69 g, 23.6 mmol) were added after 4 and 7 h. After the final addition. Stirring was continued at 75 °C for 16 h. The mixture was partially concentrated under reduced pressure, diluted with EtOAc (100 mL), washed with brine (2 x 150 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0 to 30% EtOAc in hexanes) gave the title compound (7.27 g, 78%) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.43 (9H, s), 1.80 - 1.94 (4H, m), 2.23 (3H, s), 2.93 (2H, br s), 4.10 (2H, br s), 4.69 - 4.92 (1H, m), 7.51 (1H, s), 8.16 (1H, d), 8.26 (1H, d); m/z (ES⁺) [M+H]⁺ = 394.2.

Intermediate 125f:

tert-Butyl 4-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]piperidine-1-carboxylate

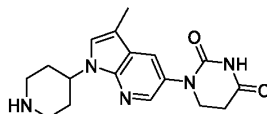


[1838] 1,4-Dioxane (82 mL) was added to a mixture of Intermediate 125e (5.48 g, 13.9 mmol), hexahydropyrimidine-2,4-dione (3.17 g, 27.8 mmol), K₃PO₄ (5.90 g, 27.8 mmol), [Pd(cinnamyl)Cl]₂ (0.36

g, 0.69 mmol) and *t*BuBrettPhos (0.67 g, 1.39 mmol). The flask was evacuated and backfilled with nitrogen (5x). The mixture was stirred at 90 °C for 15 h. After cooling to r.t., sat. aq. NH₄Cl (150 mL) was added, and the mixture was extracted with DCM (3 x 200 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was triturated with hexanes/DCM (5:1), H₂O, and hexanes to give the title compound (4.61 g, 78%) as a grey solid. ¹H NMR (DMSO-*d*₆): δ 1.42 (9H, s), 1.77 - 1.98 (4H, m), 2.23 (3H, s), 2.75 (2H, t), 2.94 (2H, br d), 3.79 (2H, t), 4.10 (2H, br d), 4.71 - 4.87 (1H, m), 7.49 (1H, s), 7.87 (1H, d), 8.16 (1H, d), 10.36 (1H, br s); *m/z* (ES⁺) [M+H]⁺ = 428.4.

Intermediate 125g:

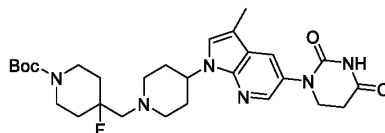
1-[3-Methyl-1-(4-piperidyl)pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1839] TFA (5.41 mL, 70.2 mmol) was added to a solution of Intermediate 125f (1.50 g, 3.51 mmol) in DCM (17 mL). The mixture was stirred at r.t. for 30 min. and concentrated under reduced pressure. DCM (100 mL), IPA (30 mL) and sat. aq. K₂CO₃ (100 mL) were added, and the phases were separated. The organic layer was washed with sat. aq. K₂CO₃ (100 mL), dried over Na₂SO₄, and concentrated under reduced pressure to give the title compound (1.17 g, 102%, 92% purity) as a yellowish salt which was used for the next step without further purification. ¹H NMR (DMSO-*d*₆): δ 1.72 - 1.93 (4H, m), 2.26 (3H, s), 2.61 - 2.71 (2H, m), 2.76 (2H, t), 3.07 (2H, br d), 3.81 (2H, t), 4.63 - 4.72 (1H, m), 7.45 (1H, s), 7.88 (1H, d), 8.17 (1H, d), 10.38 (1H, br s), (one NH proton not observed); *m/z* (ES⁺) [M+H]⁺ = 328.2.

Intermediate 125h:

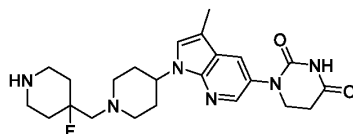
tert-Butyl 4-[[4-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-1-piperidyl]methyl]-4-fluoro-piperidine-1-carboxylate



[1840] Prepared in an analogous method to Intermediate 25f using Intermediate 25e (3.71 g, 10.2 mmol) and Intermediate 125g (1.66 g, 5.08 mmol), stirring at 85 °C for 23 h. Purification by FSC (elution gradient: 0 to 15% MeOH in DCM) gave the title compound (1.42 g, 51%) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.40 (9H, s), 1.51 - 1.69 (2H, m), 1.77 - 1.89 (4H, m), 1.98 - 2.10 (2H, m), 2.24 (3H, s), 2.34 (2H, br t), 2.52 - 2.64 (2H, m), 2.74 (2H, t), 3.02 (4H, br d), 3.68 - 3.76 (2H, m), 3.79 (2H, t), 4.58 (1H, tt), 7.48 (1H, s), 7.86 (1H, d), 8.16 (1H, d), 10.36 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 543.5.

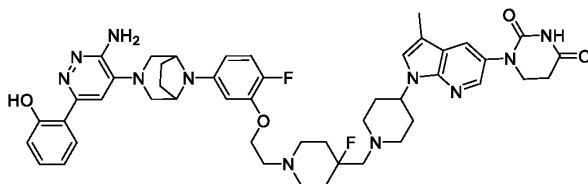
Intermediate 125i:

1-[1-[1-[(4-Fluoro-4-piperidyl)methyl]-4-piperidyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1841] TFA (4.0 mL) was added to a solution of Intermediate 125h (1.42 g, 2.61 mmol) in DCM (12.1 mL). The resulting mixture was stirred at r.t. for 30 min. and concentrated under reduced pressure. The residue was azeotroped with DCM (3x) and dried *in vacuo*. DCM (90 mL), IPA (30 mL), sat. aq. K_2CO_3 (50 mL) and water (20 mL) were added, and the phases were separated. The organic layer was washed with sat. aq. K_2CO_3 (50 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to give the title compound (1.01 g, 78%) as a white solid. 1H NMR (DMSO-*d*₆): δ 1.55 - 1.70 (2H, m), 1.73 - 1.88 (4H, m), 2.04 (2H, qd), 2.24 (3H, s), 2.33 (2H, br t), 2.51 - 2.58 (2H, m), 2.68 - 2.85 (6H, m), 3.02 (2H, br d), 3.79 (2H, t), 4.58 (1H, tt), 7.48 (1H, s), 7.86 (1H, d), 8.16 (1H, d), 10.36 (1H, br s), (one NH proton not observed); m/z (ES^+) $[M+H]^+ = 443.4$.

1-[1-[1-[1-[2-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenoxy]ethyl]-4-fluoro-4-piperidyl]methyl]-4-piperidyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

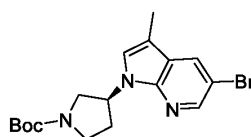


[1842] A mixture of Intermediate 125d (28.0 mg, 0.04 mmol), Intermediate 125i (16 mg, 0.04 mmol), and DIPEA in DMF (0.2 mL) was stirred at 80 °C overnight. Purification by RPC (elution gradient: 20-60% MeCN in water with 0.1% FA) gave the alkylated product. The alkylated product was dissolved in DCM (0.5 mL) and HCl (4N in dioxane, 0.5 ml) was added. The mixture was stirred at r. t. for 30 min. The solvent was removed, and the material was dissolved in MeOH, and carbonate resin was added, stirred for 1h. The resin were filtered off, and the filtrate was concentrated. Purification by RPC (elution gradient: 5-35% MeCN in water with 0.1% FA) gave the title compound (10.40 mg, 32.8 %) as a white solid. 1H NMR (DMSO-*d*₆): δ 1.57 - 1.77 (2H, m), 1.79 - 1.88 (4H, m), 1.90 - 1.98 (2H, m), 2.00 - 2.10 (2H, m), 2.10 - 2.16 (2H, m), 2.21 - 2.25 (3H, m), 2.29 - 2.39 (4H, m), 2.70 - 2.78 (6H, m), 2.99 - 3.05 (2H, m), 3.06 - 3.11 (2H, m), 3.17 - 3.24 (4H, m), 3.78 - 3.82 (2H, m), 4.12 - 4.18 (2H, m), 4.37 - 4.43 (2H, m), 4.55 - 4.63 (1H, m), 5.93 (2H, s), 6.40 (1H, dt), 6.67 (1H, dd), 6.82 - 6.89 (2H, m), 7.00 (1H, dd), 7.19 - 7.23 (1H, m), 7.45 (1H, s), 7.48 (1H, s), 7.85 - 7.91 (2H, m), 8.13 - 8.17 (1H, m), 10.35 (1H, s), 13.75 - 14.58 (1H, m); m/z (ES^+) $[M+H]^+ = 876.4$.

EXAMPLE 126

Intermediate 126a:

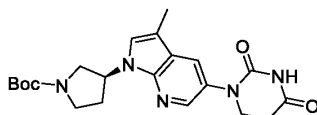
tert-Butyl (3*S*)-3-(5-bromo-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl)pyrrolidine-1-carboxylate



[1843] 5-Bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (1 g, 4.74 mmol) was added to *tert*-butyl (*R*)-3-hydroxypyrrolidine-1-carboxylate (0.887 g, 4.74 mmol) and 2-(tributyl- λ^5 -phosphaneylidene)acetonitrile (1.372 g, 5.69 mmol) in toluene (10 mL) under nitrogen. The resulting mixture was stirred at 100 °C for 24 h. The reaction mixture was concentrated under reduced pressure. Purification by RPC (elution gradient: 5 to 100% MeCN in water with 0.1% NH_4HCO_3) gave the title compound (1.0 g, 56%) as a brown gum. ^1H NMR ($\text{DMSO}-d_6$): δ 1.38 – 1.42 (9H, s), 2.24 (3H, s), 2.29 – 2.33 (2H, m), 3.40 – 3.49 (2H, m), 3.50 – 3.54 (1H, m), 3.75 – 3.79 (1H, m), 5.28 – 5.35 (1H, m), 7.44 (1H, d), 8.20 (1H, d), 8.30 (1H, d); m/z (ES^+) $[\text{M}+\text{H}]^+ = 380.1$.

Intermediate 126b:

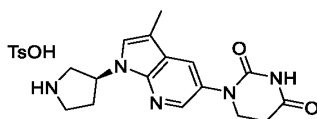
tert-Butyl (3*S*)-3-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]pyrrolidine-1-carboxylate



[1844] Prepared in an analogous method to Intermediate 114d starting from Intermediate 126a (900 mg, 2.37 mmol). Purification by FSC (elution gradient: 0 to 50% EtOAc in petroleum ether, then 0 to 10% MeOH in DCM) gave the title compound (600 mg, 61%) as a white solid. ^1H NMR ($\text{DMSO}-d_6$): δ 1.41 (9H, d), 2.26 (3H, d), 2.29 – 2.35 (2H, m), 2.76 (2H, t), 3.38 – 3.50 (2H, m), 3.52 – 3.57 (1H, m), 3.76 – 3.81 (1H, m), 3.83 (2H, t), 5.31 – 5.39 (1H, m), 7.42 (1H, d), 7.92 (1H, d), 8.21 (1H, d), 10.41 (1H, s); m/z (ES^+) $[\text{M}+\text{H}]^+ = 414.2$.

Intermediate 126c:

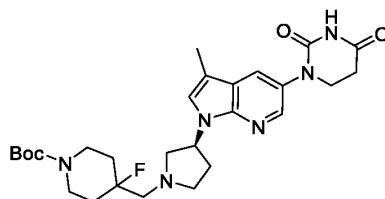
1-[3-Methyl-1-[(3*S*)-pyrrolidin-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1845] Prepared in an analogous method to Intermediate 6c starting from Intermediate 126b (600 mg, 1.45 mmol). The mixture was concentrated under reduced pressure. MTBE was added (3 mL). The solids were collected by filtration, washed with MTBE (1 mL), and dried *in vacuo* to give title compound (690 mg, 98%) as a yellow solid in the form of the TsOH salt, which was used without further purification. m/z (ES^+) $[\text{M}+\text{H}]^+ = 314.1$.

Intermediate 126d:

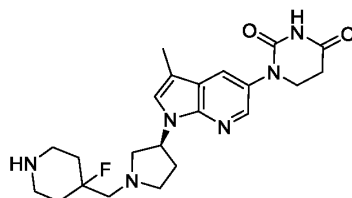
tert-Butyl 4-[[[(3*S*)-3-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]pyrrolidin-1-yl]methyl]-4-fluoro-piperidine-1-carboxylate



[1846] Prepared in an analogous method to Intermediate 25f starting from Intermediate 25e (1224 mg, 3.35 mmol) and Intermediate 126c (700 mg, 2.23 mmol). Purification by FSC (elution gradient: 0 to 10% MeOH in DCM) gave the title compound (580 mg, 49%) as a yellow solid. ^1H NMR (DMSO- d_6): δ 1.41 (9H, s), 1.56 – 1.68 (3H, m), 1.80 – 1.92 (3H, m), 2.27 (3H, s), 2.38 – 2.42 (1H, m), 2.53 – 2.57 (1H, m), 2.69 – 2.72 (1H, m), 2.74 – 2.78 (3H, m), 2.86 (1H, d), 2.99 – 3.10 (3H, m), 3.72 – 3.77 (2H, m), 3.81 (2H, t), 5.37 – 5.41 (1H, m), 7.47 (1H, s), 7.89 (1H, d), 8.16 (1H, s), 10.39 (1H, s); m/z (ES^+) $[\text{M}+\text{H}]^+ = 529.3$.

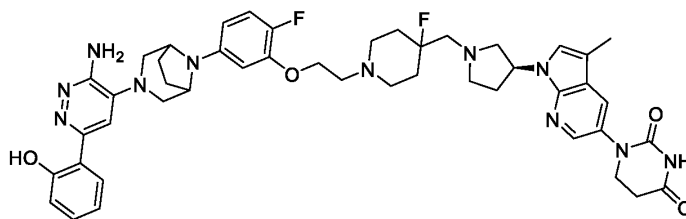
Intermediate 126e:

1-[1-[(3S)-1-[(4-Fluoro-4-piperidyl)methyl]pyrrolidin-3-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1847] Prepared in an analogous method to Intermediate 1i starting from Intermediate 126d (570 mg, 1.08 mmol). The crude residue was triturated with MTBE (5 mL) and dried *in vacuo* to give the title compound (300 mg, 65%) as a white solid in TFA salt form. m/z (ES^+) $[\text{M}+\text{H}]^+ = 429.2$.

1-[1-[(3S)-1-[[1-[2-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenoxy]ethyl]-4-fluoro-4-piperidyl)methyl]pyrrolidin-3-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione



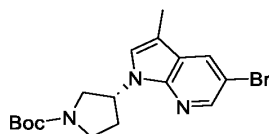
[1848] Prepared in an analogous method to EXAMPLE 125 starting from Intermediate 125d (40 mg, 0.05 mmol) and Intermediate 126e (22 mg, 0.05 mmol). Purification by RPC (elution gradient: 0-60% MeCN in water with 0.1% FA) gave the title compound (11.8 mg, 26.7 %) as a white solid. ^1H NMR (DMSO- d_6) δ 1.60 - 1.76 (2H, m), 1.79 - 1.91 (3H, m), 1.92 - 2.01 (2H, m), 2.10 - 2.20 (2H, m), 2.20 - 2.27 (3H, m), 2.33 - 2.43 (3H, m), 2.52 - 2.56 (1H, m), 2.63 - 2.67 (1H, m), 2.67 - 2.79 (8H, m), 2.80 - 2.86 (2H, m), 3.01 - 3.13 (4H, m), 3.20 - 3.24 (2H, m), 3.77 - 3.81 (2H, m), 4.13 - 4.19 (2H, m), 4.35 - 4.42 (2H, m), 5.33 -

5.41 (1H, m), 6.39 (1H, dt), 6.66 (1H, dd), 6.81 - 6.90 (2H, m), 6.99 (1H, dd), 7.15 - 7.24 (1H, m), 7.46 (2H, d), 7.85 - 7.91 (2H, m), 8.16 (1H, d), 10.36 (1H, s), 13.78 - 14.48 (1H, m); m/z (ES^+ $[M+H]^+$) = 862.4.

EXAMPLE 127

Intermediate 127a:

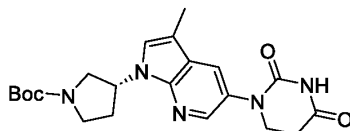
tert-Butyl (3*R*)-3-(5-bromo-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl)pyrrolidine-1-carboxylate



[1849] Prepared in an analogous manner to Intermediate 114a starting from 5-bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (0.939 g, 4.45 mmol) and *tert*-butyl (3*S*)-3-hydroxypyrrolidine-1-carboxylate (1 g, 5.34 mmol). Purification by RPC (elution gradient: 5 to 100% MeCN in water with 0.5% NH_4HCO_3) gave the title compound (1.0 g, 59 %) as a yellow solid. 1H NMR (DMSO-*d*₆): δ 1.41 (9H, d), 2.28 – 2.39 (3H, m), 2.31 (2H, q), 3.38 – 3.57 (3H, m), 3.73 – 3.79 (1H, m), 5.26 – 5.37 (1H, m), 7.44 (1H, d), 8.20 (1H, d), 8.30 (1H, d); m/z (ES^+) $[M+H]^+$ = 324.1.

Intermediate 127b:

tert-Butyl (3*R*)-3-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]pyrrolidine-1-carboxylate

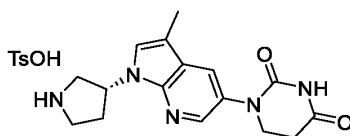


[1850] Prepared in an analogous manner to Intermediate 4b starting from Intermediate 127a (900 mg, 2.37 mmol).

[1851] Purification by FSC (elution gradient: 0 to 10% MeOH in DCM) gave the title compound (500 mg, 51.1 %) as a yellow solid. 1H NMR (DMSO-*d*₆): δ 1.42 (9H, d), 2.29 – 2.37 (3H, m), 2.77 (2H, t), 3.45 – 3.58 (3H, m), 3.78 (1H, t), 3.82 (2H, t), 5.28 – 5.39 (1H, m), 7.42 (1H, d), 7.92 (1H, d), 8.21 (1H, d), 10.41 (1H, s); m/z (ES^+) $[M+H]^+$ = 414.2.

Intermediate 127c:

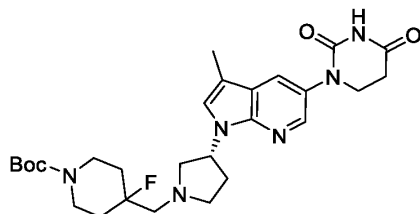
1-[3-Methyl-1-[(3*R*)-pyrrolidin-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1852] Prepared in an analogous manner to Intermediate 6c starting from Intermediate 127b (490 mg, 1.19 mmol) gave the title compound (540 mg, 69.3 %) as a yellow solid in the form of the TsOH salt. The crude product was used for the next step without further purification. m/z (ES^+) $[M+H]^+$ = 314.

Intermediate 127d:

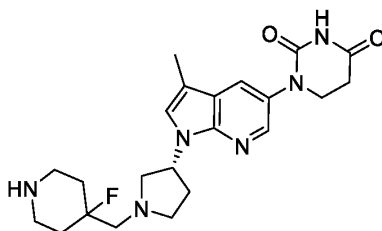
4-[[[(3*R*)-3-[5-(2,4-Dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]pyrrolidin-1-yl]methyl]-4-fluoro-piperidine-1-carboxylate



[1853] Prepared in an analogous manner to Intermediate 25f starting from Intermediate 127c (530mg, 1.09 mmol) and Intermediate 25e (479 mg, 1.31 mmol). Purification by FSC (elution gradient: 0 to 10% MeOH in DCM) gave the title compound (300 mg, 52.0 %) as a yellow solid. ¹H NMR (DMSO-*d*₆): δ 1.41 (9H, s), 1.57 – 1.71 (2H, m), 1.80 – 1.93 (3H, m), 2.27 (3H, s), 2.52 – 2.59 (1H, m), 2.70 (1H, d), 2.76 (3H, t), 2.83 – 2.89 (2H, m), 3.12 – 3.17 (2H, m), 3.59 – 3.66 (2H, m), 3.74 (2H, d), 3.81 (2H, t), 5.34 – 5.45 (1H, m), 7.47 (1H, s), 7.89 (1H, d), 8.18 (1H, d), 10.40 (1H, s); *m/z* (ES⁺), [M+H]⁺ = 529.0

Intermediate 127e:

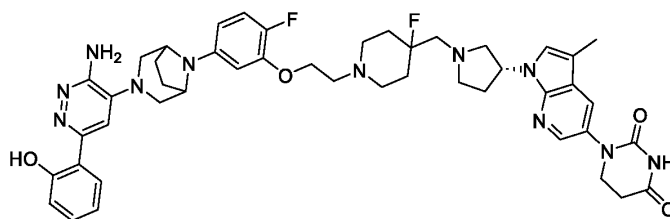
1-[1-[(3*R*)-1-[(4-Fluoro-4-piperidyl)methyl]pyrrolidin-3-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1854] Prepared in an analogous manner to Intermediate 1i starting from Intermediate 127d (70 mg, 0.16 mmol).

[1855] Purification by RPC (elution gradient 5 to 70% MeCN in water with 0.5 % NH₄HCO₃) gave the title compound (30.0 mg, 42.9 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.53 – 1.67 (2H, m), 1.69 – 1.81 (2H, m), 1.84 – 1.95 (1H, m), 2.26 (3H, s), 2.36 – 2.45 (1H, m), 2.53 – 2.58 (1H, m), 2.63 – 2.68 (1H, m), 2.69 – 2.74 (4H, m), 2.76 (3H, t), 2.83 – 2.89 (2H, m), 3.05 – 3.11 (1H, m), 3.81 (2H, t), 5.32 – 5.43 (1H, m), 7.49 (1H, s), 7.89 (1H, d), 8.18 (1H, d), 10.39 (1H, s); *m/z* (ES⁺), [M+H]⁺ = 429.

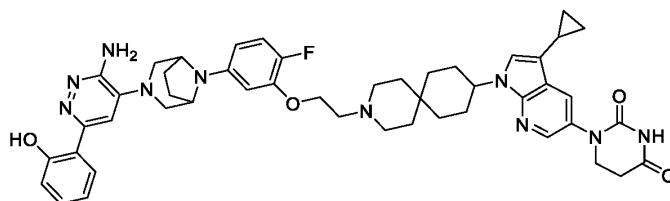
1-[1-[(3*R*)-1-[[1-[2-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenoxy]ethyl]-4-fluoro-4-piperidyl)methyl]pyrrolidin-3-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1856] Prepared in an analogous method to example 125 starting from Intermediate 125d (29 mg, 0.04 mmol) and intermediate 127e (16 mg, 0.04mmol). Purification by RPC (elution gradient: 0-60% MeCN in water with 0.1% FA) gave the title compound (6.7 mg, 20.82 %) as a white solid. ¹H NMR (DMSO-*d*₆) δ 1.58 - 1.76 (2H, m), 1.77 - 1.91 (3H, m), 1.92 - 1.99 (2H, m), 2.09 - 2.19 (2H, m), 2.19 - 2.25 (3H, m), 2.31 - 2.38 (2H, m), 2.53 - 2.56 (1H, m), 2.62 - 2.68 (1H, m), 2.69 - 2.79 (7H, m), 2.82 - 2.88 (2H, m), 3.01 - 3.15 (4H, m), 3.20 - 3.24 (2H, m), 3.77 - 3.81 (2H, m), 4.13 - 4.19 (2H, m), 4.37 - 4.43 (2H, m), 5.34 - 5.40 (1H, m), 5.93 (2H, s), 6.39 (1H, dt), 6.66 (1H, dd), 6.80 - 6.89 (2H, m), 6.99 (1H, dd), 7.18 - 7.24 (1H, m), 7.42 - 7.49 (2H, m), 7.84 - 7.91 (2H, m), 8.16 (1H, d), 10.36 (1H, s), 13.38 - 14.98 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 862.4.

EXAMPLE 128

1-[1-[3-[2-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenoxy]ethyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

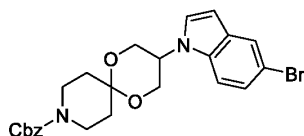


[1857] Prepared in an analogous method to EXAMPLE 125 starting from Intermediate 125d (26 mg, 0.05 mmol) and Intermediate 36a (31 mg, 0.06mmol). Purification by RPC (elution gradient: 0-60% MeCN in water with 0.1% FA) gave the title compound (4 mg, 9.36 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 0.64 (2H, dd), 0.82 - 0.86 (2H, m), 1.21 - 1.32 (3H, m), 1.33 - 1.39 (2H, m), 1.62 - 1.71 (4H, m), 1.74 - 1.82 (2H, m), 1.87 - 2.01 (6H, m), 2.11 - 2.16 (2H, m), 2.69 - 2.73 (2H, m), 2.73 - 2.77 (2H, m), 3.08 - 3.13 (2H, m), 3.20 - 3.26 (3H, m), 3.77 - 3.83 (2H, m), 4.13 - 4.18 (2H, m), 4.37 - 4.42 (2H, m), 4.55 - 4.61 (1H, m), 5.91 - 5.96 (2H, m), 6.38 - 6.42 (1H, m), 6.66 - 6.69 (1H, m), 6.82 - 6.88 (2H, m), 6.97 - 7.03 (1H, m), 7.19 - 7.24 (1H, m), 7.43 - 7.47 (1H, m), 7.49 (1H, s), 7.87 (1H, s), 7.92 (2H, d), 8.14 (1H, d), 10.35 (1H, s), 13.96 - 14.35 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 855.6.

EXAMPLE 129

Intermediate 129a:

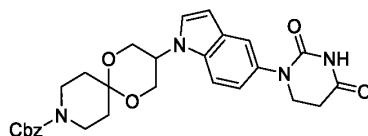
Benzyl 3-(5-bromoindol-1-yl)-1,5-dioxo-9-azaspiro[5.5]undecane-9-carboxylate



[1858] A 250 mL flask was charged with Intermediate 99b (4.12 g, 15.3 mmol) and Intermediate 64c (5.54 g, 19.8 mmol). PPTS (0.19 g, 0.76 mmol) and toluene (76 mL) were added. The resulting mixture was stirred at 110 °C for 15 h. After cooling to r.t., the mixture was washed with sat. aq. NaHCO₃ (100 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by FSC (1st purification: 0-30% acetone in hexanes; 2nd purification: 0-50% EtOAc in hexanes) gave the title compound (5.06 g, 68%) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.83 (2H, br s), 1.98 (2H, s), 3.37 - 3.53 (4H, m), 3.94 - 4.01 (2H, m), 4.32 (2H, br d), 4.59 (1H, br t), 5.08 (2H, s), 6.48 (1H, d), 7.20 - 7.26 (1H, m), 7.28 - 7.33 (1H, m), 7.33 - 7.40 (4H, m), 7.48 (1H, d), 7.75 (1H, d), 7.81 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 485.2.

Intermediate 129b:

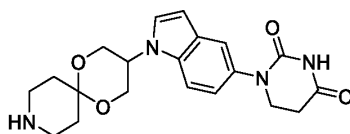
Benzyl 3-[5-(2,4-dioxohexahydropyrimidin-1-yl)indol-1-yl]-1,5-dioxo-9-azaspiro[5.5]undecane-9-carboxylate



[1859] A 250 mL flask was charged with Intermediate 129a (4.04 g, 8.32 mmol), K₃PO₄ (5.30 g, 25.0 mmol), hexahydropyrimidine-2,4-dione (1.42 g, 12.5 mmol) and *t*BuBrettPhos Pd G3 (0.71 g, 0.83 mmol). The flask was evacuated and backfilled with argon (2x). 1,4-dioxane (49 mL) was added. The flask was evacuated and backfilled with argon (3x). The resulting mixture was stirred at 100 °C for 4 h. After cooling to r.t., the mixture was concentrated under reduced pressure. Water (70 mL) and EtOAc (70 mL) were added. The resulting suspension was stirred at r.t. for 15 min. The mixture was filtered. The filter-cake was washed with EtOAc (2 x 20 mL) and dried in vacuo to give 2.90 g of a grey solid. The filtrate was concentrated under reduced pressure. EtOAc–MeOH (9:1, 20 mL) was added. The resulting mixture was stirred at r.t. for 1 hour and filtered. The solids were washed with EtOAc–MeOH (9:1, 10 mL) and dried in vacuo to give 0.72 g of an off-white solid. The two filter-cakes were combined and purified by FSC (0-12% MeOH in EtOAc) to give the title compound (2.98 g, 69%) as an off-white solid. ¹H NMR (DMSO-*d*₆): δ 1.88 (2H, br s), 1.99 (2H, br s), 2.73 (2H, t), 3.47 (4H, br s), 3.77 (2H, t), 4.02 (2H, br dd), 4.33 (2H, br d), 4.54 - 4.72 (1H, m), 5.10 (2H, s), 6.50 (1H, d), 7.09 (1H, dd), 7.27 - 7.43 (5H, m), 7.46 - 7.56 (2H, m), 7.81 (1H, d), 10.29 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 519.2.

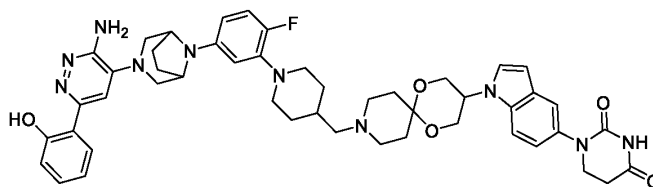
Intermediate 129c:

1-[1-(1,5-Dioxo-9-azaspiro[5.5]undecan-3-yl)indol-5-yl]hexahydropyrimidine-2,4-dione



[1860] A 40 mL vial was charged with Intermediate 129b (100 mg, 0.19 mmol) and Pd/C (41 mg, 0.04 mmol, 10 wt% Pd). DMF (3.9 mL) was added. Hydrogen was bubbled through the mixture for 5 minutes. The resulting mixture was stirred under an atmosphere of hydrogen for 2 h. The mixture was filtered through a pad of Celite® with DMF. The filtrate was concentrated under reduced pressure. Lyophilization from water–MeCN gave the title compound as an off-white solid. ¹H NMR (DMSO-*d*₆): δ 1.63 - 2.12 (5H, m), 2.62 - 2.77 (6H, m), 3.76 (2H, t), 3.97 (2H, dd), 4.29 (2H, dd), 4.53 - 4.59 (1H, m), 6.47 (1H, d), 7.07 (1H, dd), 7.44 - 7.52 (2H, m), 7.80 (1H, d), 10.24 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 385.3.

1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]indol-5-yl]hexahydropyrimidine-2,4-dione

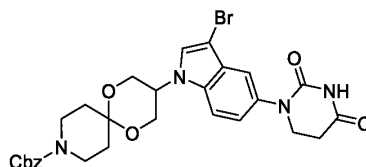


[1861] Prepared in an analogous manner to EXAMPLE 64 using Intermediate 129c (31 mg, 0.08 mmol) and Intermediate 13d (34 mg, 0.07 mmol). Purification by RPC (0-40% MeCN in water with 0.1% HCOOH) gave the title compound (31.9 mg, 53%) as an off-white solid. ¹H NMR (DMSO-*d*₆): δ 1.16 - 1.30 (2H, m), 1.61 (1H, br s), 1.78 (2H, br d), 1.83 - 2.06 (6H, m), 2.12 (2H, br d), 2.20 (2H, br d), 2.33 - 2.47 (4H, m), 2.63 (2H, br t), 2.71 (2H, t), 3.09 (2H, br d), 3.25 (2H, br d), 3.34 (2H, br d), 3.76 (2H, t), 3.94 - 4.01 (2H, m), 4.24 - 4.41 (4H, m), 4.53 - 4.61 (1H, m), 5.92 (2H, s), 6.38 - 6.44 (1H, m), 6.44 - 6.51 (2H, m), 6.81 - 6.96 (3H, m), 7.08 (1H, dd), 7.18 - 7.27 (1H, m), 7.42 - 7.51 (3H, m), 7.80 (1H, d), 7.89 (1H, br d), 10.24 (1H, s), 13.97 (1H, br s); *m/z* (ES⁺) [M+H]⁺ = 871.5.

EXAMPLE 130

Intermediate 130a:

Benzyl 3-[3-bromo-5-(2,4-dioxohexahydropyrimidin-1-yl)indol-1-yl]-1,5-dioxo-9-azaspiro[5.5]undecane-9-carboxylate

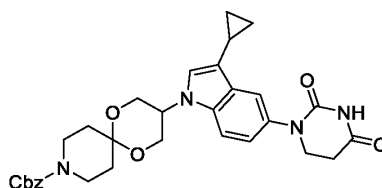


[1862] NBS (177 mg, 0.99 mmol) was added to a solution of Intermediate 129b (491 mg, 0.95 mmol) in DCM (19 mL). The resulting mixture was stirred at r.t. for 12 min. The mixture was washed with sat. aq.

$\text{Na}_2\text{S}_2\text{O}_3$ (2 x 20 mL) and sat. aq. NaHCO_3 (20 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to give the title compound (529 mg, 94%) as a brown solid. ^1H NMR ($\text{DMSO}-d_6$): δ 1.81 - 1.91 (2H, m), 1.97 (2H, br s), 2.73 (2H, t), 3.36 - 3.55 (4H, m), 3.79 (2H, t), 4.02 (2H, br dd), 4.24 - 4.40 (2H, m), 4.66 (1H, br t), 5.08 (2H, s), 7.19 (1H, dd), 7.28 - 7.43 (6H, m), 7.60 (1H, d), 7.93 (1H, s), 10.29 (1H, s); m/z (ES^+) $[\text{M}+\text{H}]^+ = 597.2$.

Intermediate 130b:

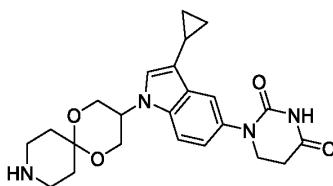
Benzyl 3-[3-cyclopropyl-5-(2,4-dioxohexahydropyrimidin-1-yl)indol-1-yl]-1,5-dioxo-9-azaspiro[5.5]undecane-9-carboxylate



[1863] A 20 mL vial was charged with Intermediate 130a (243 mg, 0.41 mmol), cyclopropylboronic acid (87 mg, 1.02 mmol), $\text{PdCl}_2(\text{dtbpf})$ (27 mg, 0.04 mmol) and K_3PO_4 (259 mg, 1.22 mmol). Toluene (3.7 mL) and water (0.37 mL) were added. Argon was bubbled through the mixture for 5 minutes. The resulting mixture was stirred at 70 °C for 6 hours. After cooling to r.t., DCM (30 mL), sat. aq. NaHCO_3 (10 mL) and brine (15 mL) were added. The phases were separated. The aqueous layer was extracted with DCM (2 x 20 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. Purification by FSC (1st purification: 80-100% EtOAc in hexanes, then 0-10% MeOH in EtOAc; 2nd purification: 0-6% MeOH in EtOAc) gave the title compound (157 mg, 69%) as an off-white solid. ^1H NMR ($\text{DMSO}-d_6$): δ 0.48 - 0.65 (2H, m), 0.78 - 0.93 (2H, m), 1.78 - 2.03 (5H, m), 2.72 (2H, t), 3.45 (4H, br s), 3.77 (2H, t), 4.00 (2H, br dd), 4.20 (2H, br d), 4.51 - 4.60 (1H, m), 5.08 (2H, s), 7.06 (1H, dd), 7.26 - 7.41 (5H, m), 7.41 - 7.49 (2H, m), 7.51 (1H, d), 10.23 (1H, s); m/z (ES^+) $[\text{M}+\text{H}]^+ = 559.3$.

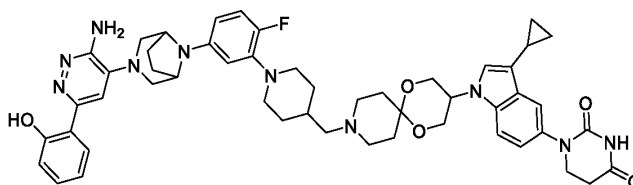
Intermediate 130c:

1-[3-Cyclopropyl-1-(1,5-dioxo-9-azaspiro[5.5]undecan-3-yl)indol-5-yl]hexahydropyrimidine-2,4-dione



[1864] Prepared in an analogous method to Intermediate 129c starting from Intermediate 130b (153 mg, 0.27 mmol) gave the title compound (116 mg, 100%) as an off-white solid. ^1H NMR ($\text{DMSO}-d_6$): δ 0.53 - 0.61 (2H, m), 0.81 - 0.88 (2H, m), 1.74 - 1.84 (4H, m), 1.86 - 1.93 (1H, m), 2.18 (1H, br s), 2.64 - 2.76 (6H, m), 3.77 (2H, t), 3.96 (2H, dd), 4.18 (2H, dd), 4.47 - 4.54 (1H, m), 7.01 - 7.09 (1H, m), 7.40 - 7.48 (2H, m), 7.49 - 7.53 (1H, m), 10.23 (1H, br s); m/z (ES^+) $[\text{M}+\text{H}]^+ = 425.4$.

1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3-azabicyclo[3.2.1]octan-8-yl]-2-fluorophenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-cyclopropyl-indol-5-yl]hexahydropyrimidine-2,4-dione

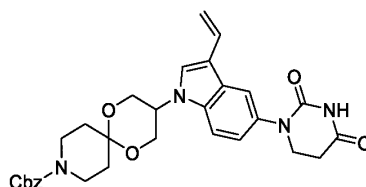


[1865] Prepared in an analogous manner to EXAMPLE 64 using Intermediate 130c (30 mg, 0.07 mmol) and Intermediate 13d (30 mg, 0.06 mmol). Purification by RPC (elution gradient: 0-50% MeCN in water with 0.1% HCOOH) gave the title compound (23.6 mg, 43%) as an off-white solid. ¹H NMR (DMSO-*d*₆): δ 0.54 - 0.60 (2H, m), 0.82 - 0.88 (2H, m), 1.24 (2H, q), 1.60 (1H, br s), 1.73 - 1.81 (2H, m), 1.84 - 2.01 (7H, m), 2.08 - 2.15 (2H, m), 2.19 (2H, br d), 2.33 - 2.47 (4H, m), 2.59 - 2.67 (2H, m), 2.72 (2H, t), 3.09 (2H, br d), 3.25 (2H, br d), 3.34 (2H, br d), 3.77 (2H, t), 3.97 (2H, dd), 4.18 (2H, br dd), 4.33 (2H, br s), 4.47 - 4.54 (1H, m), 5.92 (2H, s), 6.37 - 6.44 (1H, m), 6.45 - 6.50 (1H, m), 6.82 - 6.93 (3H, m), 7.03 - 7.09 (1H, m), 7.18 - 7.25 (1H, m), 7.41 - 7.49 (3H, m), 7.49 - 7.54 (1H, m), 7.78 - 8.01 (1H, m), 10.24 (1H, s), 14.07 (1H, br s); *m/z* (ES⁺) [M+H]⁺ = 911.5.

EXAMPLE 131

Intermediate 131a:

Benzyl 3-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-vinyl-indol-1-yl]-1,5-dioxo-9-azaspiro[5.5]undecane-9-carboxylate

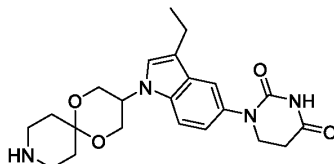


[1866] A 20 mL vial was charged with Intermediate 130a (226 mg, 0.38 mmol), K₃PO₄ (241 mg, 1.13 mmol) and PdCl₂(dtbpf) (25 mg, 0.04 mmol). Toluene (3.3 mL), water (0.3 mL) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (0.16 mL, 0.95 mmol) were added. Argon was bubbled through the mixture for 5 minutes. The resulting mixture was stirred at 70 °C for 135 min and at 100 °C for 90 min. After cooling to r.t., sat. aq. NaHCO₃ (20 mL) was added. The mixture was extracted with DCM (3 x 20 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by FSC (elution gradient: 0-6% MeOH in EtOAc) and RPC (elution gradient: 40-70% MeCN in water with 0.1% NH₄OH) gave the title compound (51 mg, 25%) as a white solid and 8:1 mixture with Intermediate 130a. ¹H NMR (DMSO-*d*₆): δ 1.83 - 1.92 (2H, m), 1.94 - 2.02 (2H, m), 2.73 (2H, t), 3.40 - 3.54 (4H, m), 3.78 (2H, t), 4.01 (2H, dd), 4.31 (2H, br d), 4.56 - 4.62 (1H, m), 5.02 - 5.15 (3H, m), 5.62

(1H, br d), 6.86 (1H, dd), 7.08 - 7.15 (1H, m), 7.30 - 7.40 (5H, m), 7.46 - 7.57 (1H, m), 7.76 (1H, s), 7.93 (1H, s), 10.29 (1H, s); m/z (ES^+) $[M+H]^+ = 545.3$.

