

2-(3,8-DIAZABICYCLO[3.2.1]OCTAN-3-YL)-1,3,5-TRIAZINE DERIVATIVES AS
KRAS G12D INHIBITORS FOR THE TREATMENT OF CANCER

Compounds are provided which can inhibit KRAS G12D. Also provided are pharmaceutical compositions and medical uses of the same, including the use in treating or preventing conditions such as cancers.

SUMMARY

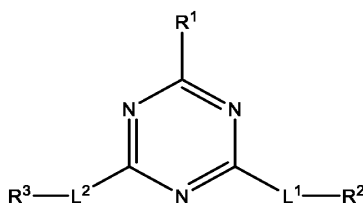
Kirsten Rat Sarcoma 2 Viral Oncogene Homolog (“KRas” or “KRAS”) is a small GTPase and a member of the Ras family of oncogenes. KRAS serves as a molecular switch cycling between inactive (GDP-bound) and active (GTP-bound) states to transduce upstream cellular signals received from multiple tyrosine kinases to downstream effectors to regulate a wide variety of processes, including cellular proliferation.

Aberrant expression of KRAS accounts for up to 20% of all cancers and oncogenic KRAS mutations that stabilize GTP binding and lead to constitutive activation of KRAS and downstream signaling have been reported in 25 -30% of lung adenocarcinomas. KRAS G12D mutation is present in 25.0% of all pancreatic ductal adenocarcinoma patients, 13.3% of all colorectal carcinoma patients, 10.1% of all rectal carcinoma patients, 4.1% of all non-small cell lung carcinoma patients, and 1.7% of all small cell lung carcinoma patients (e.g., see The AACR Project GENIE Consortium, (2017) Cancer Discovery;7(8):818-831. Dataset Version 4).

The well-known role of KRAS in malignancy and the discovery of these frequent mutations in KRAS in various tumor types made KRAS a highly attractive target of the pharmaceutical industry for cancer therapy. WO 2021/041671, WO 2023/098425, and WO 2023/274324 disclose KRAS G12D inhibitors which are based on a bicyclic (pyrido[4,3-d]pyrimidine) core.

Clearly there remains a continued interest and effort to develop inhibitors of KRAS, particularly inhibitors of activating KRAS mutants, especially KRAS G12D, e.g., for treating KRAS G12D-mediated cancer.

Accordingly, in a first aspect the present disclosure provides a compound of Formula (0):

**(Formula (0))**

or a pharmaceutically acceptable salt thereof, wherein:

R¹ is a 6- to 10-membered, monocyclic or bicyclic heterocycloalkyl or heterocycloalkenyl group comprising at least one ring atom which is N, and wherein R¹ is optionally substituted by one or more groups independently selected from =O, CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)OH, C(O)NH₂, C(O)ONH₂, C(O)R*, C(O)OR*, OC(O)R*, C(O)NHR*, CH₂C(O)NHR*, C(O)NR*₂, CH₂C(O)NR*₂, C(O)ONHR*, CH₂C(O)ONHR*, C(O)ONR*₂ and CH₂C(O)ONR*₂; or wherein R¹ is -L³-R^{1'}, wherein R^{1'} is a 5-membered, monocyclic heterocycloalkyl or heterocycloalkenyl group comprising at least one ring atom which is N, and wherein R^{1'} is optionally substituted by one or more groups independently selected from =O, CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)OH, C(O)NH₂, C(O)ONH₂, C(O)R*, C(O)OR*, C(O)NHR*, C(O)NR*₂, C(O)ONHR*, and C(O)ONR*₂;

R² is a 5- to 9-membered (*e.g.* 5- to 8-membered), monocyclic or bicyclic heterocycloalkyl or heterocycloalkenyl group comprising at least one ring atom which is N or O; a 5- or 6-membered monocyclic heteroaryl group comprising at least one ring atom which is N; a fused, 8- to 10-membered bicyclic group wherein one or both rings are aromatic, and wherein at least one ring comprises at least one ring atom which is N; or a fused, 11- to 14-membered tricyclic group wherein at least one ring is aromatic, and wherein at least one ring comprises at least one ring atom which is N;

and wherein R² may be substituted by one or more groups independently selected from CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)R*, C(O)OH, C(O)OR*, C(O)NH₂, C(O)NHR*, C(O)NR*₂, C(O)ONH₂, C(O)ONHR*, C(O)ONR*₂, =O, (C₂-C₃)alkenyl, and (C₂-C₃)alkynyl;

R³ is a phenyl or naphthalenyl group which is substituted by OH and optionally by one or more additional groups independently selected from CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)R*, C(O)OH, C(O)OR*, C(O)NH₂, C(O)NHR*, C(O)NR*₂, C(O)ONH₂, C(O)ONHR*, C(O)ONR*₂, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl; or R³ is a fused, 8-to-10-membered bicyclic group comprising a saturated carbocyclic ring fused to a heterocyclic ring, wherein the carbocyclic ring, the heterocyclic ring, or both, may optionally be substituted by one or more groups independently selected from CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)R*, C(O)OH, C(O)OR*, C(O)NH₂, C(O)NHR*, C(O)NR*₂, C(O)ONH₂, C(O)ONHR*, C(O)ONR*₂, NHC(O)R*, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl; or R³ is a fused, 8- to 10-membered bicyclic group comprising a saturated carbocyclic ring fused to an aryl ring, wherein the carbocyclic ring, the aryl ring, or both, may be optionally substituted by one or more groups independently selected from CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)R*, C(O)OH, C(O)OR*, C(O)NH₂, C(O)NHR*, C(O)NR*₂, C(O)ONH₂, C(O)ONHR*, C(O)ONR*₂, NHC(O)R*, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl; or R³ is a fused, 8- to 10-membered bicyclic group comprising a saturated heterocyclic ring fused to an aryl or heteroaryl ring, wherein the carbocyclic ring, the aryl or heteroaryl ring, or both, may be optionally substituted by one or more

groups independently selected from CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)R*, C(O)OH, C(O)OR*, C(O)NH₂, C(O)NHR*, C(O)NR*₂, C(O)ONH₂, C(O)ONHR*, C(O)ONR*₂, NHC(O)R*, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl;

L¹ is a bond or is -O-, -(C₁-C₃)alkyl-, *-O-(C₁-C₃)alkyl-**, *-(C₁-C₃)alkyl-O-**, *-C(O)NR'-**, or *-NR'C(O)-**, wherein R' is H, OH, CN, Cl, F, or (C₁-C₃)alkyl, and * denotes a point of attachment to the triazole moiety of the compound of Formula (0) and ** denotes a point of attachment to R²;

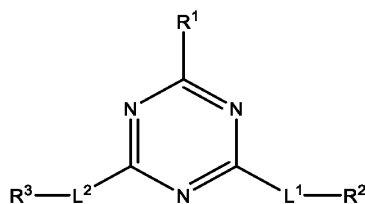
L² is -(C₁-C₃)alkyl-, C₅-heteroaryl optionally substituted with one or more R'', *-O-(C₁-C₃)alkyl-**, *-(C₁-C₃)alkyl-O-**, -(C₂-C₃)alkenyl-, -(C₂-C₃)alkynyl-, *-C(O)NR''-**, *-NR''(C₁-C₃)alkyl-**, *-C(O)NR''-**, *-NR''C(O)-**, *-NR''-(C₁-C₃)alkyl-**, or *-C(O)NR''-**, wherein R'' is H, OH, CN, Cl, F, or (C₁-C₃)alkyl, and wherein * denotes a point of attachment to R³ and ** denotes a point of attachment to the triazole moiety of the compound of Formula (0);

L³ is a bond or is -(C₁-C₃)alkyl-, -O-, -NH- or -N(C₁-C₃)alkyl;

and

wherein in R¹, R², and R³, each R* is independently selected from (C₁-C₄)alkyl (*e.g.* C₁-C₃)alkyl), (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkenyl, and 5- or 6-membered monocyclic heteroaryl, wherein said (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkenyl or 5- or 6-membered monocyclic heteroaryl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, NH₂, NH((C₁-C₃)alkyl), (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or O(C₁-C₃)alkyl.

In embodiments, the present disclosure provides a compound of Formula (0) which is a compound of Formula (I):



(Formula (I))

or a pharmaceutically acceptable salt thereof, wherein in Formula (I):

R¹ is a 6- to 10-membered bridged bicyclic heterocycloalkyl or heterocycloalkenyl group comprising at least one ring atom which is N, and wherein R¹ is optionally substituted by one or more groups

independently selected from =O, CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)OH, C(O)NH₂, C(O)ONH₂, C(O)R*, C(O)OR*, C(O)NHR*, C(O)NR*₂, C(O)ONHR*, and C(O)ONR*₂;

R² is a 5- to 8-membered, monocyclic or bicyclic heterocycloalkyl or heterocycloalkenyl group comprising at least one ring atom which is N or O; a 5- or 6-membered monocyclic heteroaryl group comprising at least one ring atom which is N; or a fused, 8- to 10-membered bicyclic group wherein one or both rings are aromatic, and wherein at least one ring comprises at least one ring atom which is N;

and wherein R² may be substituted by one or more groups independently selected from CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)R*, C(O)OH, C(O)OR*, C(O)NH₂, C(O)NHR*, C(O)NR*₂, C(O)ONH₂, C(O)ONHR*, C(O)ONR*₂, =O, (C₂-C₃)alkenyl, and (C₂-C₃)alkynyl;

R³ is a phenyl or naphthalenyl group which is substituted by OH and optionally by one or more additional groups independently selected from CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)R*, C(O)OH, C(O)OR*, C(O)NH₂, C(O)NHR*, C(O)NR*₂, C(O)ONH₂, C(O)ONHR*, C(O)ONR*₂, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl; or R³ is a fused, 8-to-10-membered bicyclic group comprising a saturated carbocyclic ring fused to a heterocyclic ring, wherein the carbocyclic ring, the heterocyclic ring, or both, may optionally be substituted by one or more groups independently selected from CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)R*, C(O)OH, C(O)OR*, C(O)NH₂, C(O)NHR*, C(O)NR*₂, C(O)ONH₂, C(O)ONHR*, C(O)ONR*₂, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl;

L¹ is -O-, -(C₁-C₃)alkyl-, *-O-(C₁-C₃)alkyl-**, *-(C₁-C₃)alkyl-O-**, *-C(O)NR'-**, or *-NR'C(O)-**, wherein R' is H, OH, CN, Cl, F, or (C₁-C₃)alkyl, and * denotes a point of attachment to the triazole moiety of the compound of Formula (I) and ** denotes a point of attachment to R²;

L² is -(C₁-C₃)alkyl-, C₅-heteroaryl optionally substituted with one or more R'', *-O-(C₁-C₃)alkyl-**, *-(C₁-C₃)alkyl-O-**, -(C₂-C₃)alkenyl-, -(C₂-C₃)alkynyl-, *-(C₁-C₃)alkyl-NR''-**, *-NR''(C₁-C₃)alkyl-**, *-C(O)NR''-**, *-NR''C(O)-**, *-NR''-(C₁-C₃)alkyl-**, or *-(C₁-C₃)alkyl-NR''-**, wherein R'' is H, OH, CN, Cl, F, or (C₁-C₃)alkyl, and wherein * denotes a point of attachment to R³ and ** denotes a point of attachment to the triazole moiety of the compound of Formula (I);

and

wherein in R¹, R², and R³, each R* is independently selected from (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, and (C₃-C₆)cycloalkenyl, wherein said (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, or (C₃-C₆)cycloalkenyl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, NH₂, NH((C₁-C₃)alkyl), (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or O(C₁-C₃)alkyl.

A further aspect provides a pharmaceutical composition comprising a compound described herein (e.g., a compound of Formula (0) or Formula (I) or a pharmaceutically acceptable salt thereof) and at least one pharmaceutically acceptable excipient or carrier.

5 A further aspect provides a method of treatment comprising administering to a subject in need thereof a therapeutically effective amount of a compound of the disclosure (e.g., a compound of Formula (0) or Formula (I) or a pharmaceutically acceptable salt thereof). In a related aspect, the disclosure provides the use of a compound of the disclosure (e.g., a compound of Formula (0) or Formula (I) or a pharmaceutically acceptable salt thereof) in the manufacture of a medicament. In a further related aspect, the disclosure provides a compound of the disclosure (e.g., a compound of Formula (0) or
10 Formula (I) or a pharmaceutically acceptable salt thereof) for use in therapy.

A further aspect provides a method of treating or preventing a disease or disorder mediated by KRAS G12D, or a disease or disorder in which KRAS G12D is implicated, in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound of the disclosure (e.g., a compound of Formula (0) or Formula (I) or a pharmaceutically acceptable salt thereof). In a
15 related aspect, the disclosure provides the use of a compound of the disclosure (e.g., a compound of Formula (0) or Formula (I) or a pharmaceutically acceptable salt thereof) in the manufacture of a medicament for the treatment or prevention of a disease or disorder mediated by KRAS G12D, or a disease or disorder in which KRAS G12D is implicated. In a further related aspect, the disclosure provides a compound of the disclosure (e.g., a compound of Formula (0) or Formula (I) or a
20 pharmaceutically acceptable salt thereof) for use in the treatment or prevention of a disease or disorder mediated by KRAS G12D, or a disease or disorder in which KRAS G12D is implicated.

In another aspect, the present disclosure provides a method of treating or preventing a disease or disorder associated with KRAS G12D (e.g., cancer) in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound of the disclosure (e.g., a
25 compound of Formula (0) or Formula (I) or a pharmaceutically acceptable salt thereof). In a related aspect, the disclosure provides the use of a compound of the disclosure (e.g., a compound of Formula (0) or Formula (I) or a pharmaceutically acceptable salt thereof) in the manufacture of a medicament for the treatment or prevention of a disease or disorder associated with KRAS G12D (e.g., cancer). In a further related aspect, the disclosure provides a compound of the disclosure (e.g., a compound of
30 Formula (0) or Formula (I) or a pharmaceutically acceptable salt thereof) for use in the treatment or prevention of a disease or disorder associated with KRAS G12D (e.g., cancer).

In another aspect, the present disclosure provides a method of treating or preventing cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound of the disclosure (e.g., a compound of Formula (0) or Formula (I) or a pharmaceutically acceptable

salt thereof). In a related aspect, the disclosure provides the use of a compound of the disclosure (e.g., a compound of Formula (I) or a pharmaceutically acceptable salt thereof) in the manufacture of a medicament for the treatment or prevention of cancer. In a further related aspect, the disclosure provides a compound of the disclosure (e.g., a compound of Formula (I) or a pharmaceutically acceptable salt thereof) for use in the treatment or prevention of cancer.

In another aspect, the disclosure provides a method of inhibiting KRAS G12D activity, the method comprising contacting KRAS G12D (e.g., a cell comprising KRAS G12D) with a compound of the present disclosure (e.g., a compound of Formula (0) or Formula (I) or a pharmaceutically acceptable salt thereof). In embodiments, the method is an *in vitro* or *ex vivo* method. In other embodiments the method is an *in vivo* method. In a related aspect, the disclosure provides an *in vitro* method of inhibiting KRAS G12D activity in a cell, the method comprising contacting the cell with a compound of the present disclosure (e.g., a compound of Formula (0) or Formula (I) or a pharmaceutically acceptable salt thereof).

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 (**Fig. 1**) shows a synthesis of compound (**1**) as described in further detail herein in Example 20.

Figure 2 (**Fig. 2**) shows a synthesis of compound (**55**) as described in further detail herein in Example 21.

Figure 3 (**Fig. 3**) shows a synthesis of compound (**56**) as described in further detail herein in Example 22.

DETAILED DESCRIPTION

Although specific embodiments of the present disclosure will now be described with reference to the description and examples, it should be understood that such embodiments are by way of example only and merely illustrative of but a small number of the many possible specific embodiments which can represent applications of the principles of the present disclosure. Various changes and modifications will be obvious to those of skill in the art given the benefit of the present disclosure and are deemed to be within the spirit and scope of the present disclosure as further defined in the appended claims.

Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice

or testing of the present disclosure, exemplary methods, devices, and materials are now described. All technical and patent publications cited herein are incorporated herein by reference in their entirety.

The practice of the present disclosure will employ, unless otherwise indicated, conventional techniques of chemical synthesis, tissue culture, immunology, molecular biology, microbiology, cell biology, recombinant DNA, etc., which are within the skill of the art. See, e.g., Michael R. Green and Joseph Sambrook, *Molecular Cloning* (4th ed., Cold Spring Harbor Laboratory Press 2012); the series Ausubel *et al.* eds. (2007) *Current Protocols in Molecular Biology*; the series *Methods in Enzymology* (Academic Press, Inc., N.Y.); MacPherson *et al.* (1991) *PCR 1: A Practical Approach* (IRL Press at Oxford University Press); MacPherson *et al.* (1995) *PCR 2: A Practical Approach*; Harlow and Lane eds. (1999) *Antibodies, A Laboratory Manual*; Freshney (2005) *Culture of Animal Cells: A Manual of Basic Technique*, 5th edition; Gait ed. (1984) *Oligonucleotide Synthesis*; U.S. Patent No. 4,683,195; Hames and Higgins eds. (1984) *Nucleic Acid Hybridization*; Anderson (1999) *Nucleic Acid Hybridization*; Hames and Higgins eds. (1984) *Transcription and Translation*; Immobilized Cells and Enzymes (IRL Press (1986)); Perbal (1984) *A Practical Guide to Molecular Cloning*; Miller and Calos eds. (1987) *Gene Transfer Vectors for Mammalian Cells* (Cold Spring Harbor Laboratory); Makrides ed. (2003) *Gene Transfer and Expression in Mammalian Cells*; Mayer and Walker eds. (1987) *Immunochemical Methods in Cell and Molecular Biology* (Academic Press, London); Herzenberg *et al.* eds (1996) *Weir's Handbook of Experimental Immunology*; *Manipulating the Mouse Embryo: A Laboratory Manual*, 3rd edition (Cold Spring Harbor Laboratory Press (2002)); Sohail (ed.) (2004) *Gene Silencing by RNA Interference: Technology and Application* (CRC Press).

All numerical designations, e.g., pH, temperature, time, concentration, molecular weight, etc., including ranges, are approximations which are varied (+) or (-) by increments of, e.g., 0.1 or 1.0, where appropriate. It is to be understood, although not always explicitly stated, that all numerical designations are preceded by the term “about”, which is used to denote a conventional level of variability. For example, a numerical designation which is “about” a given value may vary by $\pm 10\%$ of said value; alternatively, the variation may be $\pm 5\%$, $\pm 2\%$, or $\pm 1\%$ of the value. It also is to be understood, although not always explicitly stated, that the reagents described herein are merely exemplary and that equivalents of such are known in the art.

As used herein, the term “room temperature” means an ambient temperature in the range of about 20 to about 25 °C, e.g., about 20, about 21, about 22, about 23, about 24 or about 25 °C.

As used in the specification and claims, the singular forms “a”, “an”, and “the” include plural references unless the context clearly dictates otherwise. For example, the term “a cell” includes a plurality of cells, including mixtures thereof. Unless specifically stated or obvious from context, as

used herein, the term “or” is understood to be inclusive. The term “including” is used herein to mean, and is used interchangeably with, the phrase “including but not limited to”.

As used herein, the term “comprising” or “comprises” is intended to mean that the compositions and methods include the recited elements, without excluding other elements. “Consisting essentially of”
5 when used to define compositions and methods, shall mean excluding other elements of any essential significance for the stated purpose. Thus, a composition consisting essentially of the elements as defined herein would not exclude trace contaminants from the isolation and purification method and pharmaceutically acceptable carriers, such as phosphate buffered saline, preservatives, and the like. “Consisting of” shall mean excluding more than trace elements of other ingredients and substantial
10 method steps for administering the compositions of this disclosure or process steps to produce a composition or achieve an intended result. Embodiments defined by each of these transition terms are within the scope of this disclosure. Use of the term “comprising” herein is intended to encompass, and to disclose, the corresponding statements in which the term “comprising” is replaced by “consisting essentially of” or “consisting of”.

15 A “subject,” “individual”, or “patient” is used interchangeably herein, and refers to a vertebrate, such as a mammal. Mammals include, but are not limited to, rodents, farm animals, sport animals, pets, and primates; for example, murines, rats, rabbit, simians, bovines, ovines, porcines, canines, felines, equines, and humans. In a particular embodiment, the mammal is a human.

“Administering” is defined herein as a means of providing an agent or a composition containing the
20 agent to a subject in a manner that results in the agent being contacted with (e.g., being inside) the subject’s body. Such an administration can be by any route including, without limitation, oral, transdermal, transmucosal, (e.g., by the vagina, rectum, or oral mucosa), by injection (e.g., subcutaneous, intravenous, parenteral, intraperitoneal, or into the central nervous system), or by inhalation (e.g., oral or nasal). Administration may also involve providing a substance or composition
25 to a part of the surface of the subject’s body, for example by topical administration to the skin. Pharmaceutical preparations are, of course, given by forms suitable for each administration route.

“Treating” or “treatment” of a disease includes: (1) preventing the disease, i.e., causing the clinical symptoms of the disease not to develop in a patient that may be predisposed to the disease but does not yet experience or display symptoms of the disease; (2) inhibiting the disease, i.e., arresting or
30 reducing the development of the disease or its clinical symptoms; and/or (3) relieving the disease, i.e., causing regression of the disease or its clinical symptoms.

The term “suffering” as it relates to the term “treatment” refers to a patient or individual who has been diagnosed with or is predisposed to the disease. A patient may also be referred to being “at risk of

suffering” from a disease because of a history of disease in their family lineage or because of the presence of genetic mutations associated with the disease. A patient at risk of a disease has not yet developed all or some of the characteristic pathologies of the disease.