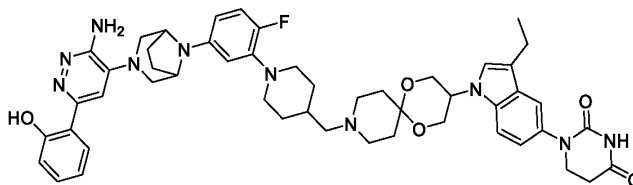
Intermediate 131b:

1-[1-(1,5-Dioxa-9-azaspiro[5.5]undecan-3-yl)-3-ethyl-indol-5-yl]hexahydropyrimidine-2,4-dione



[1867] Prepared in an analogous method to Intermediate 129c starting from Intermediate 131a (49 mg, 0.09 mmol). Purification by RPC (elution gradient: 0-90% MeCN in water with 0.1% NH_4OH) gave the title compound (29 mg, 78%) as a white solid. 1H NMR ($DMSO-d_6$): δ 1.25 (3H, t), 1.83 (4H, br d), 2.64 - 2.77 (8H, m), 3.76 (2H, t), 3.97 (2H, br dd), 4.22 (2H, dd), 4.47 - 4.57 (1H, m), 7.05 (1H, dd), 7.38 - 7.48 (2H, m), 7.58 (1H, s), 10.26 (1H, br s), (one NH proton not observed); m/z (ES^+) $[M+H]^+ = 413.4$.

1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxa-9-azaspiro[5.5]undecan-3-yl]-3-ethyl-indol-5-yl]hexahydropyrimidine-2,4-dione

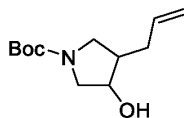


[1868] Prepared in an analogous manner to EXAMPLE 64 using Intermediate 131b (28 mg, 0.07 mmol) and Intermediate 13d (28 mg, 0.06 mmol). Purification by RPC (elution gradient: 0-50% MeCN in water with 0.1% $HCOOH$) gave the title compound (23.6 mg, 43%) as an off-white solid. 1H NMR ($DMSO-d_6$): δ 1.19 - 1.30 (5H, m), 1.57 - 1.65 (1H, m), 1.78 (2H, br d), 1.85 - 2.02 (6H, m), 2.08 - 2.15 (2H, m), 2.20 (2H, br d), 2.33 - 2.47 (4H, m), 2.59 - 2.75 (6H, m), 3.09 (2H, br d), 3.25 (2H, br d), 3.34 (2H, br d), 3.76 (2H, br t), 3.97 (2H, br dd), 4.23 (2H, br d), 4.30 - 4.38 (2H, m), 4.52 (1H, br d), 5.92 (2H, br s), 6.38 - 6.43 (1H, m), 6.44 - 6.49 (1H, m), 6.82 - 6.88 (2H, m), 6.91 (1H, dd), 7.03 - 7.08 (1H, m), 7.22 (1H, t), 7.41 - 7.47 (3H, m), 7.57 (1H, s), 7.89 (1H, br d), 10.23 (1H, s), 14.04 (1H, br s); m/z (ES^+) $[M+H]^+ = 899.5$.

EXAMPLE 132

Intermediate 132a

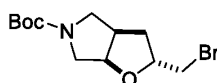
tert-Butyl 3-allyl-4-hydroxy-pyrrolidine-1-carboxylate



[1869] Lithium tri-*sec*-butylhydroborate solution (11.3 ml, 11.3 mmol, 1M in THF) was added slowly to a stirred solution of *tert*-butyl 3-allyl-4-oxopyrrolidine-1-carboxylate (2.31 g, 10.25 mmol) in 2-methyl tetrahydrofuran (37.9 ml) cooled to 0°C under nitrogen. The resulting mixture was stirred as it slowly warmed to r.t. The reaction was stirred at r.t. for 17 h. An additional portion of lithium tri-*sec*-butylhydroborate (2.05 ml, 2.05 mmol, 1M in THF) was added and the reaction was stirred for and additional 15 mins. The reaction mixture was diluted with EtOAc and quenched with sat. aq. NH₄Cl. The organic layer was dried over Na₂SO₄, filtered, and concentrated. Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) afforded the title compound (1.10 g, 47.2 %) as a pale-yellow oil. ¹H NMR (CDCl₃): δ 1.48 (9H, s), 2.08 - 2.29 (2H, m), 2.34 (1H, dt), 3.07 - 3.16 (1H, m), 3.40 - 3.55 (2H, m), 3.61 (1H, br t), 4.28 (1H, br s), 5.01 - 5.10 (1H, m), 5.15 (1H, br d), 5.74 - 5.90 (1H, m).

Intermediate 132b:

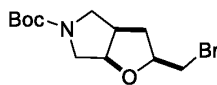
tert-Butyl *rac*-(2*R*,3*aR*,6*aR*)-2-(bromomethyl)-2,3,3*a*,4,6,6*a*-hexahydrofuro[2,3-*c*]pyrrole-5-carboxylate



and

Intermediate 132c:

tert-Butyl *rac*-(2*S*,3*aR*,6*aR*)-2-(bromomethyl)-2,3,3*a*,4,6,6*a*-hexahydrofuro[2,3-*c*]pyrrole-5-carboxylate

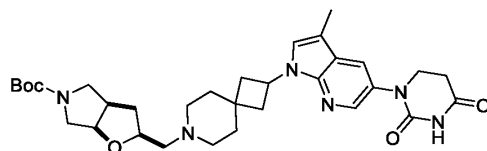


[1870] NBS (0.941 g, 5.28 mmol) was added in one portion to a stirred solution of Intermediate 132a (1.09 g, 4.80 mmol) in DCM (24.0 ml) under air. The resulting mixture was stirred at r.t. for 20 h. The reaction was quenched with sat. aq. Na₂SO₃. The reaction was diluted with EtOAc, the layers were separated, and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated. Purification by FSC (elution gradient 0 to 61% EtOAc in hexanes) gave the title compounds Intermediate 132b (0.581 g, 39.5 %) and Intermediate 132c (0.346 g, 23.5 %).

[1871] Compound were a racemic mixture of enantiomers but a known diastereomers. Relative stereochemistry of the diastereomers was assessed by comparing spectra to that of similar products and derivatives. Intermediate 132b: ¹H NMR (CD₂Cl₂): δ 1.46 (9H, s), 1.94 - 2.03 (1H, m), 2.04 - 2.11 (1H, m), 2.91 - 3.03 (1H, m), 3.17 (1H, dd), 3.40 (1H, dd), 3.47 (2H, d), 3.55 - 3.63 (2H, m), 4.42 (1H, dq), 4.65 (1H, t). Intermediate 132c: ¹H NMR (CD₂Cl₂): δ 1.47 (9H, s), 1.54 - 1.68 (1H, m), 2.30 - 2.41 (1H, m), 2.84 - 2.95 (1H, m), 3.31 (1H, br s), 3.39 (1H, br dd), 3.46 - 3.55 (3H, m), 3.63 (1H, d), 4.11 - 4.20 (1H, m), 4.53 (1H, t).

Intermediate 132d:

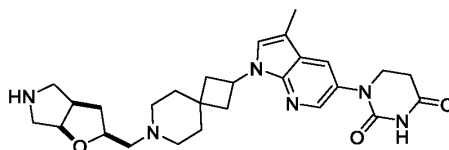
tert-Butyl *rac*-(2*S*,3*aR*,6*aR*)-2-[[2-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-7-azaspiro[3.5]nonan-7-yl)methyl]-2,3,3*a*,4,6,6*a*-hexahydrofuro[2,3-*c*]pyrrole-5-carboxylate



[1872] DIPEA (282 μ l, 1.62 mmol) was added in one portion to a stirred mixture of Intermediate 132c (198 mg, 0.54 mmol) and Intermediate 124a (248 mg, 0.81 mmol) in DMF (3767 μ l). The resulting suspension was stirred at 100 °C for 15 h and cooled to r.t. Purification by RPC (elution gradient: 10-100% water with 0.1% formic acid in MeOH) gave the title compound (152 mg, 47%) as a solid. ^1H NMR (DMSO-*d*₆): δ 1.40 (9H, s), 1.64 - 1.77 (4H, m), 2.20 (3H, br s), 2.27 (3H, s), 2.31 - 2.50 (7H, m), 2.76 (3H, br t), 3.15 (1H, br dd), 3.24 - 3.36 (2H, m), 3.36 - 3.47 (3H, m), 3.80 (2H, t), 4.00 (1H, br s), 4.34 (1H, br s), 5.25 (1H, quin), 7.61 (1H, s), 7.88 (1H, d), 8.17 (1H, s), 10.40 (1H, s); m/z (ES⁺) [M+H]⁺ = 593.5.

Intermediate 132e

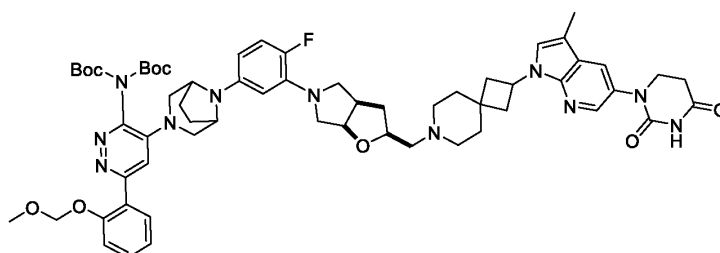
1-[1-[7-[[*rac*-(2*S*,3*aR*,6*aR*)-3,3*a*,4,5,6,6*a*-Hexahydro-2*H*-furo[2,3-*c*]pyrrol-2-yl)methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1873] Prepared from an analogous method to Intermediate 2c starting from Intermediate 132d (149 mg, 0.25 mmol). Purification by ion exchange chromatography (PoraPak Rxn CX cartridge) eluting with 1.5 N NH₃ in MeOH and 1.5 N NH₃ in MeOH/DCM gave the title compound (109 mg, 88 %) as a yellow solid. ^1H NMR (DMSO-*d*₆): δ 1.58 - 1.76 (4H, m), 2.09 - 2.23 (3H, m), 2.23 - 2.47 (12H, m), 2.53 - 2.70 (2H, m), 2.72 - 2.79 (2H, m), 2.87 (1H, br d), 3.17 (1H, br s), 3.69 - 3.86 (3H, m), 4.31 (1H, br d), 5.25 (1H, br t), 7.61 (1H, s), 7.88 (1H, s), 8.16 (1H, s), 10.40 (1H, br s); m/z (ES⁺) [M+H]⁺ = 493.3.

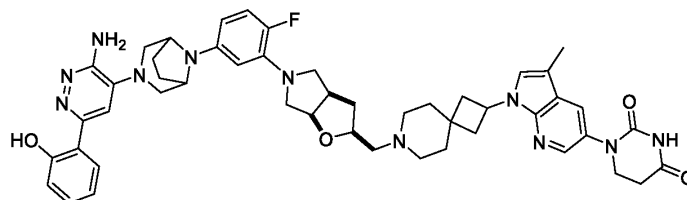
Intermediate 132f:

tert-Butyl *N*-[4-[8-[3-[*rac*-(2*S*,3*aR*,6*aR*)-2-[[2-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-7-azaspiro[3.5]nonan-7-yl)methyl]-2,3,3*a*,4,6,6*a*-hexahydrofuro[2,3-*c*]pyrrol-5-yl]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]-6-[2-(methoxymethoxy)phenyl]pyridazin-3-yl]-*N*-*tert*-butoxycarbonyl-carbamate



[1874] Prepared from an analogous method to Intermediate 56f starting with Intermediate 57a (148 mg, 0.22 mmol) and Intermediate 132c (109 mg, 0.22 mmol). Purification by FSC (elution gradient: 75 - 100% EtOAc in hexanes and then 0 - 100% MeOH in EtOAc) gave the title compound (63.7 mg, 25.6 %) as a yellow solid. *m/z*: ES+ [M+H]⁺ = 1126.8.

1-[3-Methyl-1-[7-[[*rac*-(2*S*,3*aR*,6*aR*)-5-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-2,3,3*a*,4,6,6*a*-hexahydrofuro[2,3-*c*]pyrrol-2-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

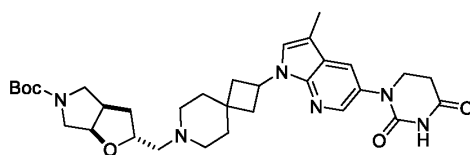


[1875] Sulfuric acid, 2 M in water (1.12 mL, 2.24 mmol) was added to a stirred solution of Intermediate 132f (63 mg, 0.06 mmol) in THF (1.12 mL). The resulting solution was stirred at 50 °C for 2.5 h. The reaction was diluted with DCM (20 mL), basified with sat. aq. NaHCO₃. The aqueous layer was extracted with additional DCM/IPA (4:1). The combined extracts were dried over Na₂SO₄, filtered, and concentrated. Purification by FSC (elution gradient: 0 -100% MeOH in EtOAc) gave the title compound (16.9 mg, 34.3 %) as an off-white solid. ¹H NMR (DMSO-*d*₆): δ 1.33 - 1.47 (1H, m), 1.66 (4H, br d), 1.94 (2H, br s), 2.08 - 2.21 (4H, m), 2.26 (5H, s), 2.33 (3H, br s), 2.36 - 2.50 (5H, m), 2.76 (2H, br t), 2.85 (1H, br s), 3.04 - 3.15 (4H, m), 3.21 - 3.29 (2H, m), 3.48 - 3.60 (1H, m), 3.80 (2H, br t), 3.89 - 3.99 (1H, m), 4.35 (2H, br s), 4.43 - 4.51 (1H, m), 5.24 (1H, br t), 5.95 (2H, br s), 6.25 (1H, br d), 6.29 (1H, br d), 6.81 - 6.96 (3H, m), 7.22 (1H, br t), 7.47 (1H, s), 7.60 (1H, s), 7.88 (1H, s), 7.91 (1H, br d), 8.16 (1H, s), 10.41 (1H, br s), 14.14 (1H, br s). ¹⁹F NMR (DMSO-*d*₆) δ -137.23 (1F, s); *m/z* (ES⁺) [M+H]⁺ = 882.5.

EXAMPLE 133

Intermediate 133a:

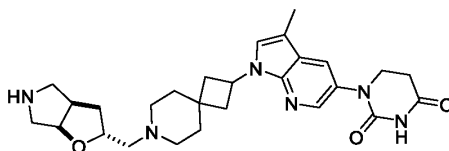
tert-Butyl *rac*-(2*R*,3*aR*,6*aR*)-2-[[2-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-7-azaspiro[3.5]nonan-7-yl]methyl]-2,3,3*a*,4,6,6*a*-hexahydrofuro[2,3-*c*]pyrrole-5-carboxylate



[1876] Prepared from an analogous method to Intermediate 132d starting with Intermediate 132b (240 mg, 0.65 mmol) and Intermediate 124a (300 mg, 0.98 mmol). Purification by RPC (elution gradient: 10 - 100% MeOH in water with 0.1% formic acid) gave the formic acid salt of the title compound (144 mg, 34.4 %) as a tan solid. ¹H NMR (DMSO-*d*₆): δ 1.39 (9H, s), 1.65 - 1.77 (5H, m), 1.91 (1H, br dd), 2.17 - 2.24 (2H, m), 2.26 (3H, s), 2.34 (2H, br d), 2.40 - 2.64 (5H, m, overlaps with residual solvent), 2.72 - 2.78 (2H, m), 2.81 - 2.93 (1H, m), 3.05 (1H, br s), 3.25 - 3.56 (4H, m, overlaps with residual water), 3.80 (2H, br t), 4.25 (1H, br s), 4.48 (1H, br t), 5.25 (1H, quin), 7.61 (1H, s), 7.88 (1H, d), 8.14 - 8.17 (2H, m), 10.40 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 593.5.

Intermediate 133b:

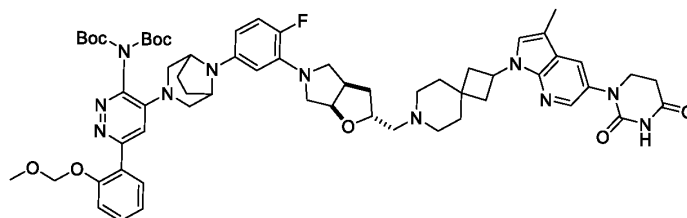
1-[1-[7-[[*rac*-(2*R*,3*aR*,6*aR*)-3*a*,4,5,6,6*a*-Hexahydro-2*H*-furo[2,3-*c*]pyrrol-2-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1877] Prepared from an analogous method to Intermediate 132e starting from Intermediate 133a (143 mg, 0.24 mmol) gave the title compound (112 mg, 94 %) as an off-white solid. ¹H NMR (DMSO-*d*₆): δ 1.61 - 1.76 (6H, m), 2.14 - 2.23 (2H, m), 2.24 - 2.47 (11H, m), 2.59 - 2.69 (3H, m), 2.71 - 2.83 (4H, m), 3.80 (2H, t), 4.16 (1H, quin), 4.46 (1H, br t), 5.25 (1H, quin), 7.61 (1H, s), 7.88 (1H, d), 8.17 (1H, d), 10.41 (1H, br s); *m/z* (ES⁺) [M+H]⁺ = 493.4

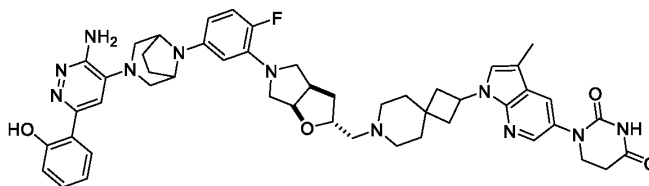
Intermediate 133c:

tert-Butyl *N*-[4-[8-[3-[[*rac*-(2*R*,3*aR*,6*aR*)-2-[[2-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methylpyrrolo[2,3-*b*]pyridin-1-yl]-7-azaspiro[3.5]nonan-7-yl]methyl]-2,3,3*a*,4,6,6*a*-hexahydrofuro[2,3-*c*]pyrrol-5-yl]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]-6-[2-(methoxymethoxy)phenyl]pyridazin-3-yl]-*N*-*tert*-butoxycarbonyl-carbamate



[1878] Prepared from an analogous method to Intermediate 56f starting with Intermediate 57a (152 mg, 0.23 mmol) and Intermediate 133b (112 mg, 0.23 mmol). Purification by FSC (elution gradient: 0 - 50% MeOH in EtOAc) gave the title compound (93 mg, 36.5 %) as a yellow solid. m/z (ES^+) $[M+H]^+ = 1126.6$.

1-[3-Methyl-1-[7-[[*rac*-(2*S*,3*aR*,6*aR*)-5-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-2,3,3*a*,4,6,6*a*-hexahydrofuro[2,3-*c*]pyrrol-2-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

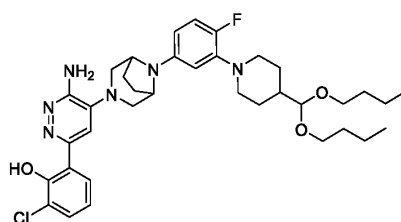


[1879] Prepared from an analogous method to EXAMPLE 132 starting with Intermediate 133c (35 mg, 0.03 mmol). Purification by RPC (elution gradient: 10 - 100% MeOH in water with 0.1% NH_4OH) gave the title compound (5.6 mg, 20.43 %) as a white solid. 1H NMR ($DMSO-d_6$): δ 1.59 - 1.80 (5H, m), 1.85 - 2.01 (3H, m), 2.09 - 2.23 (4H, m), 2.27 (3H, s), 2.29 - 2.50 (7H, m, some slight overlap with residual solvent), 2.76 (2H, br t), 2.93 (1H, br s), 3.07 - 3.15 (2H, m), 3.17 - 3.31 (5H, m), 3.39 - 3.47 (2H, m), 3.80 (2H, br t), 4.22 (1H, br s), 4.36 (2H, br s), 4.64 (1H, br t), 5.25 (1H, quin), 5.96 (2H, br s), 6.24 (1H, br d), 6.30 (1H, br d), 6.81 - 6.96 (3H, m), 7.23 (1H, br t), 7.48 (1H, s), 7.61 (1H, s), 7.85 - 7.90 (1H, m), 7.92 (1H, br d), 8.13 - 8.20 (1H, m), 10.41 (1H, br s), 14.20 (1H, br s). ^{19}F NMR ($DMSO-d_6$): δ -137.39 (1F, s); m/z (ES^+) $[M+H]^+ = 882.5$.

EXAMPLE 134

Intermediate 134a:

2-[6-Amino-5-[8-[3-[4-(dibutoxymethyl)-1-piperidyl]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-yl]-6-chloro-phenol

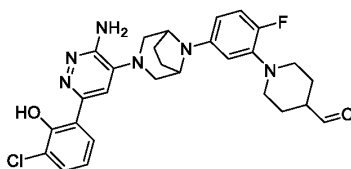


[1880] Prepared in an analogous manner to Intermediate 2h from (3-chloro-2-hydroxyphenyl)boronic acid (71.9 mg, 0.42 mmol) and Intermediate 11f (200 mg, 0.35 mmol). Purification by FSC (elution gradient: 0-100% EtOAc in hexanes) gave the title compound (83 mg, 35.8 %) as an orange solid. 1H NMR ($DMSO-d_6$): δ 0.89 (6H, t), 1.33 - 1.43 (6H, m), 1.47 - 1.53 (4H, m), 1.61 - 1.70 (1H, m), 1.73 (2H, br d), 1.89 - 1.99 (2H, m), 2.13 (2H, br d), 2.60 (2H, br t), 3.12 (2H, br d), 3.27 (2H, br d), 3.35 - 3.43 (4H, m),

3.53 - 3.60 (2H, m), 4.22 (1H, d), 4.35 (2H, br s), 6.08 (2H, s), 6.45 (2H, br dd), 6.84 - 6.98 (2H, m), 7.36 - 7.43 (1H, m), 7.52 (1H, s), 7.94 (1H, br d), 15.69 (1H, br s); m/z (ES⁺) [M+H]⁺ = 667.5.

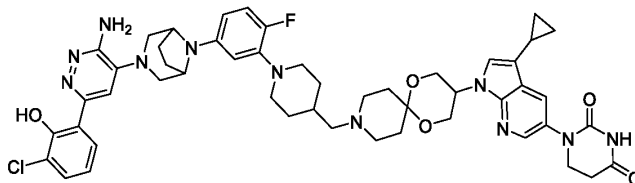
Intermediate 134b:

1-[5-[3-[3-Amino-6-(3-chloro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]piperidine-4-carbaldehyde



[1881] Prepared in an analogous manner to Intermediate 83c from Intermediate 134a (80 mg, 0.12 mmol) gave the title compound (60.0 mg, 93 %) as a solid. The crude product was used for the next step. m/z (ES⁺) [M+H]⁺ = 537.3.

1-[1-[9-[[1-[5-[3-[3-Amino-6-(3-chloro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

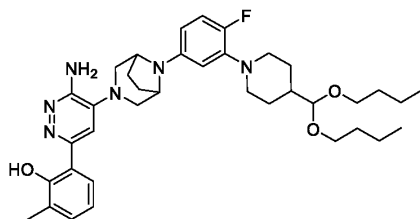


[1882] Prepared in an analogous manner to EXAMPLE 64 from Intermediate 134b (37.9 mg, 0.07 mmol) and Intermediate 87c (30 mg, 0.07 mmol). Purification by RPC (elution gradient: 0-100% MeCN in water with 0.1% NH₄OH) gave the title compound (28.0 mg, 42.0 %) as a light yellow solid following lyophilization. ¹H NMR (DMSO-*d*₆): δ 0.64 (2H, br d), 0.89 (2H, br d), 1.13 - 1.31 (4H, m), 1.57 - 1.68 (1H, m), 1.79 (2H, br d), 1.95 (6H, br s), 2.14 (2H, br d), 2.21 (2H, br d), 2.42 (4H, br s), 2.65 (2H, br t), 2.77 (2H, br t), 3.07 - 3.17 (2H, m), 3.28 (2H, br d), 3.37 (1H, br s), 3.83 (2H, br t), 4.05 (2H, br dd), 4.24 (2H, br d), 4.35 (2H, br s), 4.83 (1H, br s), 6.09 (2H, br s), 6.40 - 6.50 (2H, m), 6.86 (1H, br t), 6.93 (1H, br dd), 7.40 (1H, br d), 7.52 (1H, s), 7.64 (1H, s), 7.94 (1H, br d), 7.99 (1H, s), 8.20 (1H, s), 10.39 (1H, s), 15.69 (1H, br s); m/z (ES⁺) [M+H]⁺ = 946.8.

EXAMPLE 135

Intermediate 135a:

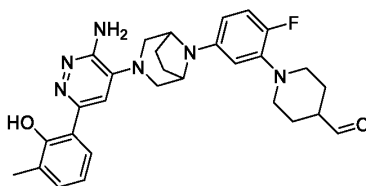
2-[6-Amino-5-[8-[3-[4-(dibutoxymethyl)-1-piperidyl]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-yl]-6-methyl-phenol



[1883] Prepared in an analogous manner to Intermediate 2h from (2-hydroxy-3-methylphenyl)boronic acid (63.4 mg, 0.42 mmol) and Intermediate 11f (200 mg, 0.35 mmol). Purification by FSC (elution gradient: 0-100% EtOAc in hexanes) gave the title compound (105 mg, 46.7 %) as an orange solid. ¹H NMR (DMSO-*d*₆): δ 0.89 (6H, t), 1.36 (6H, dt), 1.45 - 1.54 (4H, m), 1.60 - 1.68 (1H, m), 1.73 (2H, br d), 1.91 - 1.99 (2H, m), 2.13 (2H, br d), 2.19 (3H, s), 2.60 (2H, br t), 3.10 (2H, br d), 3.26 (2H, br d), 3.35 - 3.45 (4H, m), 3.56 (2H, dt), 4.22 (1H, d), 4.34 (2H, br s), 5.94 (2H, s), 6.45 (2H, br dd), 6.76 (1H, t), 6.92 (1H, dd), 7.13 (1H, br d), 7.45 (1H, s), 7.74 (1H, br d), 14.58 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 647.6.

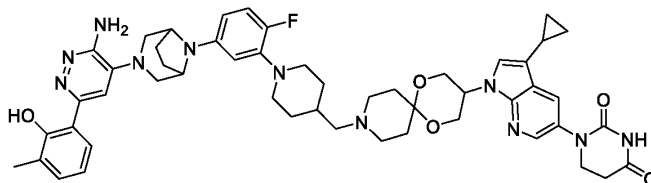
Intermediate 135b:

1-[5-[3-[3-Amino-6-(2-hydroxy-3-methyl-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]piperidine-4-carbaldehyde



[1884] Prepared in an analogous manner to Intermediate 83c from Intermediate 135a (100 mg, 0.15 mmol) gave the title compound (73.0 mg, 91 %) as a solid. The crude product was used for the next step. *m/z* (ES⁺) [M+H]⁺ = 517.4.

1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxy-3-methyl-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

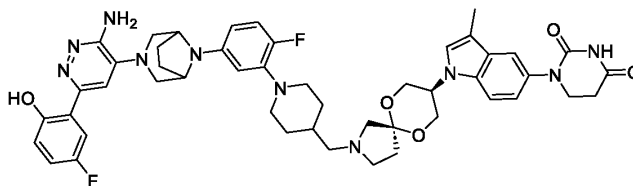


[1885] Prepared in an analogous manner to EXAMPLE 64 from Intermediate 135b (30.4 mg, 0.06 mmol) and Intermediate 87e (25 mg, 0.06 mmol). Purification by RPC (elution gradient: 0-100% MeCN in water with 0.1% NH₄OH) gave the title compound (20.00 mg, 36.8 %) as a white solid following lyophilization. ¹H NMR (DMSO-*d*₆): δ 0.65 (2H, br d), 0.89 (2H, br d), 1.25 (2H, br d), 1.62 (1H, br s), 1.79 (2H, br d), 1.95 (6H, br s), 2.13 (2H, br d), 2.20 (5H, br s), 2.42 (4H, br s), 2.65 (2H, br t), 2.77 (2H, br t), 3.11 (2H, br d), 3.27 (2H, br d), 3.36 (3H, br d), 3.83 (2H, br t), 4.05 (2H, br d), 4.24 (2H, br d), 4.35

(2H, br s), 4.83 (1H, br s), 5.94 (2H, br s), 6.39 - 6.54 (2H, m), 6.77 (1H, br t), 6.87 - 7.01 (1H, m), 7.13 (1H, br d), 7.46 (1H, s), 7.65 (1H, s), 7.75 (1H, br d), 7.99 (1H, br s), 8.20 (1H, br s), 10.39 (1H, s), 14.58 (1H, br s); m/z (ES^+) $[M+H]^+ = 926.8$.

EXAMPLE 136

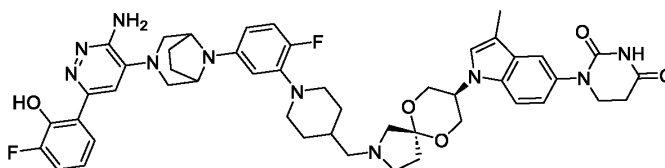
1-[1-[(5*s*,8*s*)-2-[[1-[5-[3-[3-Amino-6-(5-fluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione



[1886] Prepared in an analogous manner to EXAMPLE 64 from Intermediate 103b (20 mg, 0.04 mmol) and Intermediate 106e (22.15 mg, 0.06 mmol). Purification by RPC (elution gradient: 0-60% MeCN in water with 0.1% formic acid) gave the title compound (9.00 mg, 26.4 %) as a white solid following lyophilization. 1H NMR (DMSO-*d*₆): δ 1.27 (2H, q), 1.60 (1H, br s), 1.81 (2H, br d), 1.90 - 2.00 (2H, m), 2.13 (4H, br d), 2.26 (3H, s), 2.31 (2H, br d), 2.57 - 2.70 (4H, m), 2.74 (2H, br t), 2.82 (2H, s), 3.12 (2H, br d), 3.26 (2H, br d), 3.36 (2H, br d), 3.78 (2H, t), 3.98 (2H, br dd), 4.25 (2H, br d), 4.35 (2H, br s), 4.55 (1H, br s), 6.01 (2H, br s), 6.39 - 6.55 (2H, m), 6.85 - 6.98 (2H, m), 7.03 - 7.10 (2H, m), 7.41 - 7.51 (3H, m), 7.55 (1H, s), 7.85 (1H, dd), 10.26 (1H, s), 13.35 - 14.84 (1H, m); m/z (ES^+) $[M+H]^+ = 889.5$.

EXAMPLE 137

1-[1-[(5*s*,8*s*)-2-[[1-[5-[3-[3-Amino-6-(3-fluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione

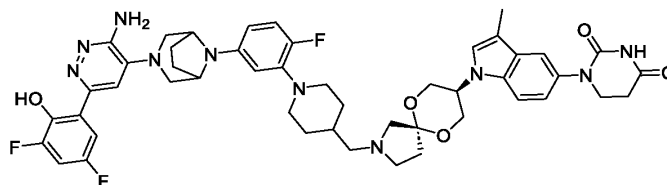


[1887] Prepared in an analogous manner to EXAMPLE 64 from Intermediate 105b (20 mg, 0.04 mmol) and Intermediate 106e (21.41 mg, 0.06 mmol). Purification by RPC (elution gradient: 0-60% MeCN in water with 0.1% formic acid) gave the title compound (8.0 mg, 23.4 %) as a white solid following lyophilization. 1H NMR (DMSO-*d*₆): δ 1.27 (2H, q), 1.60 (1H, br s), 1.81 (2H, br d), 1.95 (2H, br d), 2.13 (4H, br d), 2.26 (3H, s), 2.31 (2H, br d), 2.58 - 2.70 (4H, m), 2.74 (2H, br t), 2.82 (2H, s), 3.12 (2H, br d), 3.27 (2H, br d), 3.36 (2H, br d), 3.78 (2H, br t), 3.98 (2H, br dd), 4.25 (2H, br d), 4.35 (2H, br s), 4.55 (1H, br s), 6.05 (2H, br s), 6.38 - 6.55 (2H, m), 6.78 - 6.87 (1H, m), 6.93 (1H, br dd), 7.08 (1H, br d), 7.15 - 7.26

(1H, m), 7.41 - 7.51 (3H, m), 7.55 (1H, s), 7.77 (1H, br d), 10.25 (1H, s), 14.35 (1H, br s); m/z (ES^+) $[M+H]^+ = 889.6$.

EXAMPLE 138

1-[1-[(5*S*,8*S*)-2-[[1-[5-[3-[3-Amino-6-(3,5-difluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione

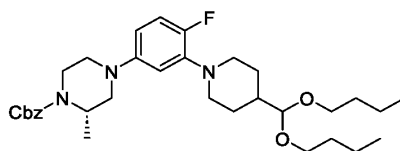


[1888] Prepared in an analogous manner to EXAMPLE 64 from Intermediate 104b (20 mg, 0.04 mmol) and Intermediate 106e (21.41 mg, 0.06 mmol). Purification by RPC (elution gradient: 0-60% MeCN in water with 0.1% formic acid) gave the title compound (10.00 mg, 29.7 %) as a white solid following lyophilization. 1H NMR (DMSO- d_6): δ 1.27 (2H, q), 1.60 (1H, br s), 1.81 (2H, br d), 1.92 - 1.99 (2H, m), 2.09 - 2.17 (4H, m), 2.26 (3H, s), 2.31 (2H, br d), 2.58 - 2.70 (4H, m), 2.74 (2H, t), 2.82 (2H, s), 3.13 (2H, br d), 3.26 (2H, br d), 3.36 (2H, br d), 3.78 (2H, br t), 3.98 (2H, br dd), 4.25 (2H, br d), 4.35 (2H, br s), 4.55 (1H, br s), 6.12 (2H, br s), 6.41 - 6.51 (2H, m), 6.93 (1H, dd), 7.08 (1H, br d), 7.22 - 7.29 (1H, m), 7.43 (1H, s), 7.46 (1H, d), 7.51 (1H, s), 7.55 (1H, s), 7.78 (1H, br d), 10.25 (1H, s), 14.01 (1H, br.s); m/z (ES^+) $[M+H]^+ = 907.7$.

EXAMPLE 139

Intermediate 139a:

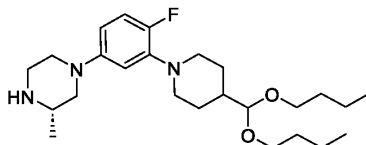
Benzyl (2*S*)-4-[3-[4-(dibutoxymethyl)-1-piperidyl]-4-fluoro-phenyl]-2-methyl-piperazine-1-carboxylate



[1889] A mixture of $[Pd(allyl)Cl]_2$ (4.92 mg, 0.01 mmol), Xphos (25.6 mg, 0.05 mmol), benzyl (2*S*)-2-methylpiperazine-1-carboxylate (378 mg, 1.61 mmol), Intermediate 11c (500 mg, 1.34 mmol) and Cs_2CO_3 (1095 mg, 3.36 mmol) in dioxane (6.5 mL) was degassed for 5 min. and heated to 90°C for 4 h under nitrogen. The reaction mixture was diluted with EtOAc (50 mL) and filtered through celite®. The filtrate was concentrated. Purification by FSC (elution gradient: 0-30% ethyl acetate in hexanes) gave the title compound (570 mg, 74.4 %) as an orange gum. 1H NMR (DMSO- d_6): δ 0.90 (6H, t), 1.24 (3H, d), 1.30 - 1.44 (6H, m), 1.45 - 1.54 (4H, m), 1.66 (1H, dt), 1.73 (2H, br d), 2.54 - 2.64 (3H, m), 2.77 (1H, dd), 3.18 - 3.28 (1H, m), 3.32 - 3.44 (5H, m), 3.49 (1H, br d), 3.56 (2H, dt), 3.88 (1H, br d), 4.22 (1H, d), 4.29 (1H, br d), 5.06 - 5.20 (2H, m), 6.39 - 6.59 (2H, m), 6.95 (1H, dd), 7.30 - 7.44 (5H, m); m/z (ES^+) $[M+H]^+ = 570.6$.

Intermediate 139b:

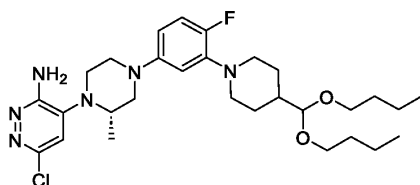
(3*S*)-1-[3-[4-(Dibutoxymethyl)-1-piperidyl]-4-fluoro-phenyl]-3-methyl-piperazine



[1890] Pd/C (213 mg, 0.20 mmol) was added to a solution of Intermediate 139a (570mg, 1.00 mmol) in THF (10 mL). The reaction was sparged with hydrogen and stirred at r.t. under hydrogen for overnight. The reaction was filtered through a plug of celite®, eluting with EtOAc and MeOH. Filtrate was concentrated gave the title compound (390 mg, 89 %) as an orange gum. The crude product was used for the next step. m/z (ES^+) $[M+H]^+ = 436.4$.

Intermediate 139c:

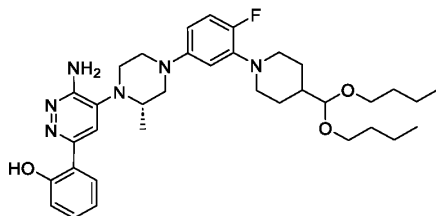
6-Chloro-4-[(2*S*)-4-[3-[4-(dibutoxymethyl)-1-piperidyl]-4-fluoro-phenyl]-2-methyl-piperazin-1-yl]pyridazin-3-amine



[1891] A mixture of 4-bromo-6-chloropyridazin-3-amine (215 mg, 1.03 mmol), Intermediate 139b (450mg, 1.03 mmol) and potassium fluoride (120 mg, 2.07 mmol) in DMSO (4 mL) was heated at 130 °C for two days. The reaction mixture was diluted with water (20 mL) and extracted with DCM (2 x 25 mL). The combined extracts were dried over Na₂SO₄, filtered and concentrated. Purification by FSC (elution gradient: 0-100% ethyl acetate in hexanes) gave the title compound (150 mg, 25.8 %) as an orange gum. ¹H NMR (DMSO-*d*₆): δ 0.90 (6H, t), 0.99 (3H, d), 1.31 - 1.45 (6H, m), 1.46 - 1.54 (4H, m), 1.66 (1H, dt), 1.74 (2H, br d), 2.60 (2H, br t), 2.75 - 2.84 (1H, m), 2.96 - 3.04 (2H, m), 3.08 - 3.13 (1H, m), 3.33 - 3.44 (6H, m), 3.57 (2H, dt), 3.77 (1H, br dd), 4.23 (1H, d), 6.21 (2H, s), 6.50 (1H, dt), 6.56 (1H, dd), 6.93 - 7.01 (1H, m), 7.07 (1H, s).

Intermediate 139d:

2-[6-Amino-5-[(2*S*)-4-[3-[4-(dibutoxymethyl)-1-piperidyl]-4-fluoro-phenyl]-2-methyl-piperazin-1-yl]pyridazin-3-yl]phenol

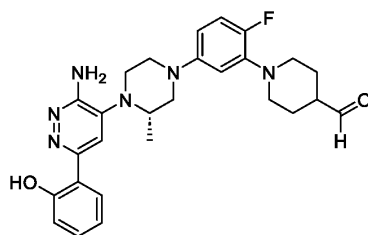


[1892] Prepared in an analogous manner to Intermediate 2h from Intermediate 139c (150 mg, 0.27 mmol). Purification by FSC (elution gradient: 0-100% EtOAc in hexane) gave the title compound (75 mg,

45.4 %) as an orange solid. ^1H NMR (DMSO- d_6): δ 0.90 (7H, t), 1.02 (3H, d), 1.32 - 1.43 (7H, m), 1.47 - 1.52 (4H, m), 1.75 (2H, br d), 2.58 - 2.66 (2H, m), 2.85 - 2.93 (1H, m), 3.01 (1H, br dd), 3.15 - 3.23 (1H, m), 3.37 - 3.50 (6H, m), 3.57 (2H, dt), 3.84 - 3.91 (1H, m), 4.23 (1H, d), 6.38 (2H, s), 6.54 (1H, dt), 6.57 - 6.61 (1H, m), 6.88 - 6.94 (2H, m), 6.98 (1H, dd), 7.23 - 7.29 (1H, m), 7.70 (1H, s), 7.93 - 7.98 (1H, m), 14.12 (1H, br s); m/z (ES^+) $[\text{M}+\text{H}]^+ = 621.5$.

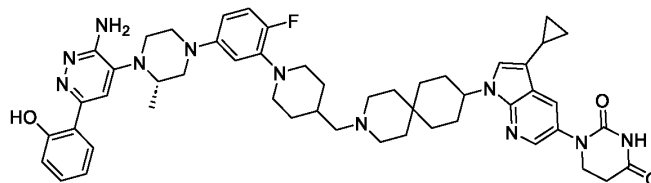
Intermediate 139e

1-[5-[(3*S*)-4-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3-methyl-piperazin-1-yl]-2-fluoro-phenyl]piperidine-4-carbaldehyde



[1893] Prepared in an analogous manner to Intermediate 83c from Intermediate 139d (75 mg, 0.12 mmol) gave the title compound (55.0 mg, 93 %) as a solid. The crude product was used for the next step. m/z (ES^+) $[\text{M}+\text{H}]^+ = 491.4$.

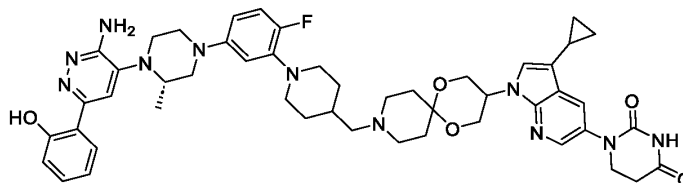
1-[1-[3-[[1-[5-[(3*S*)-4-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3-methyl-piperazin-1-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1894] Prepared in an analogous manner to EXAMPLE 64 from Intermediate 139e (20 mg, 0.04 mmol) and Intermediate 36a (21.41 mg, 0.06 mmol). Purification by RPC (elution gradient: 0-60% MeCN in water with 0.1% formic acid) gave the title compound (15.00 mg, 41.1 %) as a white solid following lyophilization. ^1H NMR (DMSO- d_6): δ 0.66 (2H, br d), 0.86 (2H, br d), 1.03 (3H, br d), 1.23 - 1.35 (4H, m), 1.41 (2H, br s), 1.63 - 1.74 (5H, m), 1.80 (4H, br d), 1.89 - 2.04 (3H, m), 2.27 (2H, br d), 2.43 (4H, br s), 2.67 (2H, br d), 2.77 (2H, br t), 2.86 - 2.95 (1H, m), 3.01 (1H, br dd), 3.20 (1H, br d), 3.36 (3H, br d), 3.44 - 3.52 (2H, m), 3.82 (2H, br t), 3.88 (1H, br d), 4.60 (1H, br t), 6.38 (2H, br s), 6.50 - 6.66 (2H, m), 6.89 - 7.05 (3H, m), 7.26 (1H, t), 7.50 (1H, s), 7.70 (1H, s), 7.88 - 8.00 (2H, m), 8.15 - 8.19 (1H, m), 10.38 (1H, s), 15.66 (1H, br s); m/z (ES^+) $[\text{M}+\text{H}]^+ = 896.8$.

EXAMPLE 140

1-[1-[9-[[1-[5-[(3*S*)-4-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3-methyl-piperazin-1-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

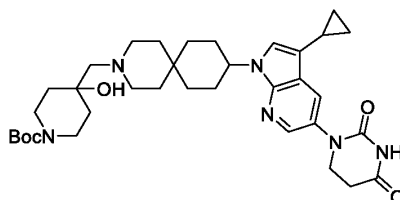


[1895] Prepared in an analogous manner to EXAMPLE 64 from Intermediate 139e (20 mg, 0.04 mmol) and Intermediate 87e (21.41 mg, 0.06 mmol). Purification by RPC (elution gradient: 0-100% MeCN in water with 0.1% NH₄OH) gave the title compound (17.00 mg, 46.3 %) as a white solid following lyophilization. ¹H NMR (DMSO-*d*₆): δ 0.64 (2H, q), 0.83 - 0.94 (2H, m), 1.03 (3H, d), 1.22 - 1.25 (3H, m), 1.25 - 1.33 (2H, m), 1.64 (1H, br s), 1.81 (2H, br d), 1.96 (4H, br d), 2.22 (2H, br d), 2.42 (3H, br d), 2.67 (2H, br d), 2.77 (2H, t), 2.87 - 2.93 (1H, m), 3.01 (1H, br dd), 3.16 - 3.23 (1H, m), 3.36 (2H, br d), 3.42 - 3.50 (2H, m), 3.83 (2H, t), 3.86 - 3.92 (1H, m), 4.05 (2H, br dd), 4.25 (2H, br dd), 4.79 - 4.88 (1H, m), 6.38 (2H, br s), 6.51 - 6.57 (1H, m), 6.57 - 6.63 (1H, m), 6.88 - 6.94 (2H, m), 6.98 (1H, dd), 7.26 (1H, t), 7.65 (1H, s), 7.71 (1H, s), 7.90 - 8.00 (2H, m), 8.20 (1H, d), 10.39 (1H, s), 14.12 (1H, br s); *m/z* (ES⁺) [M+H]⁺ = 900.7.

EXAMPLE 141

Intermediate 141a:

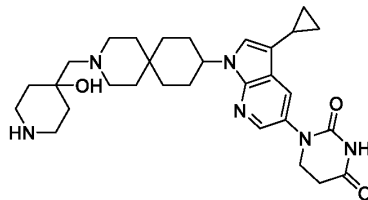
tert-Butyl 4-[[9-[3-cyclopropyl-5-(2,4-dioxohexahydropyrimidin-1-yl)pyrrolo[2,3-*b*]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl]methyl]-4-hydroxy-piperidine-1-carboxylate



[1896] A mixture of Intermediate 36a (527 mg, 1.25mmol), *tert*-butyl 1-oxa-6-azaspiro[2.5]octane-6-carboxylate (533 mg, 2.50 mmol), and DIPEA (437 μl, 2.50 mmol) in *n*BuOH (0.5 ml) was heated at 85 °C for 6 h. The solvent was removed, and the residue was partitioned between DCM and water. The organic phase was dried over MgSO₄, filtered and concentrated. The residue was triturated in ether to give the title compound (601 mg, 76%) as a solid. ¹H NMR (DMSO-*d*₆): δ 0.64 (2H, br s), 0.82 - 0.88 (2H, m), 1.20 - 1.27 (2H, m), 1.30 - 1.48 (18H, m), 1.65 (4H, br s), 1.77 (2H, br d), 1.88 - 2.01 (4H, m), 2.23 (2H, s), 2.75 (2H, t), 2.98 - 3.15 (2H, m), 3.61 (2H, br d), 3.80 (2H, t), 4.10 (1H, s), 4.52 - 4.63 (1H, m), 7.48 (1H, s), 7.92 (1H, d), 8.14 (1H, d), 10.35 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 635.5

Intermediate 141b:

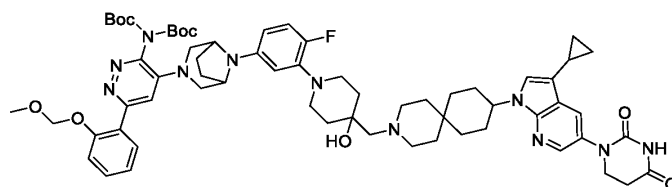
1-[3-Cyclopropyl-1-[3-[(4-hydroxy-4-piperidyl)methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1897] TFA (1.5 ml, 18.93 mmol) was added to stirred solution of Intermediate 141a (601 mg, 0.95 mmol) in DCM (5 mL). The reaction was stirred at r.t. for 1h. The solvent was removed, and residue was triturated with ether, and the solids were collected by filtration. The solids were dissolved in MeOH (20 mL) and carbonate resin (2.5-3.5 mmol/g, 1g) was added. The reaction was stirred at r.t. for 2h. The resin was filtered off gave the title compound (495 mg, 98 %) as beige solid. ¹H NMR (DMSO-*d*₆): δ 0.60 - 0.68 (2H, m), 0.80 - 0.88 (2H, m), 1.24 - 1.32 (2H, m), 1.32 - 1.39 (2H, m), 1.54 - 1.59 (2H, m), 1.63 - 1.73 (6H, m), 1.73 - 1.81 (2H, m), 1.87 - 1.92 (1H, m), 1.96 - 2.02 (1H, m), 2.27 (2H, s), 2.75 (2H, t), 2.99 - 3.11 (4H, m), 3.23 - 3.35 (6H, m), 3.80 (2H, t), 4.38 - 4.50 (1H, m), 4.57 (1H, br t), 7.47 (1H, s), 7.92 (1H, d), 8.14 (1H, d), 10.35 (1H, br s); *m/z* (ES⁺) [M+H]⁺ = 535.5

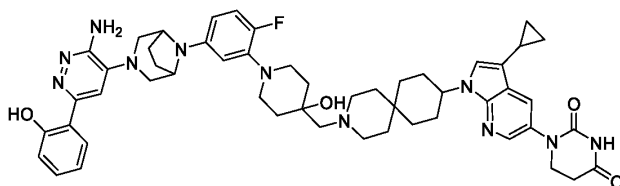
Intermediate 141c:

tert-Butyl *N*-*tert*-butoxycarbonyl-*N*-[4-[8-[3-[4-[[9-[3-cyclopropyl-5-(2,4-dioxohexahydropyrimidin-1-yl)pyrrolo[2,3-*b*]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl]methyl]-4-hydroxy-1-piperidyl]-4-fluorophenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]-6-[2-(methoxymethoxy)phenyl]pyridazin-3-yl]carbamate



[1898] Prepared in an analogous method to Intermediate 56f starting with Intermediate 141b (96 mg, 0.18 mmol), and Intermediate 57a (101 mg, 0.15 mmol). Purification by FSC (elution gradient:10-50% MeOH in EtOAc), followed by RPC (elution gradient:25-60% MeCN in water with 0.1% FA) gave the title compound (17.0 mg, 9.7 %) as a brown gum. *m/z* (ES⁺) [M+H]⁺ = 1168.6.

1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-hydroxy-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

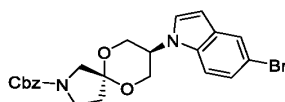


[1899] Intermediate 141c (17 mg, 0.01 mmol) in DCM (0.5 mL) was added HCl (4N in Dioxane) (0.5 mL, 2.00 mmol). The reaction was stirred at r.t. 2h. The solvent was removed, the HCl salt was free based by dissolving in MeOH (2 mL) and quenched with the addition of carbonate resin. The resin was filtered off and filtrate was concentrated. Purification by RPC (elution gradient: 25-60% MeCN in water with 0.1% FA) gave the title compound (5.0 mg, 37 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 0.64 (2H, br d), 0.84 (2H, br d), 1.26 (2H, br t), 1.31 - 1.43 (2H, m), 1.53 (2H, br d), 1.63 - 1.81 (8H, m), 1.81 - 2.02 (6H, m), 2.12 (2H, br d), 2.32 (2H, br s), 2.54 - 2.59 (3H, m), 2.75 (2H, br t), 2.94 - 3.01 (2H, m), 3.03 - 3.11 (4H, m), 3.21 - 3.26 (2H, m), 3.77 - 3.81 (2H, m), 4.30 - 4.36 (2H, m), 4.57 (1H, br t), 5.91 (2H, br s), 6.36 - 6.44 (1H, m), 6.49 (1H, br d), 6.82 - 6.94 (3H, m), 7.21 (1H, br t), 7.47 (2H, br d), 7.87 - 7.95 (2H, m), 8.15 (1H, s), 10.35 (1H, s), (two OH protons not observed); *m/z* (ES⁺) [M+H]⁺ = 924.6.

EXAMPLE 142

Intermediate 142a:

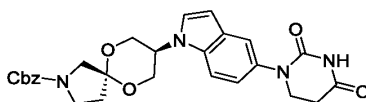
Benzyl (5*s*,8*s*)-8-(5-bromoindol-1-yl)-6,10-dioxaspiro[4.5]decane-2-carboxylate



[1900] Prepared in an analogous manner to Intermediate 64d starting from Intermediate 99b (2.1 g, 7.77 mmol) and Intermediate 65a (2.475 g, 9.33 mmol). Purification by FSC (elution gradient: 0 to 100% ethyl acetate in hexanes) gave the title compound, cis isomer which eluted second off the column, (1.260 g, 34.4 %) as an orange gum. ¹H NMR (DMSO-*d*₆): δ 2.29 - 2.37 (2H, m), 3.38 - 3.52 (2H, m), 3.59 (2H, s), 4.00 - 4.06 (2H, m), 4.27 - 4.38 (2H, m), 4.63 (1H, br s), 5.07 (2H, s), 6.47 (1H, br s), 7.20 - 7.27 (1H, m), 7.28 - 7.34 (1H, m), 7.36 (4H, d), 7.50 (1H, br t), 7.75 (1H, d), 7.80 (1H, br d); *m/z* (ES⁺) [M+H]⁺ = 471.3.

Intermediate 142b:

Benzyl (5*s*,8*s*)-8-[5-(2,4-dioxohexahydropyrimidin-1-yl)indol-1-yl]-6,10-dioxaspiro[4.5]decane-2-carboxylate

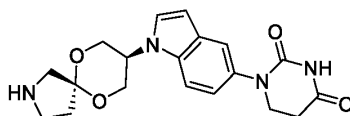


[1901] Prepared in an analogous manner to Intermediate 2b starting from Intermediate 142a (943 mg, 2 mmol).

[1902] Purification by FSC (elution gradient: 10-60% MeOH in DCM with 1% NH₄OH) gave the title compound (496 mg, 49.2 %) as a white solid. ¹H NMR (CD₂Cl₂): δ 2.28 - 2.38 (2H, m), 2.75 - 2.85 (2H, m), 3.54 - 3.60 (2H, m), 3.63 - 3.75 (2H, m), 3.83 - 3.88 (2H, m), 4.10 - 4.17 (2H, m), 4.31 - 4.42 (2H, m), 4.44 - 4.59 (1H, m), 5.12 (2H, s), 6.56 (1H, br s), 7.13 (1H, br d), 7.27 - 7.40 (6H, m), 7.49 - 7.56 (1H, m), 7.60 - 7.76 (2H, m); *m/z* (ES⁺) [M+H]⁺ = 505.4.

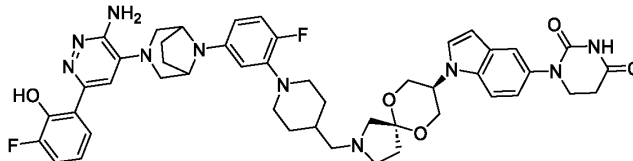
Intermediate 142c:

1-[1-((5*s*,8*s*)-6,10-dioxo-2-azaspiro[4.5]decan-8-yl)indol-5-yl]hexahydropyrimidine-2,4-dione



[1903] Prepared in an analogous manner to Intermediate 139b starting from Intermediate 142b (492 mg, 0.98 mmol) gave the title compound (295 mg, 82 %) as an off-white solid. m/z (ES^+) $[M+H]^+ = 371.6$.

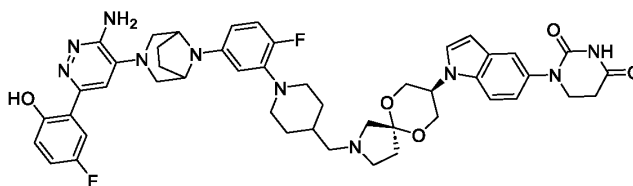
1-[1-[(5*s*,8*s*)-2-[[1-[5-[3-[3-Amino-6-(3-fluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]indol-5-yl]hexahydropyrimidine-2,4-dione



[1904] Prepared in an analogous method to EXAMPLE 64 starting from Intermediate 105b (21 mg, 0.04 mmol) and Intermediate 142c (22 mg, 0.06 mmol). Purification by RPC (elution gradient: 0-60% MeCN in water with 0.1% FA) gave the title compound (18 mg, 51.4 %) as a white solid. 1H NMR (DMSO- d_6): δ 1.26 (2H, q), 1.62 (1H, br s), 1.80 (2H, br d), 1.90 - 1.96 (2H, m), 2.04 - 2.13 (2H, m), 2.14 - 2.24 (2H, m), 2.26 - 2.47 (2H, m), 2.59 - 2.79 (6H, m), 2.80 - 3.00 (2H, m), 3.10 (2H, br d), 3.18 - 3.26 (2H, m), 3.34 - 3.44 (2H, m), 3.76 (2H, t), 4.01 (2H, br dd), 4.22 - 4.41 (4H, m), 4.60 (1H, br s), 6.03 (2H, s), 6.39 - 6.52 (3H, m), 6.81 (1H, td), 6.91 (1H, dd), 7.08 (1H, br d), 7.14 - 7.20 (1H, m), 7.44 - 7.52 (3H, m), 7.73 - 7.78 (2H, m), 10.24 (1H, s), 13.75 - 15.20 (1H, m); m/z (ES^+) $[M+H]^+ = 875.5$.

EXAMPLE 143

1-[1-[(5*s*,8*s*)-2-[[1-[5-[3-[3-Amino-6-(5-fluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]indol-5-yl]hexahydropyrimidine-2,4-dione

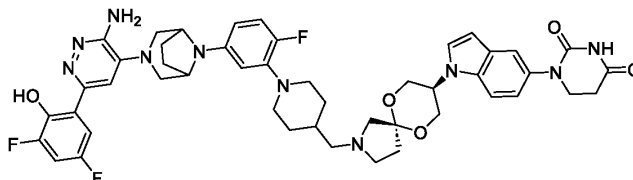


[1905] Prepared in an analogous method to EXAMPLE 64 starting from Intermediate 103b (21 mg, 0.04 mmol) and Intermediate 142c (22mg, 0.06 mmol). Purification by RPC (gradient: 0-60% MeCN in water with 0.1% FA) gave the title compound (21 mg, 60 %) as a white solid. 1H NMR (DMSO- d_6): δ 1.26 (2H, q), 1.60 (1H, br s), 1.79 (2H, br d), 1.87 - 1.99 (2H, m), 2.08 - 2.22 (4H, m), 2.24 - 2.43 (2H, m), 2.55 - 2.70 (4H, m), 2.70 - 2.76 (2H, m), 2.76 - 2.93 (2H, m), 3.10 (2H, br d), 3.20 - 3.25 (2H, m), 3.33 - 3.41 (2H, m), 3.76 (2H, t), 4.00 (2H, br dd), 4.24 - 4.38 (4H, m), 4.60 (1H, br s), 5.99 (2H, s), 6.38 - 6.52 (3H,

m), 6.84 - 6.95 (2H, m), 7.03 - 7.10 (2H, m), 7.43 - 7.53 (3H, m), 7.76 (1H, d), 7.83 (1H, dd), 10.24 (1H, s), 13.45 - 14.88 (1H, m); m/z (ES^+) $[M+H]^+ = 875.5$.

EXAMPLE 144

1-[1-[(5*s*,8*s*)-2-[[1-[5-[3-[3-Amino-6-(3,5-difluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]indol-5-yl]hexahydropyrimidine-2,4-dione

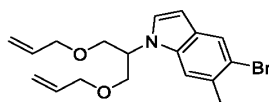


[1906] Prepared in an analogous method to EXAMPLE 64 starting from Intermediate 104b (22 mg, 0.04 mmol) and Intermediate 142c (22 mg, 0.06 mmol). Purification by RPC (elution gradient: 0-60% MeCN in water with 0.1% FA) gave the title compound (26 mg, 72.8 %) as a white solid. 1H NMR ($DMSO-d_6$): δ 1.18 - 1.33 (2H, m), 1.59 (1H, br s), 1.79 (2H, br d), 1.88 - 1.98 (2H, m), 2.07 - 2.19 (4H, m), 2.27 - 2.39 (2H, m), 2.59 - 2.68 (4H, m), 2.71 (2H, br t), 2.82 (2H, br s), 3.11 (2H, br d), 3.19 - 3.26 (2H, m), 3.33 - 3.41 (2H, m), 3.76 (2H, t), 4.00 (2H, br dd), 4.24 - 4.37 (4H, m), 4.59 (1H, br s), 6.10 (2H, s), 6.37 - 6.51 (3H, m), 6.91 (1H, dd), 7.08 (1H, br d), 7.19 - 7.28 (1H, m), 7.43 - 7.54 (3H, m), 7.73 - 7.79 (2H, m), 10.24 (1H, s), 14.14 - 15.30 (1H, m); m/z (ES^+) $[M+H]^+ = 893.5$.

EXAMPLE 145

Intermediate 145a:

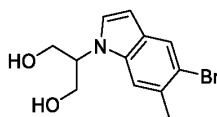
1-[2-Allyloxy-1-(allyloxymethyl)ethyl]-5-bromo-6-methyl-indole



[1907] Prepared in an analogous method to Intermediate 113a using 5-bromo-4-fluoro-1*H*-indole (1.00 g, 4.67 mmol). Purification by FSC (1st purification: 0-10% acetone in hexanes; 2nd purification: 30-100% DCM in hexanes) gave the title compound (0.62 g, 36%) as a yellow oil. 1H NMR ($DMSO-d_6$): δ 2.42 (3H, s), 3.73 - 3.82 (4H, m), 3.90 (4H, d), 4.82 (1H, quin), 5.05 - 5.11 (2H, m), 5.11 - 5.18 (2H, m), 5.70 - 5.85 (2H, m), 6.39 (1H, d), 7.44 (1H, d), 7.56 (1H, s), 7.73 (1H, s); m/z (ES^+) $[M+H]^+ = 364.2$.

Intermediate 145b:

2-(5-Bromo-6-methyl-indol-1-yl)propane-1,3-diol

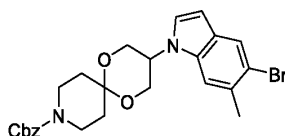


[1908] Prepared in an analogous method to Intermediate 64b using Intermediate 145a (613 mg, 1.68 mmol). Purification by FSC (1st purification: elution gradient 0-80% acetone in hexanes; 2nd purification:

50-100% EtOAc in hexanes) gave the title compound (398 mg, 83%) as a red solid. ^1H NMR ($\text{DMSO}-d_6$): δ 2.43 (3H, s), 3.68 - 3.86 (4H, m), 4.42 (1H, quin), 4.85 (2H, br s), 6.36 (1H, d), 7.42 (1H, d), 7.47 (1H, s), 7.73 (1H, s); m/z (ES^+) $[\text{M}+\text{H}]^+ = 284.0$.

Intermediate 145c:

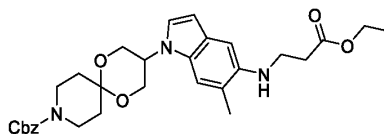
Benzyl 3-(5-bromo-6-methyl-indol-1-yl)-1,5-dioxo-9-azaspiro[5.5]undecane-9-carboxylate



[1909] Prepared in an analogous method to Intermediate 64d using Intermediate 145b (496 mg, 1.78 mmol). Purification by FSC (elution gradient: 0-15% EtOAc in DCM) gave the title compound (469 mg, 69%) as a white foam. ^1H NMR ($\text{DMSO}-d_6$): δ 1.81 - 1.90 (2H, m), 1.94 - 1.99 (2H, m), 2.42 (3H, s), 3.34 - 3.55 (4H, m), 3.98 (2H, dd), 4.23 - 4.36 (2H, m), 4.50 - 4.61 (1H, m), 5.08 (2H, s), 6.42 (1H, d), 7.26 - 7.40 (5H, m), 7.52 (1H, s), 7.73 (1H, d), 7.77 (1H, s); m/z (ES^+) $[\text{M}+\text{H}]^+ = 499.0$.

Intermediate 145d:

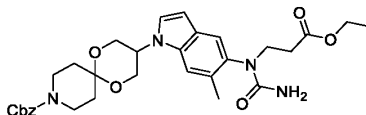
Benzyl 3-[5-[(3-ethoxy-3-oxo-propyl)amino]-6-methyl-indol-1-yl]-1,5-dioxo-9-azaspiro[5.5]undecane-9-carboxylate



[1910] Prepared in an analogous method to Intermediate 113d using Intermediate 145c (467 mg, 0.94 mmol). Purification by FSC (1st purification: elution gradient 0-100% EtOAc in hexanes; 2nd purification: 0-40% acetone in hexanes) gave the title compound (352 mg, 70%) as a yellow wax. ^1H NMR ($\text{DMSO}-d_6$): δ 1.18 (3H, t), 1.82 - 1.89 (2H, m), 1.89 - 1.96 (2H, m), 2.17 (3H, s), 2.63 (2H, t), 3.27 - 3.35 (2H, m), 3.44 (4H, br s), 3.97 (2H, br dd), 4.08 (2H, q), 4.23 (2H, br d), 4.31 - 4.39 (1H, m), 4.40 - 4.50 (1H, m), 5.08 (2H, s), 6.23 (1H, d), 6.66 (1H, s), 7.15 (1H, s), 7.28 - 7.40 (5H, m), 7.48 (1H, d); m/z (ES^+) $[\text{M}+\text{H}]^+ = 536.3$.

Intermediate 145e:

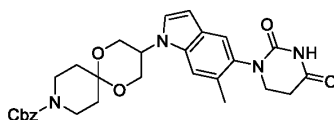
Benzyl 3-[5-[carbamoyl-(3-ethoxy-3-oxo-propyl)amino]-6-methyl-indol-1-yl]-1,5-dioxo-9-azaspiro[5.5]undecane-9-carboxylate



[1911] Prepared in an analogous method to Intermediate 113e using Intermediate 145d (0.34 g, 0.64 mmol) to give the title compound as a yellowish foam which was used for the next step without further purification. Quantitative yield was assumed. m/z (ES^+) $[\text{M}+\text{H}]^+ = 579.4$.

Intermediate 145f:

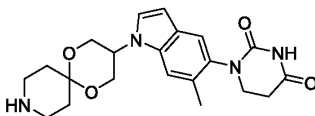
Benzyl 3-[5-(2,4-dioxohexahydropyrimidin-1-yl)-6-methyl-indol-1-yl]-1,5-dioxo-9-azaspiro[5.5]undecane-9-carboxylate



[1912] Prepared in an analogous method to Intermediate 113f using Intermediate 145e (0.37 g, 0.64 mmol) to give the title compound (0.27 g, 81%) as an orange solid. ^1H NMR (DMSO- d_6): δ 1.83 - 1.90 (2H, m), 1.96 (2H, br s), 2.26 (3H, s), 2.64 - 2.79 (2H, m), 3.39 - 3.58 (5H, m), 3.69 - 3.80 (1H, m), 3.96 - 4.05 (2H, m), 4.30 (2H, br d), 4.53 - 4.60 (1H, m), 5.08 (2H, s), 6.43 (1H, d), 7.27 - 7.40 (6H, m), 7.43 (1H, s), 7.72 (1H, d), 10.24 (1H, s); m/z (ES^+) $[\text{M}+\text{H}]^+ = 533.3$.

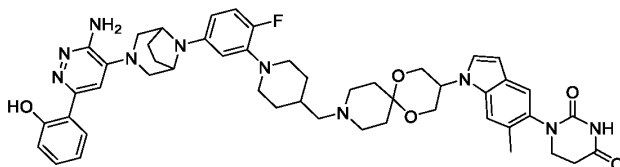
Intermediate 145g:

1-[1-(1,5-Dioxo-9-azaspiro[5.5]undecan-3-yl)-6-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione



[1913] Prepared in an analogous manner to Intermediate 129c starting from Intermediate 145f (262 mg, 0.49 mmol) to give the title compound (182 mg, 93%) as a white solid. ^1H NMR (DMSO- d_6): δ 1.80 (2H, br s), 1.84 - 1.93 (2H, m), 2.26 (3H, s), 2.69 - 2.76 (6H, m), 3.53 (1H, dt), 3.70 - 3.80 (1H, m), 3.91 - 4.02 (2H, m), 4.27 (2H, dd), 4.50 - 4.57 (1H, m), 6.42 (1H, d), 7.38 (1H, s), 7.43 (1H, s), 7.72 (1H, d), 10.24 (1H, br s), one nitrogen-bound proton not observed; m/z (ES^+) $[\text{M}+\text{H}]^+ = 399.3$.

1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-6-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione



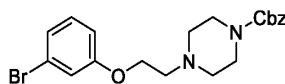
[1914] Prepared in an analogous manner to EXAMPLE 64 using Intermediate 145g (25 mg, 0.06 mmol) and Intermediate 13d (26 mg, 0.05 mmol). Purification by RPC (elution gradient: 10-40% MeCN in water with 0.1% HCOOH) gave the title compound (26.8 mg, 57%) as a white solid. ^1H NMR (DMSO- d_6): δ 1.18 - 1.32 (2H, m), 1.61 (1H, br s), 1.72 - 1.81 (2H, m), 1.83 - 2.05 (6H, m), 2.08 - 2.15 (2H, m), 2.20 (2H, d), 2.26 (3H, s), 2.33 - 2.47 (4H, m), 2.63 (2H, t), 2.67 - 2.81 (2H, m), 3.09 (2H, d), 3.25 (2H, d), 3.34 (2H, br d), 3.50 - 3.57 (1H, m), 3.72 - 3.79 (1H, m), 3.91 - 4.02 (2H, m), 4.24 - 4.30 (2H, m), 4.33 (2H, br s), 4.48 - 4.60 (1H, m), 5.92 (2H, br s), 6.37 - 6.52 (3H, m), 6.82 - 6.88 (2H, m), 6.91 (1H, dd), 7.22 (1H,

t), 7.38 (1H, s), 7.43 (1H, s), 7.45 (1H, s), 7.73 (1H, d), 7.89 (1H, br d), 10.24 (1H, s), 14.12 (1H, br s); m/z (ES⁺) [M+H]⁺ = 885.5.

EXAMPLE 146

Intermediate 146a:

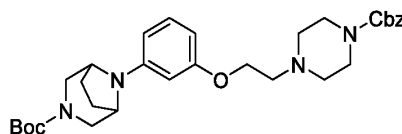
Benzyl 4-[2-(3-bromophenoxy)ethyl]piperazine-1-carboxylate



[1915] Di-*tert*-butyl azodicarboxylate (1.900 g, 8.25 mmol) in DCM (5 mL) was added dropwise to a solution of 3-bromophenol (1.298 g, 7.5 mmol), benzyl 4-(2-hydroxyethyl)piperazine-1-carboxylate (1.982 g, 7.50 mmol) and triphenylphosphine (2.361 g, 9.00 mmol) in DCM (30 mL) at r.t. The resulting solution was stirred at r.t. for 2 h. The solvent was concentrated. Purification by FSC (elution gradient: 10-20% MeOH in DCM with 1% NH₄OH) gave the title compound (2.74 g, 87 %) as a colorless oil. ¹H NMR (CD₂Cl₂): δ 2.51 (4H, br s), 2.78 (2H, br t), 3.50 (4H, br s), 4.02 - 4.12 (2H, m), 5.10 (2H, s), 6.83 - 6.87 (1H, m), 7.05 - 7.11 (2H, m), 7.12 - 7.19 (1H, m), 7.29 - 7.41 (5H, m); m/z (ES⁺) [M+H]⁺ = 419.2.

Intermediate 146b:

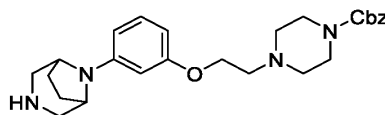
tert-Butyl 8-[3-[2-(4-benzyloxycarbonylpiperazin-1-yl)ethoxy]phenyl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



[1916] A mixture of Intermediate 146a (1.677 g, 4 mmol), *tert*-butyl 3,8-diazabicyclo[3.2.1]octane-3-carboxylate (0.849 g, 4.00 mmol), RuPhosPdG3 (0.167 g, 0.20 mmol), and KO^{*t*}Bu (0.673 g, 6.00 mmol) in toluene (20 mL) was flushed with nitrogen and backfilled with nitrogen. The mixture was stirred under nitrogen at 105 °C for 2 h and then cooled to r.t., filtered through Celite®, and the filtrate was evaporated. Purification by FSC (elution gradient: 0-10% MeOH in EtOAc) gave the title compound (1.670 g, 76 %) as a light yellow solid. ¹H NMR (CD₂Cl₂): δ 1.42 (9H, s), 1.80 (2H, br d), 1.95 - 2.00 (2H, m), 2.51 (4H, br s), 2.76 (2H, br t), 3.14 (1H, br d), 3.20 - 3.31 (1H, m), 3.47 - 3.53 (4H, m), 3.57 (1H, br d), 3.67 (1H, br d), 4.01 - 4.06 (2H, m), 4.10 - 4.19 (2H, m), 5.10 (2H, s), 6.24 - 6.30 (1H, m), 6.32 (1H, s), 6.40 (1H, br d), 7.11 (1H, t), 7.26 - 7.38 (5H, m); m/z (ES⁺) [M+H]⁺ = 551.6.

Intermediate 146c:

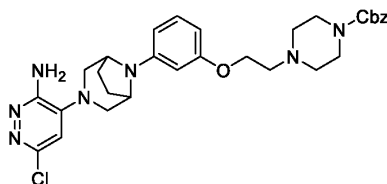
Benzyl 4-[2-[3-(3,8-diazabicyclo[3.2.1]octan-8-yl)phenoxy]ethyl]piperazine-1-carboxylate



[1917] Intermediate 146b (1.48 g, 2.69 mmol) in DCM (10 ml) was added TFA (4 ml, 53.75 mmol). The reaction was stirred at r.t. for 1h. The solvent was removed, and residue was partitioned between CHCl_3/IPA (3:1) (70 mL) and washed with saturated Na_2CO_3 solution. The organic phase was separated, dried over MgSO_4 , filtered and concentrated to give the title compound (1.320 g, 109 %) as a beige gum. ^1H NMR ($\text{DMSO}-d_6$): δ 1.85 - 1.95 (4H, m), 2.40 - 2.46 (4H, m), 2.50 - 2.57 (2H, m), 2.68 (2H, br t), 2.96 (2H, br d), 3.72 - 3.80 (2H, m), 3.96 - 4.08 (2H, m), 4.13 (2H, br s), 4.31 (2H, br s), 5.06 (2H, s), 6.22 (1H, br d), 6.28 - 6.34 (1H, m), 6.37 (1H, br d), 7.04 (1H, t), 7.27 - 7.41 (5H, m), (NH proton not observed); m/z (ES^+) $[\text{M}+\text{H}]^+ = 451.4$.

Intermediate 146d:

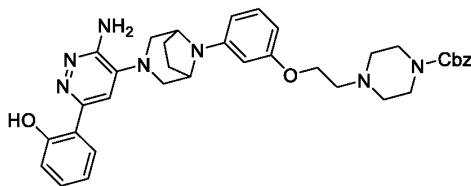
Benzyl 4-[2-[3-[3-(3-amino-6-chloro-pyridazin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl]phenoxy]ethyl]piperazine-1-carboxylate



[1918] Prepared in an analogous manner to Intermediate 3c starting from Intermediate 146c (1.172 g, 2.6 mmol). Purification by FSC (elution gradient: 5-30% solvent MeOH in DCM then 10% MeOH in DCM with 1% NH_4OH) gave the title compound (1.090 g, 72.5 %) as a light yellow solid. ^1H NMR (CD_2Cl_2): δ 2.01 - 2.05 (2H, m), 2.09 - 2.20 (2H, m), 2.31 - 2.74 (4H, m), 2.77 - 3.01 (2H, m), 3.04 - 3.12 (2H, m), 3.12 - 3.21 (2H, m), 3.34 - 3.77 (4H, m), 4.07 - 4.21 (2H, m), 4.31 (2H, br s), 4.61 - 4.77 (2H, m), 5.11 (2H, s), 6.28 - 6.35 (1H, m), 6.37 (1H, br s), 6.44 (1H, br d), 6.69 (1H, s), 7.14 (1H, t), 7.26 - 7.42 (5H, m); m/z (ES^+) $[\text{M}+\text{H}]^+ = 578.4$.

Intermediate 146e:

Benzyl 4-[2-[3-[3-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl]phenoxy]ethyl]piperazine-1-carboxylate

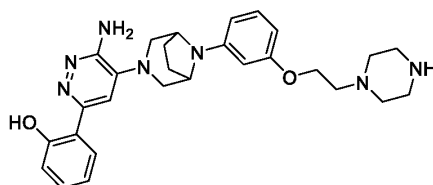


[1919] Prepared in an analogous manner to Intermediate 2h starting from Intermediate 146d (0.504 g, 0.87 mmol). Purification by FSC (elution gradient: 0-10% MeOH in DCM with 1% NH_4OH) gave the title compound (0.294 g, 53.0 %) as a beige solid. ^1H NMR ($\text{DMSO}-d_6$): δ 1.91 - 1.97 (2H, m), 2.13 (2H, br d), 2.41 - 2.45 (2H, m), 2.69 (2H, br t), 3.07 (2H, br d), 3.20 - 3.25 (2H, m), 3.26 - 3.29 (2H, m), 3.39 (4H, br s), 4.02 - 4.08 (2H, m), 4.39 (2H, br s), 5.06 (2H, s), 5.89 - 5.95 (2H, m), 6.25 (1H, br d), 6.40 - 6.46 (1H,

m), 6.48 (1H, br d), 6.77 - 6.92 (2H, m), 7.07 (1H, t), 7.15 - 7.26 (1H, m), 7.29 - 7.37 (5H, m), 7.44 (1H, s), 7.89 (1H, d), 14.14 (1H, br s); m/z (ES⁺) [M+H]⁺ = 636.4.

Intermediate 146f:

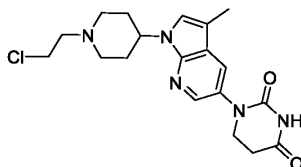
2-[6-Amino-5-[8-[3-(2-piperazin-1-ylethoxy)phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-yl]phenol



[1920] Prepared in an analogous manner to Intermediate 123c starting from Intermediate 146e (309 mg, 0.49 mmol) gave the title compound (261 mg, 107 %) as a beige solid. ¹H NMR (CD₂Cl₂) δ 2.05 - 2.13 (2H, m), 2.12 - 2.19 (2H, m), 2.52 (4H, br s), 2.74 (2H, br t), 2.88 (4H, br t), 3.23 (4H, s), 4.06 (2H, br t), 4.36 (2H, br s), 4.82 (2H, br s), 6.27 - 6.37 (1H, m), 6.41 (1H, br s), 6.46 (1H, br d), 6.81 - 6.94 (1H, m), 6.94 - 6.98 (1H, m), 7.15 (1H, br t), 7.25 (2H, br t), 7.59 (1H, br d); m/z (ES⁺) [M+H]⁺ = 502.2.

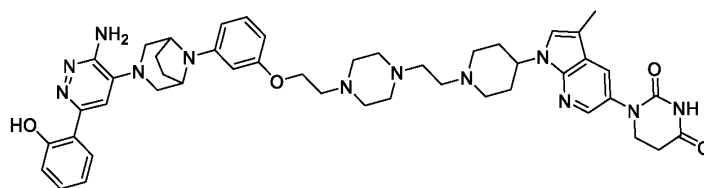
Intermediate 146g:

1-[1-[1-(2-Chloroethyl)-4-piperidyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1921] Intermediate 125g (327 mg, 1 mmol) and 2-chloroacetaldehyde (50% w. in water) (314 mg, 2.00 mmol) in DCM (5 mL) were stirred at r.t. for 30 min. Sodium triacetoxyhydroborate (424 mg, 2.00 mmol) was added and the mixture was stirred at r.t. for 30 min. The reaction was partitioned between sat. aq. NaHCO₃ solution and DCM (50 mL). The organic phase was dried over MgSO₄, filtered, concentrated. The residue was triturated with ether, solids were filtered, dried to give the title compound (315 mg, 81 %) as a light yellow solid. ¹H NMR (DMSO-*d*₆): δ 1.85 (2H, br d), 1.97 - 2.06 (2H, m), 2.23 - 2.32 (5H, m), 2.70 - 2.77 (4H, m), 3.04 (2H, br d), 3.71 (2H, br t), 3.79 (2H, t), 4.53 - 4.67 (1H, m), 7.49 (1H, s), 7.87 (1H, d), 8.16 (1H, d), 10.36 (1H, s); m/z (ES⁺) [M+H]⁺ = 390.2.