5 An “effective amount” or “therapeutically effective amount” is an amount sufficient to effect beneficial or desired results. An effective amount can be administered in one or more administrations, applications, or dosages. Such delivery is dependent on a number of variables including the time period for which the individual dosage unit is to be used, the bioavailability of the therapeutic agent, the route of administration, etc. It is understood, however, that specific dose levels of the therapeutic agents of the present disclosure for any particular subject depends upon a variety of factors including, for
10 example, the activity of the specific compound employed, the age, body weight, general health, sex, and diet of the subject, the time of administration, the rate of excretion, the drug combination, the severity of the particular disorder being treated, and the form of administration. Treatment dosages generally may be titrated to optimize safety and efficacy. Typically, dosage-effect relationships from *in vitro* and/or *in vivo* tests initially can provide useful guidance on the proper doses for patient
15 administration. In general, one will desire to administer an amount of the compound that is effective to achieve a serum level commensurate with the concentrations found to be effective *in vitro*. Determination of these parameters is well within the skill of the art. These considerations, as well as effective formulations and administration procedures, are well known in the art and are described in standard textbooks. Consistent with this definition, as used herein, the term “therapeutically effective
20 amount” is an amount sufficient to treat (e.g., improve) one or more symptoms associated with the condition. The total daily dose may be administered in single or divided doses and may, at the physician’s discretion, fall outside of the typical range given herein.

As used herein, the terms “increased” and “elevated” are used interchangeably and encompass any measurable increase in a biological function, and/or a biological activity, and/or a concentration. For
25 example, an increase can be by at least about 10%, e.g., at least about 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%, such as at least about 95%, 96%, 97%, 98%, 99%, or 100%. Thus, an increase can be by at least about 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, or 10-fold, such as at least about 20-fold, 25-fold, 50-fold, 100-fold, or higher, relative to a control or baseline amount or function, or activity, or concentration.

30 As used herein, the terms “increased expression” and/or “increased activity” of a substance, such as KRAS G12D, in a sample or cancer or patient, typically refers to an increase in the amount of the substance (e.g., of the KRAS G12D mutant protein), although it may also denote an increase in the biological activity of the substance. For example, an increase can be by an amount of about 5%, e.g., about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%,

90%, or 95%, such as about 96%, 97%, 98%, 99%, or 100%. Thus, the increase can be about 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, or 10-fold, such as about 20-fold, 25-fold, 50-fold, 100-fold, or higher, relative to the amount (or activity) of the substance, such as KRAS G12D, in a control sample or control samples, such as an individual or group of individuals who are not suffering from the disease or disorder (e.g., cancer) or an internal control, as determined by techniques known in the art. A subject can also be determined to have an "increased expression" or "increased activity" of KRAS G12D if the expression and/or activity of KRAS G12D is increased by one standard deviation, two standard deviations, three standard deviations, four standard deviations, five standard deviations, or more, relative to the mean (average) or median amount of KRAS G12D in a control group of samples or a baseline group of samples or a retrospective analysis of patient samples. As practiced in the art, such control or baseline expression levels can be previously determined, or measured prior to the measurement in the sample or cancer or subject, or can be obtained from a database of such control samples.

As used herein, the term "pharmaceutically acceptable excipient" encompasses any of the standard pharmaceutical excipients, for example as described in Remington's Pharmaceutical Sciences (20th ed., Mack Publishing Co. 2000). Such excipients include carriers such as a phosphate buffered saline solution, water, and emulsions, such as an oil/water or water/oil emulsion, and various types of wetting agents. Pharmaceutical compositions also can include stabilizers, preservatives, adjuvants, fillers, binders, lubricants, and the like.

As used herein, the term "alkyl" means a saturated linear or branched functional group consisting essentially of carbon atoms and a corresponding number of hydrogen atoms. Exemplary alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, etc. Other alkyl groups will be readily apparent to those of skill in the art given the benefit of the present disclosure. The terms "(C₁-C₃)alkyl", "(C₁-C₆)alkyl", etc., have equivalent meanings, i.e., a saturated linear or branched functional group consisting essentially of 1 to 3 (or 1 to 6) carbon atoms and a corresponding number of hydrogen atoms. The definition of "alkyl" also applies in the context of other functional groups which comprise alkyl groups, such as "-O(C₁-C₃)alkyl-". The term "haloalkyl" means an alkyl group which is substituted by one or more halogens. Exemplary haloalkyl groups include trifluoromethyl, trifluoroethyl, difluoroethyl, pentafluoroethyl, chloromethyl, etc. One or more carbon atoms in the backbone of the alkyl group may be substituted by (or bonded to) a heteroatom by a multiple bond (e.g., a double bond); for example, a carbon atom of the alkyl group may be bonded to oxygen via a double bond (i.e., substituted by oxo to provide a carbonyl function). The presence of such a substituent does not prevent the carbon backbone of the group being considered as an alkyl group.

As used herein, the term “alkenyl” means an unsaturated linear or branched functional group consisting essentially of carbon atoms and a corresponding number of hydrogen atoms and comprising at least one carbon-carbon double bond. Exemplary alkenyl groups include ethenyl, 1-propenyl, 2-propenyl (isopropenyl), etc. Other alkenyl groups will be readily apparent to those of skill in the art given the benefit of the present disclosure. The terms “(C₂-C₃)alkenyl”, “(C₂-C₆)alkenyl”, etc., have equivalent meanings, i.e., an unsaturated linear or branched functional group consisting essentially of 2 to 3 (or 2 to 6) carbon atoms and a corresponding number of hydrogen atoms. The definition of “alkenyl” also applies in the context of other functional groups which comprise alkenyl groups, such as “-O(C₂-C₃)alkenyl-”. The term “haloalkenyl” means an alkenyl group which is substituted by one or more halogens. Where valency permits, one or more carbon atoms in the backbone of the alkenyl group may be substituted by (or bonded to) a heteroatom by a multiple bond (e.g., a double bond); for example, a carbon atom of the alkenyl group may be bonded to oxygen via a double bond (i.e., substituted by oxo to provide a carbonyl function), provided that such carbon atom is not participating in a carbon-carbon double bond. The presence of such a substituent does not prevent the carbon backbone of the group being considered as an alkenyl group.

As used herein, the term “alkynyl” means an unsaturated linear or branched functional group consisting essentially of carbon atoms and a corresponding number of hydrogen atoms and comprising at least one carbon-carbon triple bond. Exemplary alkynyl groups include ethynyl, 1-propynyl, 2-propynyl (propargyl), etc. Other alkynyl groups will be readily apparent to those of skill in the art given the benefit of the present disclosure. The terms “(C₂-C₃)alkynyl”, “(C₂-C₆)alkynyl”, etc., have equivalent meanings, i.e., an unsaturated linear or branched functional group consisting essentially of 2 to 3 (or 2 to 6) carbon atoms and a corresponding number of hydrogen atoms. The definition of “alkynyl” also applies in the context of other functional groups which comprise alkynyl groups, such as “-O(C₂-C₃)alkynyl-”. The term “haloalkynyl” means an alkynyl group which is substituted by one or more halogens. Where valency permits, one or more carbon atoms in the backbone of the alkynyl group may be substituted by (or bonded to) a heteroatom by a multiple bond (e.g., a double bond); for example, a carbon atom of the alkynyl group may be bonded to oxygen via a double bond (i.e., substituted by oxo to provide a carbonyl function), provided that such carbon atom is not participating in a carbon-carbon double or triple bond. The presence of such a substituent does not prevent the carbon backbone of the group being considered as an alkynyl group.

As used herein, the term “cyclic group” means a saturated, partially or fully unsaturated, or aromatic group having at least 3 to 10 atoms (i.e., ring atoms) that form a ring. Where a cyclic group is defined as having a certain number of members, the term “members”, “membered” and the like is used to denote the number of ring atoms in said cyclic group. For example, a 5-membered cyclic group (e.g.,

a 5-membered heterocyclic group) contains 5 ring atoms. It will be appreciated that a cyclic group may be part of a larger cyclic system; for example, bicyclo[4.3.0]nonane comprises two carbocyclic groups, namely a cyclohexane group and a cyclopentane group, which are fused to form the carbocyclic system which makes up the molecule. The term “cyclic group” is intended to encompass both carbocyclic groups as well as heterocyclic groups. The term “carbocyclic” refers to a group having at least 3 to 10 carbon atoms that form a ring. The term “heterocyclic” refers to a group having at least 3 to 10 atoms that form a ring, wherein at least 1 to 9 of said ring atoms are carbon and the remaining at least 1 to 9 ring atom(s) (i.e., hetero ring atom(s)) are selected independently from the group consisting of nitrogen, sulfur, and oxygen. The term “heterocyclic group” thus encompasses saturated, unsaturated and aromatic (i.e. heteroaryl) groups unless context clearly dictates otherwise (e.g. by specifically requiring a “saturated heterocyclic” group, an “unsaturated heterocyclic” group, or an “aromatic heterocyclic” group), whereas e.g. a “heterocycloalkyl” group must be saturated, a “heterocycloalkenyl” group must be unsaturated, and a “heteroaryl” group must be aromatic.

The term “spiro” or “spirocyclic” as used herein in relation to cyclic groups denotes that a first cyclic group within a multicyclic system is attached to a second cyclic group within said multicyclic system, wherein the ring atoms of said first cyclic group and the ring atoms of said second cyclic group have only one atom in common, i.e., said first and second cyclic groups share only one common ring atom. For example, the spiro[5.5]undecanyl group comprises two cyclohexane rings which have a single carbon ring atom in common.

The term “fused” as used herein in relation to cyclic groups denotes that a first cyclic group within a multicyclic system is attached to a second cyclic group within said multicyclic system, wherein the ring atoms of said first cyclic group and the ring atoms of said second cyclic group have two adjacent atoms in common, i.e., said first and second cyclic groups share two common ring atoms. For example, the bicyclo[4.4.0]decanyl group comprises two cyclohexane rings which have two adjacent carbon ring atoms in common.

The term “bridged” as used herein in relation to cyclic groups denotes that a first cyclic group within a multicyclic system is attached to a second cyclic group within said multicyclic system, wherein the ring atoms of said first cyclic group and the ring atoms of said second cyclic group have more than two adjacent atoms in common, i.e., said first and second cyclic groups share three or more common ring atoms. For example, the bicyclo[3.3.1]nonanyl group comprises two cyclohexane rings which have three adjacent carbon ring atoms in common.

Within the structural formulae described herein, any ring system (including any spiro, fused, or bridged ring system) may be connected to other parts of a molecule through any atom having suitable valency. For example, a bicyclic ring may be connected to another part of the molecule through a ring atom

(e.g., a secondary carbon atom or heteroatom such as N), or a bridgehead (e.g., a tertiary carbon atom). Spiro, fused, and bridged rings may be fully unsaturated, partially unsaturated, or fully saturated, and may have aromatic character in one or more of their constituent rings.

As used herein, the term “cycloalkyl” means a saturated group having at least 3 to 10 carbon atoms (i.e., ring atoms) that form a ring. Exemplary cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. It will be appreciated that the cycloalkyl group may be monocyclic or multicyclic (e.g., fused, bridged, or spirocyclic). In the case of multicyclic cycloalkyl groups, there are further rings, e.g., 1 or more further rings, all of which contain from 3 to 7 carbon atoms (i.e., ring atoms). Exemplary cycloalkyl groups having such further rings include bicyclo[1.1.1]pentanyl. The term “(C₃-C₇)cycloalkyl” denotes that the cycloalkyl group contains from 3 to 7 carbon atoms in the ring portion of the group, which may be monocyclic or multicyclic (e.g., fused, bridged, or spirocyclic), for example cyclopropanyl (having 3 ring carbon atoms) or bicyclo[1.1.1]pentanyl (having 5 ring carbon atoms). One or more ring atoms of the cycloalkyl group may be substituted by (i.e., bonded to) a heteroatom by a double bond (e.g., cycloalkyl substituted by oxo). The presence of such a substituent does not prevent the carbon backbone of the group being considered as a cycloalkyl group.

As used herein, the term “cycloalkenyl” means an unsaturated (i.e., partially or fully unsaturated) group having at least 3 to 10 carbon atoms (i.e., ring atoms) that form a ring. The term “cycloalkenyl” is not intended to encompass cyclic groups having aromatic character (those being considered as aryl groups as defined herein). Exemplary cycloalkenyl groups include cyclohexenyl. It will be appreciated that the cycloalkenyl group may be monocyclic or multicyclic (e.g., bridged). In the case of multicyclic cycloalkenyl groups, there are further rings, e.g., 1 or more further rings, all of which contain from 3 to 10 carbon atoms (i.e., ring atoms). Those further rings may be saturated or unsaturated. Exemplary cycloalkenyl groups having such further rings include bicyclo[2.2.1]hept-5-enyl. The term “(C₄-C₈)cycloalkenyl” denotes that the cycloalkenyl group contains from 4 to 8 carbon atoms in the ring portion of the group, for example cyclohexenyl (having 6 ring carbon atoms) or bicyclo[2.2.1]hept-5-enyl (having 7 ring carbon atoms). The double bond (or bonds) within the cycloalkenyl group is/are typically between ring carbon atoms (i.e., endocyclic), although may also be between one ring carbon atom and an adjacent non-ring carbon atom (i.e., exocyclic).

As used herein, the term “aryl” means an aromatic group having at least 6 carbon atoms (i.e., ring atoms) that form a ring. It will be appreciated that the aryl group may be monocyclic or multicyclic (e.g., fused). In the case of multicyclic aryl groups, there are further rings, e.g. 1 or more further rings, all of which contain at least 3 carbon atoms (i.e., ring atoms). The further rings may also contain one or more heteroatoms and they may be saturated, unsaturated, or aromatic. A multicyclic aryl group is

typically attached to the rest of the molecule via an aromatic ring, and typically not via a ring containing a heteroatom. In embodiments, the multicyclic aryl group does not contain any ring heteroatoms. Examples of aryl groups include phenyl and naphthalenyl, as well as indenyl and indanyl groups. Other aryl groups include, for example, tetrahydroisoquinolinyl bonded to the rest of the molecule via its phenyl ring. The term “(C₆-C₁₀)aryl” denotes that the aryl group contains from 6 to 10 carbon atoms in the ring portion of the group, which may be monocyclic or multicyclic (e.g., fused), for example phenyl (having 6 ring carbon atoms) or indanyl (having 9 ring carbon atoms).

As used herein, the term “heterocycloalkyl” means a saturated group having at least 3 to 10 atoms (i.e., ring atoms) that form a ring, wherein at least 1 to 9 of said ring atoms are carbon and the remaining at least 1 to 9 ring atom(s) (i.e., hetero ring atom(s)) are selected independently from the group consisting of nitrogen, sulfur, and oxygen. For example, the term “4- to 10-membered heterocycloalkyl” means a saturated group containing from 4 to 10 ring atoms, of which one or more is a hetero ring atom. Heterocycloalkyl rings may have oxo substituents, typically adjacent to a heteroatom (e.g., 2-oxopyrrolidinyl), but the oxygen atom does not form part of the ring and is excluded from the number of ring atoms. The presence of such a substituent does not prevent the ring (or rings) of the group being considered as a heterocycloalkyl group. Exemplary heterocycloalkyl groups include tetrahydrofuranyl, piperidinyl, morpholinyl and piperazinyl. Any ring sulfur atom may optionally carry one or more pendant (i.e., non-ring) oxygen atoms, as found in, e.g., a sulfolanyl group. In the case of multicyclic heterocyclic groups, there are further rings, e.g., 1 or more further rings, all of which contain from 3 to 7 ring atoms selected from carbon, nitrogen, sulfur, and oxygen. The further rings may be saturated, or partially or fully unsaturated (e.g., having aromatic character). Multicyclic heterocyclic groups include fused, bridged, and spirocyclic ring systems. Where a multicyclic heterocycloalkyl group contains an unsaturated fused ring, the group is typically not bonded to the rest of the molecule via that fused ring. Exemplary heterocyclic groups having such further rings include 2-oxaspiro[3.3]heptanyl, tetrahydroisoquinolinyl, 1-azaspiro[3.3]heptan-2-onyl, and 2-azabicyclo[4.1.0]heptanyl. Where a heterocycloalkyl group is described as being “X- to Y-membered” (where X and Y are integers), this means that the heterocycloalkyl group contains a total number of ring atoms from X to Y. Thus, for example, a “4- to 7-membered heterocycloalkyl group” contains a total of 4, 5, 6, or 7 ring atoms, for example tetrahydropyranyl (6 ring atoms).

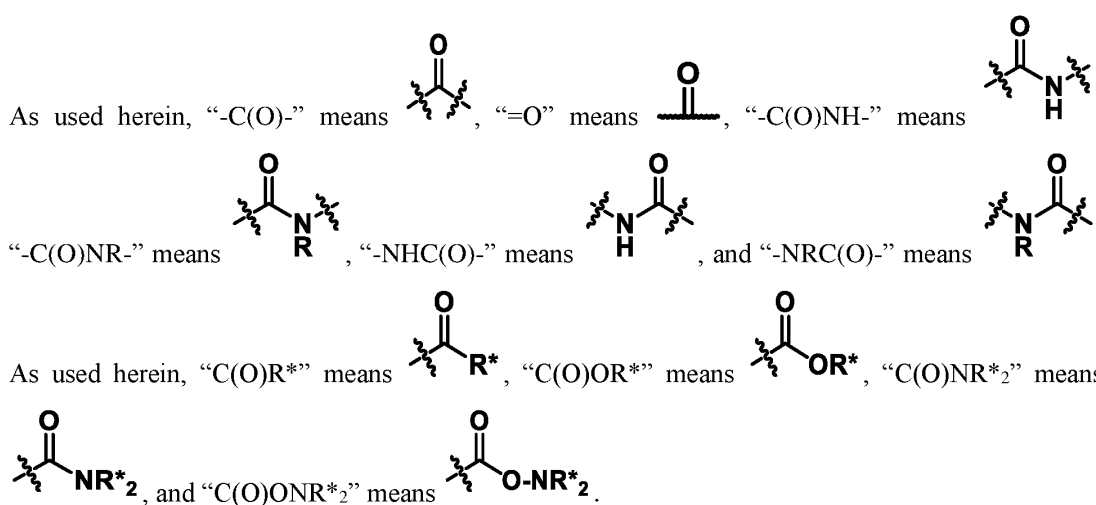
As used herein, the term “heterocycloalkenyl” means an unsaturated (i.e., partially or fully unsaturated) group having at least 3 to 6 atoms (i.e., ring atoms) that form a ring, wherein at least 1 to 5 of said ring atoms are carbon and the remaining at least 1 to 5 ring atom(s) (i.e., hetero ring atom(s)) are selected independently from the group consisting of nitrogen, sulfur, and oxygen. Heterocycloalkenyl rings may have oxo substituents, typically adjacent to a heteroatom, but the

- oxygen atom does not form part of the ring and is excluded from the number of ring atoms. Exemplary heterocycloalkenyl groups include tetrahydropyridyl. Any ring sulfur atom may optionally carry one or more pendant (i.e., non-ring) oxygen atoms. It will be appreciated that the heterocycloalkenyl group may be monocyclic or multicyclic (e.g., bridged). In the case of multicyclic heterocycloalkenyl groups,
- 5 there are further rings, e.g., 1 or more further rings, all of which contain from 3 to 6 ring atoms selected from carbon, nitrogen, sulfur, and oxygen. Said further rings may be saturated, or partially or fully unsaturated (e.g., having aromatic character). Multicyclic heterocycloalkenyl groups include fused, bridged, and spirocyclic ring systems. Where a multicyclic heterocycloalkenyl group contains an unsaturated fused ring, the group is typically not bonded to the rest of the molecule via that fused ring.
- 10 Exemplary heterocycloalkenyl groups having such further rings include tetrahydroindolyl. Where a heterocycloalkenyl group is described as being “X- to Y-membered”, this means that the heterocycloalkenyl group contains a total number of ring atoms from X to Y. Thus, for example, a “5- to 8-membered heterocycloalkenyl group” contains a total of 5, 6, 7, or 8 ring atoms, for example dihydropyranyl (6 ring atoms).
- 15 As used herein, the term “heteroaryl” means an aromatic (i.e., having aromatic character) group typically containing from 5 to 10 ring atoms, wherein 1 to 9 of said ring atoms are carbon and the remaining 1 to 9 ring atom(s) (i.e., hetero ring atom(s)) are selected independently from the group consisting of nitrogen, sulfur, and oxygen. It will be appreciated that the heteroaryl group may be monocyclic or multicyclic (e.g., fused). In the case of multicyclic heteroaryl groups, there are further
- 20 rings, e.g., 1 or more further rings, all of which contain at least 3 atoms (i.e., ring atoms), which further rings may optionally be aromatic. Examples of heteroaryl groups include monocyclic groups such as pyridyl and 2-oxopyridinyl, as well as multicyclic groups such as indolyl. Where a heteroaryl group is described as being “X- to Y-membered”, this means that the heteroaryl group contains a total number of ring atoms from X to Y. Thus, for example, a “5- to 10-membered heteroaryl group” contains a total
- 25 of 5, 6, 7, 8, 9, or 10 ring atoms, for example indolyl (9 ring atoms). A heteroaryl group may equivalently be described as a “C_x heteroaryl” group where the number corresponding to subscript x refers to the total number of ring atoms including the heteroatom(s) and carbon atoms in the ring. Thus, for example, a “C₅ heteroaryl” group contains a total of 5 ring atoms including any heteroatom(s) provided that at least one heteroatom is present.
- 30 As used herein, the term “hydrogen” or “H” includes ¹H and ²H (deuterium, “D”). Thus, references to e.g., OH, (C₁-C₆)alkyl, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl groups, etc. include such groups which are partly or fully deuterated as well as non-deuterated groups. For example, references to “OH” or “hydroxy” therefore include OD, and references to “C₁ alkyl”, “methyl”, “Me”, or “CH₃” therefore include e.g., CD₃.

As used herein, the terms “halo” and “halogen” mean fluorine, chlorine, bromine, or iodine. These terms are used interchangeably and may refer to a halogen functional group or to a halogen atom as such. Those of skill in the art will readily be able to ascertain which is intended in the context in which this term is used in the present disclosure.

- 5 As used herein, the term “CN” means a functional group having a carbon atom linked to a nitrogen atom via a triple bond. The CN group is attached via its carbon atom.

As used herein, the term “oxo” means a functional group wherein an oxygen atom is connected to the atom bearing this group via a double bond. For example, where a carbon atom carries an oxo group it forms a carbon-oxygen double bond. It will be appreciated that not all atoms within a given structure
 10 can be substituted by oxo, and that this will depend on the free valency of the atom to be substituted.



- 15 The compounds of the present disclosure are described, *inter alia*, by way of structural formulae. It will be appreciated that these formulae typically show only one form (e.g., resonance form, tautomeric form, etc.) of the compound, whereas certain compounds may exist in more than one such form. This will be readily apparent to the skilled reader. The present disclosure includes all possible tautomers of the compounds characterised by the structural formulae hereinbefore and below, including as single
 20 tautomers, or as any mixture of tautomers in any ratio. It will also be appreciated that certain of the present compounds may exist in one or more isomeric (e.g., stereoisomeric) forms. The present disclosure includes all possible stereoisomers, enantiomers, diastereomers, etc. of the compounds described hereinbefore and below, as well as cis- and trans- forms and conformers of the same. The purification and the separation of isomers may be accomplished by methods described hereinafter, as
 25 well as by techniques known in the art. For example, optical isomers of the compounds can be obtained by resolution of the racemic mixture of diastereoisomeric salts thereof (e.g., using an optically active acid or base, or by the formation of covalent diastereomers). A different process for separation of

optical isomers involves the use of chiral chromatography (e.g., HPLC columns using a chiral phase), with or without conventional derivatization. Enzymatic separation, with or without derivatisation, may also be useful, and optically active compounds of the present disclosure can likewise be obtained by chiral syntheses utilizing optically active starting materials. The present disclosure includes all possible stereoisomers of the compounds described herein as single stereoisomers, or as any mixture of said stereoisomers, e.g., (R)- or (S)- isomers, in any ratio.

The compounds of the disclosure may exist in the form of free acids or bases, or may exist as addition salts with suitable acids or bases. For example, basic compounds of Formula (0) (*e.g.* basic compounds of Formula (I)) may be provided as pharmaceutically acceptable acid addition salts with an acid such as HCl. Methods for forming salts are described below and are also known in the art (see, e.g., Berge *et al.*, J Pharm Sci. (1977) 66:1-19).

As used herein, the term “pharmaceutically acceptable” when used in connection with salts means a salt of a currently disclosed compound that may be administered without any resultant substantial undesirable biological effect(s) or any resultant deleterious interaction(s) with any other component of a pharmaceutical composition in which it may be contained.

The recitation of a listing of chemical groups in any definition of a variable herein includes definitions of that variable as any single group or combination of listed groups. The recitation of an embodiment for a variable or aspect herein includes that embodiment as any single embodiment or in combination with any other embodiments or portions thereof.

Compositions and methods provided herein may be combined with one or more of any of the other compositions and methods provided herein.

The following abbreviations and empirical formulae are used herein:

	Ac	acetyl <i>or</i> acetate (e.g., AcOK = potassium acetate)
	AcOH	acetic acid
25	aq.	aqueous
	atm	atmosphere(s)
	Bn	benzyl
	Boc <i>or</i> BOC	tert-butyloxy carbonyl
	BSA	bovine serum albumin
30	cataCXium® A-Pd-G3	Mesylate[(di(1-adamantyl)-n-butylphosphine)-2-(2'-amino-1,1'-biphenyl)]palladium(II), [(Di(1-adamantyl)-butylphosphine)-2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate; CAS number 1651823-59-4

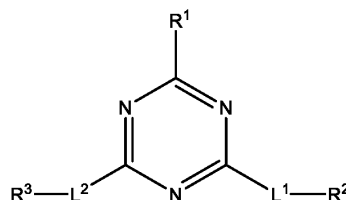
	CHAPS	3-((3-cholamidopropyl)dimethylammonio)-1-propanesulfonate
	COSY	correlation spectroscopy
	DavePhos	2-dicyclohexylphosphino-2'-(<i>N,N</i> -dimethylamino)biphenyl
	dba	dibenzylideneacetone
5	DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
	DCM	dichloromethane
	DIPA	diisopropylamine
	DIPEA <i>or</i> DIEA	diisopropylethylamine
	DMEM	Dulbecco's modified eagle medium
10	DMF	<i>N,N</i> -dimethylformamide
	DMSO	dimethyl sulfoxide
	Dppf	1,1'-bis(diphenylphosphino)ferrocene
	DPPP	1,3-bis(diphenylphosphino)propane
	DTT	dithiothreitol
15	EA	ethyl acetate
	ee	enantiomeric excess
	ELSD	evaporative light scattering detection
	eq <i>or</i> equiv	equivalent(s)
	ERK	extracellular signal-related kinase
20	ESI-MS	electrospray ionization mass spectrometry
	Et	ethyl
	EtOAc <i>or</i> AcOEt	ethyl acetate
	FBS	fetal bovine serum
	GDP	guanosine diphosphate
25	HATU	hexafluorophosphate azabenzotriazole tetramethyl uronium
	HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
	HMBC	heteronuclear multiple bond coherence
	HPLC	high performance liquid chromatography
	HSQC	heteronuclear single quantum correlation
30	<i>i</i> -PrOH	isopropyl alcohol
	KRAS G12Dhu	human KRAS G12D
	LC	liquid chromatography
	LCMS	liquid chromatography / mass spectrometry
	LDA	lithium diisopropylamide
35	LiHMDS	lithium bis(trimethylsilyl)amide

	mCPBA	meta-chloroperoxybenzoic acid
	Me	methyl
	MOM	methoxy methyl ether
	MOMBR	bromomethyl methyl ether
5	MS	mass spectrometry
	MW	molecular weight
	NBS	N-bromo succinimide
	NMR	nuclear magnetic resonance
	OTf	triflate
10	PDA	photodiode array
	PE	petroleum ether
	PE/EA	petroleum ether/ethyl acetate
	Pd/C	palladium on carbon
	Pd(OAc) ₂	palladium(II) diacetate
15	PE	petroleum ether
	Ph	phenyl
	p-Tol.	<i>para</i> -tolyl
	ROESY	rotational nuclear Overhauser effect spectroscopy
	RPMI-1640	Roswell Park Memorial Institute 1640 Medium
20	RT	room temperature; (for LCMS) retention time
	SPR	Surface Plasmon Resonance
	TBAB	tetrabutylammonium bromide
	TBSCl	<i>tert</i> -butyldimethylsilyl chloride
	TCEP	tris (2-carboxyethyl)phosphine
25	TEA	triethylamine
	TFA	trifluoroacetic acid
	THF	tetrahydrofuran
	TIPS	triisopropylsilane
	TLC	thin layer chromatography
30	TR-FRET	time-resolved Förster Resonance Energy Transfer
	UHP	urea hydrogen peroxide
	UV	ultraviolet
	w	(for cell cultures) well; thus e.g., 96w = 96-well
	WT	wild-type

	Xantphos	9,9-Dimethyl-9H-xanthene-4,5-diylbis(diphenylphosphane); CAS Registry No. 161265-03-8
5	Xantphos Pd G4 (SP-4-3)-[[5-(diphenylphosphino)-9,9-dimethyl-9H-xanthen-4-yl]diphenylphosphine-κP](methanesulfonato-κO)[2'-(methylamino-κN)[1,1'-biphenyl]-2-yl-κC]- Palladium ; CAS Registry No. 1621274-19-8	
	XPhos	2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl; CAS Registry No. 564483-18-7
10	XPhos PdG3	2-Dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate; CAS Registry No. 1445085-55-1

Compounds

In a first aspect the present disclosure provides a compound of Formula (0):



(Formula (0))

or a pharmaceutically acceptable salt thereof, wherein:

- R¹ is a 6- to 10-membered, monocyclic or bicyclic heterocycloalkyl or heterocycloalkenyl group comprising at least one ring atom which is N, and wherein R¹ is optionally substituted by one or more groups independently selected from =O, CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)OH, C(O)NH₂, C(O)ONH₂, C(O)R*, C(O)OR*, OC(O)R*, C(O)NHR*, CH₂C(O)NHR*, C(O)NR*₂, CH₂C(O)NR*₂, C(O)ONHR*, CH₂C(O)ONHR*, C(O)ONR*₂ and CH₂C(O)ONR*₂; or wherein R¹ is -L³-R^{1'}, wherein R^{1'} is a 5-membered, monocyclic heterocycloalkyl or heterocycloalkenyl group comprising at least one ring atom which is N, and wherein R^{1'} is optionally substituted by one or more groups independently selected from =O, CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)OH, C(O)NH₂, C(O)ONH₂, C(O)R*, C(O)OR*, C(O)NHR*, C(O)NR*₂, C(O)ONHR*, and C(O)ONR*₂;

R² is a 5- to 9-membered, monocyclic or bicyclic heterocycloalkyl or heterocycloalkenyl group comprising at least one ring atom which is N or O; a 5- or 6-membered monocyclic heteroaryl group comprising at least one ring atom which is N; a fused, 8- to 10-membered bicyclic group wherein one or both rings are aromatic, and wherein at least one ring comprises at least one ring atom which is N;

or a fused, 11- to 14-membered tricyclic group wherein at least one ring is aromatic, and wherein at least one ring comprises at least one ring atom which is N;

and wherein R² may be substituted by one or more groups independently selected from CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)R*, C(O)OH, C(O)OR*, C(O)NH₂, C(O)NHR*, C(O)NR*₂, C(O)ONH₂, C(O)ONHR*, C(O)ONR*₂, =O, (C₂-C₃)alkenyl, and (C₂-C₃)alkynyl;

R³ is a phenyl or naphthalenyl group which is substituted by OH and optionally by one or more additional groups independently selected from CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)R*, C(O)OH, C(O)OR*, C(O)NH₂, C(O)NHR*, C(O)NR*₂, C(O)ONH₂, C(O)ONHR*, C(O)ONR*₂, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl; or R³ is a fused, 8-to-10-membered bicyclic group comprising a saturated carbocyclic ring fused to a heterocyclic ring, wherein the carbocyclic ring, the heterocyclic ring, or both, may optionally be substituted by one or more groups independently selected from CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)R*, C(O)OH, C(O)OR*, C(O)NH₂, C(O)NHR*, C(O)NR*₂, C(O)ONH₂, C(O)ONHR*, C(O)ONR*₂, NHC(O)R*, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl; or R³ is a fused, 8- to 10-membered bicyclic group comprising a saturated carbocyclic ring fused to an aryl ring, wherein the carbocyclic ring, the aryl ring, or both, may be optionally substituted by one or more groups independently selected from CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)R*, C(O)OH, C(O)OR*, C(O)NH₂, C(O)NHR*, C(O)NR*₂, C(O)ONH₂, C(O)ONHR*, C(O)ONR*₂, NHC(O)R*, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl; or R³ is a fused, 8- to 10-membered bicyclic group comprising a saturated heterocyclic ring fused to an aryl or heteroaryl ring, wherein the carbocyclic ring, the aryl or heteroaryl ring, or both, may be optionally substituted by one or more groups independently selected from CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)R*, C(O)OH, C(O)OR*, C(O)NH₂, C(O)NHR*, C(O)NR*₂, C(O)ONH₂, C(O)ONHR*, C(O)ONR*₂, NHC(O)R*, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl;

L¹ is a bond or is -O-, -(C₁-C₃)alkyl-, *-O-(C₁-C₃)alkyl-**, *-(C₁-C₃)alkyl-O-**, *-C(O)NR'-**, or *-NR'C(O)-**, wherein R' is H, OH, CN, Cl, F, or (C₁-C₃)alkyl, and * denotes a point of attachment to the triazole moiety of the compound of Formula (0) and ** denotes a point of attachment to R²;

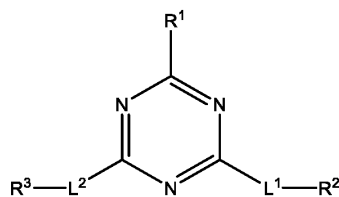
L² is -(C₁-C₃)alkyl-, C₅-heteroaryl optionally substituted with one or more R'', *-O-(C₁-C₃)alkyl-**, *-(C₁-C₃)alkyl-O-**, -(C₂-C₃)alkenyl-, -(C₂-C₃)alkynyl-, *-C(O)NR''-**, *-NR''(C₁-C₃)alkyl-**, *-C(O)NR''-**, *-NR''C(O)-**, *-NR''-(C₁-C₃)alkyl-**, or *-C(O)NR''-**, wherein R'' is H, OH, CN, Cl, F, or (C₁-C₃)alkyl, and wherein * denotes a point of attachment to R³ and ** denotes a point of attachment to the triazole moiety of the compound of Formula (0);

L³ is a bond or is -(C₁-C₃)alkyl-, -O-, -NH- or -N(C₁-C₃)alkyl;

and

- wherein in R^1 , R^2 , and R^3 , each R^* is independently selected from (C₁-C₄)alkyl (*e.g.* C₁-C₃ alkyl), (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkenyl, and 5- or 6-membered monocyclic heteroaryl, wherein said (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkenyl or 5- or 6-membered monocyclic heteroaryl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, NH₂, NH((C₁-C₃)alkyl), (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or O(C₁-C₃) alkyl.

In embodiments, the compound of Formula (0) is a compound of Formula (I):



(Formula I)

- or a pharmaceutically acceptable salt thereof, wherein in Formula (I):
- R^1 is a 6- to 10-membered bridged bicyclic heterocycloalkyl or heterocycloalkenyl group comprising at least one ring atom which is N, and wherein R^1 is optionally substituted by one or more groups independently selected from =O, CN, Cl, F, R^* , OH, OR^* , NH₂, NHR^* , NR^{*2} , CHO, C(O)OH, C(O)NH₂, C(O)ONH₂, C(O) R^* , C(O) OR^* , C(O) NHR^* , C(O) NR^{*2} , C(O)ON $H R^*$, and C(O)ON R^{*2} ;
- R^2 is a 5- to 8-membered, monocyclic or bicyclic heterocycloalkyl or heterocycloalkenyl group comprising at least one ring atom which is N or O; a 5- or 6-membered monocyclic heteroaryl group comprising at least one ring atom which is N; or a fused, 8- to 10-membered bicyclic group wherein one or both rings are aromatic, and wherein at least one ring comprises at least one ring atom which is N;
- and wherein R^2 may be substituted by one or more groups independently selected from CN, Cl, F, R^* , OH, OR^* , NH₂, NHR^* , NR^{*2} , CHO, C(O) R^* , C(O)OH, C(O) OR^* , C(O)NH₂, C(O) NHR^* , C(O) NR^{*2} , C(O)ONH₂, C(O)ON $H R^*$, C(O)ON R^{*2} , =O, (C₂-C₃)alkenyl, and (C₂-C₃)alkynyl;
- R^3 is a phenyl or naphthalenyl group which is substituted by OH and optionally by one or more additional groups independently selected from CN, Cl, F, R^* , OH, OR^* , NH₂, NHR^* , NR^{*2} , CHO, C(O) R^* , C(O)OH, C(O) OR^* , C(O)NH₂, C(O) NHR^* , C(O) NR^{*2} , C(O)ONH₂, C(O)ON $H R^*$, C(O)ON R^{*2} , (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl; or R^3 is a fused, 8-to-10-membered bicyclic group comprising a saturated carbocyclic ring fused to a heterocyclic ring, wherein the carbocyclic ring, the heterocyclic ring, or both, may optionally be substituted by one or more groups independently selected

from CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)R*, C(O)OH, C(O)OR*, C(O)NH₂, C(O)NHR*, C(O)NR*₂, C(O)ONH₂, C(O)ONHR*, C(O)ONR*₂, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl;

L¹ is -O-, -(C₁-C₃)alkyl-, *-O-(C₁-C₃)alkyl-**, *-(C₁-C₃)alkyl-O-**, *-C(O)NR'-**, or *-NR'C(O)-**, wherein R' is H, OH, CN, Cl, F, or (C₁-C₃)alkyl, and * denotes a point of attachment to the triazole moiety of the compound of Formula (I) and ** denotes a point of attachment to R²;

L² is -(C₁-C₃)alkyl-, C₅-heteroaryl optionally substituted with one or more R'', *-O-(C₁-C₃)alkyl-**, *-(C₁-C₃)alkyl-O-**, -(C₂-C₃)alkenyl-, -(C₂-C₃)alkynyl-, *-(C₁-C₃)alkyl-NR''-**, *-NR''(C₁-C₃)alkyl-**, *-C(O)NR''-**, *-NR''C(O)-**, *-NR''-(C₁-C₃)alkyl-**, or *-(C₁-C₃)alkyl-NR''-**, wherein R'' is H, OH, CN, Cl, F, or (C₁-C₃)alkyl, and wherein * denotes a point of attachment to R³ and ** denotes a point of attachment to the triazole moiety of the compound of Formula (I);

and

wherein in R¹, R², and R³, each R* is independently selected from (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, and (C₃-C₆)cycloalkenyl, wherein said (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, or (C₃-C₆)cycloalkenyl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, NH₂, NH((C₁-C₃)alkyl), (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or O(C₁-C₃)alkyl.

In the compounds of the present disclosure, R¹ may be -L³-R^{1'}, wherein R^{1'} is a 5-membered, monocyclic heterocycloalkyl or heterocycloalkenyl group comprising at least one ring atom which is N, and wherein R^{1'} is optionally substituted by one or more groups independently selected from =O, CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)OH, C(O)NH₂, C(O)ONH₂, C(O)R*, C(O)OR*, C(O)NHR*, C(O)NR*₂, C(O)ONHR*, and C(O)ONR*₂, and wherein L³ is a bond or is -(C₁-C₃)alkyl-, -O-, -NH- or -N(C₁-C₃)alkyl and wherein each R* is independently selected from (C₁-C₄)alkyl (e.g. C₁-C₃alkyl), (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkenyl, and 5- or 6-membered monocyclic heteroaryl, wherein said (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkenyl or 5- or 6-membered monocyclic heteroaryl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, NH₂, NH((C₁-C₃)alkyl), (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or O(C₁-C₃)alkyl.

In the compounds of the present disclosure, R¹ may be a 6- to 10-membered, monocyclic or bicyclic heterocycloalkyl or heterocycloalkenyl group comprising at least one ring atom which is N, and wherein R¹ is optionally substituted by one or more groups independently selected from =O, CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)OH, C(O)NH₂, C(O)ONH₂, C(O)R*, C(O)OR*,

OC(O)R*, C(O)NHR*, CH₂C(O)NHR*, C(O)NR*₂, CH₂C(O)NR*₂, C(O)ONHR*, CH₂C(O)ONHR*, C(O)ONR*₂ and CH₂C(O)ONR*₂, wherein each R* is independently selected from (C₁-C₄)alkyl (*e.g.* (C₁-C₃)alkyl), (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkenyl, and 5- or 6-membered monocyclic heteroaryl, wherein said (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkenyl or 5- or 6-membered monocyclic heteroaryl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, NH₂, NH((C₁-C₃)alkyl), (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or O(C₁-C₃) alkyl.

Where R¹ is bicyclic, R¹ may be a bridged bicyclic, fused bicyclic, or spirocyclic group. Thus, R¹ may be a 6- to 10-membered, bicyclic heterocycloalkyl or heterocycloalkenyl group which is a bridged, fused or spirocyclic group comprising at least one ring atom which is N, and wherein R¹ is optionally substituted by one or more groups independently selected from =O, CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)OH, C(O)NH₂, C(O)ONH₂, C(O)R*, C(O)OR*, C(O)NHR*, CH₂C(O)NHR*, C(O)NR*₂, CH₂C(O)NR*₂, C(O)ONHR*, CH₂C(O)ONHR*, C(O)ONR*₂ and CH₂C(O)ONR*₂, wherein each R* is independently selected from (C₁-C₄)alkyl (*e.g.* (C₁-C₃)alkyl), (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkenyl, and 5- or 6-membered monocyclic heteroaryl, wherein said (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkenyl or 5- or 6-membered monocyclic heteroaryl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, NH₂, NH((C₁-C₃)alkyl), (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or O(C₁-C₃) alkyl.

In the compounds of the present disclosure, R¹ may be a 6- to 10-membered, fused bicyclic heterocycloalkyl or heterocycloalkenyl group comprising at least one ring atom which is N, and wherein R¹ is optionally substituted by one or more groups independently selected from =O, CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)OH, C(O)NH₂, C(O)ONH₂, C(O)R*, C(O)OR*, OC(O)R*, C(O)NHR*, CH₂C(O)NHR*, C(O)NR*₂, CH₂C(O)NR*₂, C(O)ONHR*, CH₂C(O)ONHR*, C(O)ONR*₂ and CH₂C(O)ONR*₂, wherein each R* is independently selected from (C₁-C₄)alkyl (*e.g.* (C₁-C₃)alkyl), (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkenyl, and 5- or 6-membered monocyclic heteroaryl, wherein said (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkenyl or 5- or 6-membered monocyclic heteroaryl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, NH₂, NH((C₁-C₃)alkyl), (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or O(C₁-C₃) alkyl.

In the compounds of the present disclosure, R¹ may be a 6- to 10-membered, spirocyclic bicyclic heterocycloalkyl or heterocycloalkenyl group comprising at least one ring atom which is N, and wherein R¹ is optionally substituted by one or more groups independently selected from =O, CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)OH, C(O)NH₂, C(O)ONH₂, C(O)R*, C(O)OR*,

OC(O)R*, C(O)NHR*, CH₂C(O)NHR*, C(O)NR*₂, CH₂C(O)NR*₂, C(O)ONHR*, CH₂C(O)ONHR*, C(O)ONR*₂ and CH₂C(O)ONR*₂, wherein each R* is independently selected from (C₁-C₄)alkyl (*e.g.* (C₁-C₃)alkyl), (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkenyl, and 5- or 6-membered monocyclic heteroaryl, wherein said (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkenyl or 5- or 6-membered monocyclic heteroaryl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, NH₂, NH((C₁-C₃)alkyl), (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or O(C₁-C₃) alkyl.