1-[1-[1-[2-[4-[2-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenoxy]ethyl]piperazin-1-yl]ethyl]-4-piperidyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

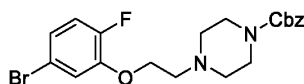


[1922] Intermediate 146f (25 mg, 0.05 mmol), Intermediate 146g (23 mg, 0.06 mmol), NaI (7.5 mg, 0.05 mmol), and NaHCO₃ (12.60 mg, 0.15 mmol) in DMF (500 μ l) were heated at 75°C overnight. The reaction was partitioned between 10% LiCl solution and CHCl₃/IPA (3:1). The organic phase separated, dried over MgSO₄, filtered, and concentrated. Purification by RPC (elution gradient: 35-70% MeCN in water with 0.1% NH₄OH) gave the title compound (15.00 mg, 35.1 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.78 - 1.86 (2H, m), 1.92 - 1.98 (2H, m), 1.98 - 2.08 (2H, m), 2.08 - 2.19 (4H, m), 2.21 - 2.26 (3H, m), 2.27 - 2.47 (10H, m), 2.51 - 2.61 (2H, m), 2.63 - 2.68 (2H, m), 2.72 - 2.78 (2H, m), 2.95 - 3.03 (2H, m), 3.03 - 3.10 (2H, m), 3.17 - 3.24 (2H, m), 3.76 - 3.83 (2H, m), 4.02 (2H, br t), 4.40 (2H, br s), 4.58 (1H, br t), 5.92 (2H, s), 6.25 (1H, br d), 6.40 - 6.51 (2H, m), 6.80 - 6.89 (2H, m), 7.07 (1H, t), 7.21 (1H, br t), 7.45 (2H, br d), 7.85 - 7.88 (1H, m), 7.90 (1H, br d), 8.16 (1H, d), 10.36 (1H, s), 13.79 - 14.63 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 855.7.

EXAMPLE 147

Intermediate 147a:

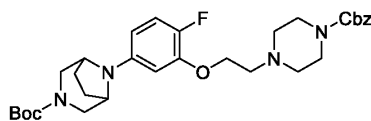
Benzyl 4-[2-(5-bromo-2-fluoro-phenoxy)ethyl]piperazine-1-carboxylate



[1923] Prepared in an analogous manner to Intermediate 146a starting from 5-bromo-2-fluorophenol (1.432 g, 7.5 mmol) and benzyl 4-(2-hydroxyethyl)piperazine-1-carboxylate (1.982 g, 7.50 mmol). Purification by FSC (elution gradient: 0-10% MeOH in DCM with 1% NH₄OH) gave the title compound (2.87 g, 88 %) as a colorless oil. ¹H NMR (CD₂Cl₂): δ 2.52 (4H, br s), 2.81 (2H, br t), 3.50 (4H, br s), 4.09 - 4.15 (2H, m), 5.10 (2H, s), 6.93 - 7.01 (1H, m), 7.01 - 7.07 (1H, m), 7.15 (1H, dd), 7.24 - 7.40 (5H, m); *m/z* (ES⁺) [M+H]⁺ = 437.2.

Intermediate 147b:

tert-Butyl 8-[3-[2-(4-benzyloxycarbonylpiperazin-1-yl)ethoxy]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate

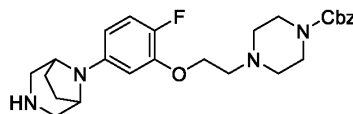


[1924] Prepared in an analogous manner to Intermediate 146b starting from a mixture of Intermediate 147a (1.749 g, 4 mmol) and *tert*-butyl 3,8-diazabicyclo[3.2.1]octane-3-carboxylate (0.849 g, 4.00 mmol). Purification by FSC (elution gradient: 0-10% MeOH in EtOAc) gave the title compound (1.56 g, 68.6 %) as light yellow solid. ¹H NMR (CD₂Cl₂): δ 1.42 (9H, s), 1.80 (2H, br d), 1.90 - 2.00 (2H, m), 2.53 (4H, br s), 2.67 - 2.93 (2H, m), 3.08 - 3.19 (1H, m), 3.24 (1H, br d), 3.41 - 3.56 (4H, m), 3.57 - 3.65 (1H, m), 3.69 (1H, br d), 4.06 - 4.18 (4H, m), 5.11 (2H, s), 6.29 (1H, br d), 6.42 (1H, br d), 6.93 (1H, dd), 7.25 - 7.40 (5H, m); *m/z* (ES⁺) [M+H]⁺ = 569.5.

Intermediate 147c:

400

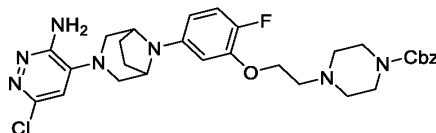
Benzyl 4-[2-[5-(3,8-diazabicyclo[3.2.1]octan-8-yl)-2-fluoro-phenoxy]ethyl]piperazine-1-carboxylate



[1925] Prepared in an analogous manner to Intermediate 146c starting from Intermediate 147b (1.46 g, 2.57 mmol) gave the title compound (1.26 g, 105 %) as a beige gum, some residual solvent remained. ¹H NMR (DMSO-*d*₆): δ 1.79 - 1.92 (4H, m), 2.38 - 2.43 (2H, m), 2.43 - 2.47 (4H, m), 2.71 (2H, t), 2.93 (2H, br d), 3.72 - 3.81 (2H, m), 4.02 - 4.07 (2H, m), 4.10 (2H, t), 4.31 (2H, br s), 5.06 (2H, s), 6.23 - 6.29 (1H, m), 6.52 (1H, dd), 6.94 (1H, dd), 7.29 - 7.38 (5H, m), (NH peak was not observed); *m/z* (ES⁺) [M+H]⁺ = 469.4.

Intermediate 147d:

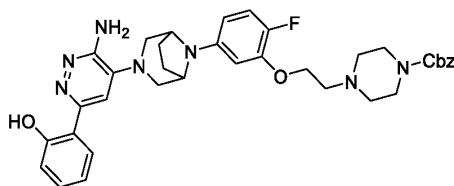
Benzyl 4-[2-[5-[3-(3-amino-6-chloro-pyridazin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenoxy]ethyl]piperazine-1-carboxylate



[1926] Prepared in an analogous manner to Intermediate 3c starting from Intermediate 147c (1.218 g, 2.6 mmol). Purification on FSC (elution gradient: 5-30% solvent B in DCM, Solvent B: 10% MeOH in DCM with 1% NH₄OH) gave the title compound (1.1 g, 71 %) as a light yellow solid. ¹H NMR (CD₂Cl₂): δ 2.01 - 2.07 (2H, m), 2.09 - 2.17 (2H, m), 2.43 - 2.75 (4H, m), 2.78 - 2.97 (2H, m), 3.04 - 3.14 (2H, m), 3.18 (2H, br d), 3.55 (4H, br s), 4.11 - 4.21 (2H, m), 4.21 - 4.27 (2H, m), 4.62 - 4.77 (2H, m), 5.11 (2H, s), 6.33 (1H, br d), 6.47 (1H, br d), 6.70 (1H, s), 6.92 - 6.98 (1H, m), 7.26 - 7.39 (5H, m); *m/z* (ES⁺) [M+H]⁺ = 596.4.

Intermediate 147e:

Benzyl 4-[2-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenoxy]ethyl]piperazine-1-carboxylate

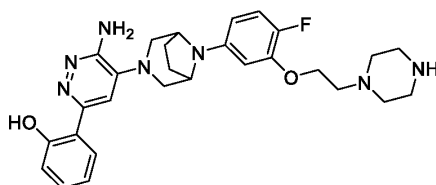


[1927] Prepared in an analogous manner to Intermediate 2h starting from Intermediate 147d (0.494 g, 0.83 mmol). Purification by FSC (elution gradient: 20-60% solvent B in DCM, solvent B: 10% MeOH in DCM with 1% NH₄OH) gave the title compound (0.304 g, 56.1 %) as a beige solid. ¹H NMR (DMSO-*d*₆): δ 1.87 - 1.96 (2H, m), 2.13 (2H, br d), 2.42 - 2.47 (2H, m), 2.73 (2H, br t), 3.09 (2H, br d), 3.19 - 3.25 (2H, m), 3.26 - 3.30 (2H, m), 3.39 (4H, br s), 4.15 (2H, br t), 4.38 (2H, br s), 5.06 (2H, s), 5.89 - 5.96 (2H, m),

6.39 (1H, br d), 6.65 (1H, br d), 6.82 - 6.88 (2H, m), 6.96 - 7.02 (1H, m), 7.17 - 7.25 (1H, m), 7.28 - 7.37 (5H, m), 7.45 (1H, s), 7.88 (1H, br d), 14.13 (1H, br s); m/z (ES⁺) [M+H]⁺ = 654.4.

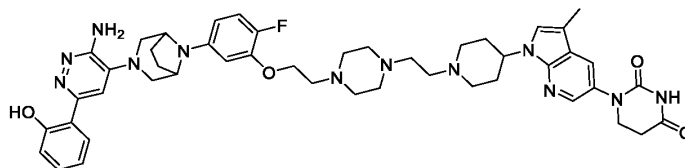
Intermediate 147f:

2-[6-Amino-5-[8-[4-fluoro-3-(2-piperazin-1-ylethoxy)phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-yl]phenol



[1928] Prepared in an analogous manner to Intermediate 123c starting from Intermediate 147e (305 mg, 0.47 mmol) gave the title compound (255 mg, 105%) as a beige solid, some residual solvent remained. ¹H NMR (CD₂Cl₂): δ 2.03 - 2.09 (2H, m), 2.59 (5H, br s), 2.80 (2H, t), 2.93 (4H, br t), 3.18 - 3.28 (5H, m), 4.14 (2H, t), 4.29 (2H, br s), 4.80 (2H, s), 6.36 (1H, br d), 6.50 (1H, br d), 6.86 - 6.91 (1H, m), 6.94 - 6.99 (2H, m), 7.23 - 7.31 (2H, m), 7.60 (1H, br d), (OH and NH protons not observed); m/z (ES⁺) [M+H]⁺ = 520.2.

1-[1-[1-[2-[4-[2-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenoxy]ethyl]piperazin-1-yl]ethyl]-4-piperidyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

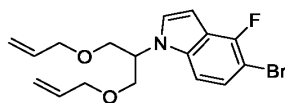


[1929] Prepared in an analogous manner to EXAMPLE 146 starting from Intermediate 147f (26 mg, 0.05 mmol) and Intermediate 146g (24 mg, 0.06 mmol) Purification by RPC (elution gradient: 35-70% MeCN in water with 0.1% NH₄OH) gave the title compound (19.00 mg, 43.5 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.76 - 1.86 (2H, m), 1.93 - 1.98 (2H, m), 1.98 - 2.06 (2H, m), 2.09 - 2.17 (4H, m), 2.23 (3H, s), 2.28 - 2.46 (9H, m), 2.46 - 2.47 (1H, m), 2.51 - 2.62 (2H, m), 2.66 - 2.72 (2H, m), 2.73 - 2.78 (2H, m), 2.95 - 3.02 (2H, m), 3.05 - 3.12 (2H, m), 3.20 - 3.25 (2H, m), 3.79 (2H, t), 4.13 (2H, br t), 4.38 (2H, br s), 4.58 (1H, br t), 5.93 (2H, s), 6.39 (1H, br d), 6.66 (1H, br d), 6.81 - 6.90 (2H, m), 6.99 (1H, dd), 7.19 - 7.19 (1H, m), 7.45 (2H, d), 7.83 - 7.91 (2H, m), 8.13 - 8.18 (1H, m), 10.36 (1H, s), 13.74 - 14.48 (1H, m); m/z (ES⁺) [M+H]⁺ = 873.6.

EXAMPLE 148

Intermediate 148a:

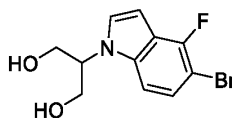
1-[2-Allyloxy-1-(allyloxymethyl)ethyl]-5-bromo-4-fluoro-indole



[1930] Prepared in an analogous method to Intermediate 113a using 5-bromo-4-fluoro-1*H*-indole (1.00 g, 4.67 mmol). Purification by FSC (elution gradient: 1st purification: 0-100% DCM in hexanes; 2nd purification: 30-100% DCM in hexanes) gave the title compound (1.01 g, 59%) as a yellow oil. ¹H NMR (DMSO-*d*₆): δ 3.74 - 3.85 (4H, m), 3.85 - 3.95 (4H, m), 4.84 - 4.95 (1H, m), 5.05 - 5.09 (2H, m), 5.10 - 5.17 (2H, m), 5.70 - 5.83 (2H, m), 6.56 (1H, d), 7.25 - 7.31 (1H, m), 7.41 (1H, d), 7.58 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 368.0.

Intermediate 148b:

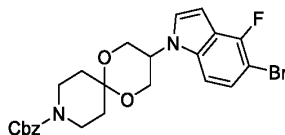
2-(5-Bromo-4-fluoro-indol-1-yl)propane-1,3-diol



[1931] Prepared in an analogous method to Intermediate 64b using Intermediate 148a (1.01 g, 2.73 mmol). Purification by FSC (elution gradient: 1st purification: 0-80% acetone in hexanes; 2nd purification: 50-100% EtOAc in hexanes) and trituration with DCM-hexanes (1:1) gave the title compound (0.51 g, 64%) as a reddish solid. ¹H NMR (DMSO-*d*₆): δ 3.69 - 3.88 (4H, m), 4.47 (1H, quin), 4.89 (2H, t), 6.53 (1H, d), 7.23 - 7.30 (1H, m), 7.30 - 7.36 (1H, m), 7.54 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 288.0.

Intermediate 148c:

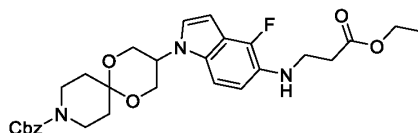
Benzyl 3-(5-bromo-4-fluoro-indol-1-yl)-1,5-dioxo-9-azaspiro[5.5]undecane-9-carboxylate



[1932] Prepared in an analogous method to Intermediate 64d using Intermediate 148b (501 mg, 1.74 mmol). Purification by FSC (elution gradient: 0-15% EtOAc in DCM) gave the title compound (797 mg, 91%) as a white foam. ¹H NMR (DMSO-*d*₆): δ 1.76 - 1.88 (2H, m), 1.98 - 2.05 (2H, m), 3.35 - 3.57 (4H, m), 3.98 (2H, dd), 4.34 (2H, br d), 4.58 - 4.66 (1H, m), 5.08 (2H, s), 6.59 (1H, d), 7.19 - 7.48 (7H, m), 7.85 (1H, d); (mass not observed).

Intermediate 148d:

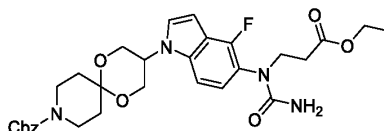
Benzyl 3-[5-[(3-ethoxy-3-oxo-propyl)amino]-4-fluoro-indol-1-yl]-1,5-dioxo-9-azaspiro[5.5]undecane-9-carboxylate



[1933] A 40 mL vial was charged with Intermediate 148c (0.79 g, 1.57 mmol), ethyl 3-aminopropanoate hydrochloride (0.36 g, 2.35 mmol), *t*BuBrettPhos Pd G3 (0.13 g, 0.16 mmol) and Cs₂CO₃ (1.84 g, 5.65 mmol). 1,4-dioxane (9.4 mL) was added. Argon was bubbled through the mixture for 5 min. The resulting mixture was stirred at 100 °C for 15 h. After cooling to r.t., the mixture was filtered through a pad of Celite® with DCM. The filtrate was concentrated under reduced pressure. Purification by FSC (elution gradient: 0-40% acetone in hexanes) gave the title compound (0.53 g, 63%) as a yellow oil. ¹H NMR (DMSO-*d*₆): δ 1.17 (3H, t), 1.76 - 1.89 (2H, m), 1.91 - 2.01 (2H, m), 2.56 (2H, t), 3.35 (2H, q), 3.39 - 3.53 (4H, m), 3.97 (2H, br dd), 4.05 (2H, q), 4.29 (2H, br d), 4.41 - 4.53 (1H, m), 4.69 (1H, br t), 5.08 (2H, s), 6.34 (1H, d), 6.75 (1H, t), 7.15 (1H, d), 7.28 - 7.45 (5H, m), 7.64 (1H, d); *m/z* (ES⁺) [M+H]⁺ = 540.3.

Intermediate 148e:

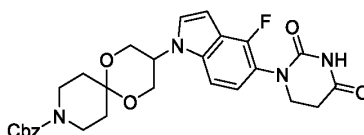
Benzyl 3-[5-[carbamoyl-(3-ethoxy-3-oxo-propyl)amino]-4-fluoro-indol-1-yl]-1,5-dioxo-9-azaspiro[5.5]undecane-9-carboxylate



[1934] Prepared in an analogous method to Intermediate 113e using Intermediate 148d (0.52 g, 0.97 mmol) to give the title compound as a yellowish foam which was used for the next step without further purification. Quantitative yield was assumed. *m/z* (ES⁺) [M+H]⁺ = 583.3.

Intermediate 148f:

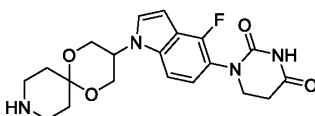
Benzyl 3-[5-(2,4-dioxohexahydropyrimidin-1-yl)-4-fluoro-indol-1-yl]-1,5-dioxo-9-azaspiro[5.5]undecane-9-carboxylate



[1935] Prepared in an analogous method to Intermediate 113f using Intermediate 148e (0.57 g, 0.97 mmol) to give the title compound (0.42 g, 81%) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.79 - 1.91 (2H, m), 1.92 - 2.04 (2H, m), 2.73 (2H, t), 3.35 - 3.56 (4H, m), 3.70 (2H, t), 4.00 (2H, br dd), 4.34 (2H, br d), 4.56 - 4.68 (1H, m), 5.08 (2H, s), 6.59 (1H, d), 7.13 (1H, t), 7.25 - 7.46 (6H, m), 7.84 (1H, d), 10.38 (1H, s); *m/z* (ES⁺) [M+H]⁺ = 537.2.

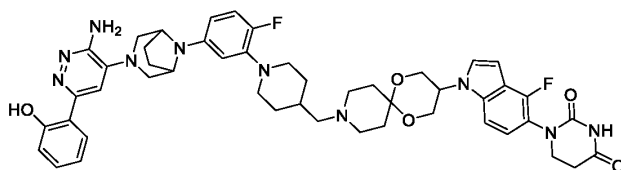
Intermediate 148g:

1-[1-(1,5-Dioxo-9-azaspiro[5.5]undecan-3-yl)-4-fluoro-indol-5-yl]hexahydropyrimidine-2,4-dione



[1936] Prepared in an analogous manner to Intermediate 129c starting from Intermediate 148f (420 mg, 0.78 mmol) to give the title compound (29 mg, 29%) as a white solid. ^1H NMR ($\text{DMSO}-d_6$): δ 1.68 - 1.82 (2H, m), 1.84 - 1.96 (2H, m), 2.67 - 2.76 (6H, m), 3.70 (2H, t), 3.96 (2H, br dd), 4.32 (2H, br dd), 4.54 - 4.64 (1H, m), 6.58 (1H, d), 7.12 (1H, t), 7.37 (1H, d), 7.85 (1H, d), 10.13 - 10.66 (1H, m), one nitrogen-bound proton not observed; m/z (ES^+) $[\text{M}+\text{H}]^+ = 403.3$.

1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-4-fluoro-indol-5-yl]hexahydropyrimidine-2,4-dione

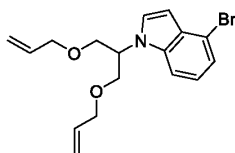


[1937] Prepared in an analogous manner to EXAMPLE 64 using Intermediate 148g (20 mg, 0.05 mmol) and Intermediate 13d (21 mg, 0.04 mmol). Purification by RPC (elution gradient: 10-40% MeCN in water with 0.1% HCOOH) gave the title compound (24.1 mg, 64%) as a white solid. ^1H NMR ($\text{DMSO}-d_6$): δ 1.16 - 1.32 (2H, m), 1.55 - 1.66 (1H, m), 1.71 - 2.06 (8H, m), 2.12 (2H, br d), 2.16 - 2.23 (2H, m), 2.33 - 2.48 (4H, m), 2.63 (2H, br t), 2.73 (2H, br t), 3.09 (2H, br d), 3.25 (2H, br d), 3.34 (2H, br d), 3.70 (2H, t), 3.97 (2H, br dd), 4.27 - 4.39 (4H, m), 4.59 (1H, br s), 5.92 (2H, s), 6.37 - 6.44 (1H, m), 6.44 - 6.50 (1H, m), 6.59 (1H, d), 6.81 - 6.95 (3H, m), 7.12 (1H, t), 7.22 (1H, t), 7.37 (1H, d), 7.45 (1H, s), 7.85 (1H, d), 7.89 (1H, br d), 10.38 (1H, s), 12.79 - 15.29 (1H, m); m/z (ES^+) $[\text{M}+\text{H}]^+ = 889.5$.

EXAMPLE 149

Intermediate 149a:

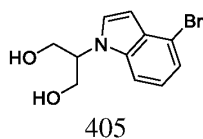
1-[2-Allyloxy-1-(allyloxymethyl)ethyl]-4-bromo-indole



[1938] Prepared in an analogous method to Intermediate 113a using 4-bromo-1*H*-indole (1.960 g, 10 mmol). Purification by FSC (elution gradient: 0 to 15% EtOAc in hexanes,) gave the title compound (1.520 g, 43.4 %) as a colorless oil. ^1H NMR (CD_2Cl_2): δ 3.85 (4H, d), 3.96 (4H, dd), 4.70 (1H, quin), 5.12 - 5.23 (4H, m), 5.79 - 5.89 (2H, m), 6.54 (1H, d), 7.06 (1H, t), 7.25 (1H, d), 7.37 (1H, d), 7.44 (1H, d); m/z (ES^+) $[\text{M}+\text{H}]^+ = 350.2$.

Intermediate 149b:

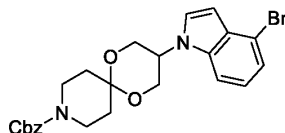
2-(4-Bromoindol-1-yl)propane-1,3-diol



[1939] Prepared in an analogous method to Intermediate 64b using Intermediate 149a (1.22 g, 3.48 mmol). Purification by FSC (elution gradient: 20-40% Solvent B in hexanes, solvent B: 10% MeOH in EtOAc) gave the title compound (0.798 g, 85 %) as a yellow oil. ^1H NMR (CD_2Cl_2): δ 1.72 - 1.90 (2H, m), 4.03 - 4.10 (4H, m), 4.59 (1H, quin), 6.60 (1H, d), 7.08 (1H, t), 7.28 (1H, d), 7.38 (1H, d), 7.41 - 7.46 (1H, m); m/z (ES^+) $[\text{M}+\text{H}]^+ = 270.1$.

Intermediate 149c:

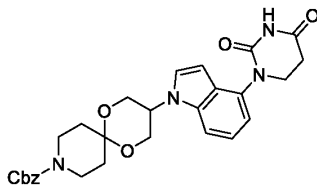
Benzyl 3-(4-bromoindol-1-yl)-1,5-dioxo-9-azaspiro[5.5]undecane-9-carboxylate



[1940] Prepared in an analogous method to Intermediate 64d using Intermediate 149b (800 mg, 2.96 mmol) and Intermediate 64c (910 mg, 3.26 mmol). The residue was triturated with ether, solids were filtered and dried to give the title compound (1.2 g, 84 %) as a white solid. ^1H NMR (CD_2Cl_2): δ 1.83 (2H, br s), 1.99 (2H, br s), 3.45 (4H, br s), 4.00 (2H, br dd), 4.34 (2H, br d), 4.61 (1H, br s), 5.05 - 5.10 (2H, m), 6.45 (1H, d), 7.07 (1H, t), 7.26 (1H, d), 7.30 - 7.38 (5H, m), 7.54 (1H, d), 7.86 - 7.91 (1H, m); m/z (ES^+) $[\text{M}+\text{H}]^+ = 485.1$.

Intermediate 149d:

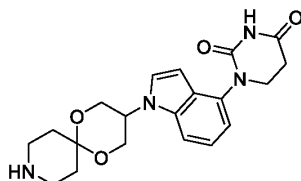
Benzyl 3-[4-(2,4-dioxohexahydropyrimidin-1-yl)indol-1-yl]-1,5-dioxo-9-azaspiro[5.5]undecane-9-carboxylate



[1941] Prepared in an analogous method to Intermediate 4b using Intermediate 149c (1.1 g, 2.27 mmol). Purification by FSC (elution gradient: 0 to 10% MeOH in DCM) gave the title compound (0.812 g, 69.1 %) as a light beige solid. ^1H NMR ($\text{DMSO}-d_6$): δ 1.85 (2H, br s), 1.98 (2H, br s), 2.75 (2H, t), 3.45 (4H, br s), 3.74 - 3.79 (1H, m), 3.78 (1H, s), 4.02 (2H, br dd), 4.33 (2H, br d), 4.61 (1H, br d), 5.08 (2H, s), 6.44 (1H, d), 6.95 - 7.00 (1H, m), 7.15 (1H, t), 7.34 - 7.39 (5H, m), 7.46 (1H, d), 7.77 (1H, d), 10.31 (1H, s); m/z (ES^+) $[\text{M}+\text{H}]^+ = 519.3$.

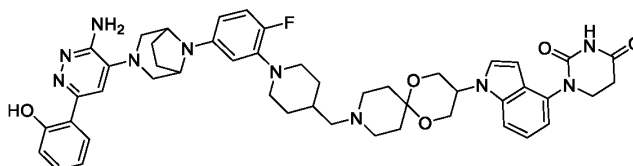
Intermediate 149e:

1-[1-(1,5-Dioxo-9-azaspiro[5.5]undecan-3-yl)indol-4-yl]hexahydropyrimidine-2,4-dione



[1942] Prepared in an analogous manner to Intermediate 129c starting from Intermediate 149d (810 mg, 1.56 mmol) gave the title compound (630 mg, 105%) as a yellow solid. m/z (ES^+) $[M+H]^+ = 385.3$.

1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]indol-4-yl]hexahydropyrimidine-2,4-dione

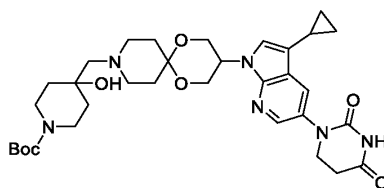


[1943] Prepared in an analogous manner to EXAMPLE 64 using Intermediate 149e (55 mg, 0.06 mmol) and Intermediate 13d (30 mg, 0.06 mmol). Purification by RPC (elution gradient: 20-50% MeCN in water with 0.1% FA) gave the title compound (24.0 mg, 45.9 %) as a white solid. 1H NMR ($DMSO-d_6$): δ 1.26 (2H, q), 1.65 (1H, br s), 1.78 (2H, br d), 1.92 (4H, br s), 2.01 - 2.10 (2H, m), 2.10 - 2.18 (2H, m), 2.27 - 2.42 (2H, m), 2.51 - 2.59 (4H, m), 2.61 - 2.69 (2H, m), 2.76 (2H, br t), 3.09 (2H, br d), 3.18 - 3.25 (2H, m), 3.35 - 3.45 (2H, m), 3.77 (2H, br t), 4.00 (2H, br d), 4.26 - 4.39 (4H, m), 4.59 (1H, br s), 5.92 (2H, br s), 6.38 - 6.51 (3H, m), 6.81 - 6.96 (3H, m), 6.96 - 7.00 (1H, m), 7.12 - 7.25 (2H, m), 7.41 - 7.48 (2H, m), 7.75 - 7.82 (1H, m), 7.89 (1H, br d), 10.32 (1H, s), 12.43 - 15.19 (1H, m); m/z (ES^+) $[M+H]^+ = 871.6$.

EXAMPLE 150

Intermediate 150a:

tert-Butyl 4-[[3-[3-cyclopropyl-5-(2,4-dioxohexahydropyrimidin-1-yl)pyrrolo[2,3-*b*]pyridin-1-yl]-1,5-dioxo-9-azaspiro[5.5]undecan-9-yl]methyl]-4-hydroxy-piperidine-1-carboxylate

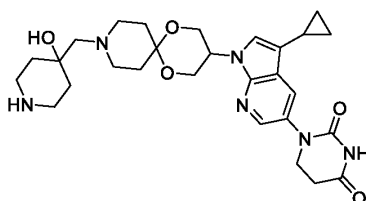


[1944] Prepared in an analogous method to Intermediate 141a starting from Intermediate 87e (740 mg, 1.74 mmol) and *tert*-butyl 1-oxa-6-azaspiro[2.5]octane-6-carboxylate (742 mg, 3.48 mmol) gave the title compound (950 mg, 86 %) as a beige solid. 1H NMR ($DMSO-d_6$): δ 0.62 (2H, q), 0.79 - 0.91 (2H, m), 1.26 - 1.39 (9H, m), 1.39 - 1.44 (4H, m), 1.82 - 2.01 (5H, m), 2.25 (2H, s), 2.52 - 2.63 (4H, m), 2.75 (2H, t), 2.95

- 3.15 (2H, m), 3.60 (2H, br d), 3.81 (2H, t), 4.01 (2H, br dd), 4.11 - 4.17 (1H, m), 4.21 (2H, br dd), 4.80 (1H, br s), 7.62 (1H, s), 7.96 (1H, d), 8.18 (1H, d), 10.36 (1H, s); m/z (ES^+) $[M+H]^+ = 639.5$.

Intermediate 150b:

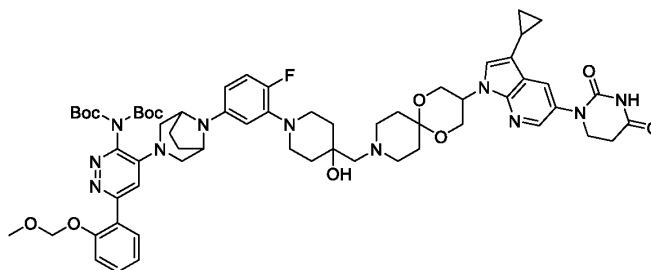
1-[3-Cyclopropyl-1-[9-[(4-hydroxy-4-piperidyl)methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1945] Prepared in an analogous method to Intermediate 141b starting from Intermediate 150a (0.95 g, 1.49 mmol) gave the title compound (0.751 g, 94 %) as a beige solid. 1H NMR ($DMSO-d_6$): δ 0.62 (2H, br d), 0.87 (2H, br d), 1.33 - 1.40 (2H, m), 1.40 - 1.48 (2H, m), 1.92 (5H, br d), 2.23 (2H, s), 2.51 - 2.60 (4H, m), 2.63 (2H, br d), 2.71 - 2.81 (4H, m), 3.76 - 3.86 (2H, m), 3.88 - 3.95 (1H, m), 3.99 - 4.05 (2H, m), 4.21 (2H, br dd), 4.80 (1H, br s), 7.62 (1H, s), 7.97 (1H, d), 8.18 (1H, d), 10.18 - 10.53 (1H, m), (one NH proton not observed); m/z (ES^+) $[M+H]^+ = 539.4$.

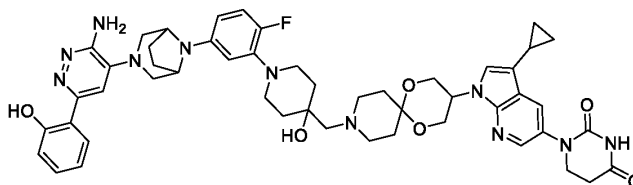
Intermediate 150c:

tert-Butyl *N-tert*-butoxycarbonyl-*N*-[4-[8-[3-[4-[[3-[3-cyclopropyl-5-(2,4-dioxohexahydropyrimidin-1-yl)pyrrolo[2,3-*b*]pyridin-1-yl]-1,5-dioxo-9-azaspiro[5.5]undecan-9-yl]methyl]-4-hydroxy-1-piperidyl]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]-6-[2-(methoxymethoxy)phenyl]pyridazin-3-yl]carbamate



[1946] Prepared in an analogous method to Intermediate 141c starting from Intermediate 150b (194 mg, 0.36 mmol) Purification by FSC (elution gradient: 10-50% hexane in Solvent B. Solvent B = 10% MeOH in EtOAc) followed by RPC (elution gradient: 20-60% MeCN in water with 0.1% FA) gave the title compound (29 mg, 8.25%) as a white solid. m/z (ES^+) $[M+H]^+ = 1172.6$.

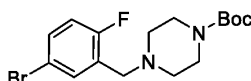
1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-hydroxy-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-cyclopropyl-

pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione

[1947] Prepared in an analogous method to EXAMPLE 141 starting from Intermediate 150c (30 mg, 0.03 mmol). Purification by RPC (elution gradient: 20-50% MeCN in water with 0.1% FA) gave the title compound (11.0 mg, 46.3 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 0.63 (2H, br d), 0.82 - 0.93 (2H, m), 1.55 (2H, br d), 1.63 - 1.75 (2H, m), 1.87 - 2.03 (7H, m), 2.12 (2H, br d), 2.32 (2H, s), 2.53 - 2.55 (1H, m), 2.55 - 2.68 (4H, m), 2.75 (2H, br t), 2.97 - 3.04 (2H, m), 3.04 - 3.14 (4H, m), 3.21 - 3.30 (2H, m), 3.81 (2H, br t), 4.02 (2H, br dd), 4.22 (2H, br d), 4.34 (2H, br s), 4.72 - 4.88 (1H, m), 5.92 (2H, s), 6.36 - 6.45 (1H, m), 6.49 (1H, br d), 6.81 - 6.94 (3H, m), 7.21 (1H, t), 7.46 (1H, s), 7.62 (1H, s), 7.85 - 7.94 (1H, m), 7.95 - 7.99 (1H, m), 8.15 - 8.21 (1H, m), 10.37 (1H, s), 13.63 - 15.01 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 928.6.

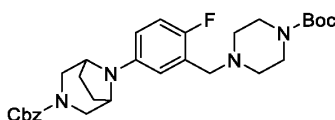
EXAMPLE 151

Intermediate 151a:

tert-Butyl 4-[(5-bromo-2-fluoro-phenyl)methyl]piperazine-1-carboxylate

[1948] Sodium triacetoxyborohydride (1.566 g, 7.39 mmol) was added to a stirred solution of 5-bromo-2-fluorobenzaldehyde (1 g, 4.93 mmol) and *tert*-butyl piperazine-1-carboxylate (0.917 g, 4.93 mmol) in DCM (15 mL). The resulting solution was stirred for 4 h at r.t. The reaction mixture was diluted with EtOAc (60 mL) and washed with sat. aq. NaHCO₃ (40 mL). The organic layer was separated, dried over Na₂SO₄, filtered, and concentrated. The residue was purified by FSC (elution gradient: 0-50% EtOAc in hexane) gave the title compound (1.350 g, 73.4 %) as an oil. ¹H NMR (DMSO-*d*₆): δ 1.39 (9H, s), 2.34 (4H, br t), 3.31 (4H, br s), 3.54 (2H, s), 7.19 (1H, t), 7.46 - 7.55 (1H, m), 7.57 - 7.64 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 373.1, 375.1.

Intermediate 151b:

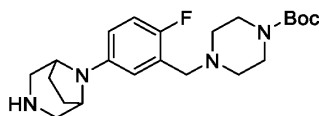
Benzyl 8-[3-[(4-*tert*-butoxycarbonylpiperazin-1-yl)methyl]-4-fluoro-phenyl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate

[1949] A 40 mL vial charged with benzyl 3,8-diazabicyclo[3.2.1]octane-3-carboxylate (0.924 g, 3.75 mmol), Intermediate 151a (1.4 g, 3.75 mmol), [Pd(allylCl)]₂ (0.014 g, 0.04 mmol), Xphos (0.072 g, 0.15

mmol) and Cs_2CO_3 (3.06 g, 9.38 mmol) and dioxane (15 mL). The reaction mixture was degassed for 5 min. and heated to 90 °C for overnight under nitrogen. The reaction mixture was filtered through celite® and washed with EtOAc (100 mL). The filtrate was concentrated. Purification by FSC (elution gradient: 0-80% EtOAc in hexanes) gave the title compound (1.420 g, 70.3 %) as an oil. ^1H NMR ($\text{DMSO-}d_6$): δ 1.38 (9H, s), 1.66 (2H, br d), 1.82 - 1.99 (2H, m), 2.33 (4H, br s), 3.06 - 3.27 (2H, m), 3.31 (4H, br d), 3.47 (2H, s), 3.61 (2H, br d), 4.23 (2H, br d), 5.08 (2H, br d), 6.74 - 6.90 (2H, m), 6.95 - 7.08 (1H, m), 7.30 - 7.45 (5H, m); m/z (ES^+) $[\text{M}+\text{H}]^+ = 539.6$.

Intermediate 151c:

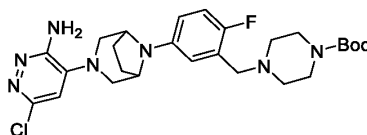
tert-Butyl 4-[[5-(3,8-diazabicyclo[3.2.1]octan-8-yl)-2-fluoro-phenyl]methyl]piperazine-1-carboxylate



[1950] Pd/C (0.277 g, 0.26 mmol) was added to a solution of Intermediate 151b (1.4 g, 2.60 mmol) in MeOH (20 mL). The reaction was sparged with H_2 (g) as stirred at r.t. under H_2 overnight. The reaction was filtered through a plug of celite® eluting with MeOH and EtOAc. The filtrate was concentrated to give the title compound (0.950 g, 90 %) as an oil. The crude product was used for the next step. m/z (ES^+) $[\text{M}+\text{H}]^+ = 405.3$.

Intermediate 151d:

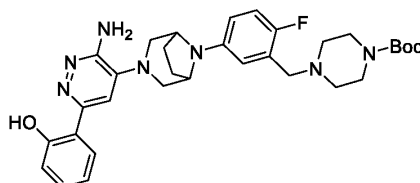
tert-Butyl 4-[[5-[3-(3-amino-6-chloro-pyridazin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]methyl]piperazine-1-carboxylate



[1951] Prepared in an analogous manner to Intermediate 3c starting from Intermediate 151c (920mg, 2.27 mmol). Purification by FSC (elution gradient: 0-100% EtOAc in hexane, then 0-30% MeOH in EtOAc) gave the title compound (1050 mg, 87 %) as a brown solid. ^1H NMR ($\text{DMSO-}d_6$): δ 1.38 (9H, s), 1.85 - 1.95 (2H, m), 2.09 (2H, br d), 2.34 (4H, br s), 2.95 (2H, br d), 3.13 - 3.23 (2H, m), 3.26 - 3.31 (4H, m), 3.48 (2H, s), 4.31 (2H, br s), 5.81 (2H, s), 6.77 - 6.89 (3H, m), 7.00 (1H, t); m/z (ES^+) $[\text{M}+\text{H}]^+ = 532.4$.

Intermediate 151e:

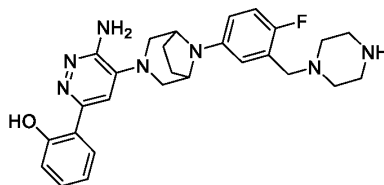
tert-Butyl 4-[[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]methyl]piperazine-1-carboxylate



[1952] Prepared in an analogous manner to Intermediate 2h starting from Intermediate 151d (500 mg, 0.94 mmol). Purification by FSC (elution gradient: 0 to 100% EtOAc in hexanes) gave the title compound (470 mg, 85 %) as a brown solid. ^1H NMR (DMSO- d_6) δ 1.37 (9H, s), 1.93 - 1.98 (2H, m), 2.15 (2H, br d), 2.35 (4H, br s), 3.09 (2H, br d), 3.23 - 3.31 (6H, m), 3.49 (2H, s), 4.36 (2H, br s), 5.95 (2H, br s), 6.83 - 6.91 (4H, m), 7.01 (1H, t), 7.23 (1H, br t), 7.46 (1H, s), 7.89 (1H, br d), 14.14 (1H, s); m/z (ES^+) $[\text{M}+\text{H}]^+ = 590.5$.

Intermediate 151f:

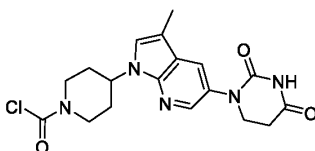
2-[6-Amino-5-[8-[4-fluoro-3-(piperazin-1-ylmethyl)phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-yl]phenol



[1953] TFA (0.901 mL, 11.70 mmol) was added to a stirred solution of Intermediate 151e (460 mg, 0.78 mmol) in DCM (6 mL). The resulting mixture was stirred at r.t. for 1 h. The mixture was concentrated under reduced pressure. The residue was basified with saturated sodium bicarbonate (20 mL) and extracted with DCM-IPA (2:1, 2 x 50 mL). The phases were separated. The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated to give title compound (320 mg, 84 %) as a white solid. The crude product was used for the next step. m/z (ES^+) $[\text{M}+\text{H}]^+ = 490.3$.