In the compounds of the present disclosure, R¹ may be a 6- to 10-membered, bridged bicyclic heterocycloalkyl or heterocycloalkenyl group comprising at least one ring atom which is N, and wherein R¹ is optionally substituted by one or more groups independently selected from =O, CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)OH, C(O)NH₂, C(O)ONH₂, C(O)R*, C(O)OR*, OC(O)R*, C(O)NHR*, CH₂C(O)NHR*, C(O)NR*₂, CH₂C(O)NR*₂, C(O)ONHR*, CH₂C(O)ONHR*, C(O)ONR*₂ and CH₂C(O)ONR*₂, wherein each R* is independently selected from (C₁-C₄)alkyl (*e.g.* (C₁-C₃)alkyl), (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkenyl, and 5- or 6-membered monocyclic heteroaryl, wherein said (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkenyl or 5- or 6-membered monocyclic heteroaryl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, NH₂, NH((C₁-C₃)alkyl), (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or O(C₁-C₃) alkyl.

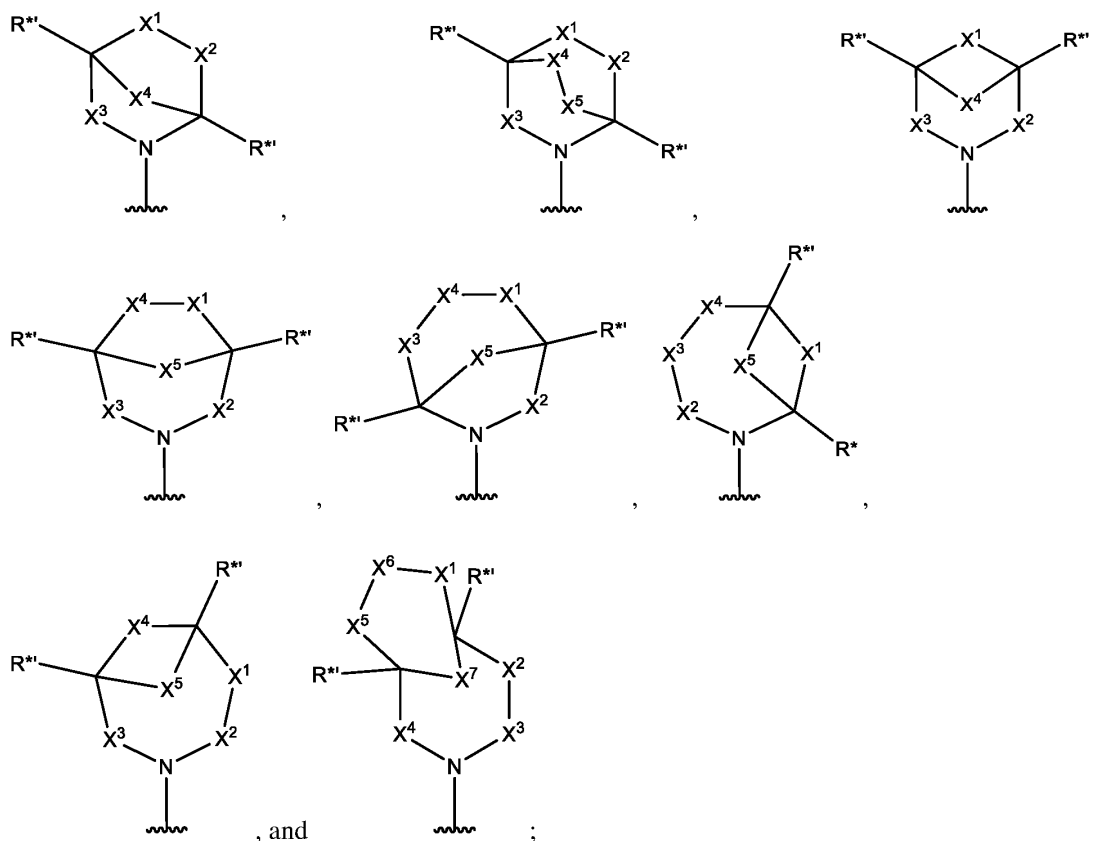
In the compounds of the present disclosure, R¹ may be a 6- to 10-membered bridged bicyclic heterocycloalkyl or heterocycloalkenyl group comprising at least one ring atom which is N, and wherein R¹ is optionally substituted by one or more groups independently selected from =O, CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)OH, C(O)NH₂, C(O)ONH₂, C(O)R*, C(O)OR*, C(O)NHR*, C(O)NR*₂, C(O)ONHR*, and C(O)ONR*₂;

wherein each R* is independently selected from (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, and (C₃-C₆)cycloalkenyl, wherein said (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, or (C₃-C₆)cycloalkenyl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, NH₂, NH((C₁-C₃)alkyl), (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or O(C₁-C₃) alkyl.

R¹ is a heterocycloalkyl or heterocycloalkenyl group as defined above, *i.e.*, R¹ is a saturated or unsaturated heterocyclic group; or R¹ is -L₃-R^{1'}, wherein R^{1'} is a heterocycloalkyl or heterocycloalkenyl group as defined above. Thus, R¹ is non-aromatic.

In embodiments, R¹ is bound to the triazole moiety of the compound of formula (0) (*e.g.* the compound of Formula (I)) through a ring atom of R¹ which is N.

In embodiments, R¹ is selected from:

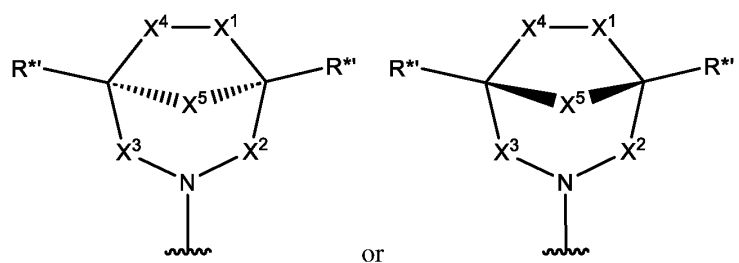


wherein each of X^1 , X^2 , X^3 , X^4 , X^5 , X^6 , and X^7 is independently selected from $C(R^{*'})_2$, $C=O$, $NR^{*'}$,

5 O, and S, and

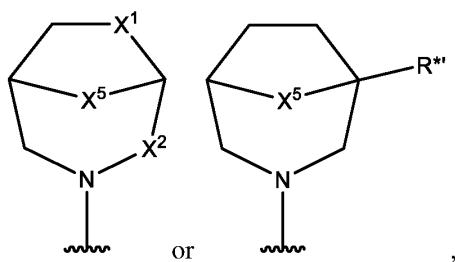
wherein each $R^{*'}$ is independently selected from H, CN, Cl, F, R^* , OR^* , $NR^{*'}_2$, CHO, $C(O)R^*$, $C(O)OR^*$, $C(O)NR^{*'}_2$, and $C(O)ONR^{*'}_2$, wherein R^* is as defined above. In embodiments of $R^{*'}$, R^* is as defined in accordance with Formula (0). In embodiments of $R^{*'}$, R^* is as defined in accordance with Formula (I). In embodiments each $R^{*'}$ is independently selected from H, CH_2CH_3 , $CH_2=CH_2$,
10 and CH_2OCH_3 .

In embodiments, R^1 is



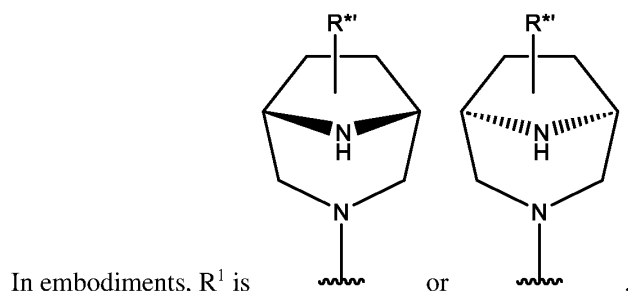
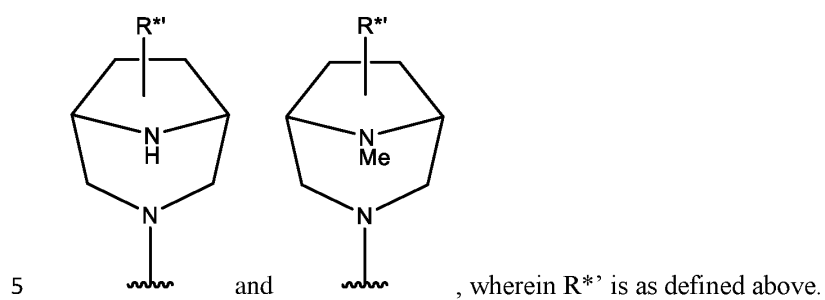
wherein each of X^1 , X^2 , X^3 , X^4 , X^5 , and $R^{*'}$ is as defined above.

In embodiments, R^1 is

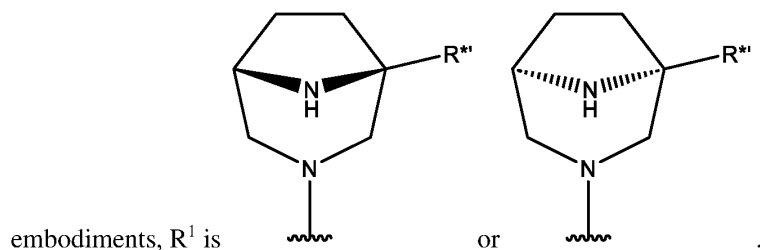
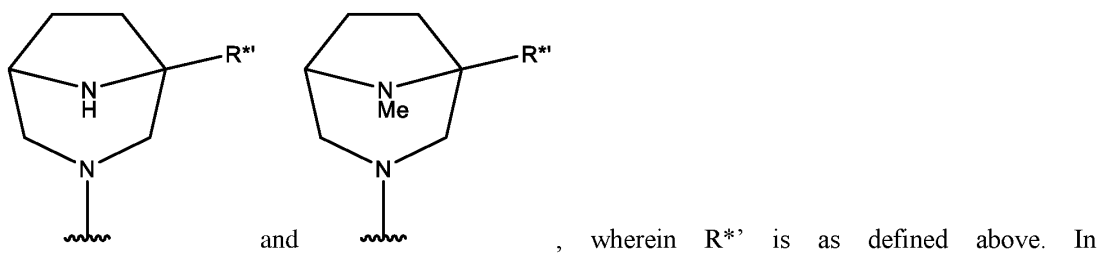


wherein X^1 , X^2 , X^5 and R^{*} are as defined above.

In embodiments, R^1 is selected from



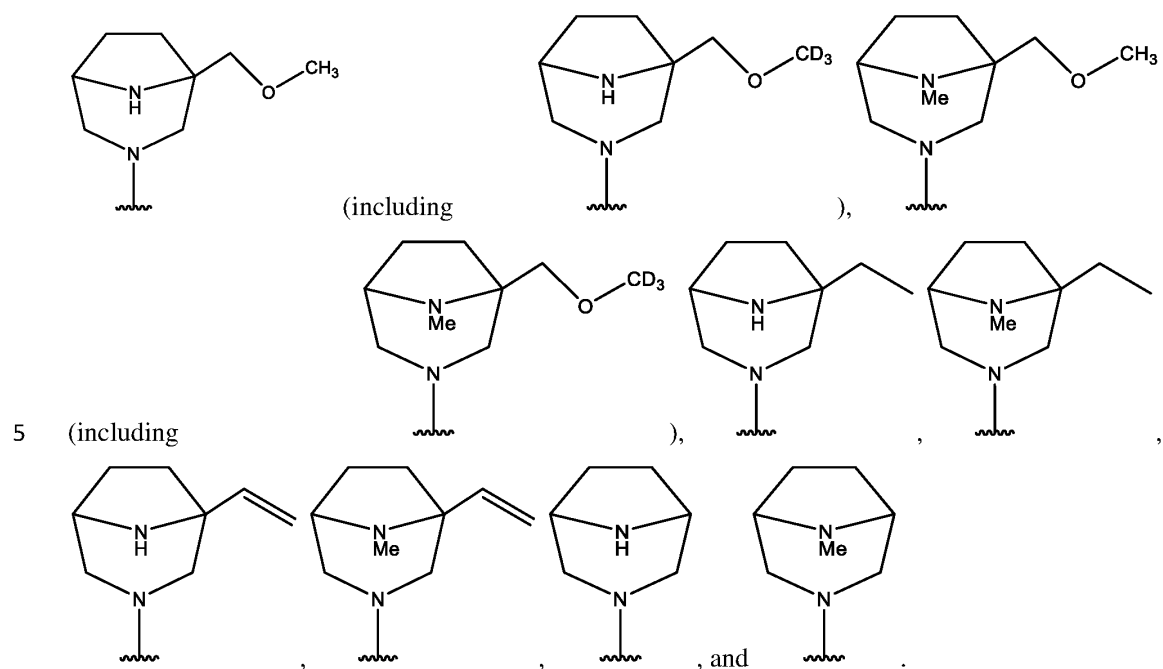
In embodiments, R^1 is selected from



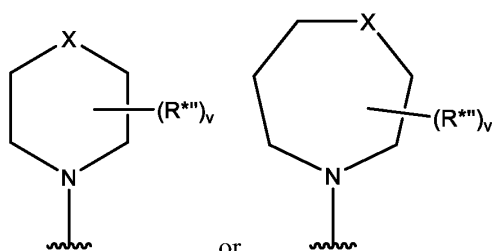
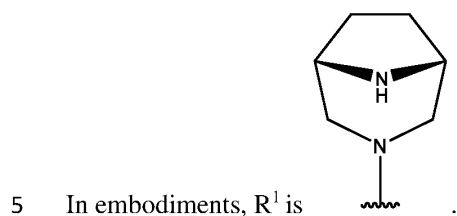
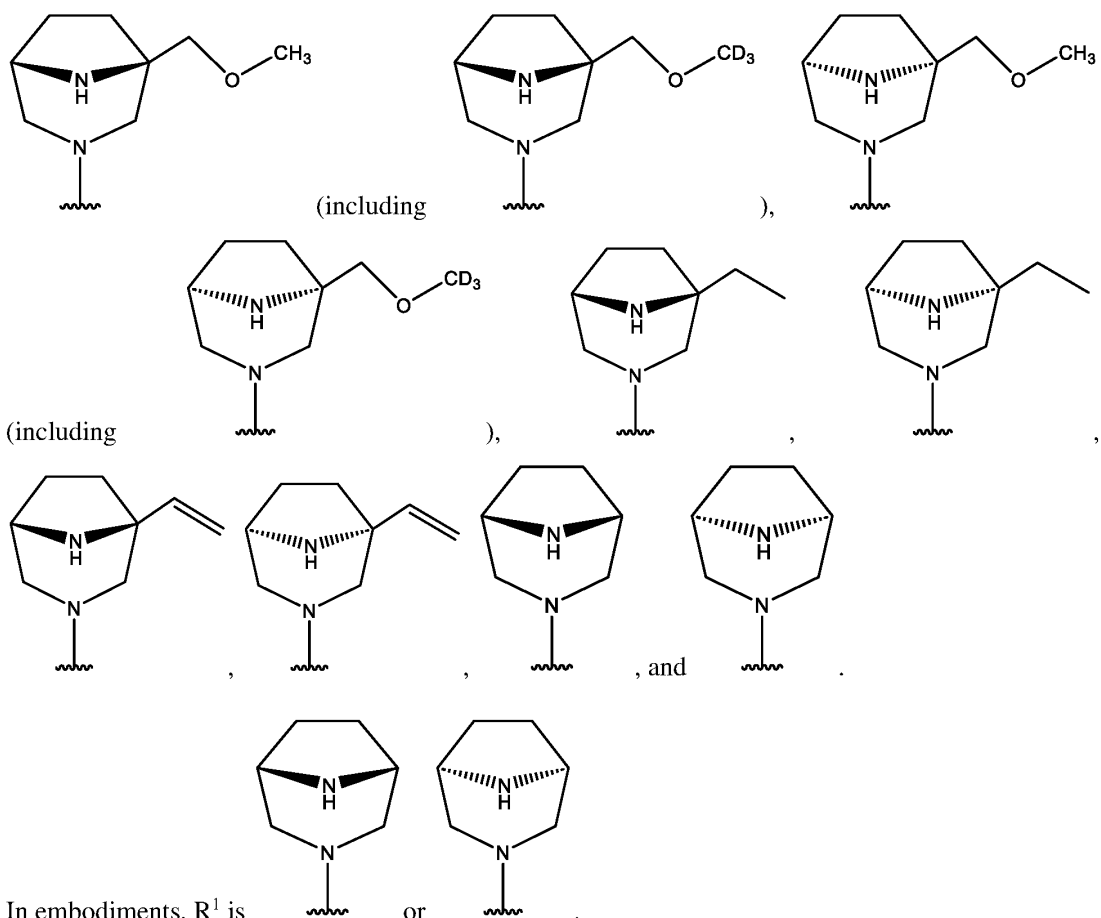
embodiments, R¹ is

or

In embodiments, R¹ is selected from

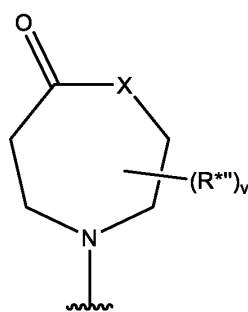


In embodiments, R¹ is selected from



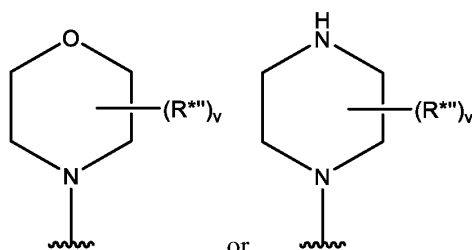
In embodiments, R¹ is  or , wherein X is selected from NH, N(C₁₋₃)alkyl, O, or CH₂; v is an integer from 0 to 4; and each R^{*} is independently selected from H, CN, Cl, F, R^{*}, OH, OR^{*}, NR^{*}₂, CHO, C(O)R^{*}, C(O)OR^{*}, C(O)NR^{*}₂, and C(O)ONR^{*}₂, wherein R^{*} is as defined above. In embodiments of R^{*}, R^{*} is as defined in accordance with Formula (0). In

embodiments of $R^{*''}$, R^* is as defined in accordance with Formula (I). In embodiments, v is 1, 2, 3 or 4. In embodiments, v is 1. In embodiments, v is 2. In embodiments, v is 3. In embodiments, v is 4.



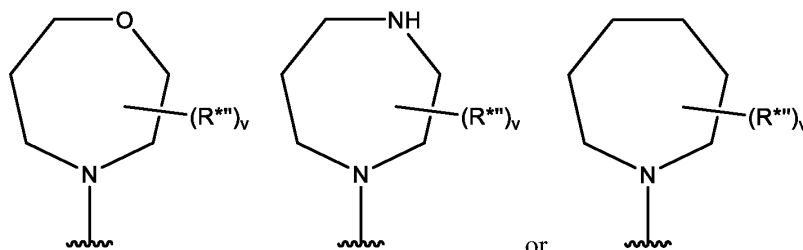
In embodiments, R^1 is , wherein X is selected from NH, $N(C_{1-3})$ alkyl, O, or CH_2 ; v is an integer from 0 to 4; and each $R^{*''}$ is independently selected from H, CN, Cl, F, R^* , OH, OR*, NR^{*}_2 , CHO, $C(O)R^*$, $C(O)OR^*$, $C(O)NR^{*}_2$, and $C(O)ONR^{*}_2$, wherein R^* is as defined above.

5 In embodiments of $R^{*''}$, R^* is as defined in accordance with Formula (0). In embodiments of $R^{*''}$, R^* is as defined in accordance with Formula (I). In embodiments, v is 1, 2, 3 or 4. In embodiments, v is 1. In embodiments, v is 2. In embodiments, v is 3. In embodiments, v is 4.



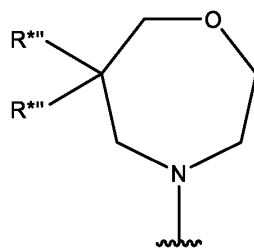
In embodiments, R^1 is  or , wherein v is an integer from 0 to 4; and each $R^{*''}$ is independently a group $R^{*''}$ as defined above. In embodiments, v is 1, 2, 3 or 4. In embodiments, v is 1. In embodiments, v is 2. In embodiments, v is 3. In embodiments, v is 4.

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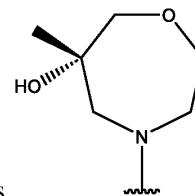
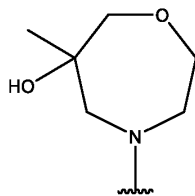
In embodiments, R^1 is , , or , wherein v is an integer from 0 to 4 and each $R^{*''}$ is independently a group $R^{*''}$ as defined above. In embodiments, v is 1, 2, 3 or 4. In embodiments, v is 1. In embodiments, v is 2. In embodiments, v is 3. In embodiments, v is 4.

15



In embodiments, R^1 is

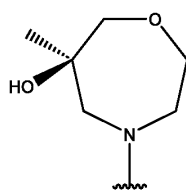
wherein each $R^{*''}$ is independently a group $R^{*''}$ as



defined above. In embodiments, R^1 is

. In embodiments, R^1 is

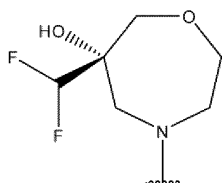
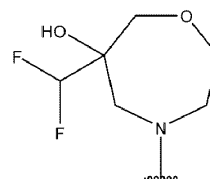
. In



embodiments, R^1 is

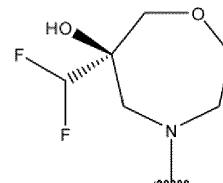
. In embodiments, R^1 is

. In embodiments, R^1

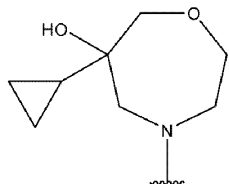


is

. In embodiments, R^1 is

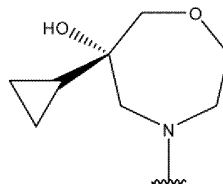


. In embodiments, R^1 is

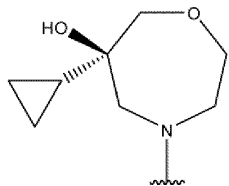


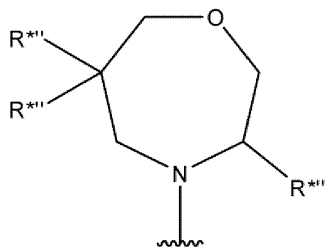
5

. In embodiments, R^1 is



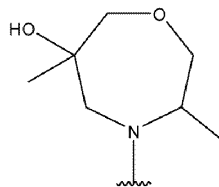
. In embodiments, R^1 is





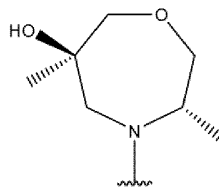
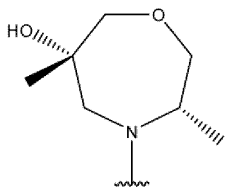
In embodiments, R^I is

wherein each R^{*II} is independently a group R^{*II}



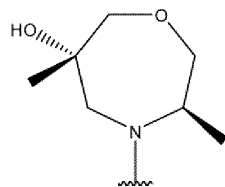
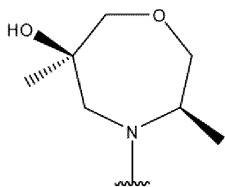
as defined above. In embodiments, R^I is

. In embodiments, R^I is



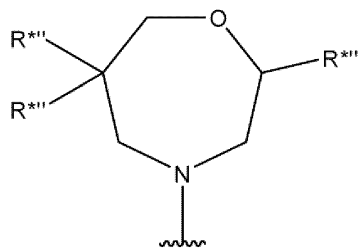
. In embodiments, R^I is

. In embodiments, R^I is



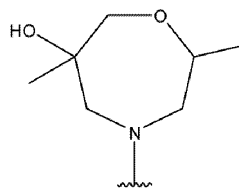
. In embodiments, R^I is

.