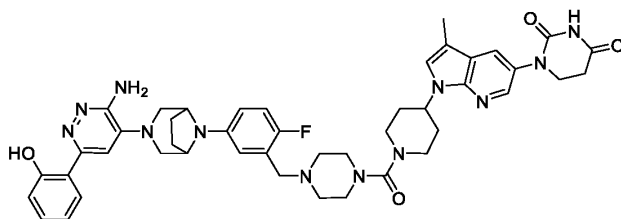
Intermediate 151g:

4-[5-(2,4-Dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]piperidine-1-carbonyl chloride



[1954] Triphosgene (181 mg, 0.61 mmol) was dissolved in DCM (5 mL), the resulting solution was cooled to -78°C then DIPEA (0.533 mL, 3.05 mmol) was added. The reaction mixture was stirred for 5 min and added Intermediate 125g (200 mg, 0.61 mmol) was added in three portions over 15 min. After the amine addition was complete, the mixture was warmed to r.t. and stirred at r.t. for 15 min. The reaction mixture diluted with DCM (20 mL) and washed with sat. aq. NH_4Cl . The organic layer was separated, dried over Na_2SO_4 , filtered, and concentrated to give title compound (205 mg, 86 %) as a light yellow solid. The crude product was used for the next step. m/z (ES^+) $[\text{M}+\text{H}]^+ = 390.2$

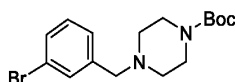
1-[1-[1-[4-[[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]methyl]piperazine-1-carbonyl]-4-piperidyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1955] Intermediate 151g (23.89 mg, 0.06 mmol) was added in DMF (1.0 mL) to a stirred solution of Intermediate 151f (30mg, 0.06 mmol) and DIPEA (0.032 mL, 0.18 mmol) in DMF (1.5 mL). The resulting mixture was stirred at r.t. overnight. The reaction mixture was directly purified by RPC (elution gradient: 0-60% MeCN in water with 0.1% FA) gave the title compound (20.0 mg, 38.7 %) as a white solid. ¹H NMR (DMSO-*d*₆): δ 1.82 - 2.06 (6H, m), 2.15 (2H, br d), 2.24 (3H, s), 2.42 (4H, br s), 2.77 (2H, br t), 2.95 (2H, br t), 3.10 (2H, br d), 3.21 - 3.45 (6H, m), 3.51 (2H, br s), 3.72 (2H, br d), 3.81 (2H, br t), 4.37 (2H, br s), 4.80 (1H, br t), 5.95 (2H, br s), 6.81 - 6.96 (4H, m), 7.02 (1H, br t), 7.23 (1H, br t), 7.47 (2H, br d), 7.89 (2H, br d), 8.18 (1H, s), 10.38 (1H, s), 13.79 - 14.47 (1H, br s); *m/z* (ES⁺) [M+H]⁺ = 843.4.

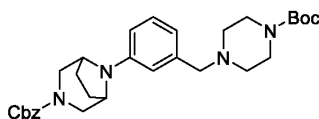
EXAMPLE 152

Intermediate 152a:

tert-Butyl 4-[(3-bromophenyl)methyl]piperazine-1-carboxylate

[1956] Prepared in an analogous manner to Intermediate 151a starting from 3-bromobenzaldehyde (1 g, 5.40 mmol). Purification by FSC (elution gradient: 0-50% EtOAc in hexanes) gave the title compound (1.270 g, 66.1 %) as an oil. ¹H NMR (DMSO-*d*₆): δ 1.39 (9H, s), 2.31 (4H, br t), 3.29 - 3.36 (4H, m), 3.48 (2H, s), 7.26 - 7.37 (2H, m), 7.46 (1H, br d), 7.49 - 7.54 (1H, m); *m/z* (ES⁺) [M+H]⁺ = 355.1, 357.1.

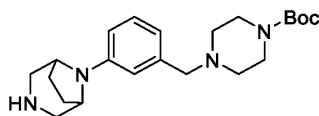
Intermediate 152b:

Benzyl 8-[3-[(4-*tert*-butoxycarbonylpiperazin-1-yl)methyl]phenyl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate

[1957] Prepared in an analogous manner to Intermediate 151b starting from Intermediate 152a (1.2 g, 3.38 mmol). Purification by FSC (elution gradient: 0-80% EtOAc in hexanes) gave the title compound (1.280 g, 72.8 %) as an oil. ¹H NMR (DMSO-*d*₆): δ 1.39 (9H, s), 1.67 (2H, br d), 1.85 - 1.95 (2H, m), 2.30 (4H, br s), 3.06 - 3.25 (2H, m), 3.32 (4H, s), 3.40 (2H, s), 3.61 (2H, br d), 4.28 (2H, br d), 5.08 (2H, br d), 6.63 (1H, br d), 6.73 - 6.83 (2H, m), 7.08 - 7.18 (1H, m), 7.29 - 7.41 (5H, m); *m/z* (ES⁺) [M+H]⁺ = 521.7.

Intermediate 152c:

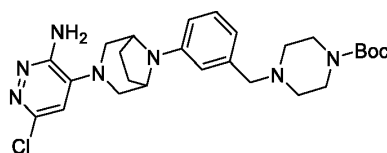
tert-Butyl 4-[[3-(3,8-diazabicyclo[3.2.1]octan-8-yl)phenyl]methyl]piperazine-1-carboxylate



[1958] Prepared in an analogous manner to Intermediate 151c starting from Intermediate 152b (1.2 g, 2.30 mmol) gave the title compound (0.820 g, 92 %) as an oil. The crude product was used for the next step. m/z (ES^+) $[M+H]^+ = 387.3$.

Intermediate 152d:

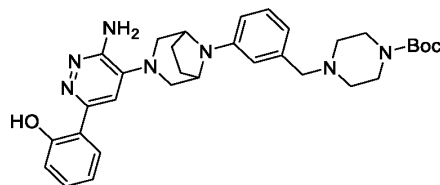
tert-Butyl 4-[[3-[3-(3-amino-6-chloro-pyridazin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]methyl]piperazine-1-carboxylate



[1959] Prepared in an analogous manner to Intermediate 3c starting from Intermediate 152c (800 mg, 2.07 mmol). Purification by FSC (elution gradient: 0-100% EtOAc in hexane, then 0-30% MeOH in EtOAc) gave the title compound (702 mg, 66.0 %) as an orange solid. 1H NMR ($DMSO-d_6$): δ 1.39 (9H, s), 1.86 - 1.95 (2H, m), 2.10 (2H, br d), 2.30 (4H, br s), 2.95 (2H, br d), 3.19 (2H, br d), 3.27 - 3.31 (4H, m), 3.41 (2H, s), 4.36 (2H, br s), 5.76 - 5.88 (2H, m), 6.63 (1H, br d), 6.75 - 6.82 (2H, m), 6.84 (1H, s), 7.10 - 7.20 (1H, m); m/z (ES^+) $[M+H]^+ = 514.3$.

Intermediate 152e:

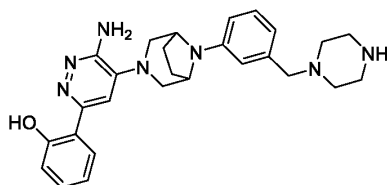
tert-Butyl 4-[[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]methyl]piperazine-1-carboxylate



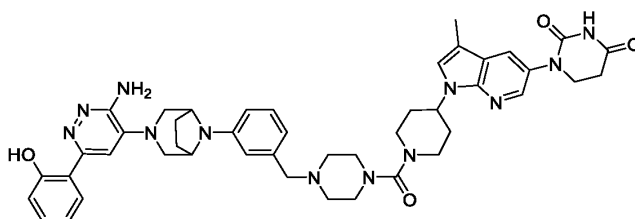
[1960] Prepared in an analogous manner to Intermediate 2h starting from Intermediate 152d (400 mg, 0.78 mmol). Purification by FSC (elution gradient: 0 to 100 % EtOAc in hexanes) gave the title compound (300 mg, 67.4 %) as a brown solid. 1H NMR ($DMSO-d_6$): δ 1.38 (9H, s), 1.90 - 2.03 (2H, m), 2.15 (2H, br d), 2.31 (4H, br s), 3.09 (2H, br d), 3.26 - 3.31 (6H, m), 3.42 (2H, s), 4.41 (2H, br s), 5.95 (2H, s), 6.63 (1H, br d), 6.79 - 6.90 (4H, m), 7.16 (1H, t), 7.23 (1H, t), 7.45 (1H, s), 7.90 (1H, br d), 14.15 (1H, s); m/z (ES^+) $[M+H]^+ = 572.4$.

Intermediate 152f:

2-[6-Amino-5-[8-[3-(piperazin-1-ylmethyl)phenyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]pyridazin-3-yl]phenol

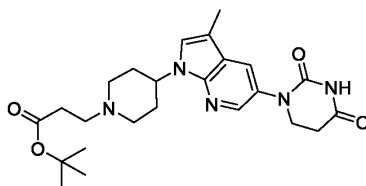


1-[1-[1-[4-[[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]methyl]piperazine-1-carbonyl]-4-piperidyl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione



EXAMPLE 153

tert-Butyl 3-[4-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-1-piperidyl]propanoate

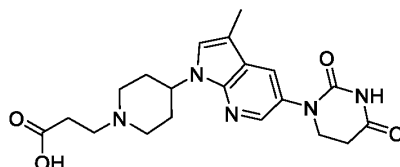


414

(3H, s), 2.37 - 2.44 (2H, m), 2.58 - 2.66 (2H, m), 2.75 (3H, br d), 2.99 (1H, br d), 3.81 (2H, t), 4.56 - 4.69 (1H, m), 7.46 (1H, s), 7.88 (1H, d), 8.17 (1H, d), 10.38 (1H, s); m/z (ES^+) $[M+H]^+ = 456.4$.

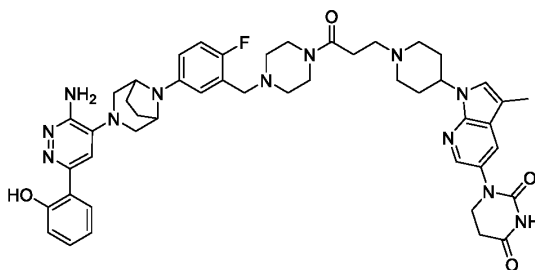
Intermediate 153b:

3-[4-[5-(2,4-Dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-1-piperidyl]propanoic acid



[1964] TFA (0.761 mL, 9.88 mmol) was added to stirred solution of Intermediate 153a (150 mg, 0.33 mmol) in DCM (4 mL). The resulting solution was stirred for 1 h. The solvent was removed under reduced pressure to give title compound (200 mg, 97 %) as a light orange solid. m/z (ES^+) $[M+H]^+ = 400.3$.

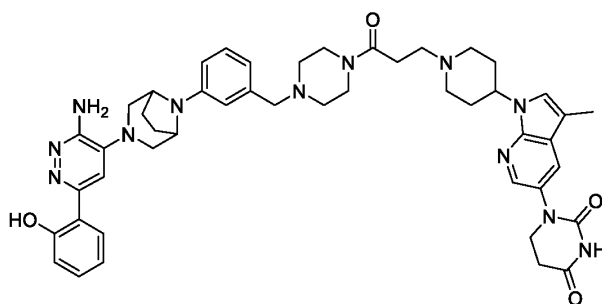
1-[1-[1-[3-[4-[[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]methyl]piperazin-1-yl]-3-oxo-propyl]-4-piperidyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1965] HATU (15.53 mg, 0.04 mmol) was added to a stirred solution of Intermediate 151f (20 mg, 0.04 mmol), Intermediate 153b (25.6 mg, 0.04 mmol) and DIPEA (0.029 mL, 0.16 mmol) in DMF (1.5 mL). The resulting solution was stirred for 1 h. The reaction mixture directly purified by RPC (elution gradient: 0-60% MeCN in water with 0.1% FA) gave the title compound (14.00 mg, 39.3 %) as a white solid following lyophilization. 1H NMR ($DMSO-d_6$): δ 1.84 (2H, br d), 1.90 - 2.06 (4H, m), 2.10 - 2.18 (4H, m), 2.26 (3H, s), 2.33 - 2.44 (4H, m), 2.46 - 2.50 (2H, m), 2.55 - 2.63 (2H, m), 2.76 (2H, t), 2.99 (2H, br d), 3.09 (2H, br d), 3.27 (2H, br d), 3.33 - 3.50 (6H, m), 3.81 (2H, t), 4.35 (2H, br s), 4.59 (1H, br t), 5.95 (2H, s), 6.79 - 6.93 (4H, m), 7.01 (1H, t), 7.23 (1H, t), 7.46 (2H, s), 7.86 - 7.93 (2H, m), 8.18 (1H, d), 10.38 (1H, s), 13.86 - 14.54 (1H, br s); m/z (ES^+) $[M+H]^+ = 871.7$.

EXAMPLE 154

1-[1-[1-[3-[4-[[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]methyl]piperazin-1-yl]-3-oxo-propyl]-4-piperidyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione



[1966] Prepared in an analogous manner to EXAMPLE 153 starting from Intermediate 152f (20 mg, 0.04 mmol) and Intermediate 153b (26.5 mg, 0.04 mmol). Purification by RPC (elution gradient: 0-60% MeCN in water with 0.1% FA) gave the title compound (15.0 mg, 41.5 %) as a white solid following lyophilization. ¹H NMR (DMSO-*d*₆): δ 1.85 (2H, br d), 1.93 - 2.06 (4H, m), 2.10 - 2.19 (4H, m), 2.26 (3H, s), 2.29 - 2.41 (4H, m), 2.57 - 2.64 (2H, m), 2.76 (2H, t), 3.00 (2H, br d), 3.09 (2H, br d), 3.28 (2H, br d), 3.34 (2H, br s), 3.46 (6H, br d), 3.81 (2H, t), 4.41 (2H, br s), 4.60 (1H, br t), 5.95 (2H, s), 6.65 (1H, br d), 6.76 - 6.91 (4H, m), 7.16 (1H, t), 7.23 (1H, t), 7.46 (2H, br d), 7.86 - 7.94 (2H, m), 8.18 (1H, d), 10.33 - 10.48 (1H, m), 14.01 - 14.32 (1H, br s); *m/z* (ES⁺) [M+H]⁺ = 853.7.

SMARCA2, SMARCA4 and PBRM1 Degradation Assays

[1967] A high throughput immunofluorescence assay was used to measure changes in SMARCA2, SMARCA4 and PBRM1 protein levels upon compound treatment. 5,000 Hela cells were seeded into each well in a 384-well plate in 30 μ L RPMI+10% FBS. Cells were incubated with increasing concentrations of compounds (10-point dose response from 1 nM to 31.7 μ M, 0.3% final DMSO) for 24h before being fixed for analysis. Cells were incubated with paraformaldehyde (2% final concentration) for 20 minutes at r.t. The plate was then aspirated using a Biotek plate washer before 30 μ L ice-cold MeOH was added to permeabilize the cells. After 5 minutes incubation in MeOH at r.t. the plate was washed once with PBS, and incubated with block solution (PBS+1%BSA+0.3% Triton-X100) for 1h at r.t. After blocking, the plate was again aspirated and 20 μ L primary antibody dilution (SMARCA2, cell signaling #11966, 1:1000; SMARCA4, cell signaling #52251, 1:1000; PBRM1, Bethyl A700-019, 1:200 diluted in blocking solution) was added into each well and the plate was left at r.t. for incubation for 2h. The plate was then washed and aspirated, and 20 μ L secondary antibody dilution (goat-anti-rabbit, Invitrogen #A-11034; goat-anti-mouse, Invitrogen #A-11032; Hoechst 33342; 1: 1000 in block solution) was added and the plate was incubated at r.t. in the dark for 1h. After a final wash, the plate was read on the Operetta CLS imager using the appropriate channels. The percentage of degradation was calculated as $F_{\text{Compound}}/F_{\text{DMSO}} \times 100\%$ (F :fluorescence intensity).

Endogenous SALL4 Degradation Assay:

[1968] The neuroblastoma cell line, Kelly, was used to monitor the degradation of the endogenous SALL4 protein using a SDS-PAGE assay. Kelly cells were grown in RPMI 1640 medium supplemented

with 10% fetal calf serum. Cells were splitted every 4 days at 1/10 ratio. Cells with less than 10 passages were used for the experiments.

[1969] For the experiment, the cells were seeded in 12 well plates at 500,000 cells per well in a final volume of 1mL of medium. The next day, the cells were dosed at 1 μ M and/or 10 μ M with the different compounds. After 24h of treatment, the cells were lysed in RIPA buffer plus protease cocktail inhibitors (100 μ L/well) for 20min on ice. Lysates were collected and spinned at 10000g for 5min. The supernatant was collected and mix with sample buffer 4X containing a sample reducing agent (25 μ L), then boil 5min at 85c. Lysates was stored at -20°C.

[1970] For the SDS-PAGE analysis, samples were loaded on precast gel (4-12%), runned at 150V constant on ice and transferred into membranes using P0 program from the fast transfer iBlot2 device (Thermofischer). Membranes were then incubated in LI-COR blocking solution (Intercept) for 30min, then with primary antibodies overnight at 4°C. The membranes were then washed for a minimum of 30min with TBS-tween 0.1% and incubated with secondary antibodies for LI-COR detection (1h diluted at 1/10000). After several washes in PBS-Tween 0.1%, the membranes were analyzed by the Li-COR Odyssey CLx imaging system for protein level detection. GAPDH was used as loading control.

List of reagents

Reagent	Source	Catalogue number
Kelly cells	Sigma-Aldrich	92110411
RPMI 1640 with Glutamine	Thermofischer	11875093
RIPA Lysis and Extraction Buffer	Thermofischer	89900
Halt™ Protease Inhibitor Cocktail (100X)	Thermofischer	78430
NuPAGE™ LDS Sample Buffer (4X)	Thermofischer	NP0007
NuPAGE™ Sample Reducing Agent (10X)	Thermofischer	NP0004
NuPAGE™ 4-12% Bis-Tris Protein Gels, 1.5 mm, 15-well	Thermofischer	NP0336BOX
iBlot™ 2 Transfer Stacks, nitrocellulose, regular size	Thermofischer	IB23001
Intercept™ Blocking Buffer	LI-COR	927-60001
SALL4 antibody	Proteintech	24500-1-AP
GAPDH antibody	Proteintech	60004-1-Ig
IRDye™ 800CW Donkey anti-Rabbit IgG Secondary Antibody	LI-COR	926-32213
IRDye™ 800CW Donkey anti-Mouse IgG Secondary Antibody	LI-COR	926-32212

Endogenous Ikaros 1 (IKZF1) Degradation Assay:

[1971] The leukemia cell line, NB4, was used to monitor the degradation of the endogenous IKZF1 protein using a SDS-PAGE assay. NB4 cells were grown in RPMI 1640 medium supplemented with 10% fetal calf serum. Cells were then split every 3 days at 1/10 ratio. Cells with less than 10 passages were used for the experiments.

[1972] For the experiment, the cells were seeded in 12 well plates at 1,000,000 cells per well in a final volume of 1mL of medium. The next day, the cells were dosed at 1 μ M and/or 10 μ M with the different

compounds. After 24h of treatment, the cells were lysed in RIPA buffer plus protease cocktail inhibitors (100 μ L/well) for 20 minutes on ice. Lysates were then collected and spun at 10000g for 5 minutes. The supernatant was then collected and mixed with sample buffer 4X containing a sample reducing agent (25 μ L), then boiled for 5 minutes at 85°C. Lysates were stored at -20°C. For the SDS-PAGE analysis, samples were loaded on precast gel (4-12%), run at 150V constant on ice and transferred into membranes using P0 program from the fast transfer iBlot2 device (Thermofischer). Membranes were then incubated in LI-COR blocking solution (Intercept) for 30 minutes, then with primary antibodies overnight at 4°C. The membranes were then washed for a minimum of 30 minutes with TBS-tween 0.1% and incubated with secondary antibodies for LI-COR detection (1h diluted at 1/10000). After several washes in PBS-Tween 0.1%, the membranes are analyzed by the Li-COR Odyssey CLx imaging system for protein level detection. GAPDH is used as loading control.

List of reagents

Reagent	Source	Catalogue number
NB4 cells	DSMZ	ACC-207
RPMI 1640 with Glutamine	Thermofischer	11875093
RIPA Lysis and Extraction Buffer	Thermofischer	89900
Halt™ Protease Inhibitor Cocktail (100X)	Thermofischer	78430
NuPAGE™ LDS Sample Buffer (4X)	Thermofischer	NP0007
NuPAGE™ Sample Reducing Agent (10X)	Thermofischer	NP0004
NuPAGE™ 4-12% Bis-Tris Protein Gels, 1.5 mm, 15-well	Thermofischer	NP0336BOX
iBlot™ 2 Transfer Stacks, nitrocellulose, regular size	Thermofischer	IB23001
Intercept™ Blocking Buffer	LI-COR	927-60001
IKZF1 antibody	Cell Signaling	14859
GAPDH antibody	Proteintech	60004-1-Ig
IRDye™ 800CW Donkey anti-Rabbit IgG Secondary Antibody	LI-COR	926-32213
IRDye™ 800CW Donkey anti-Mouse IgG Secondary Antibody	LI-COR	926-32212

Clearance Assay: Metabolic Stability Assessment using human liver microsomes (HLM)

[1973] The stability of control (phenacetin, verapamil, diclofenac, imiprimine, benzydamine and metoprolol) and test compounds was evaluated using 1 mg/mL HLM (150 mixed gender donor pool) containing 1 mM NADPH, and 1 μ M test compound/control. 222.5 μ L of HLM mixture containing 1.12 mg/mL HLM in phosphate buffer pH 7.4 was mixed with 25 μ L 10 mM NADPH and pre-warmed at 37°C for 8 minutes prior to addition of 2.5 μ L of 100 μ M test compound/control prepared in DMSO. Aliquots (20 μ L) were removed at 0.5, 5, 10, 15, 20 and 30 minutes and quenched with 100 μ L of cold stop solution (100% ACN with 100 nM of alprazolam, caffeine and tolbutamide as internal standards). Samples were centrifuged for 20 minutes at 4,000 rpm and 4°C and a 40 μ L aliquot of supernatant was mixed with 160 μ L pure water for LC-MS/MS analysis. Each incubation was conducted in singlicate. Peak areas were determined from extracted ion chromatograms and percent (%) parent remaining was calculated from peak area of test compound/control. The slope value, k, was determined by linear regression of the natural logarithm of percent parent remaining vs. incubation time curve, using Microsoft Excel. The in vitro half-

life was calculated from $-(\text{natural logarithm (ln) of } 2 / k)$, and converted to *in vitro* intrinsic clearance using Equation 1.

$$\textit{in vitro CL}_{\text{int}} = \frac{\ln 2}{t_{1/2}} \times \frac{\text{incubation volume } (\mu\text{L})}{\text{protein concentration (mg)}} \quad \text{Equation 1}$$

Human Hepatocyte Clint assay

[1974] Human Hepatocyte CL_{int}. Metabolism is initiated by addition of compound to the hepatocyte incubation giving a compound concentration of 1 μM with 1×10^6 hepatocytes/ml. Samples of the incubation at 37°C are taken regularly over 120 min into cold acetonitrile (5:1) containing internal standards. Samples are then centrifuged and 40 μL of supernatant is diluted with 160 μL of water (30 μL of supernatant is diluted with 180 μL water for human hepatocytes) before analysis by LCMSMS. The natural log of % parent remaining at each time point is plotted against time to half-life and subsequently CL_{int}.

SALL-4 and AIOLOS Luciferase degrader assays

[1975] *Cell lines:* HiBiT-IKZF3 MM.1S cells (obtained from Promega) were grown in RPMI-1640 (Gibco), supplemented with 10% FBS and GlutaMAX (Gibco). HiBiT-SALL4 SK-N-DZ cells (obtained from Promega) were grown in DMEM (high glucose) (Gibco), supplemented with 10% FBS, GlutaMAX (Gibco), Sodium Pyruvate (1mM) (Gibco) and 1% Non-essential Amino Acids (NEAA) (Sigma).

[1976] *HiBiT assay:* Compound assay-ready-plates were prepared using acoustic dispensing (Echo), generating 12-point, half-log dose-responses with a top concentration of 30 μM . Wells were backfilled with DMSO to 0.3% DMSO. DMSO and Pomalidomide (30 μM) were used as spot controls across the plates to define the scale range. HiBiT-IKZF3 MM.1S cells and HiBiT-SALL4 SK-N-DZ cells were started from cryovials into their respective media and dispensed onto compound assay-ready-plates at either 3000 (SALL4) or 20,000 (AIOLOS) cells/well using a multidrop combi. Plates were subsequently spun for 1 min at 300xg and incubated for 6h at 37°C, 5% CO₂ in a humidified incubator. HiBiT Lytic Detection Reagents (Promega) was prepared according to manufacturer's instructions, and 5 μL /well of the lytic detection mix was added to each plate using a multidrop combi. Plates were spun for 1 min at 300g, placed on an orbital shaker at 300rpm for 30 min before reading luminescence on a Envision-1 plate reader according to manufacturer's instructions.

[1977] *Data analysis:* Raw signals were analysed in Genedata Screener using 'Neutral Controls minus Inhibitors' method and dose-response curves were drawn using 'Smart Fit' condensing method to calculate DC50 values. Compounds were accepted as active when $\geq 30\%$ response was observed.

[1978] Potential cytotoxicity of PROTACs reviewed in alternative cell screen in parallel with degradation assays, enabling consolidation of whether IC50s generated in degradation assays represent true activity or whether it is inconclusive due to potential cytotoxicity associated with PROTACs.

[1979] The SMARCA2 degradation of representative Compounds of the Disclosure of provided in Table 1.

Table 1

Example No.	SMARCA2 DC ₅₀ (μM)	SMARCA2 D _{max} (%)
1	0.064	57.0
2	0.035	86.6
3	0.022	73.5
4	0.094	72.3
5	0.004	86.8
6	0.014	87.1
7	0.008	81.2
8	0.038	69.5
9	0.067	68.1
10	0.078	62.3
11	0.005	88.9
12	0.006	88.4
13	0.002	92.2
14	0.003	86.3
15	0.007	83.0
16	0.003	82.2
17	0.063	79.9
18	0.002	92.4
19	0.004	88.0
20	0.038	73.9
21	0.264	60.1
22	0.016	80.0
23	0.015	78.4
24	0.129	71.6
25	0.095	75.7
26	0.103	68.1
27	0.064	79.4
28	0.042	78.8
29	0.010	78.4
30	0.032	69.8
31	0.023	73.7
32	0.078	55.5
33	0.009	82.7

34	0.027	80.5
35	0.130	66.5
36	0.069	78.9
37	0.011	70.8
38	1.063	65.0
39	0.006	93.1
40	0.175	77.1
41	0.007	83.8
42	0.002	79.7
43	0.030	68.5
44	0.007	90.5
45	0.018	76.7
46	0.042	78.8
47	0.018	77.0
48	0.009	89.3
49	0.016	94.4
50	0.064	76.8
51	0.014	82.7
52	0.014	82.0
53	0.026	75.4
54	0.006	83.1
55	0.030	66.2
56	0.120	78.9
57	0.101	79.5
58	0.007	91.5
59	0.044	84.0
60	0.022	87.9
61	0.004	89.9
62	0.004	91.0
63	0.008	91.1
64	0.017	82.4
65	0.073	87.9
66	0.049	80.3
67	0.023	72.3
68	0.023	71.5
69	0.031	84.4
70	0.029	70.7
71	0.002	91.8
72	0.006	85.6

73	0.054	61.4
74	0.004	92.4
75	0.026	87.6
76	0.028	94.1
77	0.013	81.6
78	0.048	86.8
79	0.023	80.8
80	0.115	81.2
81	0.026	84.1
82	0.008	86.6
83	0.014	84.4
84	0.022	80.8
85	0.006	87.6
86	0.080	70.2
87	0.028	87.9
88	0.027	75.4
89	0.023	79.0
90	0.020	74.0
91	0.034	73.6
92	0.029	61.9
93	0.008	83.7
94	0.134	79.8
95	0.079	76.5
96	0.202	74.2
97	0.014	90.7
98	0.037	62.7
99	0.046	90.3
100	0.016	85.2
101	0.035	82.7
102	0.029	80.5
103	0.017	85.5
104	0.023	83.2
105	0.013	85.2
106	0.016	87.5
107	0.022	86.3
108	0.065	76.8
109	0.044	82.6
110	0.052	79.1
111	0.073	81.5

112	0.027	87.1
113	0.005	91.0
114	0.008	84.1
115	0.022	82.0
116	0.037	82.3
117	0.049	81.9
118	0.046	83.7
119	0.087	80.0
120	0.090	79.4
121	0.010	88.5
122	0.046	87.1
123	0.004	92.5
124	0.013	89.3
125	0.024	85.9
126	0.102	72.6
127	0.062	67.0
128	0.005	93.4
129	0.006	90.0
130	0.047	82.8
131	0.052	76.6
132	0.006	89.3
133	0.062	78.5
134	0.054	81.1
135	0.219	78.3
136	0.188	87.6
137	0.077	83.6
138	0.134	84.4
139	0.104	81.5
140	0.243	73.2
141	0.015	86.1
142	0.071	78.3
143	0.033	86.3
144	0.075	75.4
145	0.003	90.7
146	>0.319	48.6
147	>0.319	42.9
148	0.012	84.2
149	0.004	88.0
150	0.014	87.6

151	0.044	70.5
152	0.013	76.7
153	>0.319	31.6
154	>0.319	46.4

[1980] The SMARCA4 and PBRM1 degradation of representative Compounds of the Disclosure of provided in Table 2.

Table 2

Example No.	SMARCA4 DC ₅₀ (μM)	SMARCA4 D _{max} (%)	PBRM1 DC ₅₀ (μM)	PBRM1 D _{max} (%)
3	>0.319	22.7	0.296	55.7
7	0.319	23.2	0.319	35.6
12	1.009	36.4	0.319	45.8
13	0.319	38.7	0.167	54.0
14	0.319	22.5	0.319	33.8
15	0.319	19.1	0.319	29.4
16	0.106	18.1	0.106	31.1
18	0.319	39.9	0.899	48.0
20	1.009	8.6	0.319	22.4
21	31.67	0.3	3.33	13.6
22	0.319	25.2	1.009	35.4
26	3.33	13.6	1.009	23.8
31	0.319	12.8	1.009	16.3
33	31.67	8.8	0.319	20.3
35	1.009	9.3	3.333	28.4
36	3.333	5.9	1.009	43.6
38	31.67	9.1	10.000	15.3
39	1.009	23.1	0.319	41.6
40	>3.333	23.3	>31.67	19.1
43	>0.319	15.8	>1.009	35.5
44	>1.009	29.6	>1.009	37.6
45	>0.319	9.1	>1.009	28.3
46	>1.009	21.5	>1.009	21.8
47	>0.319	12.1	>0.319	44.0

49	>1.009	38.1	0.186	74.0
51	>0.319	18.0	>1.009	30.2
52	>0.319	8.8	>1.009	21.2
53	>1.009	18.3	>1.009	38.8
54	>0.319	19.2	>0.106	30.5
55	>31.67	12.6	>1.009	26.2
56	>0.319	16.7	2.08	55.6
62	>0.319	40.6	>0.319	45.1
64	>1.009	4.1	>1.009	25.1
65	>3.333	21.1	>3.333	33.3
66	>1.009	8.0	>31.67	54.2
67	>31.67	3.2	>0.319	14.1
68	>31.67	1.8	>1.009	18.5
69	>1.009	12.8	>1.009	22.3
70	>1.009	17.0	>1.009	35.8
71	>0.319	33.1	>0.319	39.4
72	>0.016	26.1	>0.106	35.3
73	>0.319	9.1	>1.009	26.0
75	>1.009	30.2	>0.319	40.0
77	>0.319	5.6	>1.009	26.8
79	>31.67	5.8	>1.009	17.4
80	>31.67	5.1	>1.009	14.3
83	>0.319	30.9	>0.319	33.8
85	>1.009	20.5	>0.319	41.3
87	>1.009	17.3	>1.009	32.3
91	>0.319	18.9	>1.009	27.2
92	>31.67	1.6	>1.009	22.3
93	>31.67	11.7	>0.319	23.5
94	>31.67	14.7	>31.67	10.3
97	>3.333	35.6	0.670	57.5
98	>10.0	10.9	>10.0	51.6
99	>3.333	31.2	>3.333	38.2
102	>1.009	28.2	2.09	54.2

103	>1.009	19.3	>3.333	38.4
104	>31.67	6.8	>0.319	27.4
105	>31.67	14.3	>3.333	28.9
106	>1.009	24.5	>0.319	26.3
110	>1.009	28.5	>1.009	44.5
111	>3.333	13.8	>1.009	35.5
114	>31.67	13.8	>1.009	19.3
115	>1.009	17.2	>1.009	26.6
116	>31.67	18.8	>1.009	29.3
117	>31.67	13.9	>1.009	23.7
118	>1.009	7.4	>1.009	14.6
119	>3.333	7.5	>1.009	23.1
120	>31.67	1.6	>3.333	15.1
121	>1.009	20.0	>0.319	42.7
122	>31.67	15.2	>1.009	34.4
130	>31.67	9.5	>1.009	24.9
131	>31.67	7.3	>3.333	14.7
132	>1.009	32.2	0.026	68.5
133	>0.319	21.1	0.201	62.0
134	>31.67	5.0	>1.009	16.9
135	>31.67	-0.4	>3.333	10.0
136	>1.009	20.0	>31.67	13.7
137	>31.67	7.9	>3.333	15.2
138	>31.67	8.7	>31.67	11.2
139	>10.0	12.8	0.985	63.9
140	>31.67	7.0	>10.0	43.0
142	>31.67	6.1	>3.333	17.8
143	>1.009	31.3	>3.333	23.8
144	>31.67	8.5	>3.333	19.8
148	>1.009	20.0	>0.319	43.5
151	>31.67	6.1	>0.319	31.4
152	>31.67	11.7	>0.319	39.7

[1981] The in vitro intrinsic clearance of representative Compounds of the Disclosure in human liver microsomes and hepatocytes are provided in Table 3.

Table 3

Example No.	<i>In-vitro</i> human liver microsomes intrinsic clearance (uL/min/mg)	<i>In-vitro</i> human hepatocytes intrinsic clearance (uL/min/mg) (uL/min/1x10 ⁶ cells)
1	10.7	-
2	61.6	-
3	<8.4	-
4	9.3	< 1
5	13.8	3.2
6	17.2	5.7
7	<8.3	2.5
8	<3.0	3.0
9	<4.6	2.6
10	14.2	-
11	13.1	< 1
12	<10.4	4.9
13	13.4	<2.0
14	10.5	4.6
15	11.1	1.7
16	14.3	4.1
17	16.6	5.0
18	18.8	5.1
19	17.0	-
20	<3.0	3.4
21	<3.0	-
22	11.6	3.6
23	9.1	2.8
24	11.8	-

25	<3.0	3.6
26	<3.0	-
27	12.8	-
28	20.8	-
29	10.8	2.5
30	47.3	10.3
31	<3.8	3.2
32	15.2	-
33	14.9	4.8
34	<3.0	2.9
35	<3.0	<1.0
36	4.1	-
37	19.9	-
38	NV	-
39	8.8	4.5
40	32.9	-
41	22.7	3.9
42	21.1	6.5
43	21.1	-
44	< 3	6.7
45	6.1	-
46	66.8	14.3
47	73.8	10.7
48	59.5	12.2
49	36.2	6.9
50	29.2	-
51	23.9	9.7
52	14.5	10.1
53	15.7	-

54	12.1	7.3
55	< 3	-
56	< 3	3.8
57	< 3	-
58	6.9	4.2
59	-	4.6
60	9.5	< 1
61	10.8	-
62	7.7	3.0
63	15.2	2.4
64	14.9	3.6
65	10.7	8.8
66	< 3	< 1
67	< 3	1.6
68	12.2	2.5
69	< 3	1.3
70	< 3	-
71	25.3	7.3
72	12.7	4.3
73	12.3	-
74	15.7	-
75	9.4	5.0
76	14.9	-
77	10.9	2.3
78	6.8	2.3
79	8.8	3.6
80	< 3	2.3
81	<4.4	< 1
82	-	4.6

83	8.2	< 1
84	6.8	1.2
85	15.0	< 1
86	10.2	< 1
87	9.9	< 1
88	15.6	-
89	17.3	-
90	15.8	4.3
91	< 3	-
92	< 3	-
93	< 3	<1
94	-	-
95	12.9	-
96	< 3	6.6
97	19.0	16.3
98	-	-
99	5.1	2.6
100	< 3	-
101	23.9	-
102	< 1	-
103	< 3.3	< 1
104	< 2.9	< 1
105	< 5.7	< 1
106	< 3.8	1.5
107	11.3	-
108	6.5	-
109	< 3	-
110	< 3	-
111	18.6	-

112	10.2	< 1
113	8.3	-
114	22.7	< 1
115	< 3.3	< 1
116	< 3	< 1
117	4.4	< 1
118	5.2	< 1
119	< 3	< 1
120	< 3	< 1
121	< 4.8	< 1
122	3.5	< 1
123	-	-
124	25.8	7.0
125	43.2	-
126	150	-
127	115	-
128	18.1	-
129	7.4	-
130	< 3	-
131	< 3	-
132	39.4	-
133	70.9	-
134	< 3	-
135	< 3	-
136	< 3	-
137	4.8	-
138	< 3	-
139	8.4	-
140	< 3	-

141	< 3	-
142	4.5	-
143	4.4	-
144	< 3	-
145	8.2	-
146	100.3	-
147	66.5	-
148	8.7	-
149	12.4	-
150	4.8	-
151	68.7	-
152	191.5	-
153	247.0	-
154	143.5	-

[1982] The SALL4 and IKZF1 degradation activities of representative Compounds of the Disclosure are provided in Table 4.

Table 4

Example No.	SALL4 degrader IC ₅₀ (μM)	IKZF1 degrader at 10μM
1	>30.0	
2	>30.0	No
3	>30.0	
6	>30.0	No
7	>30.0	No
8	>30.0	
9	>30.0	
10	>30.0	
11	>30.0	No
12	>30.0	No
14	>30.0	

15	>30.0	
16	>30.0	
18	>30.0	
20	>30.0	
23	>30.0	
25	>30.0	
26	>30.0	
27	>30.0	
29	>30.0	
31	>30.0	
32	>30.0	
85	>30	-

[1983] The SALL4 and AIOLOS degradation activities of representative Compounds of the Disclosure are provided in Table 5.

Table 5

Example No.	SALL4 degrader IC ₅₀ (μM)	AIOLOS degrader IC ₅₀ (μM)
1	>30.0	-
2	>30.0	-
3	>30.0	-
6	>30.0	-
7	>30.0	-
8	>30.0	-
9	>30.0	-
10	>30.0	-
11	>30.0	>21.2
12	>30.0	-
14	>30.0	-
15	>30.0	-
16	>30.0	-
18	>30.0	-
20	>30.0	-

23	>30.0	-
25	>30.0	>30.0
26	>30.0	-
27	>30.0	-
29	>16.9	-
31	>30.0	-
32	>30.0	-
33	>30.0	>30.0
36	>30.0	-
47	>30.0	>30.0
62	>30.0	-
69	>30.0	>30.0
77	>30.0	>30.0
85	>30.0	-
87	>30.0	>30.0
93	>30.0	>30.0
94	>30.0	>30.0
99	>30.0	>30.0
103	>30.0	-
104	>30.0	4.6*
105	>30.0	10.6*
106	>30.0	>30.0
107	-	>30.0
110	-	>30.0
112	>30.0	>30.0
115	>30.0	>30.0
116	>30.0	>30.0
117	>30.0	>30.0
118	>10.0	>30.0
121	-	>30.0
122	>30.0	29.5
129	-	>30.0
130	-	>30.0
132	>30.0	>30.0

137	-	>30.0
140	-	>30.0
141	-	>30.0
142	-	>30.0
143	-	>30.0

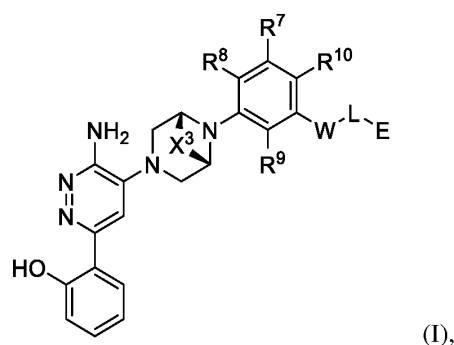
*partial response

[1984] Having now fully described the compounds, compositions, the methods herein, it will be understood by those of skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations, and other parameters without affecting the scope of the methods, compounds, and compositions provided herein or any embodiment thereof. All patents, patent applications, and publications cited herein are fully incorporated by reference herein in their entirety.

V. Statements

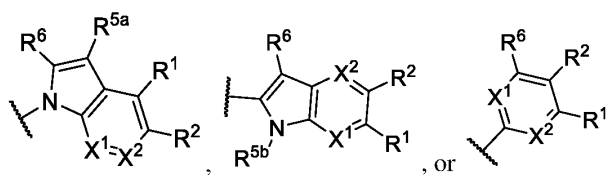
[1985] The present disclosure also provides the following particular Statements.

[1986] Statement 1. A compound of Formula (I), or pharmaceutically acceptable salt thereof:

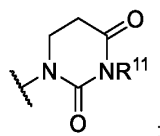


wherein:

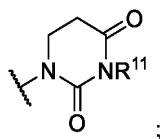
[1987] E is:



[1988] R¹ is hydrogen, halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or

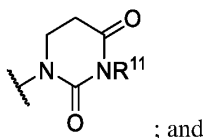


[1989] R² is hydrogen, halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or

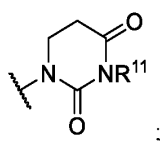


[1990] with the provisos:

[1991] (i) when R¹ is hydrogen, halogen, (C₁-C₆)alkyl, or (C₁-C₆)alkoxy, then R² is:



[1992] (ii) when R² is hydrogen, halogen, (C₁-C₆)alkyl, or (C₁-C₆)alkoxy, then R¹ is



[1993] R¹¹ is hydrogen or -(C₁-C₆)alkyl-O-P(=O)-(OH)₂;

[1994] X¹ is CR³ or N;

[1995] R³ is hydrogen, halogen, or (C₁-C₆)alkyl;

[1996] X² is CR⁴ or N;

[1997] R⁴ is hydrogen, halogen, or (C₁-C₆)alkyl;

[1998] R^{5a} is hydrogen, halogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, 4- to 6-membered heterocycloalkyl, cyano, aryl, or 5- or 6-membered heteroaryl, wherein (C₁-C₆)alkyl is optionally substituted with one, two, or three substituents independently selected from halogen or cyano; and 4- to 6-membered heterocycloalkyl, aryl, or 5- or 6-membered heteroaryl is optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or (C₁-C₆)alkyl;

[1999] R^{5b} is hydrogen, (C₁-C₆)alkyl, or (C₃-C₆)cycloalkyl;

[2000] R⁶ is hydrogen, (C₁-C₆)alkyl, or cyano;

[2001] X³ is -CH₂CH₂- or -CH₂-O-CH₂-; or

[2002] X³ is absent;

[2003] L is -G¹-G²-G³-G⁴-, wherein G¹ is attached to W;

[2004] G¹ is (C₁-C₆)alkylenyl; 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or cyano; or 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or cyano;

[2005] G² is (C₁-C₆)alkylenyl or a direct bond;

[2006] G³ is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C₁-C₆)alkyl, or (C₁-C₆)alkoxy; cyano; or 7- to 11-

membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or cyano;

[2007] G⁴ is (C₁-C₆)alkylenyl or a direct bond;

[2008] W is -C≡C- or a direct bond;

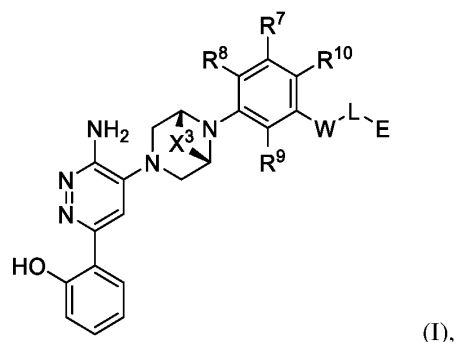
[2009] R⁷ is hydrogen, halogen, (C₁-C₆)alkyl optionally substituted with one, two, or three halogen, cyano, or (C₃-C₆)cycloalkyl;

[2010] R⁸ is hydrogen, halogen, (C₁-C₆)alkyl optionally substituted with one, two, or three halogen, cyano, or (C₃-C₆)cycloalkyl;

[2011] R⁹ is hydrogen, halogen, (C₁-C₆)alkyl optionally substituted with one, two, or three halogen, cyano, or (C₃-C₆)cycloalkyl; and

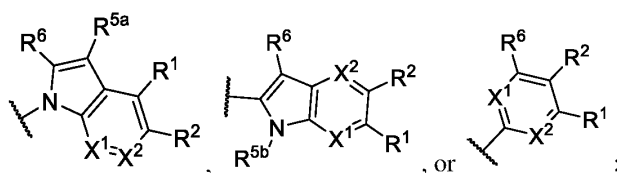
[2012] R¹⁰ is hydrogen, halogen, (C₁-C₆)alkyl optionally substituted with one, two, or three halogen, cyano, or (C₃-C₆)cycloalkyl.

[2013] Statement 2. A compound of Formula (I), or pharmaceutically acceptable salt thereof:

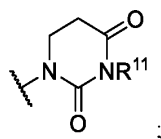


wherein:

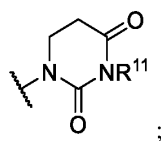
[2014] E is:



[2015] R¹ is hydrogen, halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or

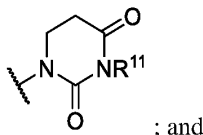


[2016] R² is hydrogen, halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or

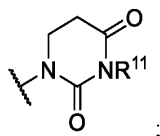


[2017] with the provisos:

[2018] (i) when R^1 is hydrogen, halogen, (C_1-C_6) alkyl, or (C_1-C_6) alkoxy, then R^2 is:



[2019] (ii) when R^2 is hydrogen, halogen, (C_1-C_6) alkyl, or (C_1-C_6) alkoxy, then R^1 is:



[2020] R^{11} is hydrogen or $-(C_1-C_6)alkyl-O-P(=O)-(OH)_2$;

[2021] X^1 is CR^3 or N;

[2022] R^3 is hydrogen, halogen, or (C_1-C_6) alkyl;

[2023] X^2 is CR^4 or N;

[2024] R^4 is hydrogen, halogen, or (C_1-C_6) alkyl;

[2025] R^{5a} is hydrogen, halogen, (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, 4- to 6-membered heterocycloalkyl, cyano, aryl, or 5- or 6-membered heteroaryl, wherein (C_1-C_6) alkyl is optionally substituted with one, two, or three substituents independently selected from halogen or cyano; and 4- to 6-membered heterocycloalkyl, aryl, or 5- or 6-membered heteroaryl is optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or (C_1-C_6) alkyl;

[2026] R^{5b} is hydrogen, (C_1-C_6) alkyl, or (C_3-C_6) cycloalkyl;

[2027] R^6 is hydrogen, (C_1-C_6) alkyl, or cyano;

[2028] X^3 is $-CH_2CH_2-$ or $-CH_2-O-CH_2-$; or

[2029] X^3 is absent;

[2030] L is $-G^1-G^2-G^3-G^4-$, wherein G^1 is attached to W;

[2031] G^1 is (C_1-C_6) alkylenyl; 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano; or 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano;

[2032] G^2 is (C_1-C_6) alkylenyl or a direct bond;

[2033] G^3 is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6) alkyl, or (C_1-C_6) alkoxy; cyano; 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano; or 5- to 10-membered heteroarylenyl;

[2034] G^4 is (C_1-C_6) alkylenyl, (C_3-C_6) cycloalkylenyl, or a direct bond;

[2035] W is $-C\equiv C-$ or a direct bond;

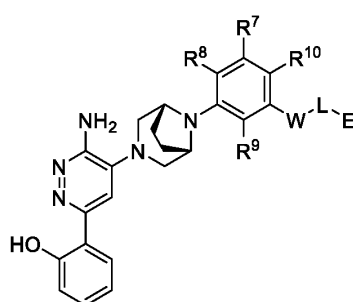
[2036] R^7 is hydrogen, halogen, (C₁-C₆)alkyl optionally substituted with one, two, or three halogen, cyano, or (C₃-C₆)cycloalkyl;

[2037] R^8 is hydrogen, halogen, (C₁-C₆)alkyl optionally substituted with one, two, or three halogen, cyano, or (C₃-C₆)cycloalkyl;

[2038] R^9 is hydrogen, halogen, (C₁-C₆)alkyl optionally substituted with one, two, or three halogen, cyano, or (C₃-C₆)cycloalkyl; and

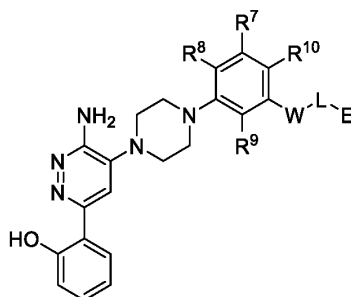
[2039] R^{10} is hydrogen, halogen, (C₁-C₆)alkyl optionally substituted with one, two, or three halogen, cyano, or (C₃-C₆)cycloalkyl.

[2040] Statement 3. The compound of statement 1 or 2, or pharmaceutically acceptable salt thereof, having Formula (II):



(II).

[2041] Statement 4. The compound of statement 1 or 2, or pharmaceutically acceptable salt thereof, having Formula (III):



(III).

[2042] Statement 5. The compound, or pharmaceutically acceptable salt thereof, according to any one of statements 1-4, wherein E is E-1.

[2043] Statement 6. The compound, or pharmaceutically acceptable salt thereof, according to statement 5, wherein R^{5a} is hydrogen.

[2044] Statement 7. The compound, or pharmaceutically acceptable salt thereof, according to statement 5, wherein R^{5a} is (C₁-C₆)alkyl optionally substituted with one, two, or three substituents independently selected from halogen or cyano.

[2045] Statement 8. The compound, or pharmaceutically acceptable salt thereof, according to statement 7, wherein R^{5a} is methyl.

[2046] Statement 9. The compound, or pharmaceutically acceptable salt thereof, according to statement 5, wherein R^{5a} is (C₃-C₆)cycloalkyl.

[2047] Statement 10. The compound, or pharmaceutically acceptable salt thereof, according to statement 9, wherein R^{5a} is cyclopropyl.

[2048] Statement 11. The compound, or pharmaceutically acceptable salt thereof, according to statement 5, wherein R^{5a} is 4- to 6-membered heterocycloalkyl optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or (C₁-C₆)alkyl.

[2049] Statement 12. The compound, or pharmaceutically acceptable salt thereof, according to statement 5, wherein R^{5a} is cyano.

[2050] Statement 13. The compound, or pharmaceutically acceptable salt thereof, according to statement 5, wherein R^{5a} is aryl optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or (C₁-C₆)alkyl.

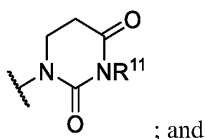
[2051] Statement 14. The compound, or pharmaceutically acceptable salt thereof, according to statement 5, wherein R^{5a} is 5- or 6-membered heteroaryl optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or (C₁-C₆)alkyl.

[2052] Statement 15. The compound, or pharmaceutically acceptable salt thereof, according to any one of statements 1-4, wherein E is E-2.

[2053] Statement 16. The compound, or pharmaceutically acceptable salt thereof, according to any one of statements 1-4, wherein E is E-3.

[2054] Statement 17. The compound, or pharmaceutically acceptable salt thereof, according to any one of statements 1-16, wherein:

[2055] R¹ is:



; and

[2056] R² is hydrogen, halogen, (C₁-C₆)alkyl, or (C₁-C₆)alkoxy.

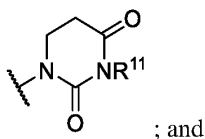
[2057] Statement 18. The compound, or pharmaceutically acceptable salt thereof, according to statement 17, wherein R² is hydrogen, halogen, or (C₁-C₆)alkyl.

[2058] Statement 19. The compound, or pharmaceutically acceptable salt thereof, according to statement 18, wherein R² is hydrogen, fluoro, or methyl.

[2059] Statement 20. The compound, or pharmaceutically acceptable salt thereof, according to any one of statements 17-19, wherein R¹¹ is hydrogen.

[2060] Statement 21. The compound, or pharmaceutically acceptable salt thereof, according to any one of statements 1-16, wherein:

[2061] R² is:



[2062] R¹ is hydrogen, halogen, (C₁-C₆)alkyl, or (C₁-C₆)alkoxy.

[2063] Statement 22. The compound, or pharmaceutically acceptable salt thereof, according to statement 21, wherein R¹ is hydrogen, halogen, or (C₁-C₆)alkyl.

[2064] Statement 23. The compound, or pharmaceutically acceptable salt thereof, according to statement 22, wherein R¹ is hydrogen, fluoro, or methyl.

[2065] Statement 24. The compound, or pharmaceutically acceptable salt thereof, according to any one of statements 21-23, wherein R¹¹ is hydrogen.

[2066] Statement 25. The compound, or pharmaceutically acceptable salt thereof, according to any one of statements 1-24, wherein X¹ is CR³.

[2067] Statement 26. The compound, or pharmaceutically acceptable salt thereof, according to statement 25, wherein R³ is hydrogen.

[2068] Statement 27. The compound, or pharmaceutically acceptable salt thereof, according to statement 25, wherein R³ is halogen.

[2069] Statement 28. The compound, or pharmaceutically acceptable salt thereof, according to statement 25, wherein R³ is (C₁-C₆)alkyl.

[2070] Statement 29. The compound, or pharmaceutically acceptable salt thereof, according to any one of statements 1-24, wherein X¹ is N.

[2071] Statement 30. The compound, or pharmaceutically acceptable salt thereof, according to any one of statements 1-29, wherein X² is CR⁴.

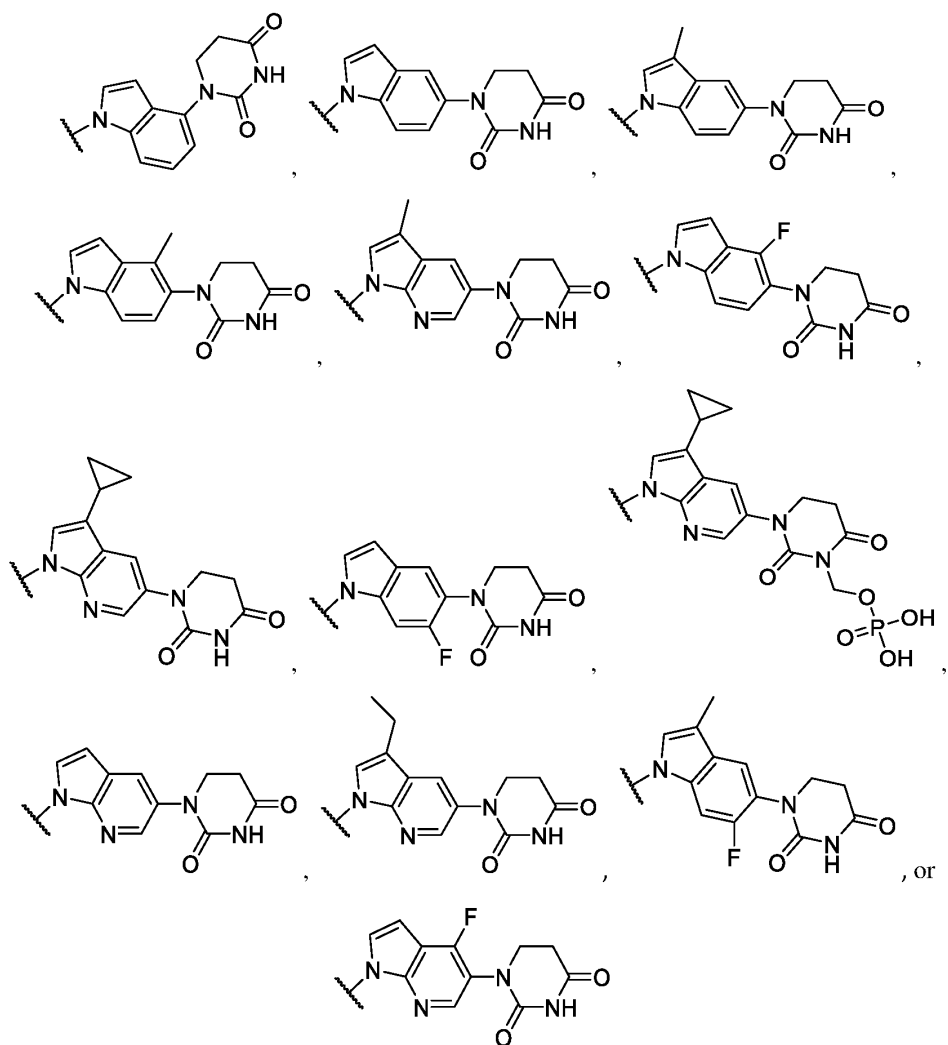
[2072] Statement 31. The compound, or pharmaceutically acceptable salt thereof, according to statement 30, wherein R⁴ is hydrogen.

[2073] Statement 32. The compound, or pharmaceutically acceptable salt thereof, according to statement 30, wherein R⁴ is halogen.

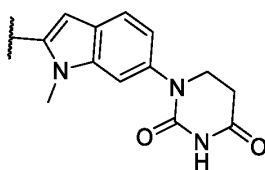
[2074] Statement 33. The compound, or pharmaceutically acceptable salt thereof, according to statement 30, wherein R⁴ is (C₁-C₆)alkyl.

[2075] Statement 34. The compound, or pharmaceutically acceptable salt thereof, according to any one of statements 1-29, wherein X² is N.

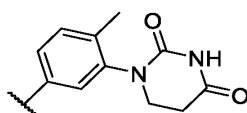
[2076] Statement 35. The compound, or pharmaceutically acceptable salt thereof, according to statement 5, wherein E-1 is:



[2077] Statement 36. The compound, or pharmaceutically acceptable salt thereof, according to statement 15, wherein E-2 is:



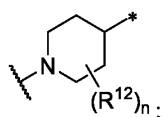
[2078] Statement 37. The compound, or pharmaceutically acceptable salt thereof, according to statement 16, wherein E-3 is:



[2079] Statement 38. The compound, or pharmaceutically acceptable salt thereof, according to any one of statements 1-37, wherein G^1 is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano.

[2080] Statement 39. The compound, or pharmaceutically acceptable salt thereof, according to statement 38, wherein:

[2081] G^1 is:



[2082] each R^{12} is independently halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano;

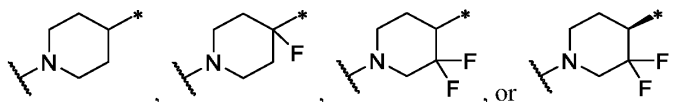
[2083] n is 0, 1, 2, or 3; and

[2084] the bond marked with an "*" is attached to G^2 .

[2085] Statement 40. The compound, or pharmaceutically acceptable salt thereof, according to statement 39, wherein each R^{12} is independently fluoro, methyl, methoxy, cyano, or $-CHF_2$; and n is 0, 1, or 2.

[2086] Statement 41. The compound, or pharmaceutically acceptable salt thereof, according to statement 38, wherein:

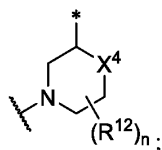
[2087] G^1 is:



[2088] and bond marked with an "*" is attached to G^2 .

[2089] Statement 42. The compound, or pharmaceutically acceptable salt thereof, according to statement 38, wherein:

[2090] G^1 is:



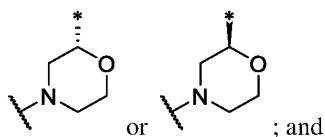
[2091] wherein X^4 is $-O-$;

[2092] each R^{12} is independently halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano; and

[2093] the bond marked with an "*" is attached to G^2 .

[2094] Statement 43. The compound, or pharmaceutically acceptable salt thereof, according to statement 42, wherein:

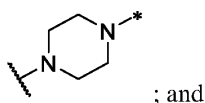
[2095] G^1 is:



[2096] the bond marked with an "*" is attached to G².

[2097] Statement 44. The compound, or pharmaceutically acceptable salt thereof, according to statement 38, wherein:

[2098] G¹ is:

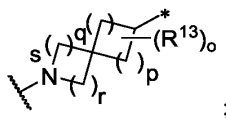


[2099] the bond marked with an "*" is attached to G².

[2100] Statement 45. The compound, or pharmaceutically acceptable salt thereof, according to any one of statements 1-37, wherein G¹ is 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or cyano.

[2101] Statement 46. The compound, or pharmaceutically acceptable salt thereof, according to statement 45, wherein:

[2102] G¹ is:



[2103] each R¹³ is independently selected from halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or cyano;

[2104] o is 0, 1, 2, or 3;

[2105] p, q, r, and s are independently 1, 2, or 3; and

[2106] the bond marked with an "*" is attached to G².

[2107] Statement 47. The compound, or pharmaceutically acceptable salt thereof, according to statement 46, wherein:

[2108] p and q are 1;

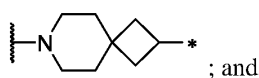
[2109] r is 1 or 2;

[2110] s is 1 or 2; and

[2111] R¹³ is halogen.

[2112] Statement 48. The compound, or pharmaceutically acceptable salt thereof, according to statement 46, wherein R¹³ is fluoro and o is 0, 1, or 2.

[2113] Statement 49. The compound, or pharmaceutically acceptable salt thereof, according to statement 46, wherein G¹ is:

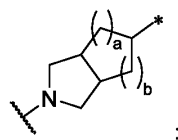


; and

[2114] the bond marked with an "*" is attached to G².

[2115] Statement 50. The compound, or pharmaceutically acceptable salt thereof, according to statement 45, wherein:

[2116] G¹ is:



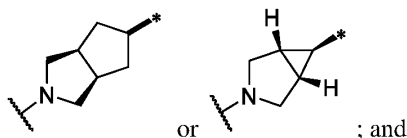
;

[2117] a is 0 or 1;

[2118] b is 0 or 1; and

[2119] the bond marked with an "*" is attached to G².

[2120] Statement 51. The compound, or pharmaceutically acceptable salt thereof, according to statement 50, wherein G¹ is:



; and

[2121] the bond marked with an "*" is attached to G².

[2122] Statement 52. The compound, or pharmaceutically acceptable salt thereof, according to any one of statements 1-49, wherein G² is a direct bond.

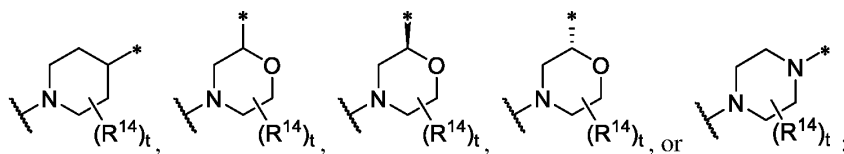
[2123] Statement 53. The compound, or pharmaceutically acceptable salt thereof, according to any one of statements 1-49, wherein G² is (C₁-C₆)alkylenyl.

[2124] Statement 54. The compound, or pharmaceutically acceptable salt thereof, according to statement 53, wherein G² is -CH₂-.

[2125] Statement 55. The compound, or pharmaceutically acceptable salt thereof, according to any one of statements 1-54, wherein G³ is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or cyano.

[2126] Statement 56. The compound, or pharmaceutically acceptable salt thereof, according to statement 55, wherein:

[2127] G³ is:



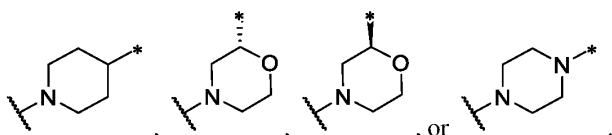
[2128] each R^{14} is independently halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano;

[2129] t is 0, 1, 2, or 3; and

[2130] the bond marked with an "*" is attached to G^4 .

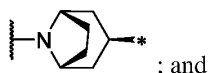
[2131] Statement 57. The compound, or pharmaceutically acceptable salt thereof, according to statement 56, wherein R^{14} is fluoro or methyl and t is 0 or 1.

[2132] Statement 58. The compound, or pharmaceutically acceptable salt thereof, according to statement 56, wherein G^3 is:



[2133] Statement 59. The compound, or pharmaceutically acceptable salt thereof, according to any one of statements 1-54, wherein G^3 is 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano.

[2134] Statement 60. The compound, or pharmaceutically acceptable salt thereof, according to statement 59, wherein G^3 is:

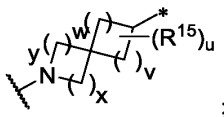


; and

[2135] the bond marked with an "*" is attached to G^4 .

[2136] Statement 61. The compound, or pharmaceutically acceptable salt thereof, according to statement 59, wherein:

[2137] G^3 is:



;

[2138] each R^{15} is independently selected from halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano;

[2139] u is 0, 1, 2, or 3;

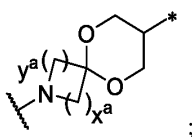
[2140] v, w, x, and y are independently 1, 2, or 3; and

[2141] the bond marked with an "*" is attached to G^4 .

[2142] Statement 62. The compound, or pharmaceutically acceptable salt thereof, according to statement 61, wherein v, w, x, and y are independently 1 or 2.

[2143] Statement 63. The compound, or pharmaceutically acceptable salt thereof, according to statement 59, wherein:

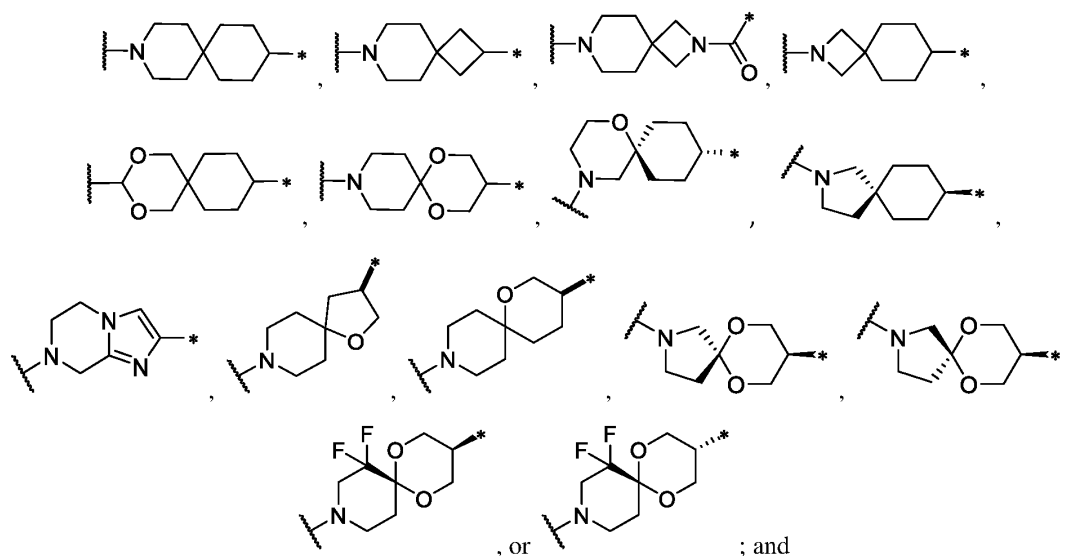
[2144] G^3 is:



[2145] x^a and y^a are independently 1, 2, or 3; and

[2146] the bond marked with an "*" is attached to G⁴.

[2147] Statement 64. The compound, or pharmaceutically acceptable salt thereof, according to statement 59, wherein G³ is:



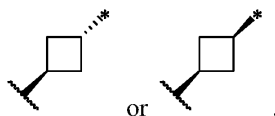
[2148] the bond marked with an “*” is attached to G⁴.

[2149] Statement 65. The compound, or pharmaceutically acceptable salt thereof, according to any one of statements 1-64, wherein G⁴ is (C₁-C₆)alkylenyl.

[2150] Statement 66. The compound, or pharmaceutically acceptable salt thereof, according to statement 65, wherein G⁴ is -CH₂- or -CH₂CH₂-.

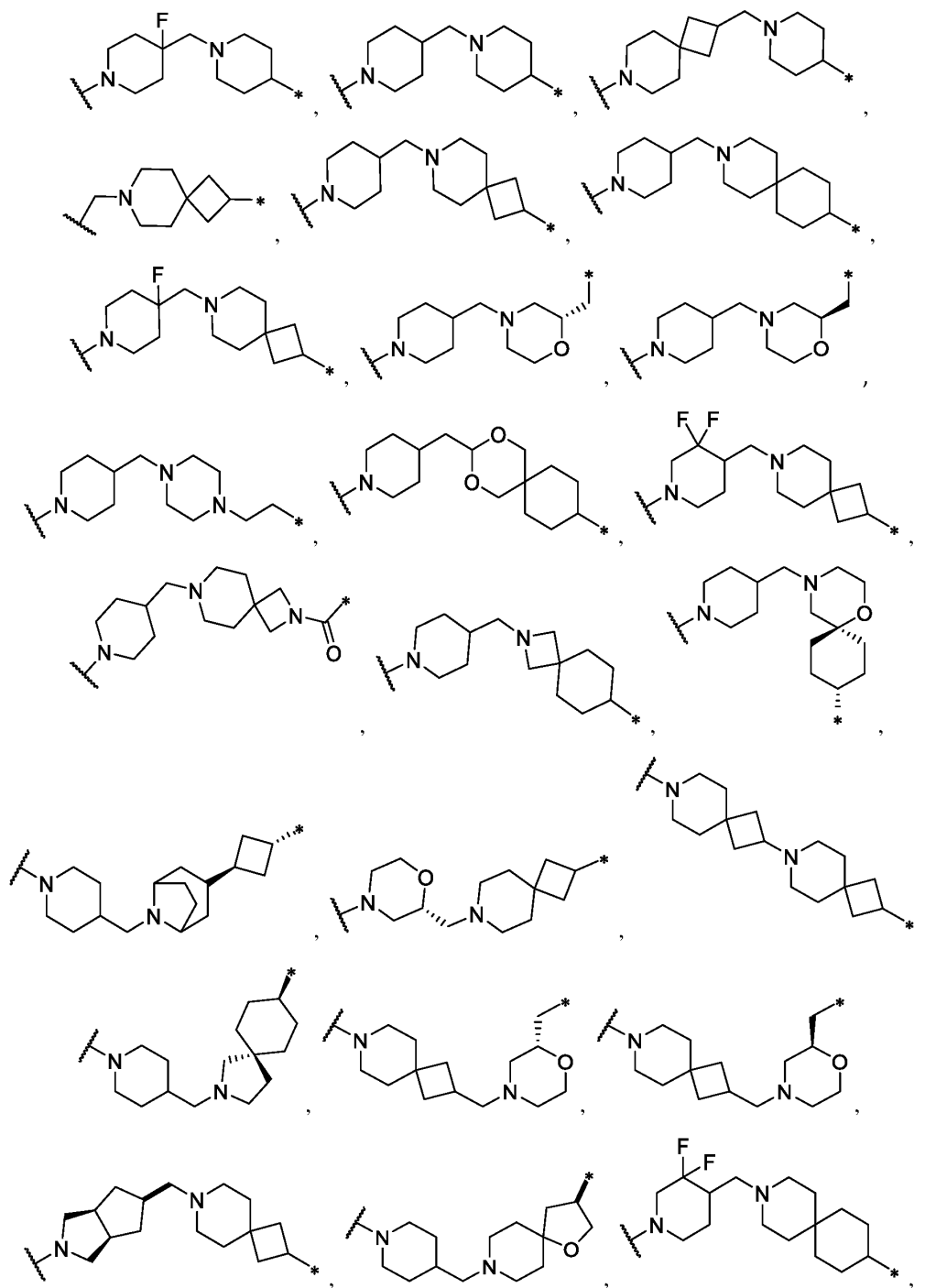
[2151] Statement 67. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 2-64, wherein G⁴ is (C₃-C₆)cycloalkylenyl.

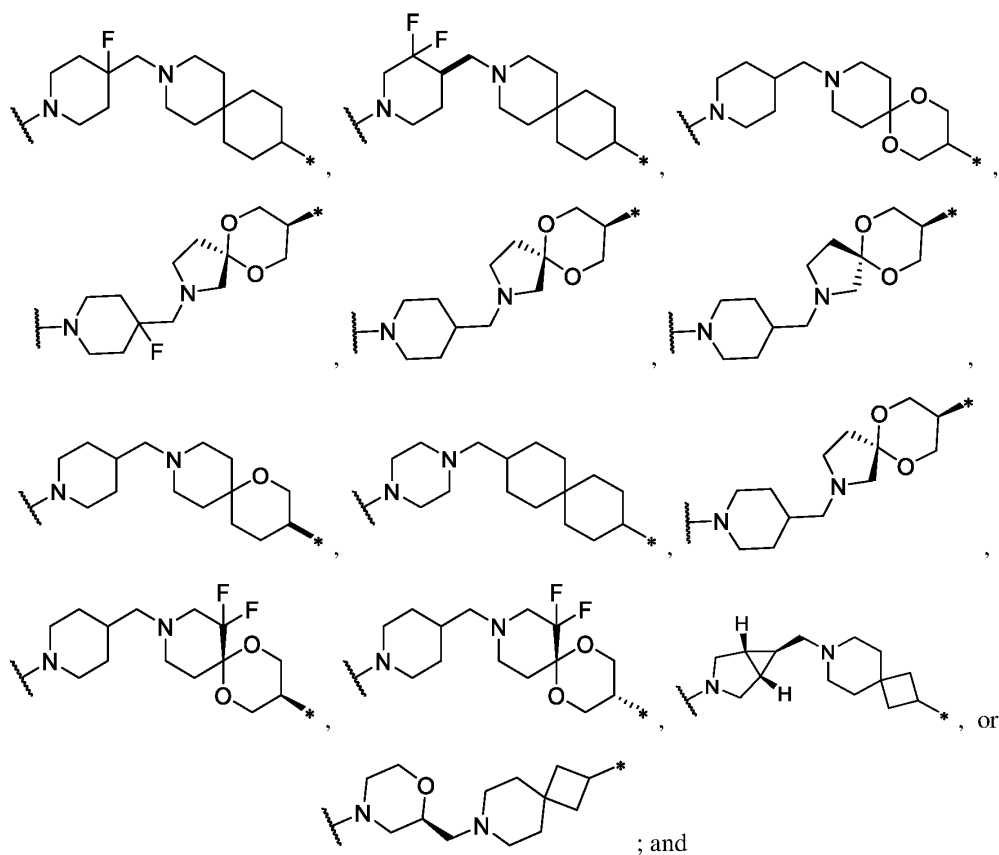
[2152] Statement 68. The compound, or pharmaceutically acceptable salt thereof, according to statement 67, wherein G⁴ is:



[2153] Statement 69. The compound, or pharmaceutically acceptable salt thereof, according to any one of statements 1-64, wherein G⁴ is a direct bond.

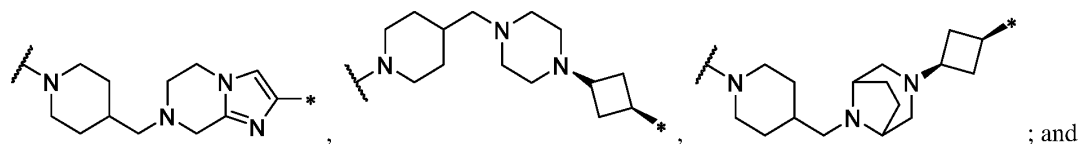
[2154] Statement 70. The compound, or pharmaceutically acceptable salt thereof, of any one of statements 1-37, wherein L is:





[2155] the bond marked with an "*" is attached to E.

[2156] Statement 71. The compound, or pharmaceutically acceptable salt thereof, of any one of statements 2-37, wherein L is:



[2157] the bond marked with an "*" is attached to E.

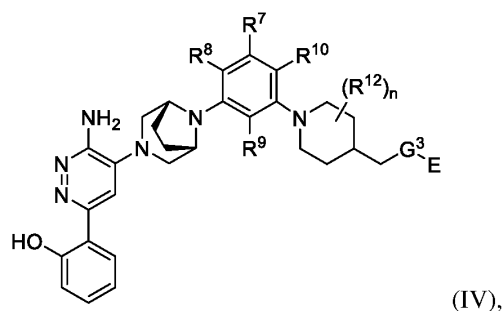
[2158] Statement 72. The compound, or pharmaceutically acceptable salt thereof, according to any one of statements 1-71, wherein W is $-C\equiv C-$.

[2159] Statement 73. The compound, or pharmaceutically acceptable salt thereof, according to any one of statements 1-71, wherein W is a direct bond.

[2160] Statement 74. The compound, or pharmaceutically acceptable salt thereof, according to any one of statements 1-73, wherein R^7 is halogen, (C_1-C_6) alkyl, cyano, or (C_3-C_6) cycloalkyl, wherein (C_1-C_6) alkyl is optionally substituted with one, two, or three halogen.

[2161] Statement 75. The compound, or pharmaceutically acceptable salt thereof, according to statement 74, wherein R^7 is halogen or (C_1-C_6) alkyl.

- [2162] Statement 76. The compound, or pharmaceutically acceptable salt thereof, according to statement 75, wherein R⁷ is fluoro or methyl.
- [2163] Statement 77. The compound, or pharmaceutically acceptable salt thereof, according to any one of statements 74-76, wherein R⁸, R⁹, and R¹⁰ are H.
- [2164] Statement 78. The compound, or pharmaceutically acceptable salt thereof, according to any one of statements 1-76, wherein R⁸ is halogen, (C₁-C₆)alkyl, cyano, or (C₃-C₆)cycloalkyl, wherein (C₁-C₆)alkyl is optionally substituted with one, two, or three halogen.
- [2165] Statement 79. The compound, or pharmaceutically acceptable salt thereof, according to statement 78, wherein R⁸ is halogen or (C₁-C₆)alkyl.
- [2166] Statement 80. The compound, or pharmaceutically acceptable salt thereof, according to statement 79, wherein R⁸ is fluoro or methyl.
- [2167] Statement 81. The compound, or pharmaceutically acceptable salt thereof, according to any one of statements 78-80, wherein R⁷, R⁹, and R¹⁰ are hydrogen.
- [2168] Statement 82. The compound, or pharmaceutically acceptable salt thereof, according to any one of statements 1-76 or 67-69, wherein R⁹ is halogen, (C₁-C₆)alkyl, cyano, or (C₃-C₆)cycloalkyl, wherein (C₁-C₆)alkyl is optionally substituted with one, two, or three halogen.
- [2169] Statement 83. The compound, or pharmaceutically acceptable salt thereof, according to statement 82, wherein R⁹ is halogen.
- [2170] Statement 84. The compound, or pharmaceutically acceptable salt thereof, according to statement 83, wherein R⁹ is fluoro.
- [2171] Statement 85. The compound, or pharmaceutically acceptable salt thereof, according to any one of statements 82-84, wherein R⁷, R⁸, and R¹⁰ are hydrogen.
- [2172] Statement 86. The compound, or pharmaceutically acceptable salt thereof, according to any one of statements 1-76, 78-80, or 82-84, wherein R¹⁰ is halogen, (C₁-C₆)alkyl, cyano, or (C₃-C₆)cycloalkyl, wherein (C₁-C₆)alkyl is optionally substituted with one, two, or three halogen.
- [2173] Statement 87. The compound, or pharmaceutically acceptable salt thereof, according to statement 86, wherein R¹⁰ is halogen.
- [2174] Statement 88. The compound, or pharmaceutically acceptable salt thereof, according to statement 87, wherein R¹⁰ is fluoro.
- [2175] Statement 89. The compound, or pharmaceutically acceptable salt thereof, according to any one of statements 86-88, wherein R⁷, R⁸, and R⁹ are hydrogen.
- [2176] Statement 90. The compound, or pharmaceutically acceptable salt thereof, according to any one of statements 1-73, wherein R⁷, R⁸, R⁹, and R¹⁰ are H.
- [2177] Statement 91. The compound, or pharmaceutically acceptable salt thereof, according to any one of statements 1-2, 5-9, or 35 having Formula (IV):



wherein:

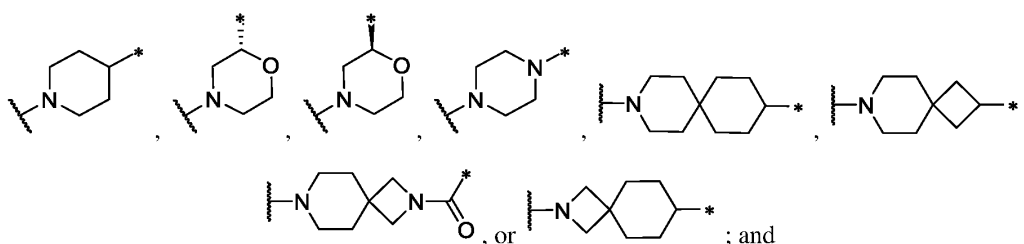
[2178] each R^{12} is independently hydrogen or fluoro;

[2179] n is 0, 1, or 2; and

[2180] R^7 , R^8 , R^9 , and R^{10} are independently hydrogen, fluoro, or methyl.