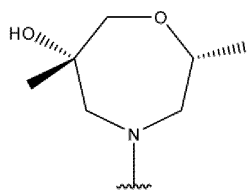
5 In embodiments, R^I is

wherein each R^{*II} is independently a group

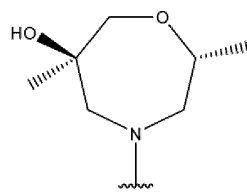


R^{*II} as defined above. In embodiments, R^I is

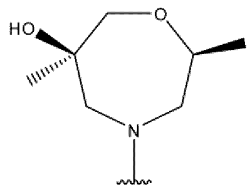
. In embodiments, R^I is



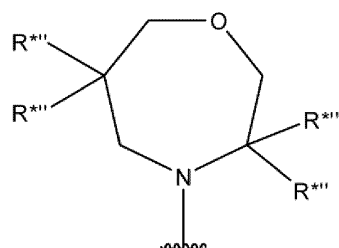
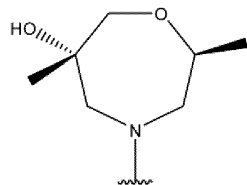
. In embodiments, R^1 is



. In embodiments, R^1 is

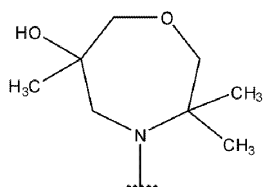


. In embodiments, R^1 is



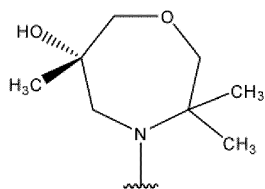
In embodiments, R^1 is

wherein each $R^{*''}$ is independently a group

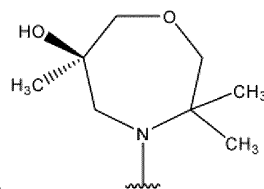


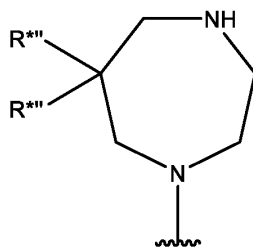
$R^{*''}$ as defined above. In embodiments, R^1 is

. In embodiments, R^1 is

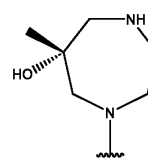
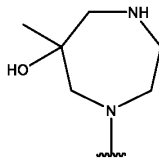


. In embodiments, R^1 is

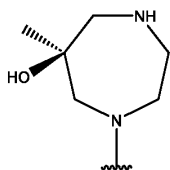




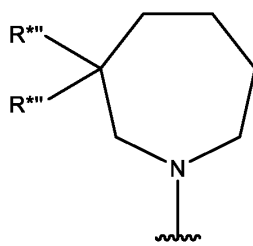
In embodiments, R^1 is  wherein each R^{*11} is independently a group R^{*11} as



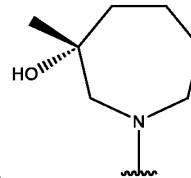
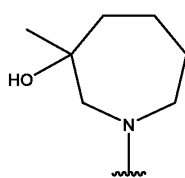
defined above. In embodiments, R^1 is  . In embodiments, R^1 is  . In



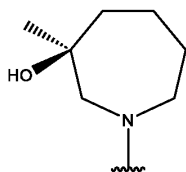
embodiments, R^1 is  .



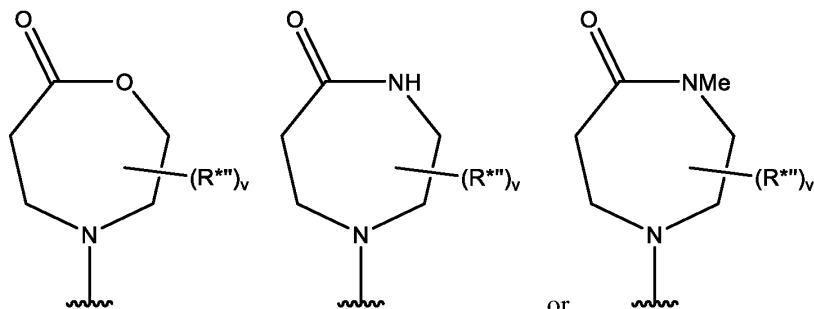
In embodiments, R^1 is  wherein each R^{*11} is independently a group R^{*11} as



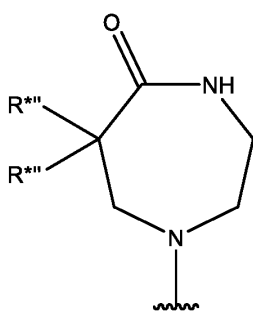
5 defined above. In embodiments, R^1 is  . In embodiments, R^1 is  . In



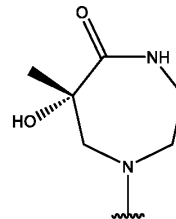
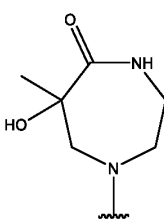
embodiments, R^1 is  .



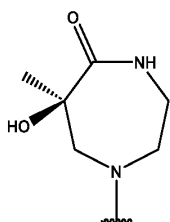
In embodiments, R^1 is , , or , wherein v is an integer from 0 to 4 and each R^{*v} is independently a group R^{*v} as defined above. In embodiments, v is 1, 2, 3 or 4. In embodiments, v is 1. In embodiments, v is 2. In embodiments, v is 3. In embodiments, v is 4.



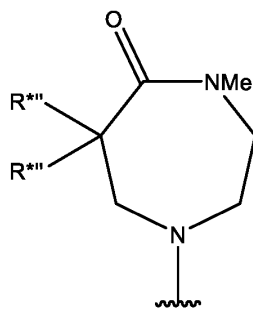
5 In embodiments, R^1 is  wherein each R^{*v} is independently a group R^{*v} as



defined above. In embodiments, R^1 is . In embodiments, R^1 is . In

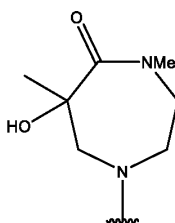


embodiments, R^1 is .

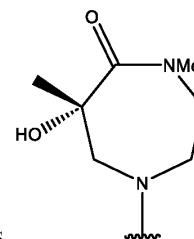


In embodiments, R^1 is

wherein each R^{*11} is independently a group R^{*11} as

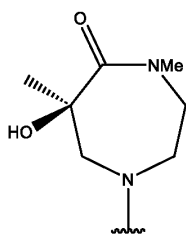


defined above. In embodiments, R^1 is

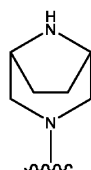


. In embodiments, R^1 is

. In



embodiments, R^1 is



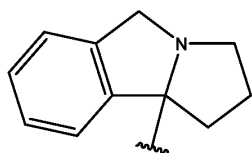
In embodiments, R^1 is not:

- 5 In the compounds of the present disclosure, R^2 is a 5- to 9-membered, monocyclic or bicyclic (*e.g.* fused, bridged or spirocyclic) heterocycloalkyl or heterocycloalkenyl group comprising at least one ring atom which is N or O; a 5- or 6-membered monocyclic heteroaryl group comprising at least one ring atom which is N; a fused, 8- to 10-membered bicyclic group wherein one or both rings are aromatic, and wherein at least one ring comprises at least one ring atom which is N; or a fused, 11- to 14-membered tricyclic group wherein at least one ring is aromatic, and wherein at least one ring comprises at least one ring atom which is N;

- and wherein R^2 may be substituted by one or more groups independently selected from CN, Cl, F, R^* , OH, OR^* , NH_2 , NHR^* , NR^{*2} , CHO, $C(O)R^*$, $C(O)OH$, $C(O)OR^*$, $C(O)NH_2$, $C(O)NHR^*$, $C(O)NR^{*2}$, $C(O)ONH_2$, $C(O)ONHR^*$, $C(O)ONR^{*2}$, =O, (C_2-C_3) alkenyl, and (C_2-C_3) alkynyl. In embodiments,
- 15 R^* is as defined in accordance with Formula (0). In embodiments, R^* is as defined in accordance with Formula (I).

In embodiments, R^2 is a fused, 11- to 14-membered tricyclic group wherein at least one ring is aromatic, and wherein at least one ring comprises at least one ring atom which is N;

- and wherein R^2 may be substituted by one or more groups independently selected from CN, Cl, F, R^* , OH, OR^* , NH_2 , NHR^* , NR^{*2} , CHO, $C(O)R^*$, $C(O)OH$, $C(O)OR^*$, $C(O)NH_2$, $C(O)NHR^*$, $C(O)NR^{*2}$, $C(O)ONH_2$, $C(O)ONHR^*$, $C(O)ONR^{*2}$, =O, (C₂-C₃)alkenyl, and (C₂-C₃)alkynyl. In embodiments, R^* is as defined in accordance with Formula (0). In embodiments, R^* is as defined in accordance with Formula (I).

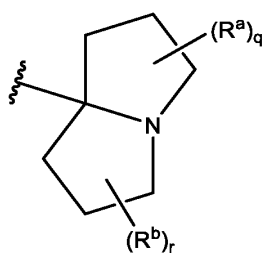


In embodiments, R^2 is

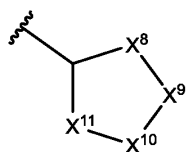
- In embodiments, R^2 is a 5- to 8-membered, monocyclic or bicyclic (*e.g.* fused, bridged, or spirocyclic) heterocycloalkyl or heterocycloalkenyl group comprising at least one ring atom which is N or O; a 5- or 6-membered monocyclic heteroaryl group comprising at least one ring atom which is N; or a fused, 8- to 10-membered bicyclic group wherein one or both rings are aromatic, and wherein at least one ring comprises at least one ring atom which is N;

- and wherein R^2 may be substituted by one or more groups independently selected from CN, Cl, F, R^* , OH, OR^* , NH_2 , NHR^* , NR^{*2} , CHO, $C(O)R^*$, $C(O)OH$, $C(O)OR^*$, $C(O)NH_2$, $C(O)NHR^*$, $C(O)NR^{*2}$, $C(O)ONH_2$, $C(O)ONHR^*$, $C(O)ONR^{*2}$, =O, (C₂-C₃)alkenyl, and (C₂-C₃)alkynyl, wherein R^* is as defined above. In embodiments, R^* is as defined in accordance with Formula (0). In embodiments, R^* is as defined in accordance with Formula (I).

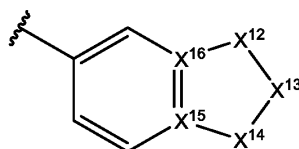
In embodiments, R^2 is selected from:



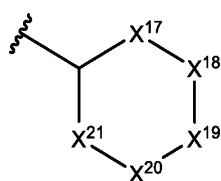
- , wherein q and r are each independently 0, 1, or 2, and each instance of R^a and R^b is independently selected from CN, Cl, F, R^* , OH, OR^* , NH_2 , NHR^* , NR^{*2} , CHO, $C(O)R^*$, $C(O)OH$, $C(O)OR^*$, $C(O)NH_2$, $C(O)NHR^*$, $C(O)NR^{*2}$, $C(O)ONH_2$, $C(O)ONHR^*$, $C(O)ONR^{*2}$, =O, (C₂-C₃)alkenyl, and (C₂-C₃)alkynyl, wherein R^* is as defined above, *e.g.* as defined in accordance with Formula (0) or as defined in accordance with Formula (I).;



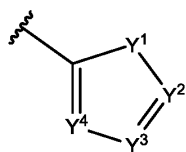
, wherein X^8 , X^9 , X^{10} , and X^{11} are each independently selected from $C(R^k)_2$, $C=O$, $N(R^k)$, O, or S, provided that at least one of X^8 , X^9 , X^{10} , and X^{11} is $N(R^k)$;



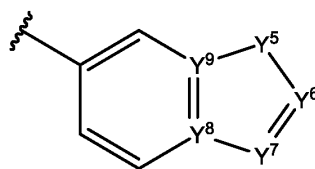
5 , wherein X^{12} , X^{13} , and X^{14} are each independently selected from $C(R^k)_2$, $C=O$, $N(R^k)$, O, or S and X^{15} and X^{16} are each independently selected from C and N, provided that at least one of X^{12} , X^{13} , and X^{14} is $N(R^k)$ and/or at least one of X^{15} and X^{16} is N;



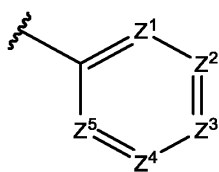
, wherein X^{17} , X^{18} , X^{19} , X^{20} , and X^{21} are each independently selected from $C(R^k)_2$, $C=O$, $N(R^k)$, O or S, provided that at least one of X^{17} , X^{18} , X^{19} , X^{20} , and X^{21} is $N(R^k)$, O, or S;



, wherein Y^1 , Y^2 , Y^3 , and Y^4 are each independently N, O, S, NR^k , or CR^k , provided that at least one of Y^1 , Y^2 , Y^3 , and Y^4 is N or NR^k ;



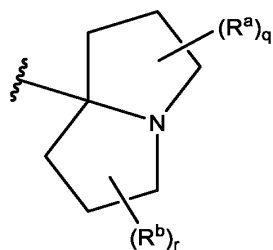
10 , wherein Y^5 , Y^6 and Y^7 are each independently N, O, S, NR^k , or CR^k , and Y^8 and Y^9 are each independently N or C, provided that at least one of Y^5 , Y^6 , and Y^7 is N or NR^k and/or at least one of Y^8 and Y^9 is N;



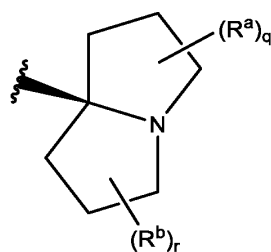
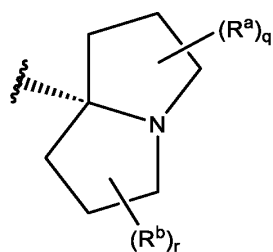
and , wherein Z^1 , Z^2 , Z^3 , Z^4 and Z^5 are each independently N, O, S or CR^k , provided that at least one of Z^1 , Z^2 , Z^3 , Z^4 and Z^5 is N;

wherein each R^k is independently selected from H, CN, Cl, F, R^* , OH, OR^* , NH_2 , NHR^* , NR^{*2} , CHO, $C(O)R^*$, $C(O)OH$, $C(O)OR^*$, $C(O)NH_2$, $C(O)NHR^*$, $C(O)NR^{*2}$, $C(O)ONH_2$, $C(O)ONHR^*$, $C(O)ONR^{*2}$, $(C_2-C_3)alkenyl$, and $(C_2-C_3)alkynyl$, and wherein R^* is as defined above. In

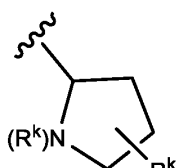
5 accordance with Formula (I).



In embodiments, R^2 is , wherein q , r , R^a , and R^b are as defined above.

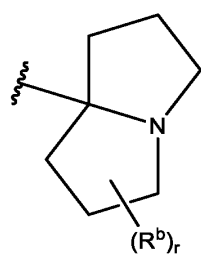


In embodiments, R^2 is or , wherein q , r , R^a , and R^b are as defined above.

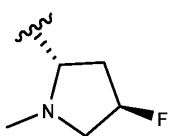
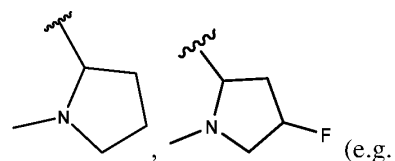


In embodiments, R^2 is $(R^k)_N$ R^k (wherein R^k is as defined above).

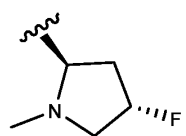
10 In embodiments, R^2 is selected from:



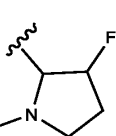
(wherein R^b and r are as defined above),



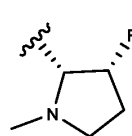
or



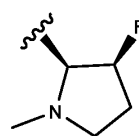
,



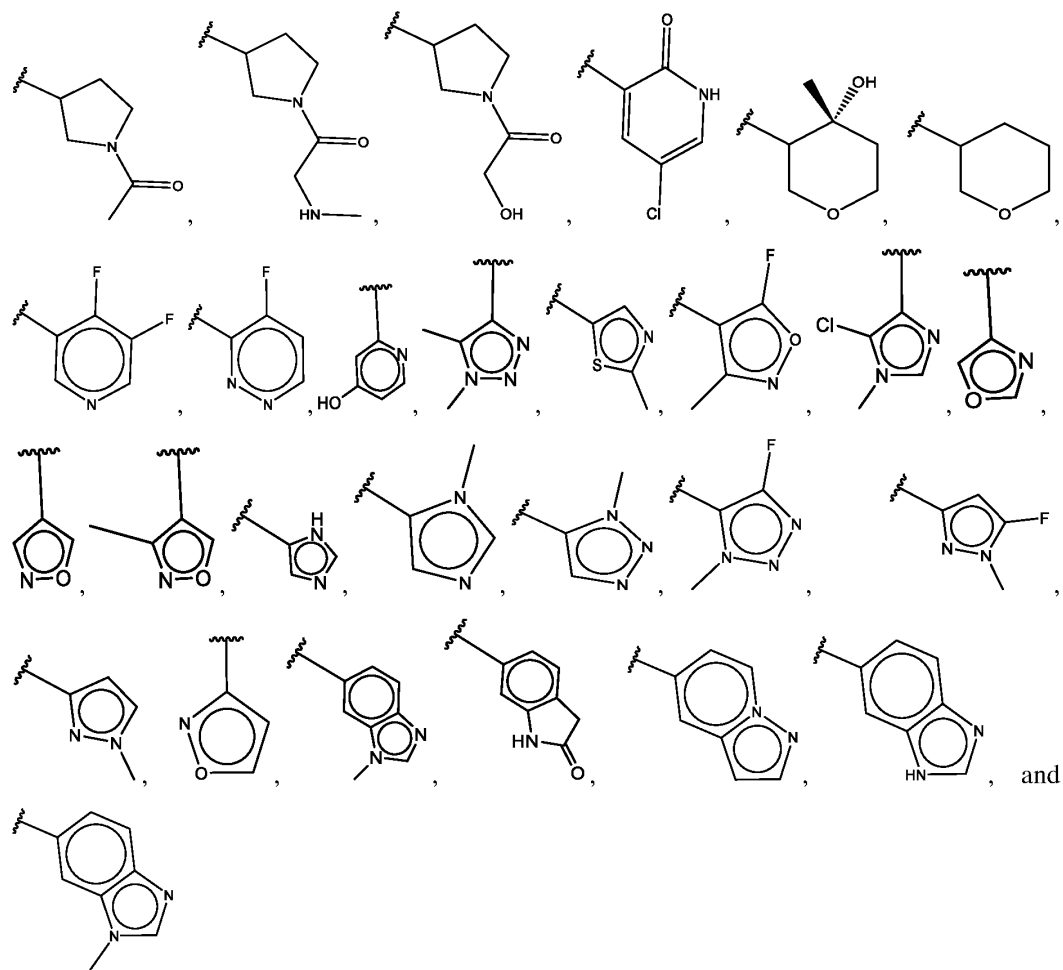
(e.g.



or

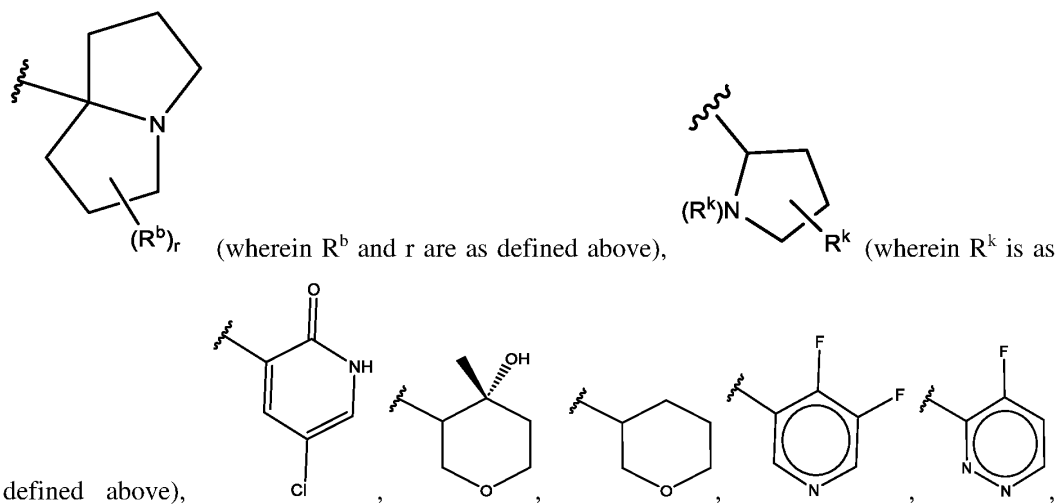


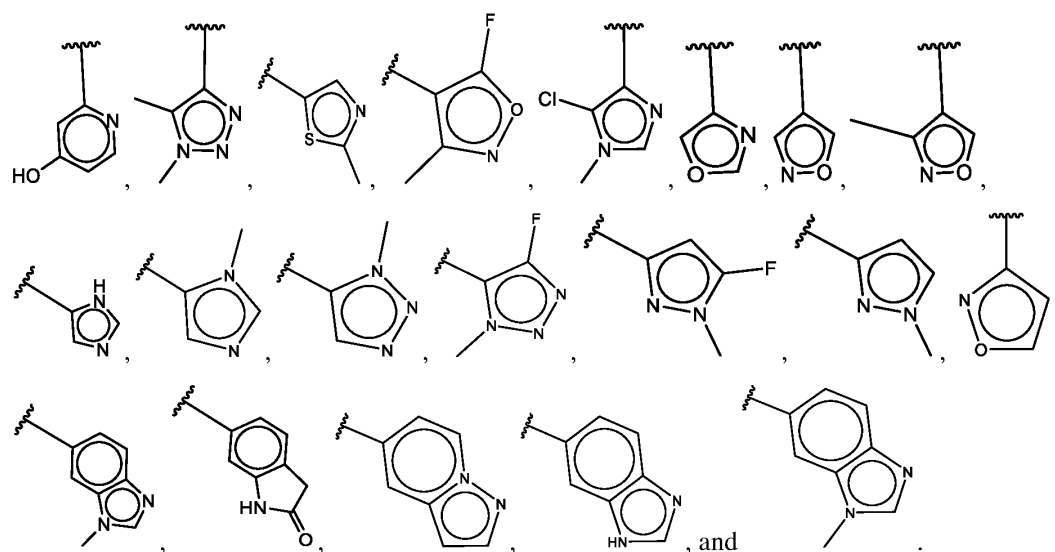
),



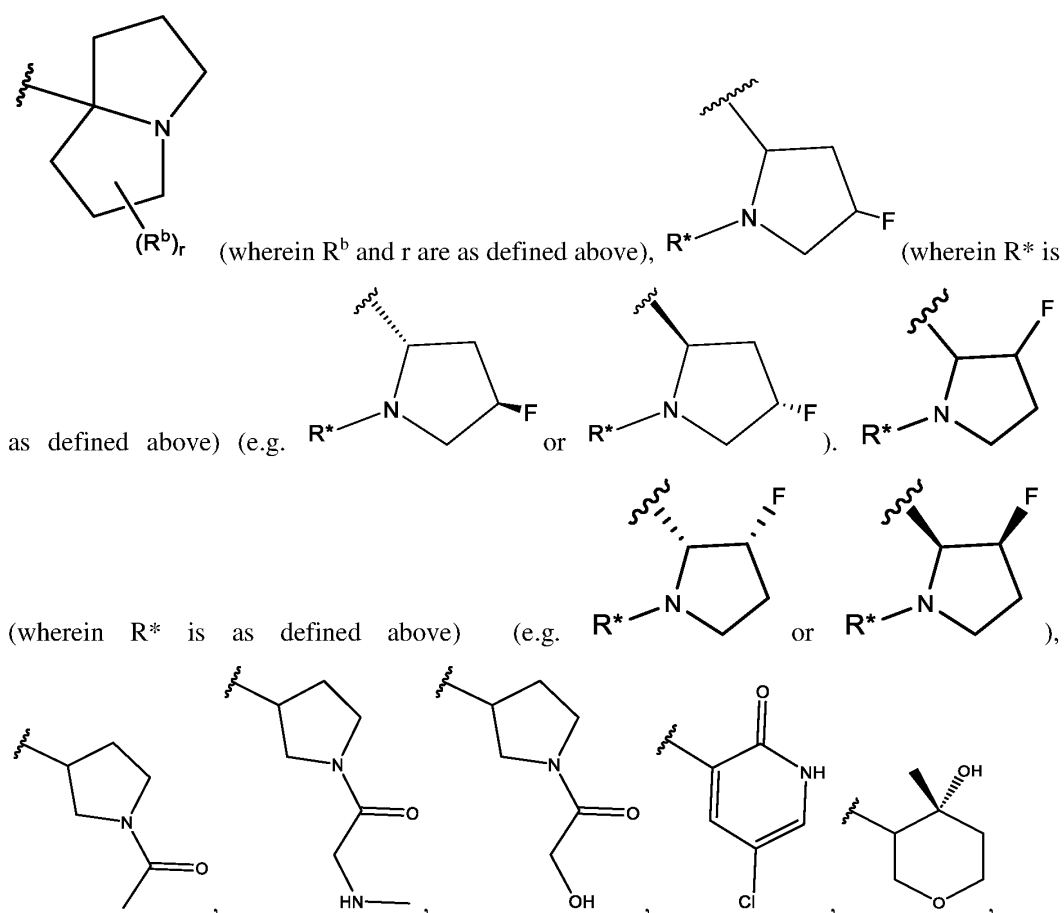
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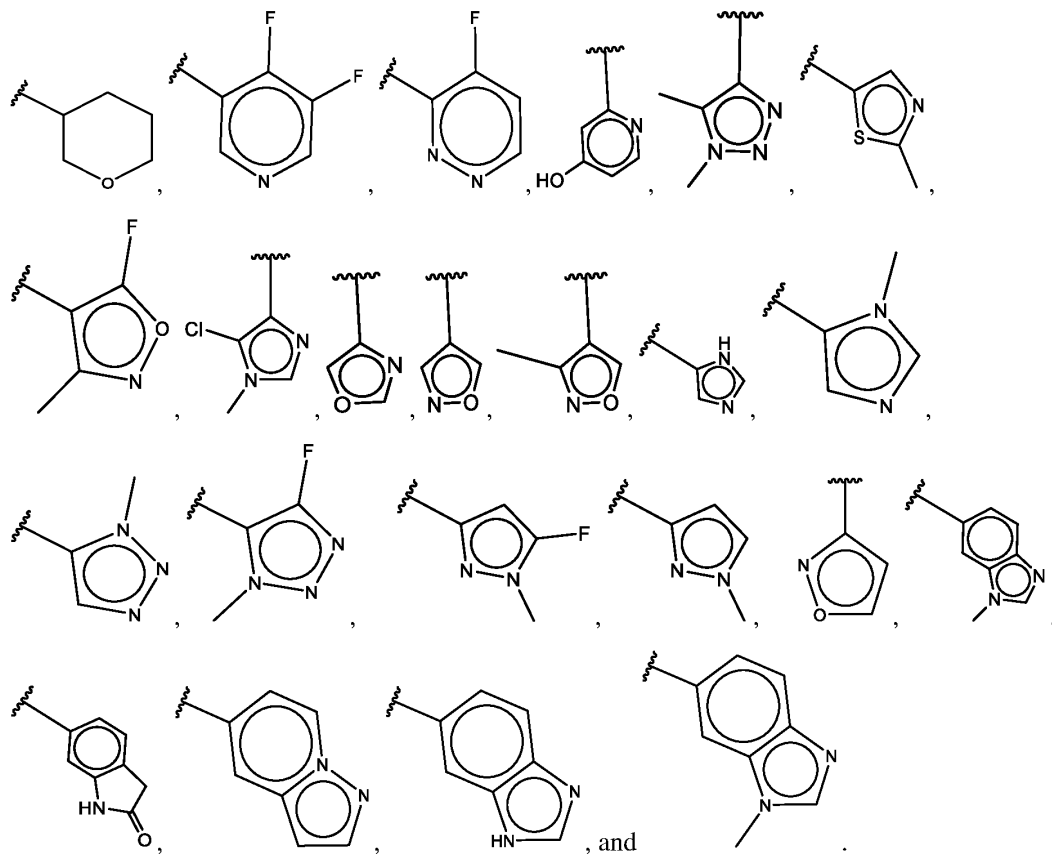
In embodiments, R^2 is selected from:



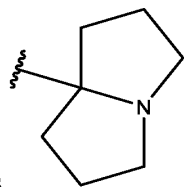
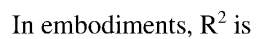
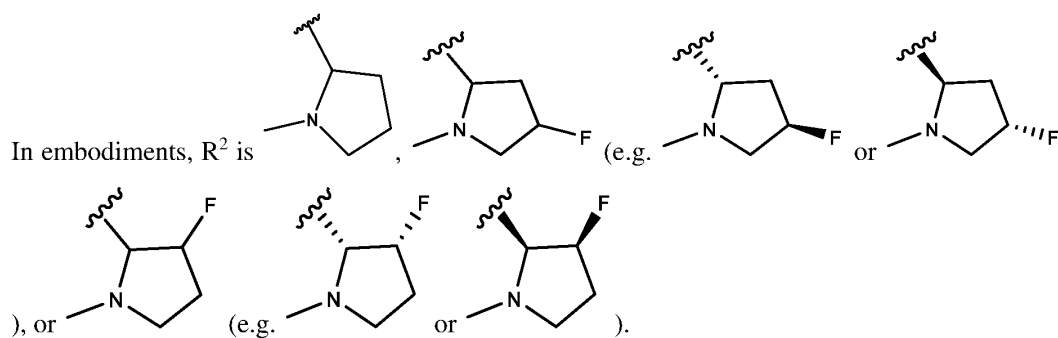


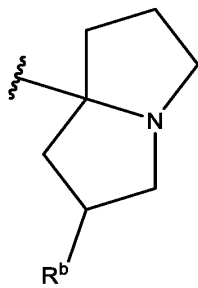
5 In embodiments, R^2 is selected from:



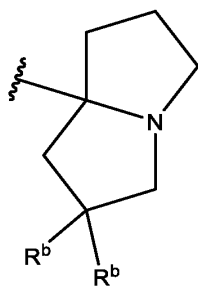


In embodiments, $\mathbf{R}^2$ is

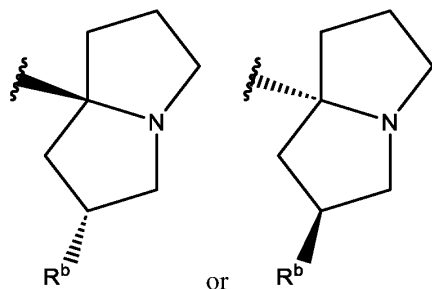




In embodiments, R^2 is R^b , wherein R^b is as defined above.

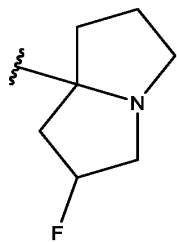


In embodiments, R^2 is R^b , wherein each R^b is independently as defined above.

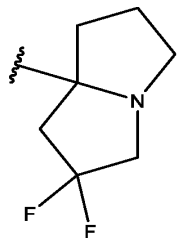


In embodiments, R^2 is R^b or R^b , wherein R^b is as defined above.

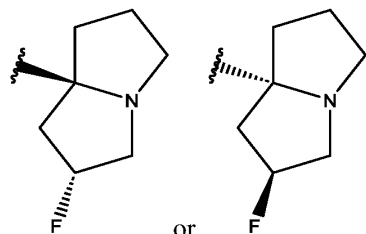
5 In embodiments, R^b is F or Cl.



In embodiments, R^2 is F.

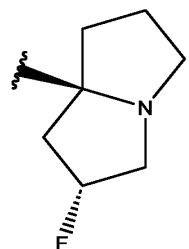


In embodiments, R^2 is F.



In embodiments, R^2 is

or



In embodiments, R^2 is

In the compounds of the present disclosure, L^1 is a bond or is -O-, -(C₁-C₃)alkyl-, *-O-(C₁-C₃)alkyl-
 , *-(C₁-C₃)alkyl-O-, *-C(O)NR'-**, or *-NR'C(O)-**, wherein R' is H, OH, CN, Cl, F, or (C₁-
 5 C₃)alkyl, and * denotes a point of attachment to the triazole moiety of the compound of formula (0)
 (e.g. a compound of Formula (I)) and ** denotes a point of attachment to R^2 . Where L^1 is (C₂-C₃) alkyl,
 *-O(C₂-C₃ alkyl)-** or *-(C₂-C₃ alkyl)O-** the C₂ or C₃ alkyl group may be linear or branched, e.g. -
 CH(CH₃)-, *-OCH(CH₃)-**, or *-CH(CH₃)O-**.

In embodiments, L^1 is -O-, -(C₁-C₃)alkyl-, *-O-(C₁-C₃)alkyl-**, *-(C₁-C₃)alkyl-O-**, *-C(O)NR'-**,
 10 or *-NR'C(O)-**, wherein R' is H, OH, CN, Cl, F, or (C₁-C₃)alkyl, and * denotes a point of attachment
 to the triazole moiety of the compound of Formula (0) (e.g. a compound of Formula (I)) and ** denotes
 a point of attachment to R^2 .

In embodiments, L^1 is -O-, -(C₂-C₃)alkyl-, *-O-(C₂-C₃)alkyl-**, *-(C₂-C₃)alkyl-O-**, *-C(O)NR'-**,
 or *-NR'C(O)-**, wherein R' is H, OH, CN, Cl, F, or (C₁-C₃)alkyl, and * denotes a point of attachment
 15 to the triazole moiety of the compound of Formula (0) (e.g. a compound of Formula (I)) and ** denotes
 a point of attachment to R^2 .

In embodiments, L^1 is -O-, -CH₂CH₂-, *-OCH₂-**, *-CH₂O-**, *-OCH(CH₃)-**, or *-CH(CH₃)O-**.

In embodiments, L^1 is -O-, -CH₂CH₂-, *-OCH₂-**, or *-CH₂O-**.

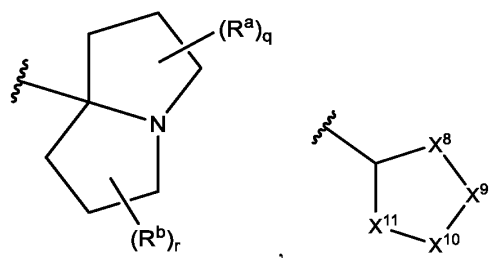
In embodiments, L^1 is -O- or *-OCH₂-**.

20 In embodiments, L^1 is -O-, -CH₂CH₂-, *-OCH₂-**, *-OCH(CH₃)-** or *-CH₂O-**.

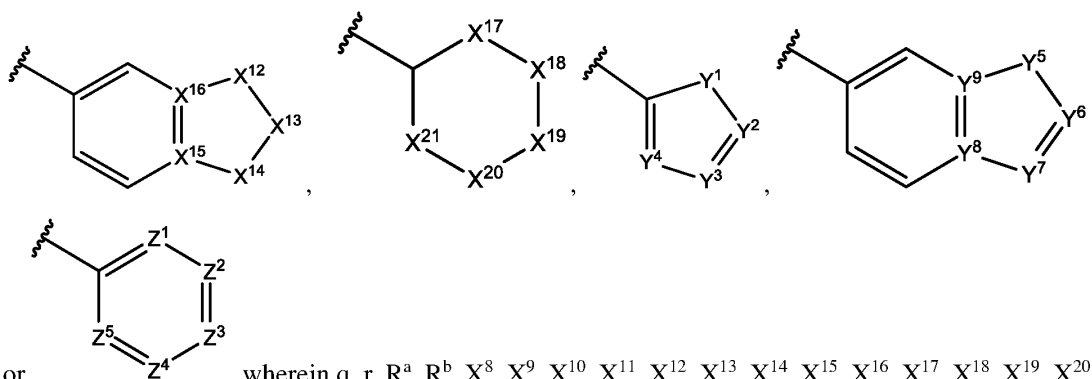
In embodiments, L^1 is -O-, *-OCH(CH₃)-** or *-OCH₂-**.

In embodiments, L^1 is -O- or *-OCH(CH₃)-**.

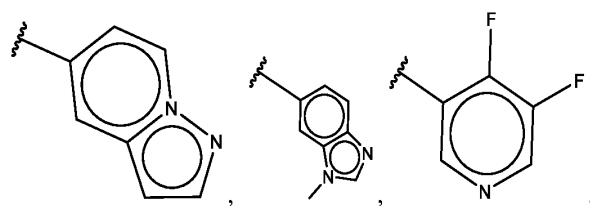
In embodiments, L^1 is $^*-OCH(CH_3)-^{**}$ or $^*-OCH_2-^{**}$.



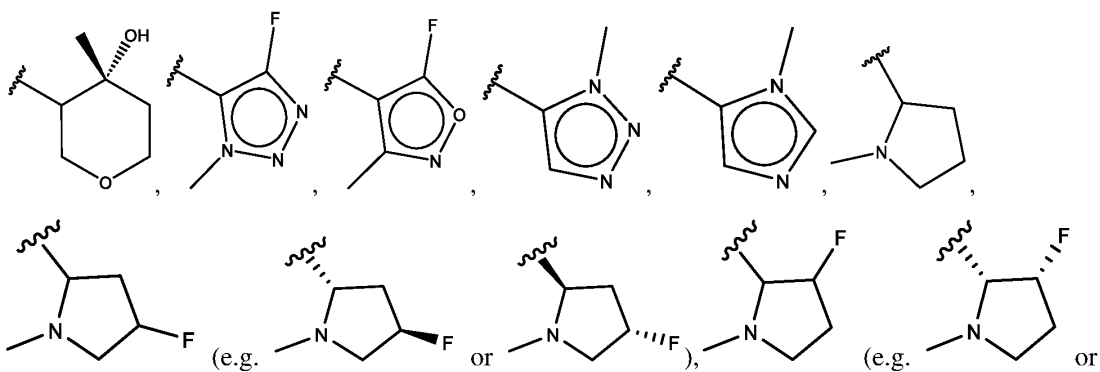
In embodiments, L^1 is $^*-OCH_2-^{**}$ and R^2 is

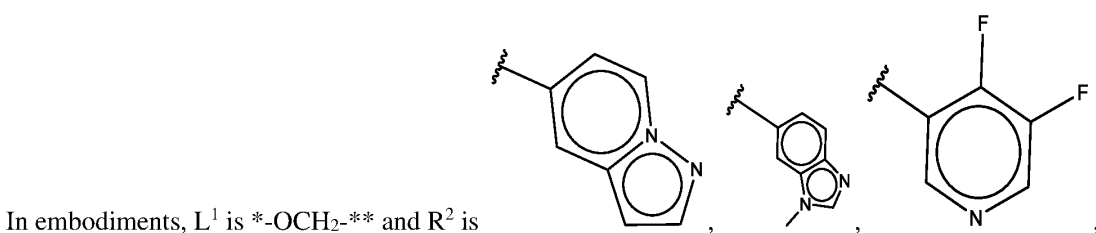


5 or , wherein q , r , R^a , R^b , X^8 , X^9 , X^{10} , X^{11} , X^{12} , X^{13} , X^{14} , X^{15} , X^{16} , X^{17} , X^{18} , X^{19} , X^{20} , X^{21} , Y^1 , Y^2 , Y^3 , Y^4 , Y^5 , Y^6 , Y^7 , Y^8 , Y^9 , Z^1 , Z^2 , Z^3 , Z^4 , and Z^5 are as defined above.