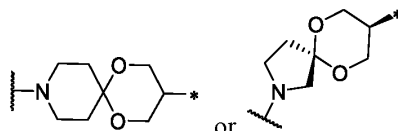
[2181] Statement 92. The compound, or pharmaceutically acceptable salt thereof, according to statement 91, wherein:

[2182] G^3 is:



[2183] G^4 is a direct bond, $-CH_2-$ or $-CH_2CH_2-$.

[2184] Statement 93. The compound, or pharmaceutically acceptable salt thereof, according to statement 91, wherein G^3 is:



[2185] Statement 94. The compound according to statement 1, or a pharmaceutically acceptable salt thereof, selected from any one or more of the compounds:

1-[1-[1-[7-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-7-azaspiro[3.5]nonan-2-yl)methyl]-4-piperidyl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[3-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]prop-2-ynyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[1-[1-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-

yl]phenyl]-4-piperidyl)methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl)methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[1-[[1-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl)methyl]-4-piperidyl]indol-4-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl)methyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl)methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-5-fluoro-phenyl]-4-piperidyl)methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-5-methyl-phenyl]-4-piperidyl)methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-methyl-phenyl]-4-piperidyl)methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl)methyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl)methyl]-7-azaspiro[3.5]nonan-2-yl]indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl)methyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl)methyl]-7-azaspiro[3.5]nonan-2-yl]-6-fluoro-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl)methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-

yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2,6-difluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[2-[1-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indol-6-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[5-[4-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]piperazin-1-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[5-[4-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]piperazin-1-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-4-fluoro-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-4-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[[3-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]methyl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-fluoro-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[1-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-fluoro-4-piperidyl]methyl]-4-piperidyl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(2S)-4-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]morpholin-2-yl]methyl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[2-[4-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]piperazin-1-yl]ethyl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[9-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-(1-(3-((1-(3-(3-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-4-fluorophenyl)piperidin-4-yl)methyl)-3-azaspiro[5.5]undecan-9-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-[1-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3-difluoro-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1-[5-[4-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]piperazin-1-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-(5-(7-((1-(5-(3-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-2-fluorophenyl)piperidin-4-yl)methyl)-2,7-diazaspiro[3.5]nonane-2-carbonyl)-2-methylphenyl)dihydropyrimidine-2,4(1H,3H)-dione;

(3-(1-(7-((1-(5-(3-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-2-fluorophenyl)piperidin-4-yl)methyl)-7-azaspiro[3.5]nonan-2-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2,6-dioxotetrahydropyrimidin-1(2H)-yl)methyl dihydrogen phosphate; and

1-(1-(2-((1-(5-(3-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-2-fluorophenyl)piperidin-4-yl)methyl)-2-azaspiro[3.5]nonan-7-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione,

or a pharmaceutically acceptable salts thereof.

Statement 95. The compound according to statement 85 selected from any one or more of the compounds:

1-[1-[1-[7-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-7-azaspiro[3.5]nonan-2-yl)methyl]-4-piperidyl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[1-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl)methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[1-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl)methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[1-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl)methyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl)methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[1-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-5-fluoro-phenyl]-4-piperidyl)methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[1-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-5-methyl-phenyl]-4-piperidyl)methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-methyl-phenyl]-4-piperidyl)methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl)methyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl)methyl]-7-azaspiro[3.5]nonan-2-yl]indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl)methyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-6-fluoro-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2,6-difluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[5-[4-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]piperazin-1-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-4-fluoro-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-4-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-fluoro-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[1-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-fluoro-4-piperidyl]methyl]-4-piperidyl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[9-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-(1-(3-((1-(3-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-4-fluorophenyl)piperidin-4-yl)methyl)-3-azaspiro[5.5]undecan-9-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl]dihydropyrimidine-2,4(1H,3H)-dione;

1-[1-[7-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3-difluoro-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1-[5-[4-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]piperazin-1-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

(3-(1-(7-((1-(5-(3-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-2-fluorophenyl)piperidin-4-yl)methyl)-7-azaspiro[3.5]nonan-2-yl)-3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2,6-dioxotetrahydropyrimidin-1(2H)-yl)methyl dihydrogen phosphate;

1-(1-(2-((1-(5-(3-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-2-fluorophenyl)piperidin-4-yl)methyl)-2-azaspiro[3.5]nonan-7-yl)-3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-[2-[1-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indol-6-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[5-[4-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]piperazin-1-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]methyl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(2S)-4-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]morpholin-2-yl]methyl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione; and

1-(5-(7-((1-(5-(3-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-

yl)-2-fluorophenyl)piperidin-4-yl)methyl)-2,7-diazaspiro[3.5]nonane-2-carbonyl)-2-methylphenyl)dihydropyrimidine-2,4(1H,3H)-dione;

or pharmaceutically acceptable salts thereof.

Statement 96. The compound according to statement 2, or a pharmaceutically acceptable salt thereof, selected from any one or more of the compounds:

1-[1-[(6r,9r)-4-[[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl]methyl]-1-oxa-4-azaspiro[5.5]undecan-9-yl]-3-methylpyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(1r,3r)-3-[8-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]cyclobutyl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[(2S)-4-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]morpholin-2-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[7-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-7-azaspiro[3.5]nonan-2-yl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(5r,8r)-2-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-2-azaspiro[4.5]decan-8-yl]-3-ethyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-ethyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(2R)-4-[[7-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-7-azaspiro[3.5]nonan-2-yl]methyl]morpholin-2-yl]methyl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazin-2-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(2S)-4-[[7-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-7-azaspiro[3.5]nonan-2-yl]methyl]morpholin-2-yl]methyl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[3-Methyl-1-[7-[[rel-(3aR,5r*,6aS)-2-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrol-5-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[3-Methyl-1-[7-[[rel-(3aR,5r*,6aS)-2-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrol-5-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[6-Fluoro-1-[rel-(3R*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[6-Fluoro-1-[rel-(3R*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[3-Cyclopropyl-1-[rel-(3R*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3-difluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[3-Cyclopropyl-1-[rel-(3R*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

4-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-[4-[[9-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-ethyl-pyrrolo[2,3-b]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl]methyl]-4-fluoro-1-piperidyl]benzonitrile;

4-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-[4-[[9-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-ethyl-pyrrolo[2,3-b]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl]methyl]-4-fluoro-1-piperidyl]benzonitrile;

1-[3-Methyl-1-[3-[[rel-(4R*)-1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3-difluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

4-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-[4-[[9-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-b]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl]methyl]-4-fluoro-1-piperidyl]benzonitrile;

1-[3-Methyl-1-[3-[[rel-(4R*)-1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3-difluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-4-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-4-fluoro-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-6-fluoro-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-ethyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(5s,8s)-2-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-fluoro-4-piperidyl]methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]-3-ethyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(5s,8s)-2-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]-3-ethyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[3-Methyl-1-[rel-(3S*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[3-Methyl-1-[rel-(3R*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione (ISOMER 1)

1-[1-[(5s,8s)-2-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(5r,8r)-2-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[3-Methyl-1-[rel-(3S*)-9-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-9-azaspiro[5.5]undecan-3-yl]pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[3-Methyl-1-[rel-(3R*)-9-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-9-azaspiro[5.5]undecan-3-yl]pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(5r,8r)-2-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[9-[[4-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]piperazin-1-yl]methyl]spiro[5.5]undecan-3-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(5s,8s)-2-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-fluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(3s,6s)-9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-11,11-difluoro-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(3r,6r)-9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-11,11-difluoro-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-fluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(1s,3s)-3-[4-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]piperazin-1-yl]cyclobutyl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

4-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-[4-[[9-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-ethyl-pyrrolo[2,3-b]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl]methyl]-1-piperidyl]benzonitrile;

4-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-[4-[[2-[3-cyclopropyl-5-(2,4-dioxohexahydropyrimidin-1-yl)pyrrolo[2,3-b]pyridin-1-yl]-7-azaspiro[3.5]nonan-7-yl]methyl]-1-piperidyl]benzonitrile;

1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-ethyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[(1R,5S,6s)-3-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3-azabicyclo[3.1.0]hexan-6-yl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione

1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[(1R,5S,6s)-3-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3-azabicyclo[3.1.0]hexan-6-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(1s,3s)-3-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]cyclobutyl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[(2R)-4-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]morpholin-2-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

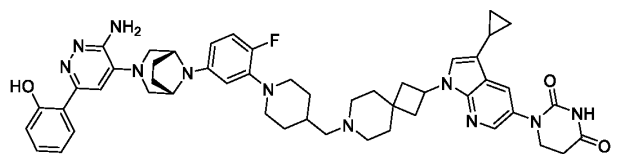
1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-6-fluoro-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3-azabicyclo[3.2.1]octan-8-yl]-2-chloro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione; and

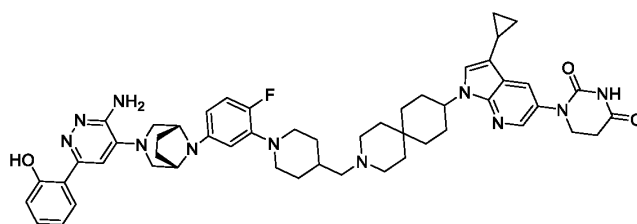
1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-6-fluoro-pyrrolo[2,3-b]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

or pharmaceutically acceptable salts thereof.

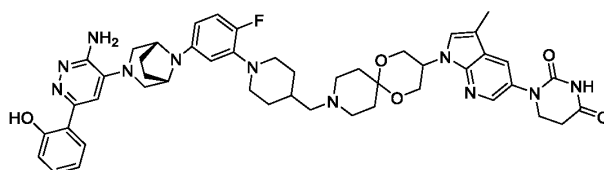
[2186] Statement 97. The compound, or pharmaceutically acceptable salt thereof, according to statement 94, wherein the compound is:



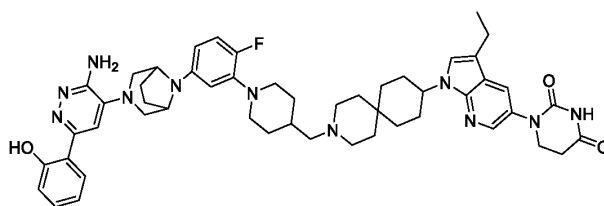
[2187] Statement 98. The compound, or pharmaceutically acceptable salt thereof, according to statement 94, wherein the compound is:



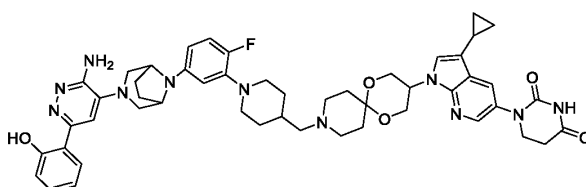
[2188] Statement 99. The compound, or pharmaceutically acceptable salt thereof, according to statement 94, wherein the compound is:



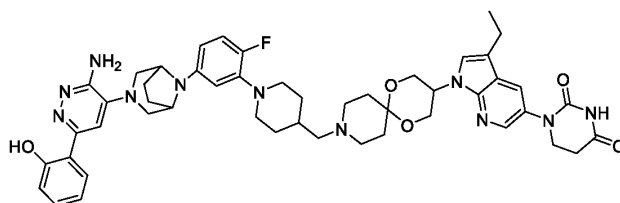
[2189] Statement 100. The compound, or pharmaceutically acceptable salt thereof, according to statement 96, wherein the compound is:



[2190] Statement 101. The compound, or pharmaceutically acceptable salt thereof, according to statement 96, wherein the compound is:



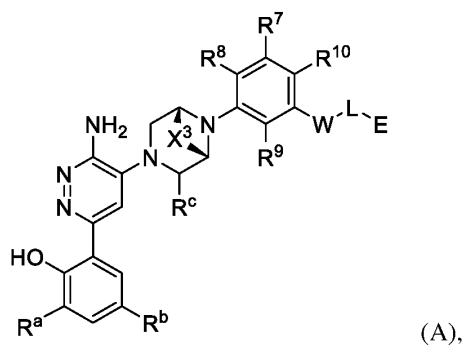
[2191] Statement 102. The compound, or pharmaceutically acceptable salt thereof, according to statement 96, wherein the compound is:



- [2202] Statement 113. A compound, or pharmaceutically acceptable salt thereof, according to any one of statements 1-104, or the composition of statement 105 for use in degrading SMARCA2 protein in a human.
- [2203] Statement 114. A compound, or pharmaceutically acceptable salt thereof, according to any one of statements 1-104, or the composition of statement 105 for use in reducing the level of SMARCA2 activity in a human.
- [2204] Statement 115. A compound, or pharmaceutically acceptable salt thereof, according to any one of statements 1-104, or the composition of statement 105 for use in treating cancer in a human.
- [2205] Statement 116. The compound for use of statement 115, wherein the cancer is a SMARCA2-sensitive cancer.
- [2206] Statement 117. The compound for use of statement 115, wherein the cancer is a SMARCA2-mutated cancer.
- [2207] Statement 118. The compound for use of any one of statements 115-117, wherein the cancer is a solid tumor.
- [2208] Statement 119. The compound for use of any one of statements 115-117, wherein the cancer is lung, liver, colon, skin, bladder, cervical or ovarian cancer.
- [2209] Statement 120. Use of a compound, or pharmaceutically acceptable salt thereof, according to any one of statements 1-104, or the composition of statement 105 in the manufacture of a medicament for degrading SMARCA2 protein in a human.
- [2210] Statement 121. Use of a compound, or pharmaceutically acceptable salt thereof, according to any one of statements 1-104, or the composition of statement 105 in the manufacture of a medicament for reducing the level of SMARCA2 activity in a human.
- [2211] Statement 122. Use of a compound, or pharmaceutically acceptable salt thereof, according to any one of statements 1-104, or the composition of statement 105 in the manufacture of a medicament for treating cancer in a human.
- [2212] Statement 123. The compound, or pharmaceutically acceptable salt thereof, for use of statement 122, wherein the cancer is a SMARCA2-sensitive cancer.
- [2213] Statement 124. The compound, or pharmaceutically acceptable salt thereof, for use of statement 122, wherein the cancer is a SMARCA2-mutated cancer.
- [2214] Statement 125. The compound, or pharmaceutically acceptable salt thereof, for use of any one of statements 122-124, wherein the cancer is a solid tumor.
- [2215] Statement 126. The compound, or pharmaceutically acceptable salt thereof, for use of any one of statements 122-124, wherein the cancer is lung, liver, colon, skin, bladder, cervical or ovarian cancer.

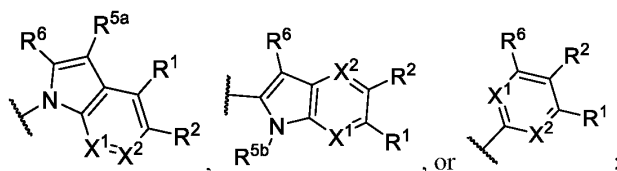
WHAT IS CLAIMED IS:

1. A compound of Formula (A), or pharmaceutically acceptable salt thereof:

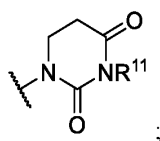


wherein:

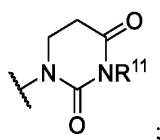
E is:



R¹ is hydrogen, halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or

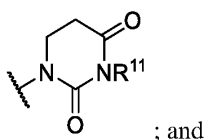


R² is hydrogen, halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or

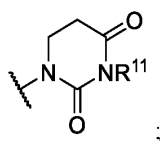


with the provisos:

- (i) when R¹ is hydrogen, halogen, (C₁-C₆)alkyl, or (C₁-C₆)alkoxy, then R² is:



- (ii) when R² is hydrogen, halogen, (C₁-C₆)alkyl, or (C₁-C₆)alkoxy, then R¹ is



R^{11} is hydrogen or $-(C_1-C_6)alkyl-O-P(=O)-(OH)_2$;

X^1 is CR^3 or N;

R^3 is hydrogen, halogen, or $(C_1-C_6)alkyl$;

X^2 is CR^4 or N;

R^4 is hydrogen, halogen, or $(C_1-C_6)alkyl$;

R^{5a} is hydrogen, halogen, $(C_1-C_6)alkyl$, $(C_3-C_6)cycloalkyl$, 4- to 6-membered heterocycloalkyl, cyano, aryl, or 5- or 6-membered heteroaryl,

wherein $(C_1-C_6)alkyl$ is optionally substituted with one, two, or three substituents independently selected from halogen or cyano; and 4- to 6-membered heterocycloalkyl, aryl, or 5- or 6-membered heteroaryl is optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or $(C_1-C_6)alkyl$;

R^{5b} is hydrogen, $(C_1-C_6)alkyl$, or $(C_3-C_6)cycloalkyl$;

R^6 is hydrogen, $(C_1-C_6)alkyl$, or cyano;

X^3 is $-CH_2CH_2-$ or $-CH_2-O-CH_2-$;

Or X^3 is absent;

L is $G^1-G^2-G^3-G^4$ -, wherein G^1 is attached to W;

G^1 is $(C_1-C_6)alkylenyl$; $(C_3-C_6)cycloalkylenyl$; $-O-CH_2-CH_2-$; 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy$, cyano, or hydroxyl; or 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy$, or cyano;

G^2 is $(C_1-C_6)alkylenyl$, $-C(=O)-$, 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three fluoro, or a direct bond;

G^3 is $-C(=O)-$; $-C(=O)-CH_2CH_2-$; $(C_1-C_6)alkylenyl$; tetrahydronaphthalenylenyl; 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy$ or cyano; 7- to 11-membered heterocycloalkyl- $C(=O)-$, or 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy$, or cyano;

G^4 is $(C_1-C_6)alkylenyl$, $(C_3-C_6)cycloalkylenyl$; 4- to 6-membered heterocycloalkylenyl; or a direct bond;

W is $-C\equiv C-$ or a direct bond;

R^7 is hydrogen; halogen; $(C_1-C_6)alkyl$ optionally substituted with one, two, or three halogen; cyano; or $(C_3-C_6)cycloalkyl$;

R^8 is hydrogen; halogen; $(C_1-C_6)alkyl$ optionally substituted with one, two, or three halogen; cyano; or $(C_3-C_6)cycloalkyl$;

R^9 is hydrogen; halogen; (C_1-C_6) alkyl optionally substituted with one, two, or three halogen; cyano; or (C_3-C_6) cycloalkyl;

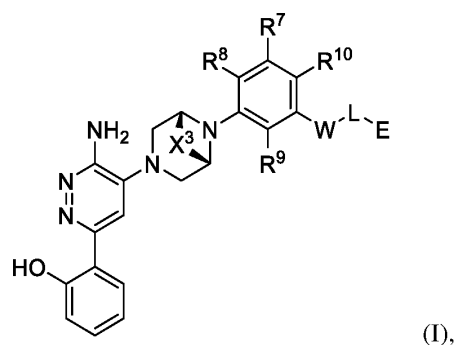
R^{10} is hydrogen; halogen; (C_1-C_6) alkyl optionally substituted with one, two, or three halogen; cyano; or (C_3-C_6) cycloalkyl;

R^a is hydrogen or halogen;

R^b is hydrogen or halogen; and

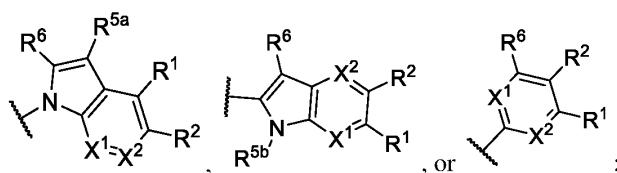
R^c is hydrogen or methyl.

2. A compound of Formula (I), or pharmaceutically acceptable salt thereof:

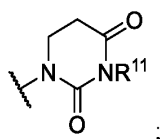


wherein:

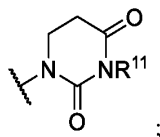
E is:



R^1 is hydrogen, halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or

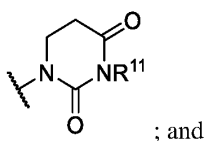


R^2 is hydrogen, halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or



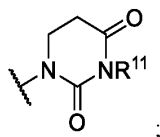
with the provisos:

- (i) when R^1 is hydrogen, halogen, (C_1-C_6) alkyl, or (C_1-C_6) alkoxy, then R^2 is:



; and

(ii) when R^2 is hydrogen, halogen, (C_1-C_6) alkyl, or (C_1-C_6) alkoxy, then R^1 is



;

R^{11} is hydrogen or $-(C_1-C_6)alkyl-O-P(=O)-(OH)_2$;

X^1 is CR^3 or N;

R^3 is hydrogen, halogen, or (C_1-C_6) alkyl;

X^2 is CR^4 or N;

R^4 is hydrogen, halogen, or (C_1-C_6) alkyl;

R^{5a} is hydrogen, halogen, (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, 4- to 6-membered heterocycloalkyl, cyano, aryl, or 5- or 6-membered heteroaryl, wherein (C_1-C_6) alkyl is optionally substituted with one, two, or three substituents independently selected from halogen or cyano; and 4- to 6-membered heterocycloalkyl, aryl, or 5- or 6-membered heteroaryl is optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or (C_1-C_6) alkyl;

R^{5b} is hydrogen, (C_1-C_6) alkyl, or (C_3-C_6) cycloalkyl;

R^6 is hydrogen, (C_1-C_6) alkyl, or cyano;

X^3 is $-CH_2CH_2-$ or $-CH_2-O-CH_2-$;

Or X^3 is absent;

L is $-G^1-G^2-G^3-G^4-$, wherein G^1 is attached to W;

G^1 is (C_1-C_6) alkylenyl; 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano; or 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano;

G^2 is (C_1-C_6) alkylenyl or a direct bond;

G^3 is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy or cyano; or 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano;

G^4 is (C_1-C_6) alkylenyl or a direct bond;

W is $-C\equiv C-$ or a direct bond;

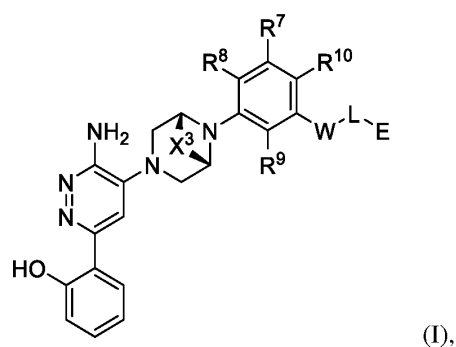
R^7 is hydrogen, halogen, (C_1-C_6) alkyl optionally substituted with one, two, or three halogen, cyano, or (C_3-C_6) cycloalkyl;

R^8 is hydrogen, halogen, (C_1-C_6) alkyl optionally substituted with one, two, or three halogen, cyano, or (C_3-C_6) cycloalkyl;

R^9 is hydrogen, halogen, (C_1-C_6) alkyl optionally substituted with one, two, or three halogen, cyano, or (C_3-C_6) cycloalkyl; and

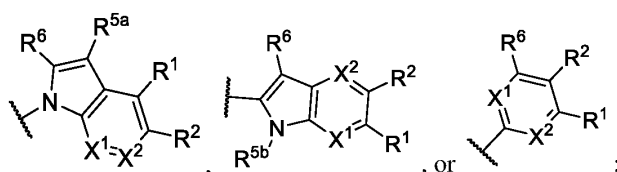
R^{10} is hydrogen, halogen, (C_1-C_6) alkyl optionally substituted with one, two, or three halogen, cyano, or (C_3-C_6) cycloalkyl.

3. A compound of Formula (I), or pharmaceutically acceptable salt thereof:

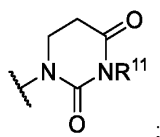


wherein:

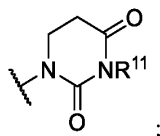
E is:



R^1 is hydrogen, halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or

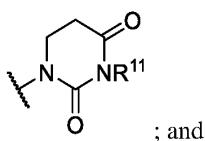


R^2 is hydrogen, halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or



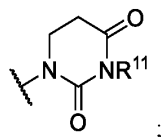
with the provisos:

(i) when R^1 is hydrogen, halogen, (C_1-C_6) alkyl, or (C_1-C_6) alkoxy, then R^2 is:



; and

(ii) when R^2 is hydrogen, halogen, (C_1-C_6) alkyl, or (C_1-C_6) alkoxy, then R^1 is:



;

R^{11} is hydrogen or $-(C_1-C_6)alkyl-O-P(=O)-(OH)_2$;

X^1 is CR^3 or N;

R^3 is hydrogen, halogen, or $(C_1-C_6)alkyl$;

X^2 is CR^4 or N;

R^4 is hydrogen, halogen, or $(C_1-C_6)alkyl$;

R^{5a} is hydrogen, halogen, $(C_1-C_6)alkyl$, $(C_3-C_6)cycloalkyl$, 4- to 6-membered heterocycloalkyl, cyano, aryl, or 5- or 6-membered heteroaryl, wherein $(C_1-C_6)alkyl$ is optionally substituted with one, two, or three substituents independently selected from halogen or cyano; and 4- to 6-membered heterocycloalkyl, aryl, or 5- or 6-membered heteroaryl is optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or $(C_1-C_6)alkyl$;

R^{5b} is hydrogen, $(C_1-C_6)alkyl$, or $(C_3-C_6)cycloalkyl$;

R^6 is hydrogen, $(C_1-C_6)alkyl$, or cyano;

X^3 is $-CH_2CH_2-$ or $-CH_2-O-CH_2-$; or

X^3 is absent;

L is $-G^1-G^2-G^3-G^4-$, wherein G^1 is attached to W;

G^1 is $(C_1-C_6)alkylenyl$; 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy$, or cyano; or 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy$, or cyano;

G^2 is $(C_1-C_6)alkylenyl$ or a direct bond;

G^3 is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy$, or cyano; 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy$, or cyano; or 5- to 10-membered heteroarylenyl;

G^4 is $(C_1-C_6)alkylenyl$, $(C_3-C_6)cycloalkylenyl$, or a direct bond;

W is $-C\equiv C-$ or a direct bond;

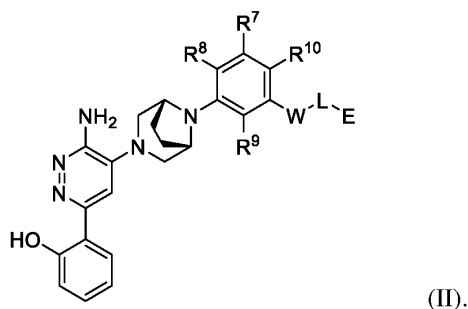
R^7 is hydrogen, halogen, $(C_1-C_6)alkyl$ optionally substituted with one, two, or three halogen, cyano, or $(C_3-C_6)cycloalkyl$;

R^8 is hydrogen, halogen, (C_1-C_6) alkyl optionally substituted with one, two, or three halogen, cyano, or (C_3-C_6) cycloalkyl;

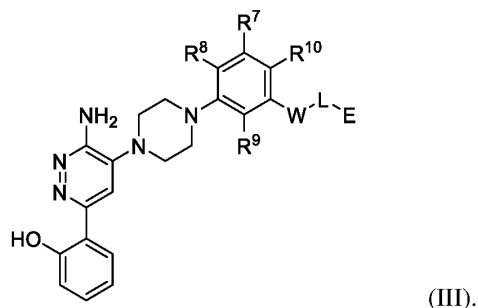
R^9 is hydrogen, halogen, (C_1-C_6) alkyl optionally substituted with one, two, or three halogen, cyano, or (C_3-C_6) cycloalkyl; and

R^{10} is hydrogen, halogen, (C_1-C_6) alkyl optionally substituted with one, two, or three halogen, cyano, or (C_3-C_6) cycloalkyl.

4. The compound, or pharmaceutically acceptable salt thereof, according to claim 2 or 3 having Formula (II):



5. The compound, or pharmaceutically acceptable salt thereof, according to claim 2 or 3 having Formula (III):



6. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-5, wherein R^{5a} is hydrogen.

7. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-5, wherein R^{5a} is (C_1-C_6) alkyl optionally substituted with one, two, or three substituents independently selected from halogen or cyano.

8. The compound, or pharmaceutically acceptable salt thereof, according to claim 7, wherein R^{5a} is methyl.

9. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-5, wherein R^{5a} is (C₃-C₆)cycloalkyl.

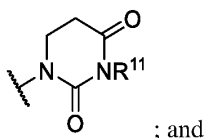
10. The compound, or pharmaceutically acceptable salt thereof, according to claim 9, wherein R^{5a} is cyclopropyl.

11. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-5, wherein R^{5a} is 4- to 6-membered heterocycloalkyl optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or (C₁-C₆)alkyl.

12. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-5, wherein R^{5a} is cyano.

13. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-5, wherein:

R¹ is:



R² is hydrogen, halogen, (C₁-C₆)alkyl, or (C₁-C₆)alkoxy.

14. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-5, wherein R² is hydrogen, halogen, or (C₁-C₆)alkyl.

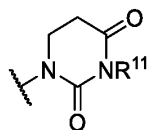
15. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-5, wherein R² is hydrogen, fluoro, or methyl.

16. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-5, wherein R¹¹ is hydrogen.

17. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-5, wherein:

R¹ is hydrogen, halogen, (C₁-C₆)alkyl, or (C₁-C₆)alkoxy; and

R² is:



18. The compound, or pharmaceutically acceptable salt thereof, according to claim 17, wherein R¹ is hydrogen, halogen, or (C₁-C₆)alkyl.

19. The compound, or pharmaceutically acceptable salt thereof, according to claim 18, wherein R¹ is hydrogen, fluoro, or methyl.

20. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 17-19, wherein R¹¹ is hydrogen.

21. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-5, wherein X¹ is CR³.

22. The compound, or pharmaceutically acceptable salt thereof, according to claim 21, wherein R³ is hydrogen.

23. The compound, or pharmaceutically acceptable salt thereof, according to claim 21, wherein R³ is halogen.

24. The compound, or pharmaceutically acceptable salt thereof, according to claim 21, wherein R³ is (C₁-C₆)alkyl.

25. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-5, wherein X¹ is N.

26. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-5, wherein X² is CR⁴.

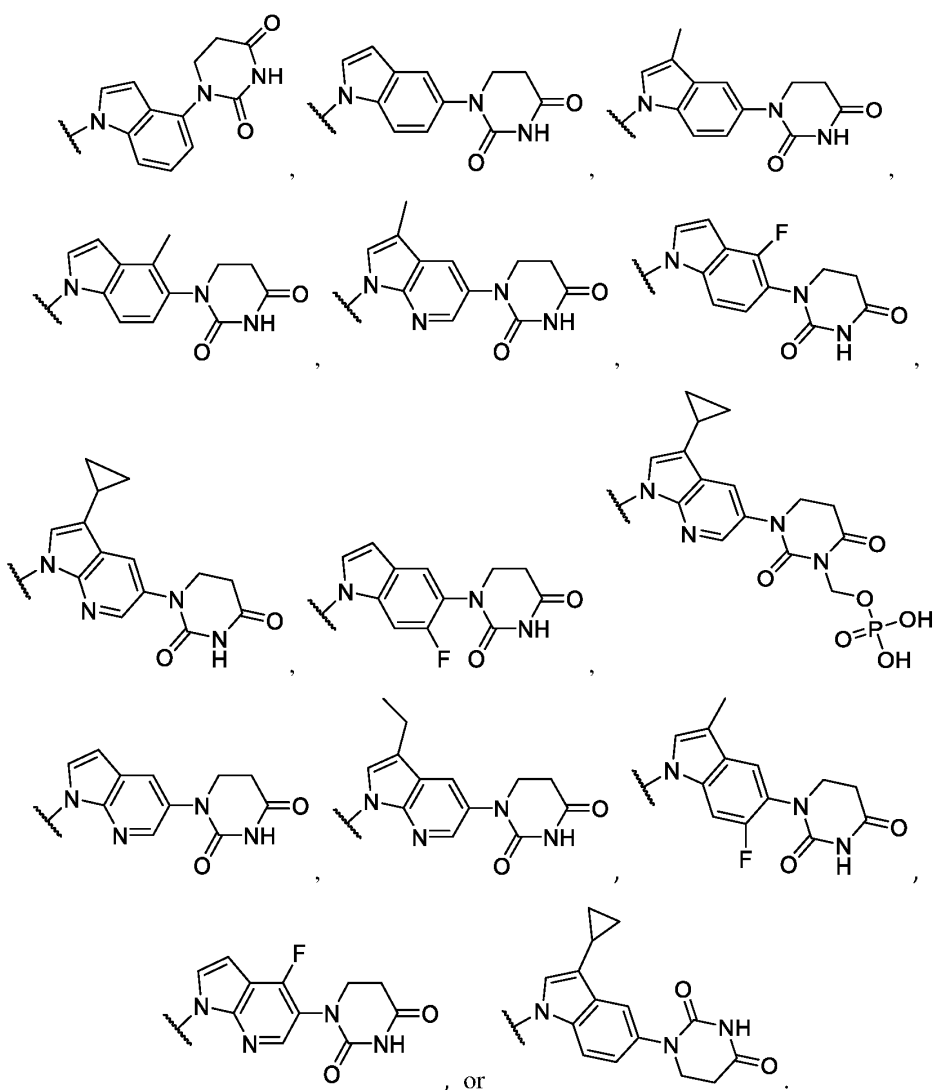
27. The compound, or pharmaceutically acceptable salt thereof, according to claim 26, wherein R⁴ is hydrogen.

28. The compound, or pharmaceutically acceptable salt thereof, according to claim 26, wherein R^4 is halogen.

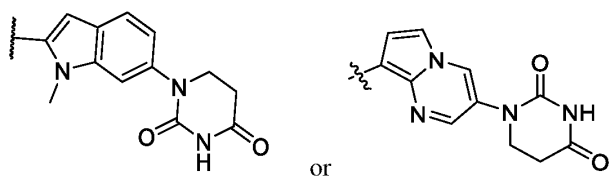
29. The compound, or pharmaceutically acceptable salt thereof, according to claim 26, wherein R^4 is (C_1-C_6) alkyl.

30. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-5, wherein X^2 is N.

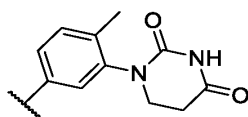
31. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-5, wherein E is:



32. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-5, wherein E is:

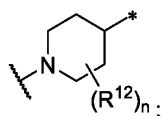


33. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-5, wherein E is:



34. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-33, wherein G^1 is (C_3-C_6) cycloalkylenyl; or 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, cyano, or hydroxyl.

35. The compound, or pharmaceutically acceptable salt thereof, according to claim 34, wherein:
 G^1 is:



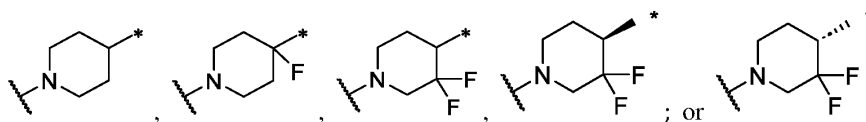
each R^{12} is independently halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, cyano, or hydroxyl;

n is 0, 1, 2, or 3; and

the bond marked with an "*" is attached to G^2 .

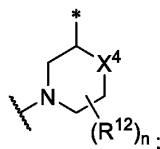
36. The compound, or pharmaceutically acceptable salt thereof, according to claim 35, wherein each R^{12} is independently fluoro, methyl, methoxy, cyano, or $-CHF_2$; and n is 0, 1, or 2.

37. The compound, or pharmaceutically acceptable salt thereof, according claim 35, wherein:
 G^1 is:



and bond marked with an "*" is attached to G^2 .

38. The compound, or pharmaceutically acceptable salt thereof, according to claim 34, wherein:
G¹ is:

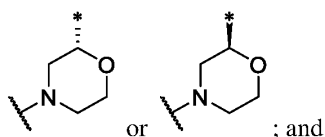


wherein X⁴ is -O-;

each R¹² is independently halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or cyano; and

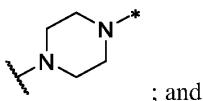
the bond marked with an "*" is attached to G².

39. The compound, or pharmaceutically acceptable salt thereof, according claim 38, wherein:
G¹ is:



the bond marked with an "*" is attached to G².

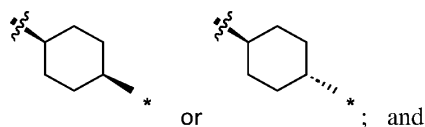
44. The compound, or pharmaceutically acceptable salt thereof, according claim 34, wherein:
G¹ is:



the bond marked with an "*" is attached to G².

41. The compound, or pharmaceutically acceptable salt thereof, according to claim 1, wherein G¹ is cyclohexylenyl.

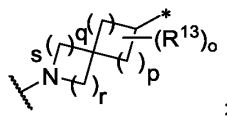
42. The compound, or pharmaceutically acceptable salt thereof, according claim 41, wherein:
G¹ is:



the bond marked with an "*" is attached to G².

43. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-33, wherein G¹ is 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or cyano.

44. The compound, or pharmaceutically acceptable salt thereof, according to claim 43, wherein:
G¹ is:

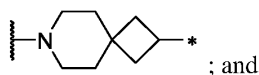


- each R¹³ is independently selected from halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or cyano;
o is 0, 1, 2, or 3;
p, q, r, and s are independently 1 or 2;
the bond marked with an "*" is attached to G².

45. The compound, or pharmaceutically acceptable salt thereof, according to claim 44, wherein:
- p and q are 1;
- r is 1 or 2;
- s is 1 or 2; and
- R¹³ is halogen.

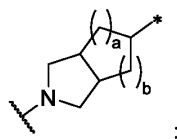
46. The compound, or pharmaceutically acceptable salt thereof, according to claim 45, wherein R¹³ is fluoro and o is 0, 1, or 2.

47. The compound, or pharmaceutically acceptable salt thereof, according claim 44, wherein G¹ is:



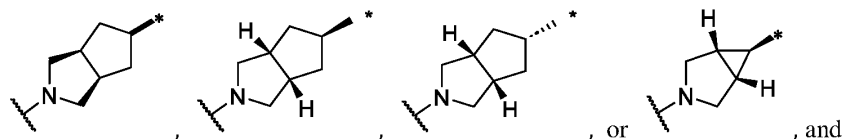
- the bond marked with an "*" is attached to G².

48. The compound, or pharmaceutically acceptable salt thereof, according to claim 43, wherein:
G¹ is:



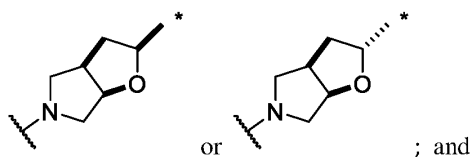
- a is 0 or 1;
b is 0 or 1; and
the bond marked with an "*" is attached to G^2 .

49. The compound, or pharmaceutically acceptable salt thereof, according claim 48, wherein G¹ is:



the bond marked with an "*" is attached to G^2 .

50. The compound, or pharmaceutically acceptable salt thereof, according claim 43, wherein G^1 is:



the bond marked with an "*" is attached to G^2 .

51. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-50, wherein G^2 is a direct bond.

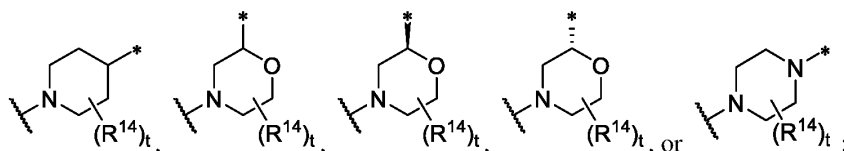
52. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1 or 6-50, wherein G^2 is a $C(=O)$.

53. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-50, wherein G^2 is (C_1-C_6) alkylenyl.

54. The compound, or pharmaceutically acceptable salt thereof, according to claim 53, wherein G^2 is $-CH_2-$.

55. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-54, wherein G^3 is 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano.

56. The compound, or pharmaceutically acceptable salt thereof, according to claim 55, wherein:
 G^3 is:



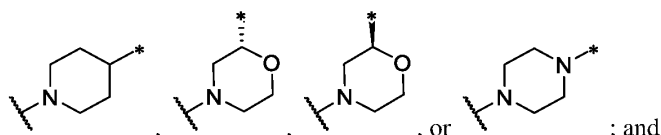
each R^{14} is independently halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano;

t is 0, 1, 2, or 3; and

the bond marked with an "*" is attached to G⁴.

57. The compound, or pharmaceutically acceptable salt thereof, according to claim 56, wherein R¹⁴ is fluoro or methyl and t is 0 or 1.

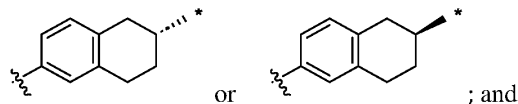
58. The compound, or pharmaceutically acceptable salt thereof, according claim 56, wherein G³ is:



the bond marked with an "*" is attached to G⁴.

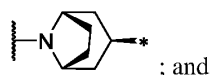
59. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-54, wherein G³ is 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or cyano.