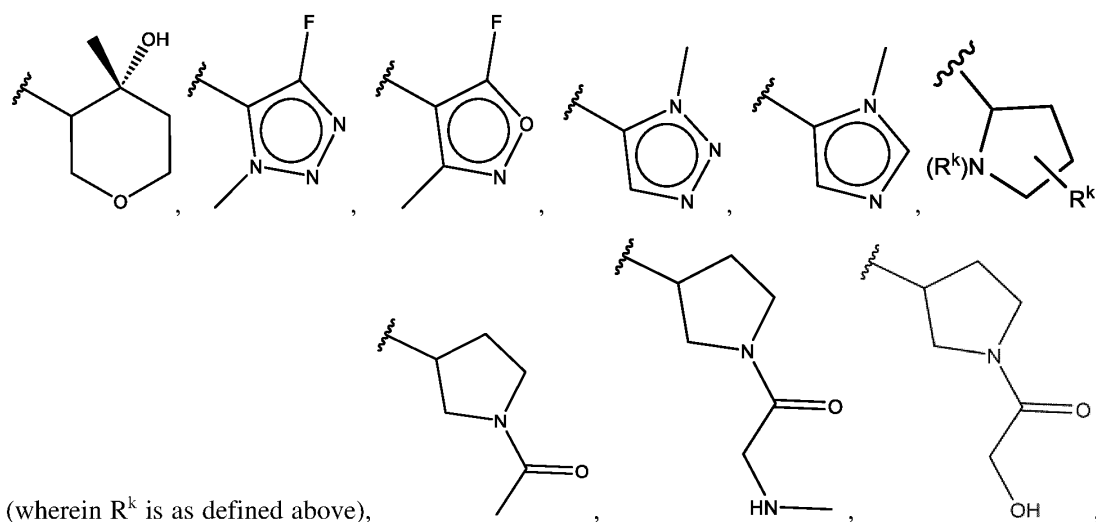


In embodiments, L^1 is $^*-OCH_2-^{**}$ and R^2 is

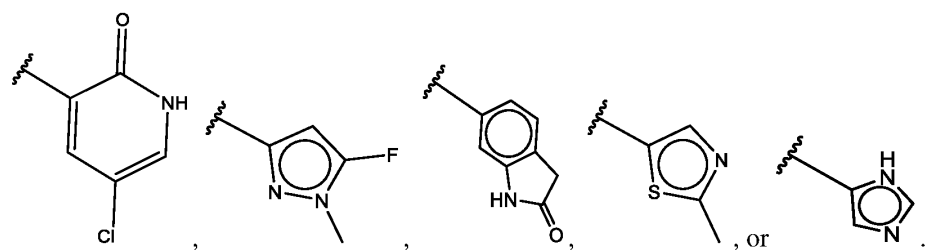


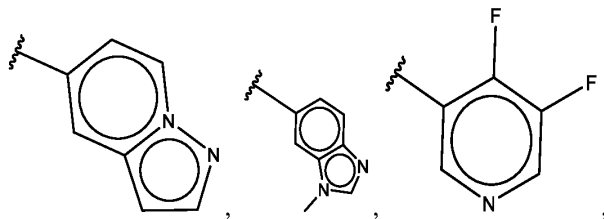


In embodiments, L¹ is *-OCH₂-** and R² is

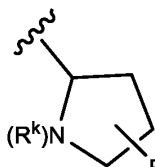
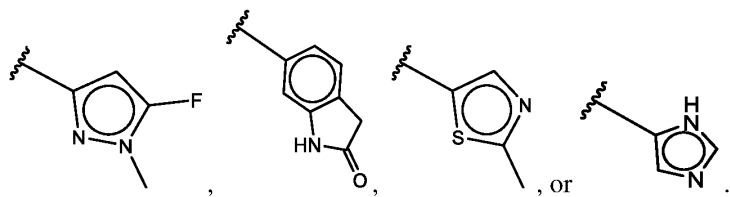
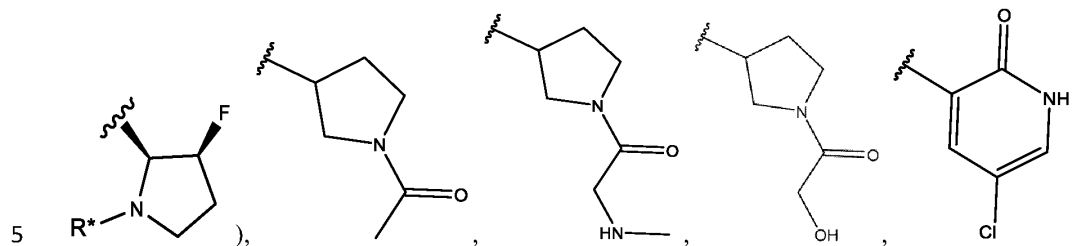
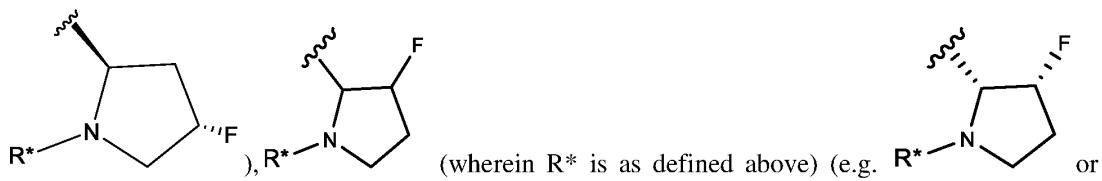
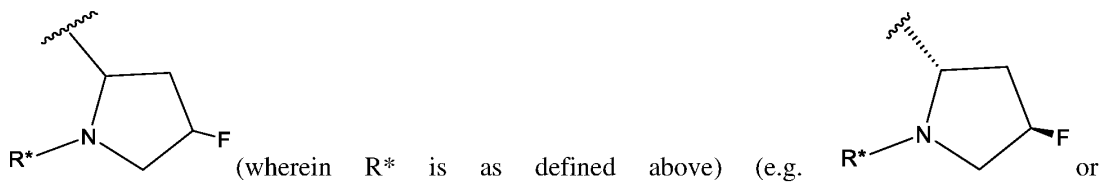
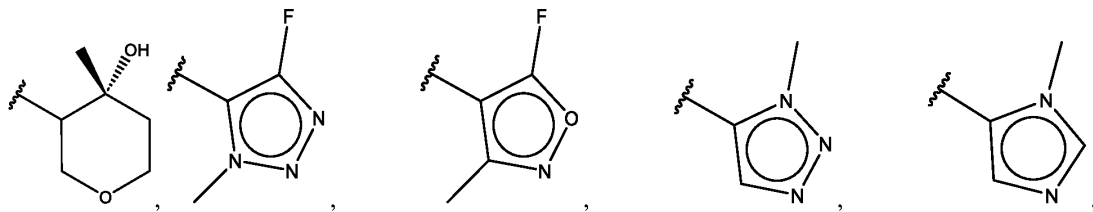


5 (wherein R^k is as defined above),

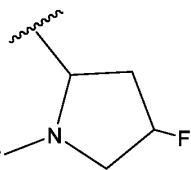


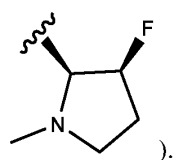
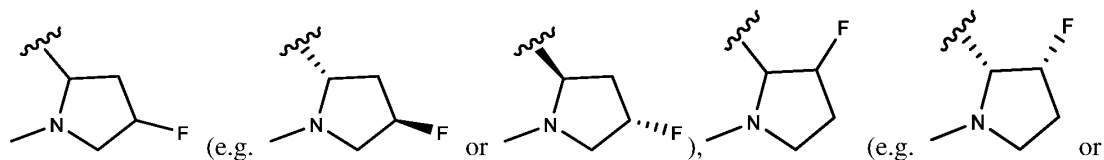
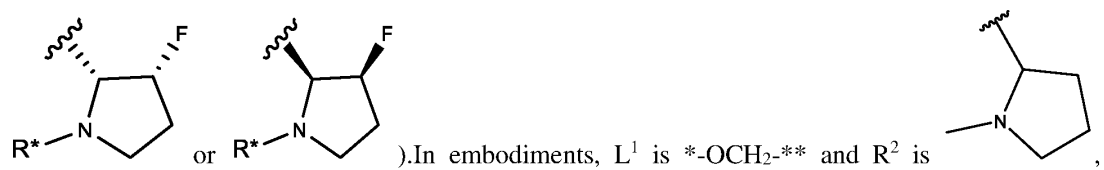
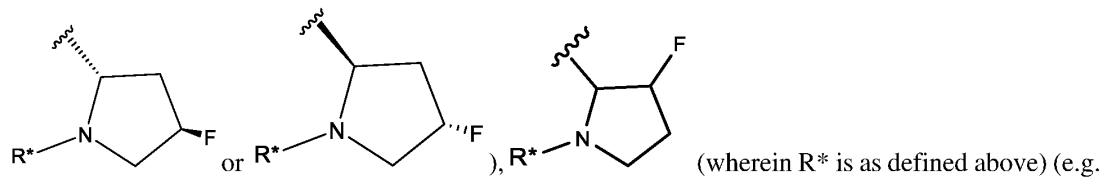


In embodiments, L¹ is *-OCH₂-** and R² is

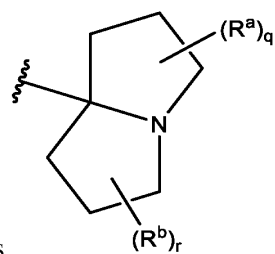


In embodiments, L¹ is *-OCH₂-** and R² is R^k (wherein R^k is as defined above).

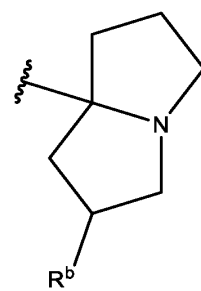
In embodiments, L^1 is $^*-OCH_2-^*$ and R^2 is  (wherein R^* is as defined above) (e.g.



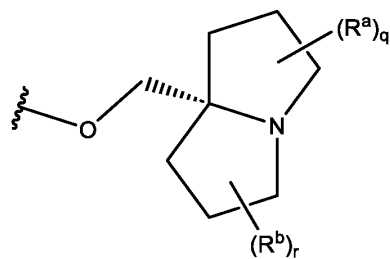
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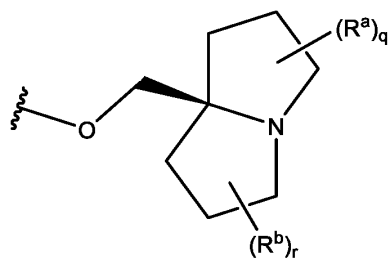
In embodiments, L^1 is $^*-OCH_2-^*$ and R^2 is defined above. , wherein q , r , R^a , and R^b are as



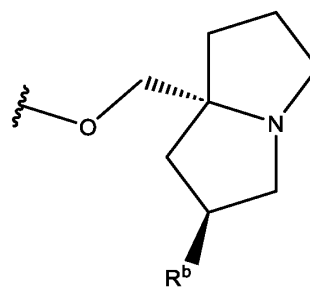
In embodiments, L^1 is $^*-OCH_2-^*$ and R^2 is , wherein R^b is as defined above.



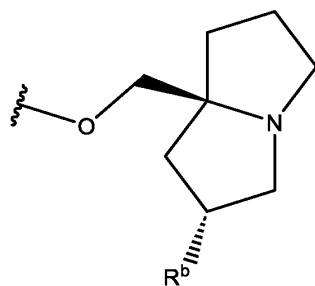
In embodiments, L^1 and R^2 together form a group



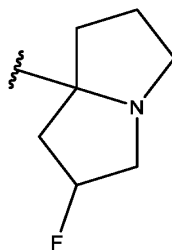
, wherein q , r , R^a , and R^b are as defined above.



In embodiments, L^1 and R^2 together form a group

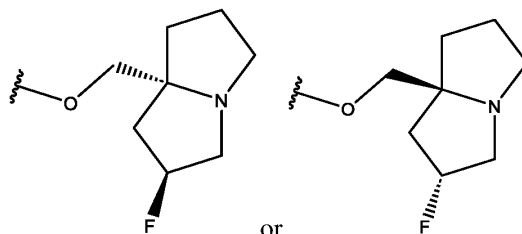


, wherein R^b is as defined above.

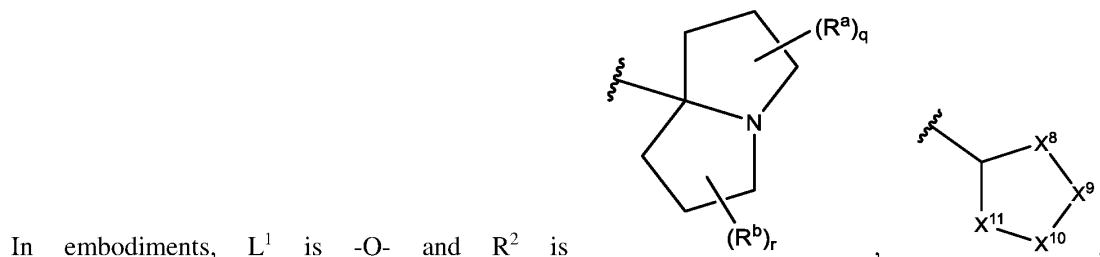


5 In embodiments, L^1 is $^*-OCH_2-^*$ and R^2 is

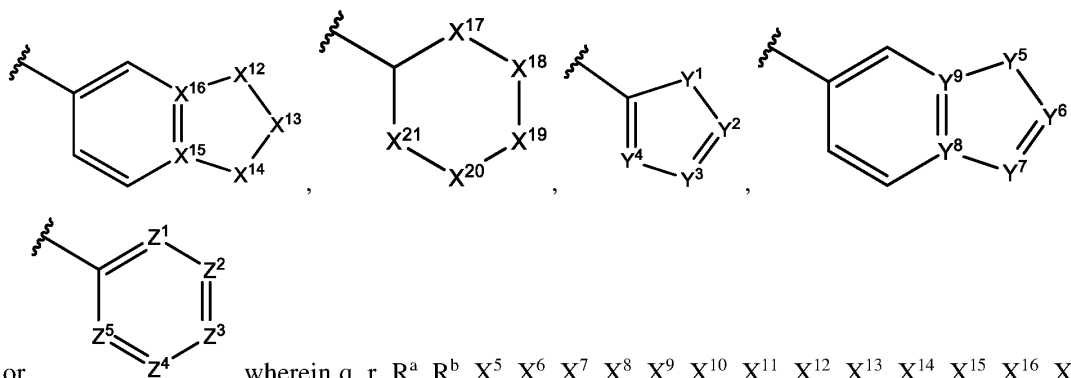
.



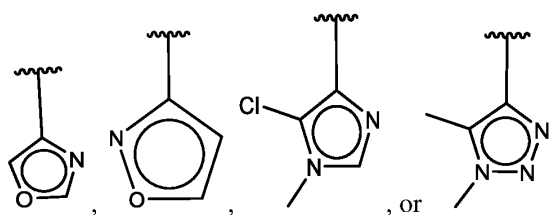
In embodiments, L^1 and R^2 together form a group



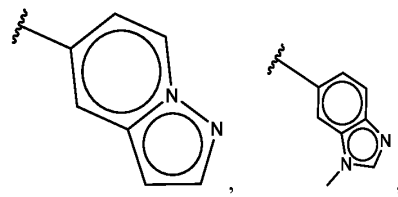
In embodiments, L^1 is -O- and R^2 is



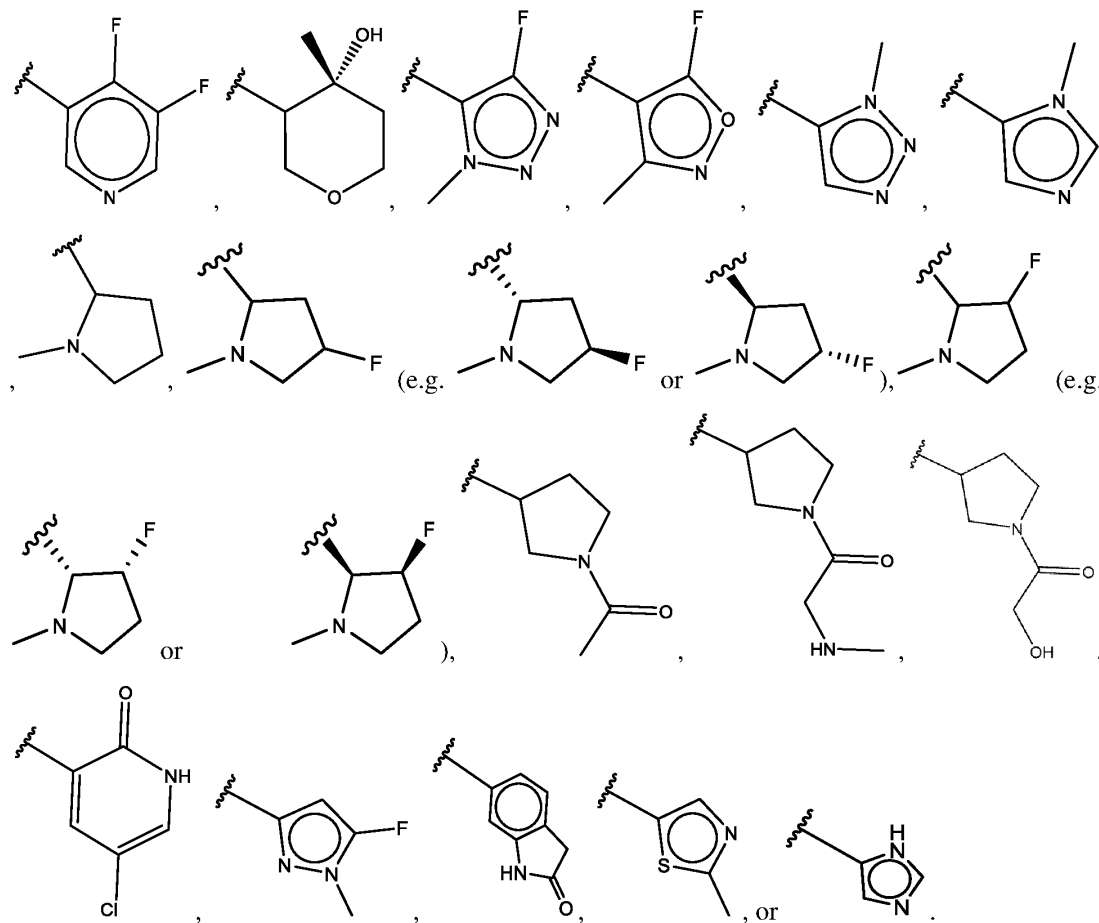
5 or , wherein q , r , R^a , R^b , X^5 , X^6 , X^7 , X^8 , X^9 , X^{10} , X^{11} , X^{12} , X^{13} , X^{14} , X^{15} , X^{16} , X^{17} , X^{18} , Y^1 , Y^2 , Y^3 , Y^4 , Y^5 , Y^6 , Y^7 , Y^8 , Y^9 , Z^1 , Z^2 , Z^3 , Z^4 , and Z^5 are as defined above.



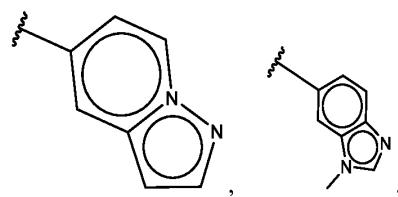
In embodiments, L^1 is -O- and R^2 is



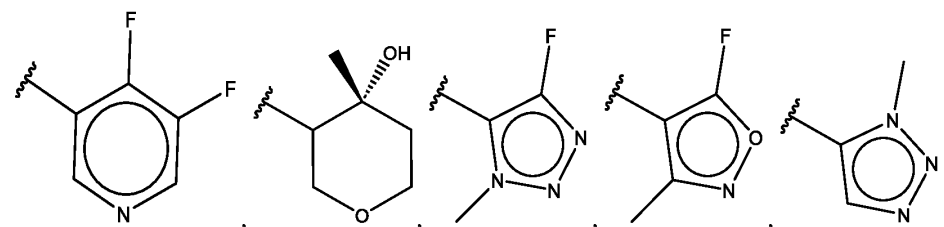
In embodiments, L^1 is $^*-OCH(CH_3)-^{**}$ and R^2 is

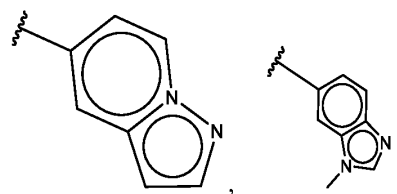
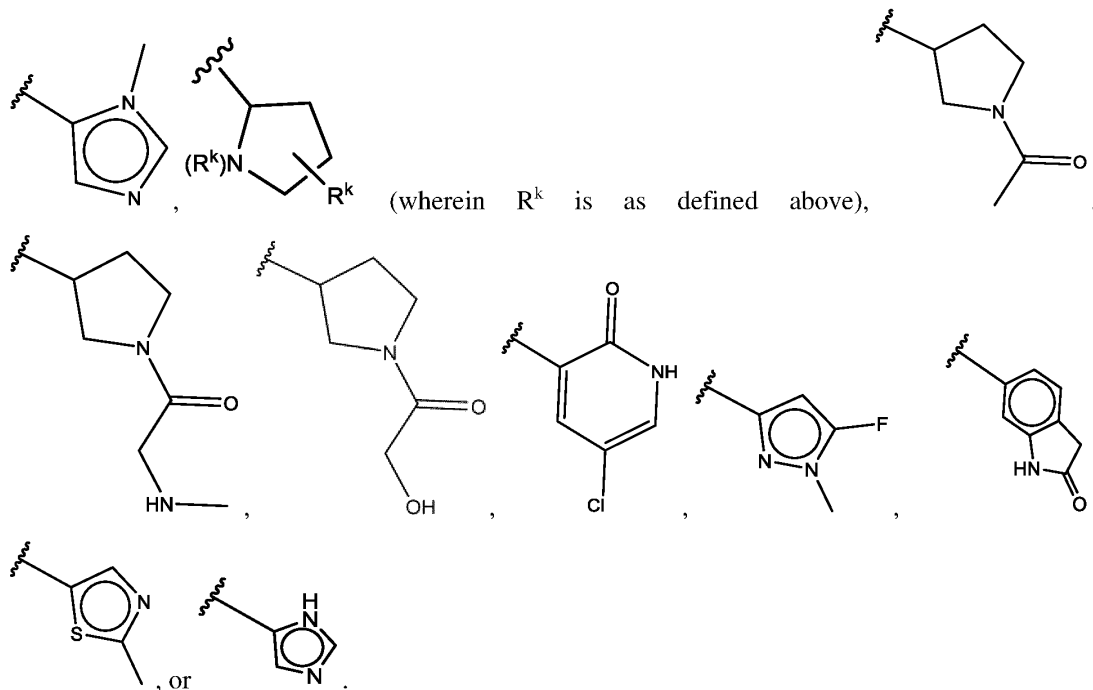


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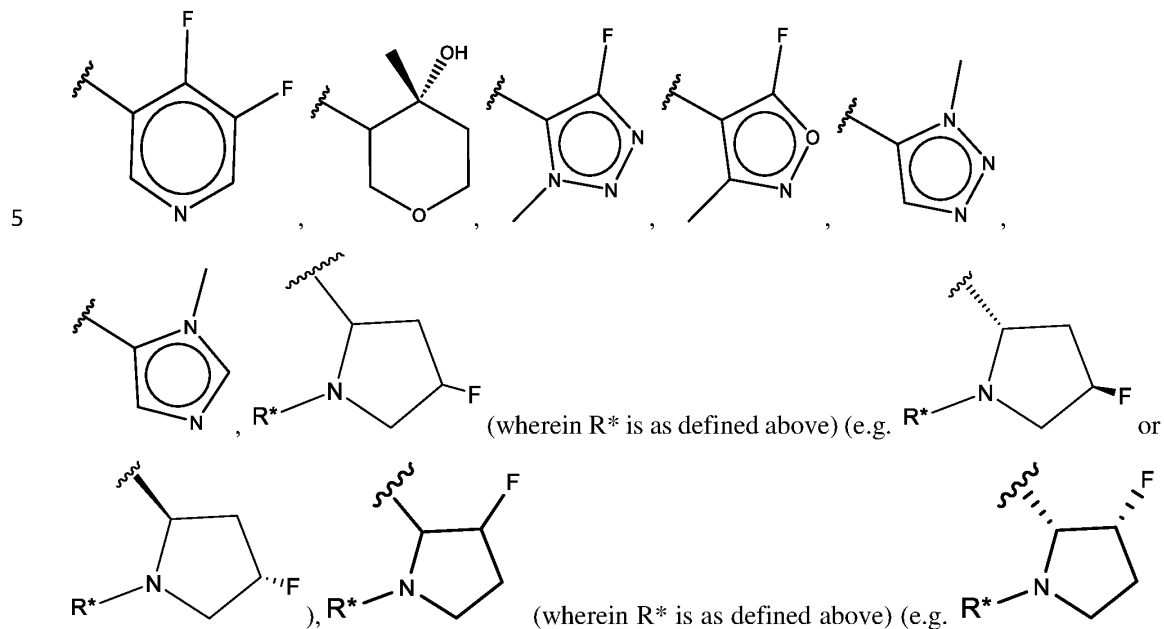