60. The compound, or pharmaceutically acceptable salt thereof, according to claim 1, wherein G³ is



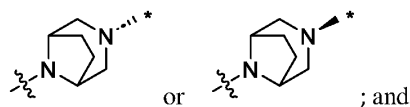
the bond marked with an "*" is attached to G⁴.

61. The compound, or pharmaceutically acceptable salt thereof, according to claim 59, wherein G³ is:



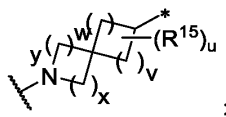
the bond marked with an "*" is attached to G⁴.

62. The compound, or pharmaceutically acceptable salt thereof, according to claim 59, wherein G³ is:



the bond marked with an "*" is attached to G⁴.

63. The compound, or pharmaceutically acceptable salt thereof, according to claim 59, wherein:
G³ is:



each R¹⁵ is independently selected from halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or cyano;

u is 0, 1, 2, or 3;

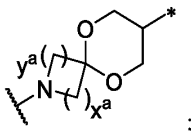
v, w, x, and y are independently 1, 2, or 3; and

the bond marked with an "*" is attached to G⁴.

64. The compound, or pharmaceutically acceptable salt thereof, according to claim 63, wherein v, w, x, and y are independently 1 or 2.

65. The compound, or pharmaceutically acceptable salt thereof, according to claim 63, wherein R¹⁵ is fluoro.

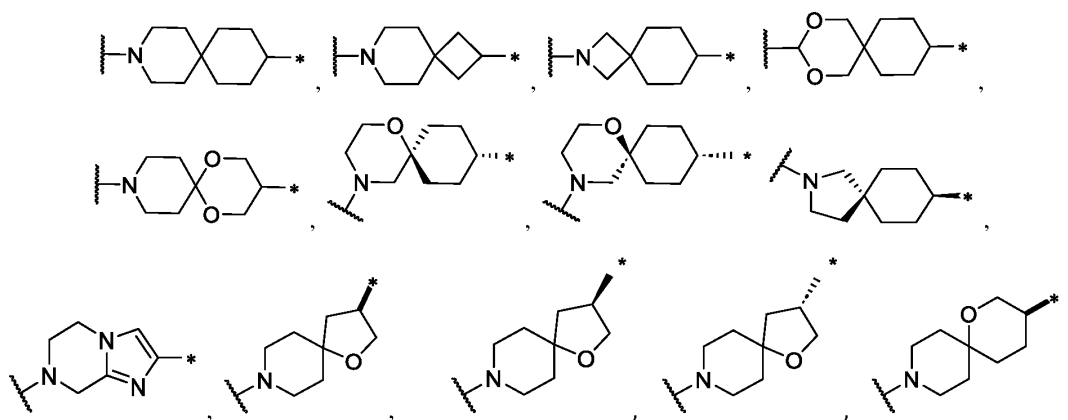
66. The compound, or pharmaceutically acceptable salt thereof, according to claim 59, wherein:
G³ is:

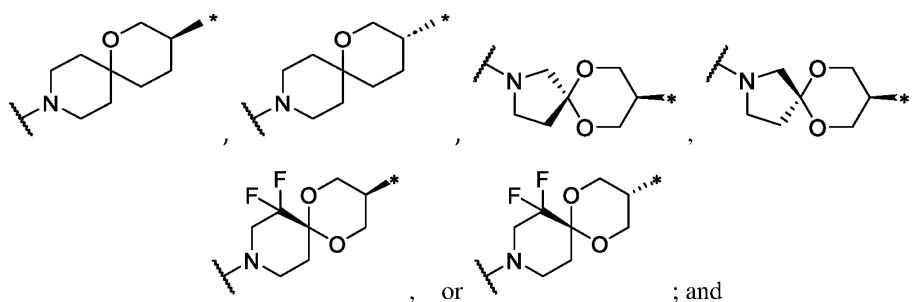


x^a and y^a are independently 1 or 2 ; and

the bond marked with an "*" is attached to G⁴.

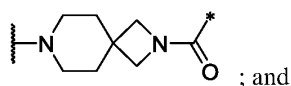
67. The compound, or pharmaceutically acceptable salt thereof, according to claim 59, wherein G³ is:





the bond marked with an “*” is attached to G^4 .

68. The compound, or pharmaceutically acceptable salt thereof, according to claim 1, wherein G^3 is



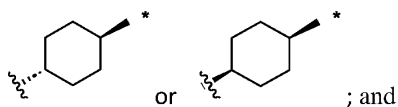
the bond marked with an “*” is attached to G^4 .

69. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-68, wherein G^4 is (C_1-C_6) alkylenyl.

70. The compound, or pharmaceutically acceptable salt thereof, according to claim 69, wherein G^4 is $-CH_2-$ or $-CH_2CH_2-$.

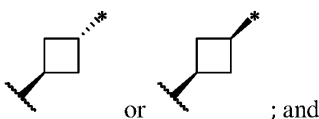
71. The compound, or pharmaceutically acceptable salt thereof, according to claim 1, wherein G^4 is (C_3-C_6) cycloalkylenyl.

72. The compound, or pharmaceutically acceptable salt thereof, according to claim 71, wherein G^4 is :



the bond marked with an “*” is attached to E.

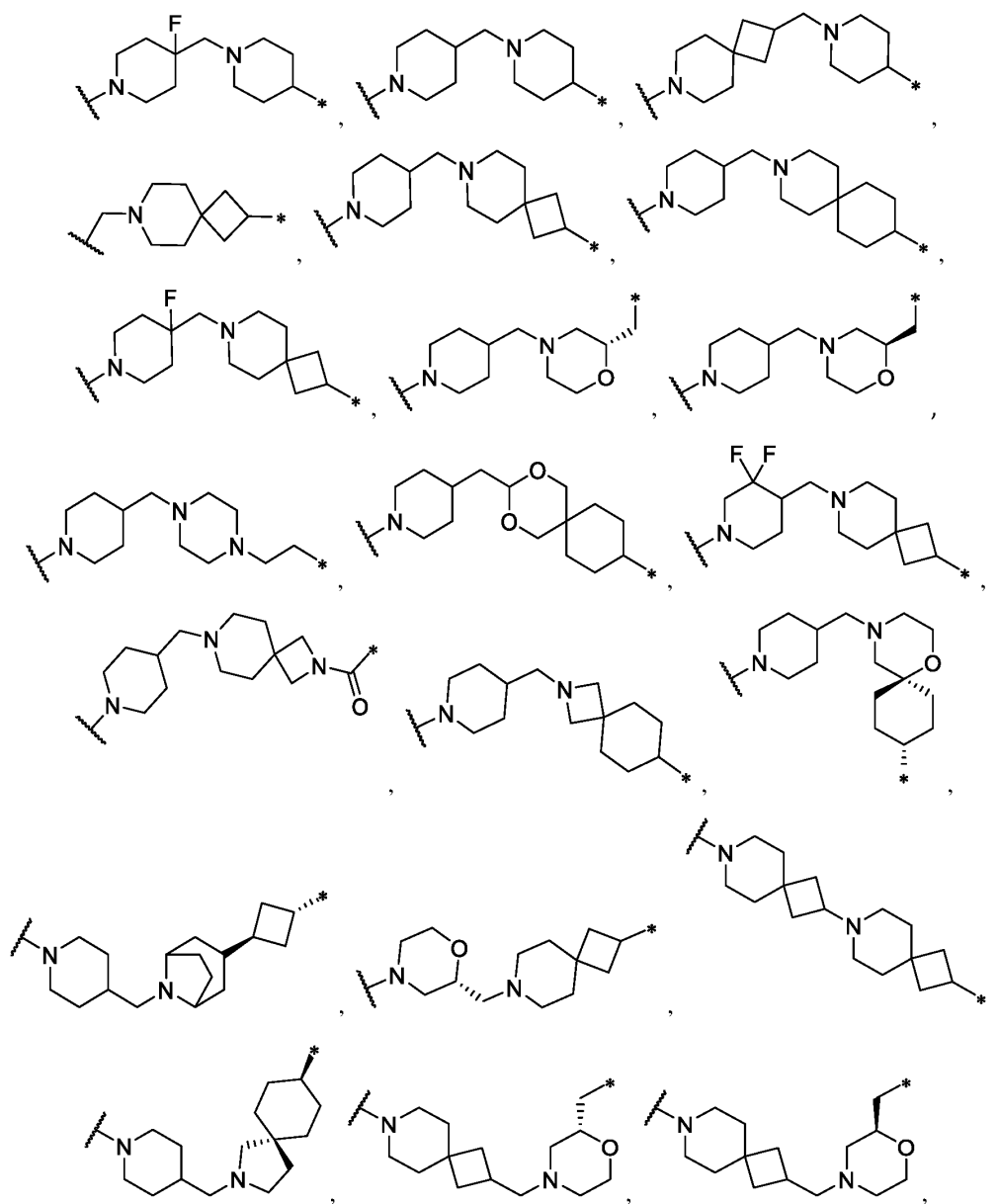
73. The compound, or pharmaceutically acceptable salt thereof, according to claim 71, wherein G^4 is:

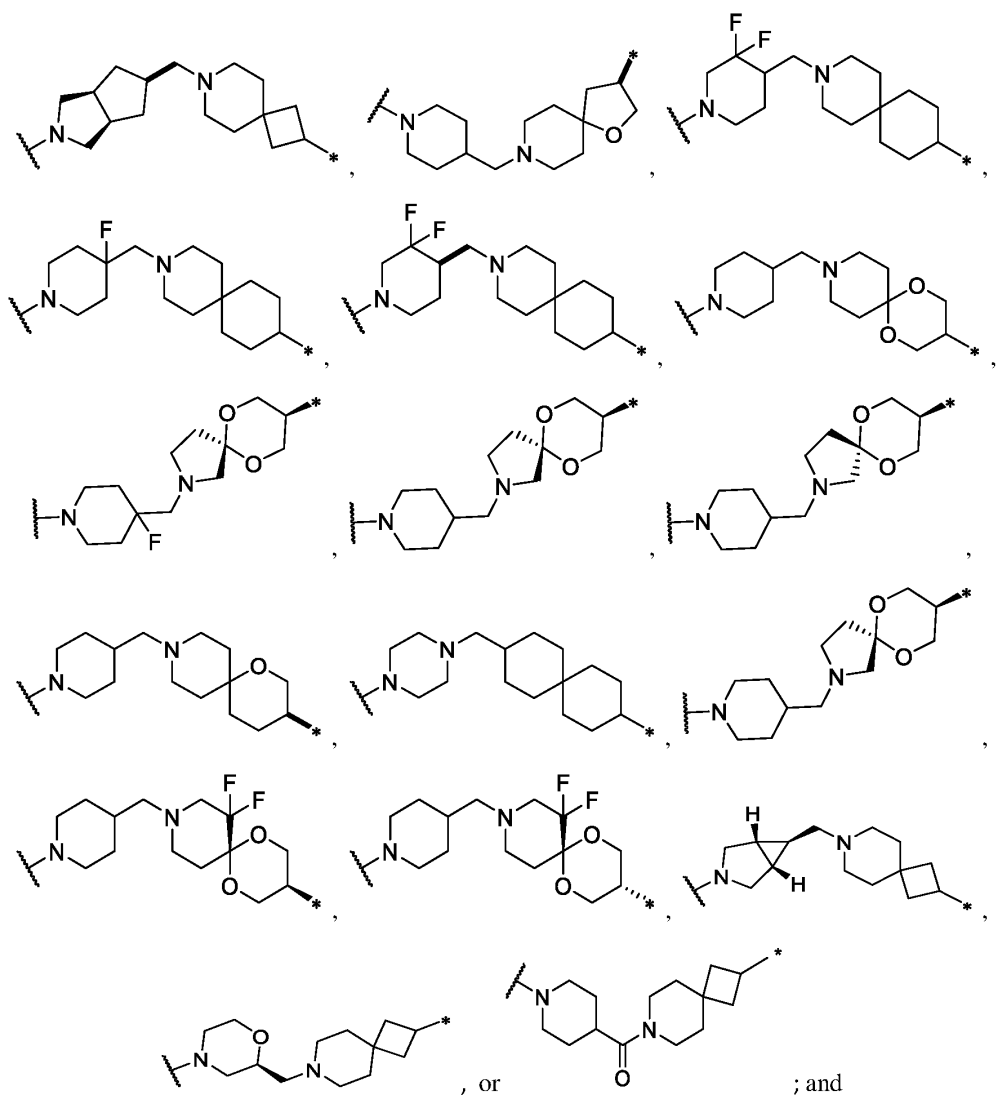


the bond marked with an “*” is attached to G^4 .

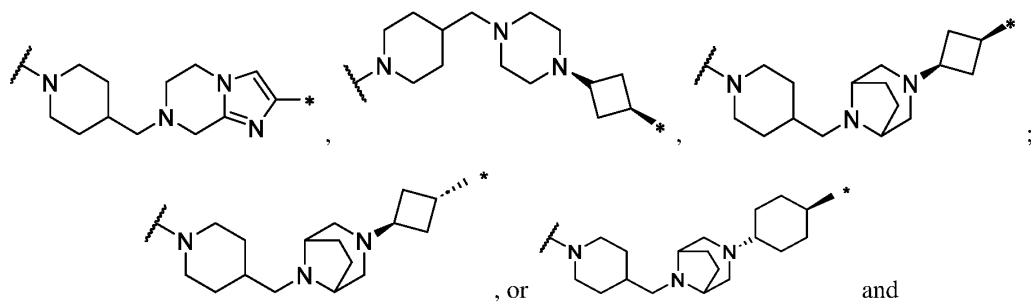
74. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-68, wherein G^4 is a direct bond.

75. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-33, wherein L is:





76. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-33, wherein L is:



the bond marked with an "*" is attached to E.

77. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-76, wherein W is $\text{-C}\equiv\text{C-}$.

78. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-76, wherein W is a direct bond.

79. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-78, wherein R^7 , R^8 , R^9 , and R^{10} are H.

80. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-78, wherein R^7 is halogen, $(\text{C}_1\text{-C}_6)\text{alkyl}$, cyano, or $(\text{C}_3\text{-C}_6)\text{cycloalkyl}$, wherein $(\text{C}_1\text{-C}_6)\text{alkyl}$ is optionally substituted with one, two, or three halogen.

81. The compound, or pharmaceutically acceptable salt thereof, according to claim 80, wherein R^7 is halogen or $(\text{C}_1\text{-C}_6)\text{alkyl}$.

82. The compound, or pharmaceutically acceptable salt thereof, according to claim 81, wherein R^7 is fluoro or methyl.

83. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 80-82, wherein R^8 , R^9 , and R^{10} are hydrogen.

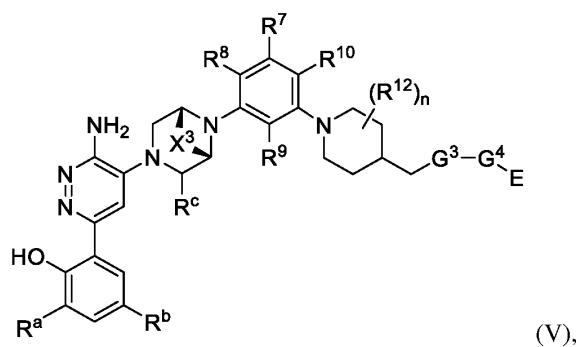
84. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-78, wherein R^8 is halogen, $(\text{C}_1\text{-C}_6)\text{alkyl}$, cyano, or $(\text{C}_3\text{-C}_6)\text{cycloalkyl}$, wherein $(\text{C}_1\text{-C}_6)\text{alkyl}$ is optionally substituted with one, two, or three halogen.

85. The compound, or pharmaceutically acceptable salt thereof, according to claim 84, wherein R^8 is halogen or $(\text{C}_1\text{-C}_6)\text{alkyl}$.

86. The compound, or pharmaceutically acceptable salt thereof, according to claim 85, wherein R^8 is fluoro or methyl.

87. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 84-86, wherein R^7 , R^9 , and R^{10} are hydrogen.

88. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-78, wherein R^9 is halogen, (C₁-C₆)alkyl, cyano, or (C₃-C₆)cycloalkyl, wherein (C₁-C₆)alkyl is optionally substituted with one, two, or three halogen.
89. The compound, or pharmaceutically acceptable salt thereof, according to claim 88, wherein R^9 is halogen.
90. The compound, or pharmaceutically acceptable salt thereof, according to claim 89, wherein R^9 is fluoro.
91. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 88-90, wherein R^7 , R^8 , and R^{10} are hydrogen.
92. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-78, wherein R^{10} is halogen, (C₁-C₆)alkyl, cyano, or (C₃-C₆)cycloalkyl, wherein (C₁-C₆)alkyl is optionally substituted with one, two, or three halogen.
93. The compound, or pharmaceutically acceptable salt thereof, according to claim 92, wherein R^{10} is halogen.
94. The compound, or pharmaceutically acceptable salt thereof, according to claim 93, wherein R^{10} is fluoro.
95. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 92-94, wherein R^7 , R^8 , and R^9 are hydrogen.
96. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-78, wherein R^{10} is cyano.
97. The compound, or pharmaceutically acceptable salt thereof, according to claim 96, wherein R^{10} is cyano; and R^7 , R^8 , and R^9 are hydrogen.
98. A compound of Formula (V), or pharmaceutically acceptable salt thereof,

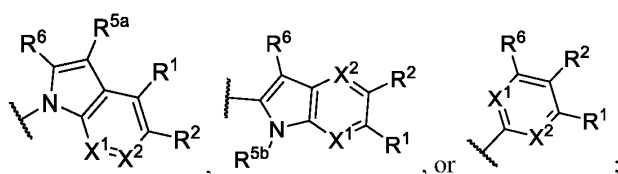


wherein:

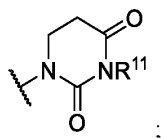
each R^{12} is fluoro or hydroxyl;

n is 0, 1, 2, or 3;

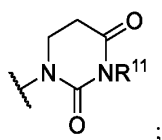
E is:



R^1 is hydrogen, halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or

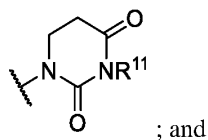


R^2 is hydrogen, halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or

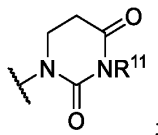


with the provisos:

(i) when R^1 is hydrogen, halogen, (C_1-C_6) alkyl, or (C_1-C_6) alkoxy, then R^2 is:



(ii) when R^2 is hydrogen, halogen, (C_1-C_6) alkyl, or (C_1-C_6) alkoxy, then R^1 is:



R^{11} is hydrogen or $-(C_1-C_6)alkyl-O-P(=O)-(OH)_2$;

X^1 is CR^3 or N;

R^3 is hydrogen, halogen, or (C_1-C_6) alkyl;

X^2 is CR^4 or N;

R^4 is hydrogen, halogen, or (C_1-C_6) alkyl;

R^{5a} is hydrogen, halogen, (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, 4- to 6-membered heterocycloalkyl, cyano, aryl, or 5- or 6-membered heteroaryl, wherein (C_1-C_6) alkyl is optionally substituted with one, two, or three substituents independently selected from halogen or cyano; and 4- to 6-membered heterocycloalkyl, aryl, or 5- or 6-membered heteroaryl is optionally substituted with one, two, or three substituents independently selected from halogen, cyano, or (C_1-C_6) alkyl;

R^{5b} is hydrogen, (C_1-C_6) alkyl, or (C_3-C_6) cycloalkyl;

R^6 is hydrogen, (C_1-C_6) alkyl, or cyano;

X^3 is $-CH_2CH_2-$ or absent;

G^3 is tetrahydronaphthalene; 4- to 6-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano; 7- to 11-membered heterocycloalkyl- $C(=O)-$, or 7- to 11-membered heterocycloalkylenyl optionally substituted with one, two, or three substituents independently selected from halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or cyano;

G^4 is absent or cyclobutylenyl;

R^7 , R^8 , R^9 , and R^{10} are independently hydrogen, fluoro, methyl, or cyano;

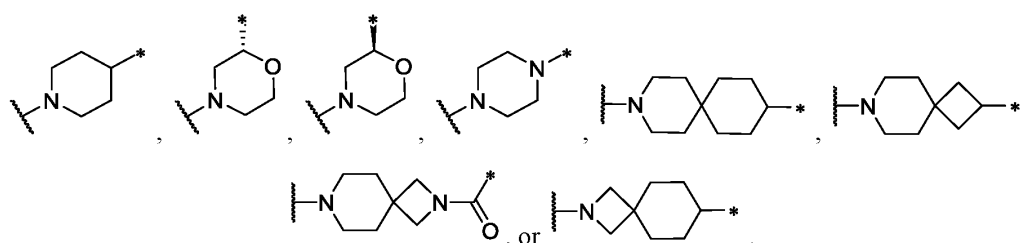
R^a is hydrogen, chloro, methyl, or fluoro;

R^b is hydrogen, chloro, methyl, or fluoro, and

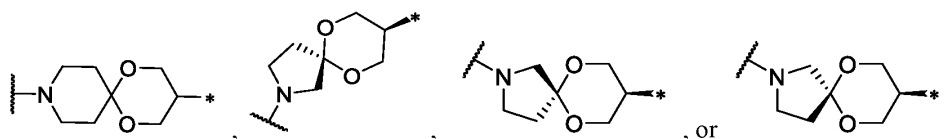
R^c is hydrogen or methyl.

99. The compound, or pharmaceutically acceptable salt thereof, according to claim 98, wherein:

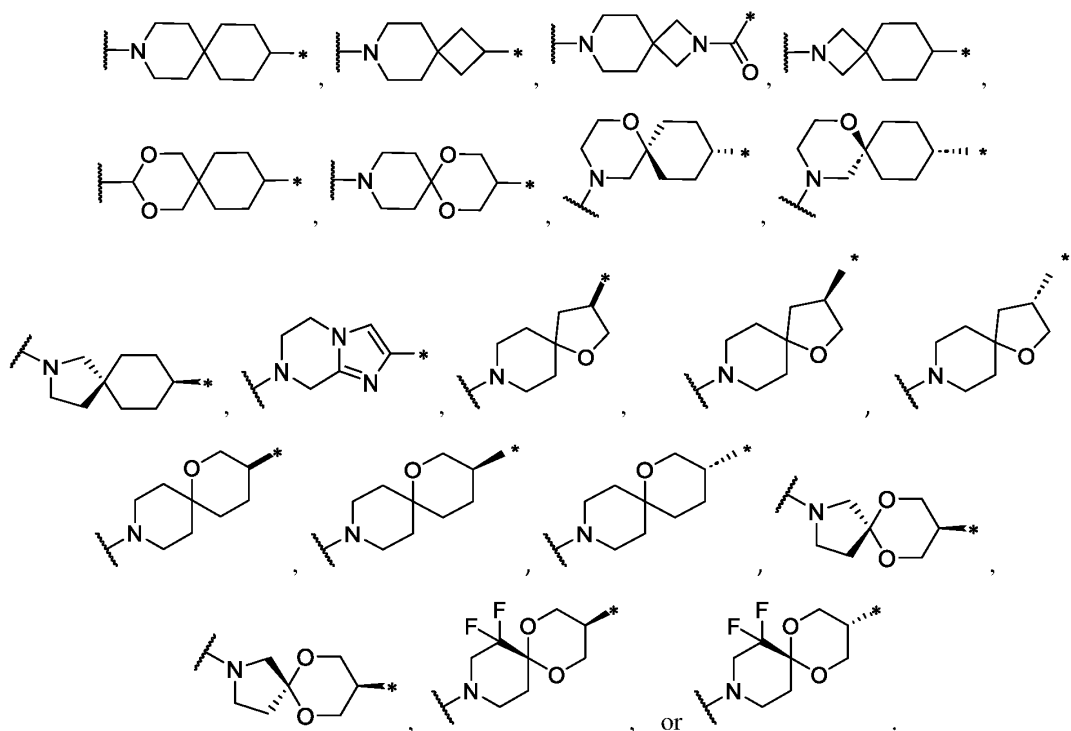
G^3 is:



100. The compound, or pharmaceutically acceptable salt thereof, according to claim 98, wherein G^3 is:



101. The compound, or pharmaceutically acceptable salt thereof, according to claim 98, wherein G^3 is:



102. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, selected from any one or more of the compounds:

1-[1-[1-[7-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-7-azaspiro[3.5]nonan-2-yl)methyl]-4-piperidyl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[3-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]prop-2-ynyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[1-[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl)methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[1-[[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl]methyl]-4-piperidyl]indol-4-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-5-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)490yridine490e-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-5-methyl-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]490yridine-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)490yridine490e-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-5-methyl-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]490yridine-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-methyl-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-6-fluoro-indol-5-yl]hexahydropyrimidine-2,4-dione

1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2,6-difluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[2-[1-[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-4-piperidyl]-1-methyl-indol-6-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[5-[4-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]piperazin-1-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[5-[4-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]piperazin-1-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-4-fluoro-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-4-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]methyl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-fluoro-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[1-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-fluoro-4-piperidyl]methyl]-4-piperidyl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[3-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[[2*S*]-4-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]morpholin-2-yl]methyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[2-[4-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]piperazin-1-yl]ethyl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-4-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3-difluoro-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1-[5-[4-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]piperazin-1-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[5-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-2,7-diazaspiro[3.5]nonane-2-carbonyl]-2-methyl-phenyl]hexahydropyrimidine-2,4-dione;

[3-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]-2,6-dioxo-hexahydropyrimidin-1-yl]methyl dihydrogen phosphate;

1-[1-[2-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-2-azaspiro[3.5]nonan-7-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(6*r*,9*r*)-4-[[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl]methyl]-1-oxa-4-azaspiro[5.5]undecan-9-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(1*r*,3*r*)-3-[8-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)493yridine493e-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]cyclobutyl]-3-methyl-pyrrolo[2,3-*b*]493yridine-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[(2*S*)-4-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]morpholin-2-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[7-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-7-azaspiro[3.5]nonan-2-yl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(5*r*,8*r*)-2-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-2-azaspiro[4.5]decan-8-yl]-3-ethyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-ethyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(2*S*)-4-[[7-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-7-azaspiro[3.5]nonan-2-yl]methyl]morpholin-2-yl]methyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazin-2-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(2*R*)-4-[[7-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-7-azaspiro[3.5]nonan-2-yl]methyl]morpholin-2-yl]methyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[3-Methyl-1-[7-[[*rel*-(3*aR*,5*r**,6*aS*)-2-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3*a*,4,5,6,6*a*-hexahydro-1*H*-cyclopenta[*c*]pyrrol-5-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione (ISOMER 1) [*absolute configuration not yet confirmed];

1-[3-Methyl-1-[7-[[*(3aR,5s,6aS)*-2-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3a,4,5,6,6a-hexahydro-1*H*-cyclopenta[*c*]pyrrol-5-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[3-Methyl-1-[7-[[*(3aR,5r,6aS)*-2-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3a,4,5,6,6a-hexahydro-1*H*-cyclopenta[*c*]pyrrol-5-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[3-Methyl-1-[7-[[*rel*-(*3aR,5r**,6*aS*)-2-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3a,4,5,6,6a-hexahydro-1*H*-cyclopenta[*c*]pyrrol-5-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione (ISOMER 2) [*absolute configuration not yet confirmed];

1-[3-Methyl-1-[7-[[*(3aR,5s,6aS)*-2-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3a,4,5,6,6a-hexahydro-1*H*-cyclopenta[*c*]pyrrol-5-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[3-Methyl-1-[7-[[*(3aR,5r,6aS)*-2-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3a,4,5,6,6a-hexahydro-1*H*-cyclopenta[*c*]pyrrol-5-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[6-Fluoro-1-[*rel*-(*3R**)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]indol-5-yl]hexahydropyrimidine-2,4-dione (ISOMER 1) [*absolute configuration not yet confirmed];

1-[6-Fluoro-1-[(*3R*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[6-Fluoro-1-[(*3S*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[6-Fluoro-1-[*rel*-(*3R**)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]indol-5-yl]hexahydropyrimidine-2,4-dione (ISOMER 2) [*absolute configuration not yet confirmed];

1-[6-Fluoro-1-[(*3R*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[6-Fluoro-1-[(3*S*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[3-Cyclopropyl-1-[(*rel*-(3*R**)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione (ISOMER 2) [*absolute configuration not yet confirmed];

1-[3-Cyclopropyl-1-[(3*R*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[3-Cyclopropyl-1-[(3*S*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-6-fluoro-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[3-Cyclopropyl-1-[(*rel*-(3*R**)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione (ISOMER 1) [*absolute configuration not yet confirmed];

1-[3-Cyclopropyl-1-[(3*R*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[3-Cyclopropyl-1-[(3*S*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

4-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-[4-[[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-ethyl-pyrrolo[2,3-*b*]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl]methyl]-4-fluoro-1-piperidyl]benzonitrile;

1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-fluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-ethyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[3-Methyl-1-[3-[[*rel*-(4*R**)-1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3-difluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione (ISOMER 2) [*absolute configuration not yet confirmed];

1-[3-Methyl-1-[3-[[*(4R)*]-1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3-difluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[3-Methyl-1-[3-[[*(4S)*]-1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3-difluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

4-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-[4-[9-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-methyl-pyrrolo[2,3-*b*]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl]methyl]-4-fluoro-1-piperidyl]benzonitrile;

1-[3-Methyl-1-[3-[[*rel*-(*4R**)]-1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3-difluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione (ISOMER 1) [*absolute configuration not yet confirmed];

1-[3-Methyl-1-[3-[[*(4R)*]-1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3-difluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[3-Methyl-1-[3-[[*(4S)*]-1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3,3-difluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-4-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-4-fluoro-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-6-fluoro-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-ethyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(*5s,8s*)-2-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-fluoro-4-piperidyl]methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]-3-ethyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(5*s*,8*s*)-2-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]-3-ethyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[3-Methyl-1-*rel*-(3*S**)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione (ISOMER 2) [*absolute configuration not yet confirmed];

1-[3-Methyl-1-[(3*S*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[3-Methyl-1-[(3*R*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[3-Methyl-1-*rel*-(3*R**)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione (ISOMER 1) [*absolute configuration not yet confirmed];

1-[3-Methyl-1-[(3*S*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[3-Methyl-1-[(3*R*)-8-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(5*s*,8*s*)-2-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(5*r*,8*r*)-2-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[3-Methyl-1-*rel*-(3*S**)-9-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-9-azaspiro[5.5]undecan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione (ISOMER 1) [*absolute configuration not yet confirmed];

1-[3-Methyl-1-[(3*S*)-9-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-9-azaspiro[5.5]undecan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[3-Methyl-1-[(3*R*)-9-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-9-azaspiro[5.5]undecan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[3-Methyl-1-[(*rel*-(3*R**)-9-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-9-azaspiro[5.5]undecan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione (ISOMER 2) [*absolute configuration not yet confirmed];

1-[3-Methyl-1-[(3*S*)-9-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-9-azaspiro[5.5]undecan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[3-Methyl-1-[(3*R*)-9-[[1-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1-oxa-9-azaspiro[5.5]undecan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(5*r*,8*r*)-2-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[9-[[4-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]piperazin-1-yl]methyl]spiro[5.5]undecan-3-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(5*s*,8*s*)-2-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-fluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(3*s*,6*s*)-9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-11,11-difluoro-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(3*r*,6*r*)-9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-11,11-difluoro-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-fluoro-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[4-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]piperazin-1-yl]cyclobutyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

4-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-[4-[[9-[5-(2,4-dioxohexahydropyrimidin-1-yl)-3-ethyl-pyrrolo[2,3-*b*]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl]methyl]-1-piperidyl]benzonitrile;

4-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-[4-[[2-[3-cyclopropyl-5-(2,4-dioxohexahydropyrimidin-1-yl)pyrrolo[2,3-*b*]pyridin-1-yl]-7-azaspiro[3.5]nonan-7-yl]methyl]-1-piperidyl]benzonitrile;

1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-ethyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1*R*,5*S*,6*s*)-3-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3-azabicyclo[3.1.0]hexan-6-yl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1*R*,5*S*,6*s*)-3-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-3-azabicyclo[3.1.0]hexan-6-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[[(1*s*,3*s*)-3-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]cyclobutyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[2*R*)-4-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]morpholin-2-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-6-fluoro-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3-azabicyclo[3.2.1]octan-8-yl]-2-chloro-phenyl]-4-piperidyl]methyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[8-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]pyrrolo[1,2-*a*]pyrimidin-3-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(2*S*)-6-[[4-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]piperazin-1-yl]methyl]tetralin-2-yl]indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(2*R*)-6-[[4-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]piperazin-1-yl]methyl]tetralin-2-yl]indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(2*S*)-6-[[4-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]piperazin-1-yl]methyl]tetralin-2-yl]indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(2*R*)-6-[[4-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]piperazin-1-yl]methyl]tetralin-2-yl]indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1*s*,4*s*)-4-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]cyclohexyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1*r*,4*r*)-4-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]cyclohexyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(3*r*,6*r*)-9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-11,11-difluoro-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(1*r*,4*r*)-4-[8-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]cyclohexyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(1*s*,4*s*)-4-[8-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]cyclohexyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(1*r*,3*r*)-3-[8-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-fluoro-4-piperidyl]methyl]-3,8-diazabicyclo[3.2.1]octan-3-yl]cyclobutyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1-[5-[3-[3-Amino-6-(5-fluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-ethyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1-[5-[3-[3-Amino-6-(3,5-difluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-ethyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1-[5-[3-[3-Amino-6-(3-fluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-ethyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(5*s*,8*s*)-2-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]piperidine-4-carbonyl]-7-azaspiro[3.5]nonan-2-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-ethyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[9-[1-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

4-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-[4-[[3-[3-cyclopropyl-5-(2,4-dioxohexahydropyrimidin-1-yl)pyrrolo[2,3-*b*]pyridin-1-yl]-1,5-dioxo-9-azaspiro[5.5]undecan-9-yl]methyl]-1-piperidyl]benzonitrile;

1-[1-[3-[[1-[5-[3-[3-Amino-6-(5-fluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-4-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[9-[[1-[5-[3-[3-Amino-6-(5-fluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[9-[[1-[5-[3-[3-Amino-6-(5-fluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[9-[[1-[5-[3-[3-Amino-6-(3-fluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[9-[[1-[5-[3-[3-Amino-6-(3-fluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[9-[[1-[5-[3-[3-Amino-6-(3,5-difluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[9-[[1-[5-[3-[3-Amino-6-(3,5-difluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1-[5-[3-[3-Amino-6-(3-fluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1-[5-[3-[3-Amino-6-(3,5-difluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[2-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenoxy]ethyl]-3-azaspiro[5.5]undecan-9-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[7-[2-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenoxy]ethyl]-7-azaspiro[3.5]nonan-2-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[1-[1-[2-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenoxy]ethyl]-4-fluoro-4-piperidyl]methyl]-4-piperidyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(3*S*)-1-[1-[2-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenoxy]ethyl]-4-fluoro-4-piperidyl]methyl]pyrrolidin-3-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(3*R*)-1-[1-[2-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenoxy]ethyl]-4-fluoro-4-piperidyl]methyl]pyrrolidin-3-yl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[2-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenoxy]ethyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[9-[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[9-[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3-azabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-cyclopropyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[9-[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-ethyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[3-Methyl-1-[7-[*rac*-(2*S*,3*aR*,6*aR*)-5-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-2,3,3*a*,4,6,6*a*-hexahydrofuro[2,3-*c*]pyrrol-2-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[3-Methyl-1-[7-[*rac*-(2*S*,3*aR*,6*aR*)-5-[5-[3-[3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-2,3,3*a*,4,6,6*a*-hexahydrofuro[2,3-*c*]pyrrol-2-yl]methyl]-7-azaspiro[3.5]nonan-2-yl]pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[9-[1-[5-[3-[3-Amino-6-(3-chloro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[9-[1-[5-[3-[3-Amino-6-(2-hydroxy-3-methyl-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(5*s*,8*s*)-2-[1-[5-[3-[3-Amino-6-(5-fluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(5*s*,8*s*)-2-[[1-[5-[3-[3-Amino-6-(3-fluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(5*s*,8*s*)-2-[[1-[5-[3-[3-Amino-6-(3,5-difluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]-3-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1-[5-[(3*S*)-4-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3-methyl-piperazin-1-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[9-[[1-[5-[(3*S*)-4-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3-methyl-piperazin-1-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[3-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-hydroxy-4-piperidyl]methyl]-3-azaspiro[5.5]undecan-9-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(5*s*,8*s*)-2-[[1-[5-[3-[3-Amino-6-(3-fluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(5*s*,8*s*)-2-[[1-[5-[3-[3-Amino-6-(5-fluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[(5*s*,8*s*)-2-[[1-[5-[3-[3-Amino-6-(3,5-difluoro-2-hydroxy-phenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-6,10-dioxo-2-azaspiro[4.5]decan-8-yl]indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-6-methyl-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[1-[2-[4-[2-[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenoxy]ethyl]piperazin-1-yl]ethyl]-4-piperidyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[1-[2-[4-[2-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenoxy]ethyl]piperazin-1-yl]ethyl]-4-piperidyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-4-fluoro-indol-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]indol-4-yl]hexahydropyrimidine-2,4-dione;

1-[1-[9-[[1-[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]-4-hydroxy-4-piperidyl]methyl]-1,5-dioxo-9-azaspiro[5.5]undecan-3-yl]-3-cyclopropyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

1-[1-[1-[4-[[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]methyl]piperazine-1-carbonyl]-4-piperidyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

-[1-[1-[4-[[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]methyl]piperazine-1-carbonyl]-4-piperidyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

-[1-[1-[3-[4-[[5-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-fluoro-phenyl]methyl]piperazin-1-yl]-3-oxo-propyl]-4-piperidyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione; or

1-[1-[1-[3-[4-[[3-[3-[3-Amino-6-(2-hydroxyphenyl)pyridazin-4-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]phenyl]methyl]piperazin-1-yl]-3-oxo-propyl]-4-piperidyl]-3-methyl-pyrrolo[2,3-*b*]pyridin-5-yl]hexahydropyrimidine-2,4-dione;

or pharmaceutically acceptable salts thereof.

103. A pharmaceutical composition comprising the compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-102, and a pharmaceutically acceptable excipient.

104. A method of degrading SMARCA2 protein in a human, comprising administering to a human in need thereof an effective amount of the compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-102, or the composition of claim 103.

105. A method of reducing the level of SMARCA2 activity in a human, comprising administering to a human in need thereof an effective amount of the compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-102, or the composition of claim 103.

106. A method of treating cancer in a human, comprising administering to a human in need thereof an effective amount of the compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-102, or the composition of claim 103.

107. The method of claim 106, wherein the cancer is a SMARCA2-sensitive cancer.

108. The method of claim 106, wherein the cancer is a SMARCA2-mutated cancer.
109. The method of any one of claims 106-108, wherein the cancer is a solid tumor.
110. The method of any one of claims 106-108, wherein the cancer is lung, liver, colon, skin, bladder, cervical or ovarian cancer.
111. A compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-102, or the composition of claim 103 for use in degrading SMARCA2 protein in a human.
112. A compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-102, or the composition of claim 103 for use in reducing the level of SMARCA2 activity in a human.
113. A compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-102, or the composition of claim 103 for use in treating cancer in a human.
114. The compound for use of claim 113, wherein the cancer is a SMARCA2-sensitive cancer.
115. The compound for use of claim 113, wherein the cancer is a SMARCA2-mutated cancer.
116. The compound for use of any one of claims 113-115, wherein the cancer is a solid tumor.
117. The compound for use of any one of claims 113-115, wherein the cancer is lung, liver, colon, skin, bladder, cervical or ovarian cancer.
118. Use of a compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-102, or the composition of claim 103 in the manufacture of a medicament for degrading SMARCA2 protein in a human.
119. Use of a compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-102, or the composition of claim 103 in the manufacture of a medicament for reducing the level of SMARCA2 activity in a human.
120. Use of a compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-102, or the composition of claim 103 in the manufacture of a medicament for treating cancer in a human.

121. The compound, or pharmaceutically acceptable salt thereof, for use of claim 120, wherein the cancer is a SMARCA2-sensitive cancer.

122. The compound, or pharmaceutically acceptable salt thereof, for use of claim 120, wherein the cancer is a SMARCA2-mutated cancer.

123. The compound, or pharmaceutically acceptable salt thereof, for use of any one of claims 120-122, wherein the cancer is a solid tumor.

124. The compound, or pharmaceutically acceptable salt thereof, for use of any one of claims 120-122, wherein the cancer is lung, liver, colon, skin, bladder, cervical or ovarian cancer.