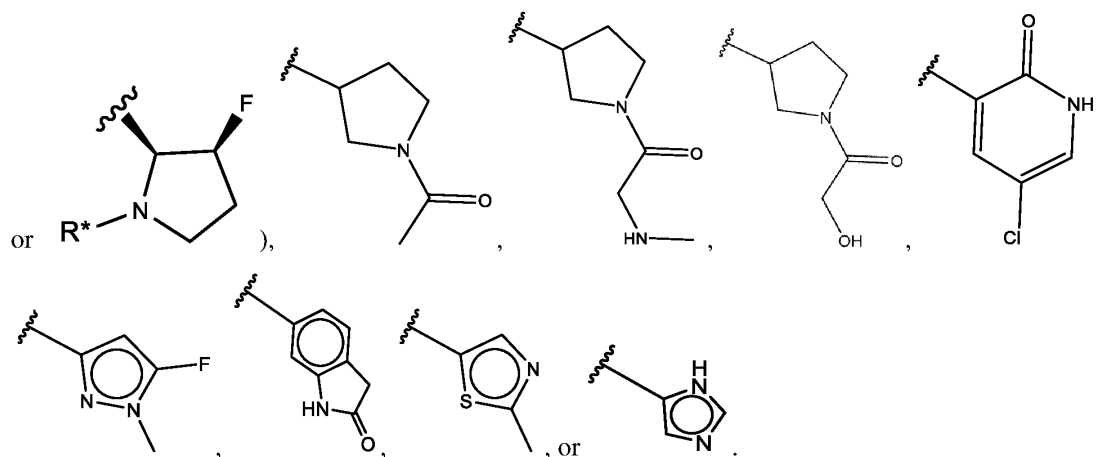
In embodiments, L^1 is $^*-OCH(CH_3)-^{**}$ and R^2 is

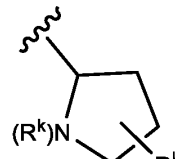


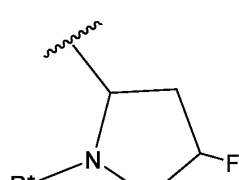


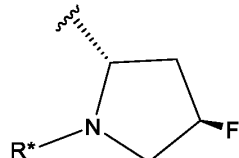
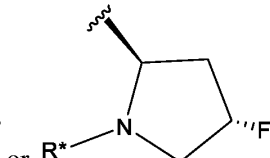
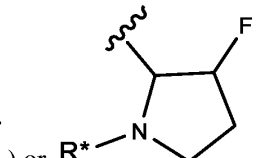
In embodiments, L¹ is *-OCH(CH₃)-** and R² is

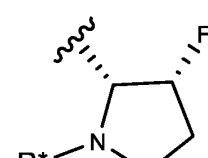
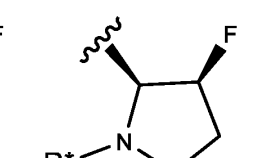


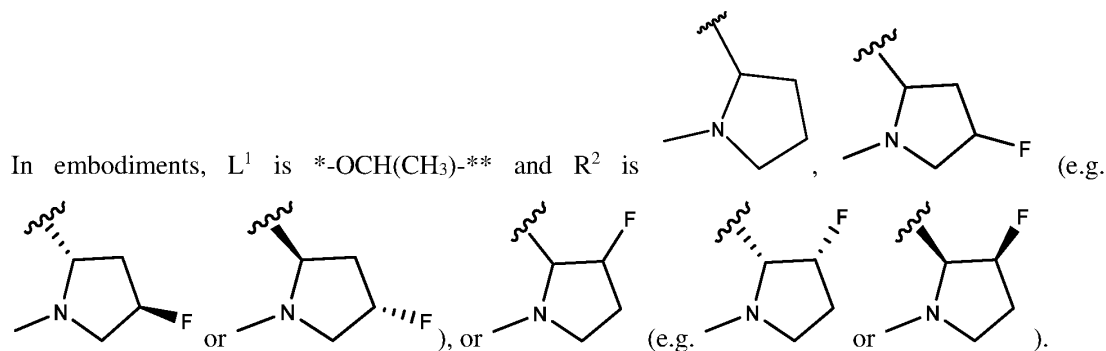


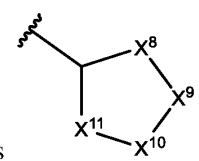
In embodiments, L^1 is $^*-OCH(CH_3)-^{**}$ and R^2 is  (wherein R^k is as defined above).

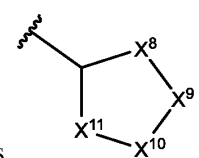
In embodiments, L^1 is $^*-OCH(CH_3)-^{**}$ and R^2 is  (wherein R^* is as defined

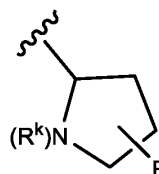
5 above) (e.g.  or ) or  (wherein R^* is as

defined above) (e.g.  or ).

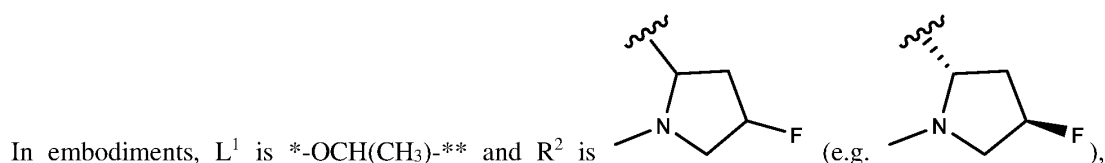


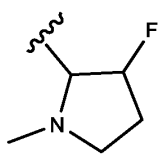
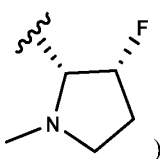
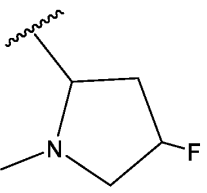
- In embodiments, L^1 is $^*\text{-OCH}(\text{CH}_3)\text{-}^{**}$ and R^2 is
- 
- , wherein X^8 , X^9 , X^{10} , and X^{11} are each independently selected from $\text{C}(\text{R}^k)_2$, $\text{C}=\text{O}$, $\text{N}(\text{R}^k)$, O , or S , provided that at least one of X^8 , X^9 , X^{10} , and X^{11} is $\text{N}(\text{R}^k)$; wherein each R^k is independently selected from H , CN , Cl , F , R^* , OH , OR^* , NH_2 , NHR^* , NR^{*2} , CHO , $\text{C}(\text{O})\text{R}^*$, $\text{C}(\text{O})\text{OH}$, $\text{C}(\text{O})\text{OR}^*$, $\text{C}(\text{O})\text{NH}_2$, $\text{C}(\text{O})\text{NHR}^*$, $\text{C}(\text{O})\text{NR}^{*2}$, $\text{C}(\text{O})\text{ONH}_2$, $\text{C}(\text{O})\text{ONHR}^*$, $\text{C}(\text{O})\text{ONR}^{*2}$, $(\text{C}_2\text{-C}_3)\text{alkenyl}$, and $(\text{C}_2\text{-C}_3)\text{alkynyl}$, and wherein each R^* is independently selected from $(\text{C}_1\text{-C}_4)\text{alkyl}$ (e.g. $\text{C}_1\text{-C}_3\text{alkyl}$), $(\text{C}_2\text{-C}_3)\text{alkenyl}$, $(\text{C}_3\text{-C}_6)\text{cycloalkyl}$, $(\text{C}_3\text{-C}_6)\text{cycloalkenyl}$, and 5- or 6-membered monocyclic heteroaryl, wherein said $(\text{C}_1\text{-C}_3)\text{alkyl}$, $(\text{C}_2\text{-C}_3)\text{alkenyl}$, $(\text{C}_3\text{-C}_6)\text{cycloalkyl}$, $(\text{C}_3\text{-C}_6)\text{cycloalkenyl}$ or 5- or 6-membered monocyclic heteroaryl may itself be substituted by one or more groups independently selected from F , Cl , CN , OH , NH_2 , $\text{NH}((\text{C}_1\text{-C}_3)\text{alkyl})$, $(\text{C}_1\text{-C}_3)\text{alkyl}$, $(\text{C}_2\text{-C}_3)\text{alkenyl}$, $(\text{C}_2\text{-C}_3)\text{alkynyl}$, or $\text{O}(\text{C}_1\text{-C}_3)\text{alkyl}$.

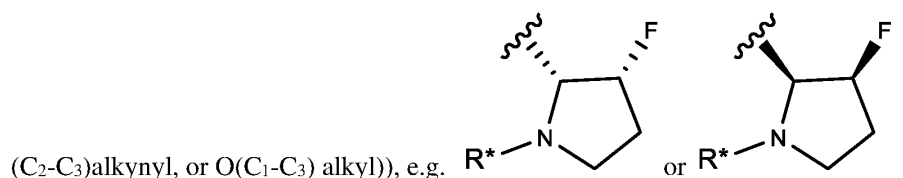
- In embodiments, L^1 is $^*\text{-OCH}(\text{CH}_3)\text{-}^{**}$ and R^2 is
- 
- , wherein X^8 , X^9 , X^{10} , and X^{11} are each independently selected from $\text{C}(\text{R}^k)_2$, $\text{C}=\text{O}$, $\text{N}(\text{R}^k)$, O , or S , provided that at least one of X^8 , X^9 , X^{10} , and X^{11} is $\text{N}(\text{R}^k)$; wherein each R^k is independently selected from H , CN , Cl , F , R^* , OH , OR^* , NH_2 , NHR^* , NR^{*2} , CHO , $\text{C}(\text{O})\text{R}^*$, $\text{C}(\text{O})\text{OH}$, $\text{C}(\text{O})\text{OR}^*$, $\text{C}(\text{O})\text{NH}_2$, $\text{C}(\text{O})\text{NHR}^*$, $\text{C}(\text{O})\text{NR}^{*2}$, $\text{C}(\text{O})\text{ONH}_2$, $\text{C}(\text{O})\text{ONHR}^*$, $\text{C}(\text{O})\text{ONR}^{*2}$, $(\text{C}_2\text{-C}_3)\text{alkenyl}$, and $(\text{C}_2\text{-C}_3)\text{alkynyl}$, and wherein each R^* is independently selected from $(\text{C}_1\text{-C}_3)\text{alkyl}$, $(\text{C}_2\text{-C}_3)\text{alkenyl}$, $(\text{C}_3\text{-C}_6)\text{cycloalkyl}$, and $(\text{C}_3\text{-C}_6)\text{cycloalkenyl}$, wherein said $(\text{C}_1\text{-C}_3)\text{alkyl}$, $(\text{C}_2\text{-C}_3)\text{alkenyl}$, $(\text{C}_3\text{-C}_6)\text{cycloalkyl}$, or $(\text{C}_3\text{-C}_6)\text{cycloalkenyl}$ may itself be substituted by one or more groups independently selected from F , Cl , CN , OH , NH_2 , $\text{NH}((\text{C}_1\text{-C}_3)\text{alkyl})$, $(\text{C}_1\text{-C}_3)\text{alkyl}$, $(\text{C}_2\text{-C}_3)\text{alkenyl}$, $(\text{C}_2\text{-C}_3)\text{alkynyl}$, or $\text{O}(\text{C}_1\text{-C}_3)\text{alkyl}$.



In embodiments, L^1 is $^*-OCH(CH_3)-^{**}$ and R^2 is
 selected from H, CN, Cl, F, R^* , OH, OR^* , NH_2 , NHR^* , NR^{*2} , CHO, $C(O)R^*$, $C(O)OH$, $C(O)OR^*$,
 $C(O)NH_2$, $C(O)NHR^*$, $C(O)NR^{*2}$, $C(O)ONH_2$, $C(O)ONHR^*$, $C(O)ONR^{*2}$, (C₂-C₃)alkenyl, and (C₂-
 5 C₃)alkynyl, and wherein each R^* is independently selected from (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₃-
 C₆)cycloalkyl, and (C₃-C₆)cycloalkenyl, wherein said (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₃-
 C₆)cycloalkyl, or (C₃-C₆)cycloalkenyl may itself be substituted by one or more groups independently
 selected from F, Cl, CN, OH, NH_2 , $NH((C_1-C_3)alkyl)$, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl,
 or $O(C_1-C_3)alkyl$.



 (e.g. , or  (wherein R^* is selected from (C₁-
 10 C₃)alkyl, (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, and (C₃-C₆)cycloalkenyl, wherein said (C₁-C₃)alkyl, (C₂-
 C₃)alkenyl, (C₃-C₆)cycloalkyl, or (C₃-C₆)cycloalkenyl may itself be substituted by one or more groups
 independently selected from F, Cl, CN, OH, NH_2 , $NH((C_1-C_3)alkyl)$, (C₁-C₃)alkyl, (C₂-C₃)alkenyl,

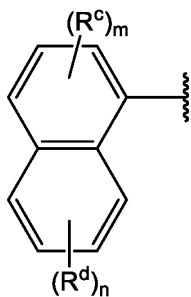


15 In the compounds of the present disclosure, R^3 is a phenyl or naphthalenyl group which is substituted
 by OH and optionally by one or more additional groups independently selected from CN, Cl, F, R^* ,
 OH, OR^* , NH_2 , NHR^* , NR^{*2} , CHO, $C(O)R^*$, $C(O)OH$, $C(O)OR^*$, $C(O)NH_2$, $C(O)NHR^*$, $C(O)NR^{*2}$,
 $C(O)ONH_2$, $C(O)ONHR^*$, $C(O)ONR^{*2}$, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl, wherein R^* is as defined
 above (e.g. in accordance with Formula (0) or in accordance with Formula (I)); or R^3 is a fused, 8-to-
 20 10-membered bicyclic group comprising a saturated carbocyclic ring fused to a heterocyclic ring,
 wherein the carbocyclic ring, the heterocyclic ring, or both, may optionally be substituted by one or
 more groups independently selected from CN, Cl, F, R^* , OH, OR^* , NH_2 , NHR^* , NR^{*2} , CHO, $C(O)R^*$,

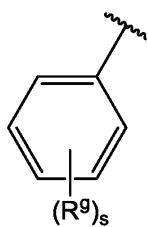
- C(O)OH, C(O)OR*, C(O)NH₂, C(O)NHR*, C(O)NR*₂, C(O)ONH₂, C(O)ONHR*, C(O)ONR*₂, NHC(O)R*, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl, wherein R* is as defined above (*e.g.* in accordance with Formula (0) or in accordance with Formula (I)); or R³ is a fused, 8- to 10-membered bicyclic group comprising a saturated carbocyclic ring fused to an aryl ring, wherein the carbocyclic ring, the aryl ring, or both, may be optionally substituted by one or more groups independently selected from CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)R*, C(O)OH, C(O)OR*, C(O)NH₂, C(O)NHR*, C(O)NR*₂, C(O)ONH₂, C(O)ONHR*, C(O)ONR*₂, NHC(O)R*, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl, wherein R* is as defined above (*e.g.* in accordance with Formula (0) or in accordance with Formula (I)); or R³ is a fused, 8- to 10-membered bicyclic group comprising a saturated heterocyclic ring fused to an aryl or heteroaryl ring, wherein the carbocyclic ring, the aryl or heteroaryl ring, or both, may be optionally substituted by one or more groups independently selected from CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)R*, C(O)OH, C(O)OR*, C(O)NH₂, C(O)NHR*, C(O)NR*₂, C(O)ONH₂, C(O)ONHR*, C(O)ONR*₂, NHC(O)R*, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl, wherein R* is as defined above (*e.g.* in accordance with Formula (0) or in accordance with Formula (I)).
- 15 In embodiments, R³ is a phenyl or naphthalenyl group which is substituted by OH and optionally by one or more additional groups independently selected from CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)R*, C(O)OH, C(O)OR*, C(O)NH₂, C(O)NHR*, C(O)NR*₂, C(O)ONH₂, C(O)ONHR*, C(O)ONR*₂, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl, wherein R* is as defined above (*e.g.* in accordance with Formula (0) or in accordance with Formula (I)); or R³ is a fused, 8-to-10-membered bicyclic group comprising a saturated carbocyclic ring fused to a heterocyclic ring, wherein the carbocyclic ring, the heterocyclic ring, or both, may optionally be substituted by one or more groups independently selected from CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)R*, C(O)OH, C(O)OR*, C(O)NH₂, C(O)NHR*, C(O)NR*₂, C(O)ONH₂, C(O)ONHR*, C(O)ONR*₂, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl.
- 25 In embodiments, R³ is a phenyl or naphthalenyl group which is substituted by OH and optionally by one or more additional groups independently selected from CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)R*, C(O)OH, C(O)OR*, C(O)NH₂, C(O)NHR*, C(O)NR*₂, C(O)ONH₂, C(O)ONHR*, C(O)ONR*₂, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl, wherein R* is as defined above (*e.g.* in accordance with Formula (0) or in accordance with Formula (I)).
- 30 In embodiments, R³ is a fused, 8-to-10-membered bicyclic group comprising a saturated carbocyclic ring fused to a heterocyclic ring, wherein the carbocyclic ring, the heterocyclic ring, or both, may optionally be substituted by one or more groups independently selected from CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)R*, C(O)OH, C(O)OR*, C(O)NH₂, C(O)NHR*, C(O)NR*₂,

C(O)ONH₂, C(O)ONHR*, C(O)ONR*₂, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl, wherein R* is as defined above (*e.g.* in accordance with Formula (0) or in accordance with Formula (I)).

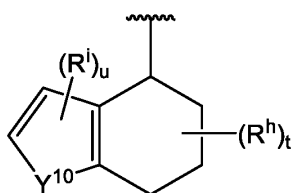
In embodiments, R³ is selected from



- wherein m is 1 or 2 and n is 0, 1, or 2; and each R^c and R^d is independently selected from F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, and (C₂-C₃)alkynyl, provided that at least one R^c is OH;



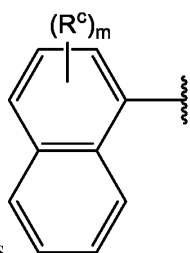
- , wherein s is 1, 2, or 3, and wherein when s is 1, R^g is OH, and when s is 2 or 3, at least one R^g is OH and each remaining R^g is independently F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or (C₃-C₆)cycloalkyl, wherein said (C₃-C₆)cycloalkyl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl; and

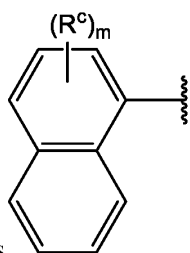


- , wherein Y¹⁰ is S, O, or NR''' wherein R''' is H, OH, CN, Cl, F, or (C₁-C₃)alkyl; t is 0, 1, 2, or 3 and u is 0, 1, or 2, with the proviso that when t is zero, u is nonzero, and that when u is zero, t is nonzero; and each R^h and Rⁱ is independently selected from CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)R*, C(O)OH, C(O)OR*, C(O)NH₂, C(O)NHR*, C(O)NR*₂, C(O)ONH₂, C(O)ONHR*, C(O)ONR*₂, (C₂-C₃)alkenyl, and (C₂-C₃)alkynyl, wherein R* is as defined above (*e.g.* in accordance with Formula (0) or in accordance with Formula (I)).

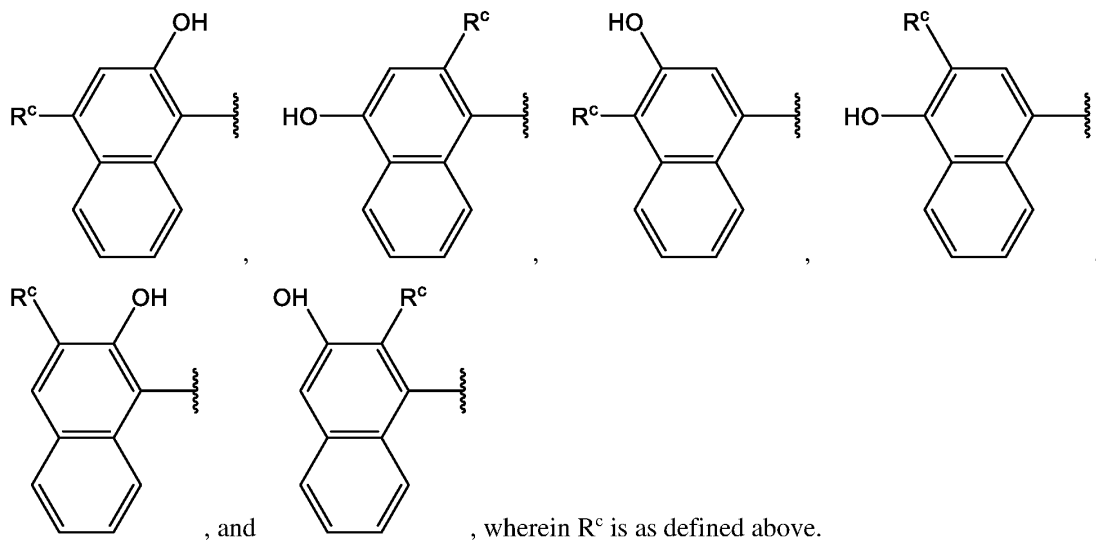
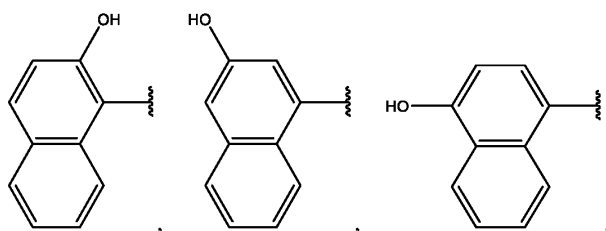
- In embodiments, R³ is a naphthalenyl group which is substituted by OH and optionally by one or more additional groups independently selected from CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)R*, C(O)OH, C(O)OR*, C(O)NH₂, C(O)NHR*, C(O)NR*₂, C(O)ONH₂, C(O)ONHR*,

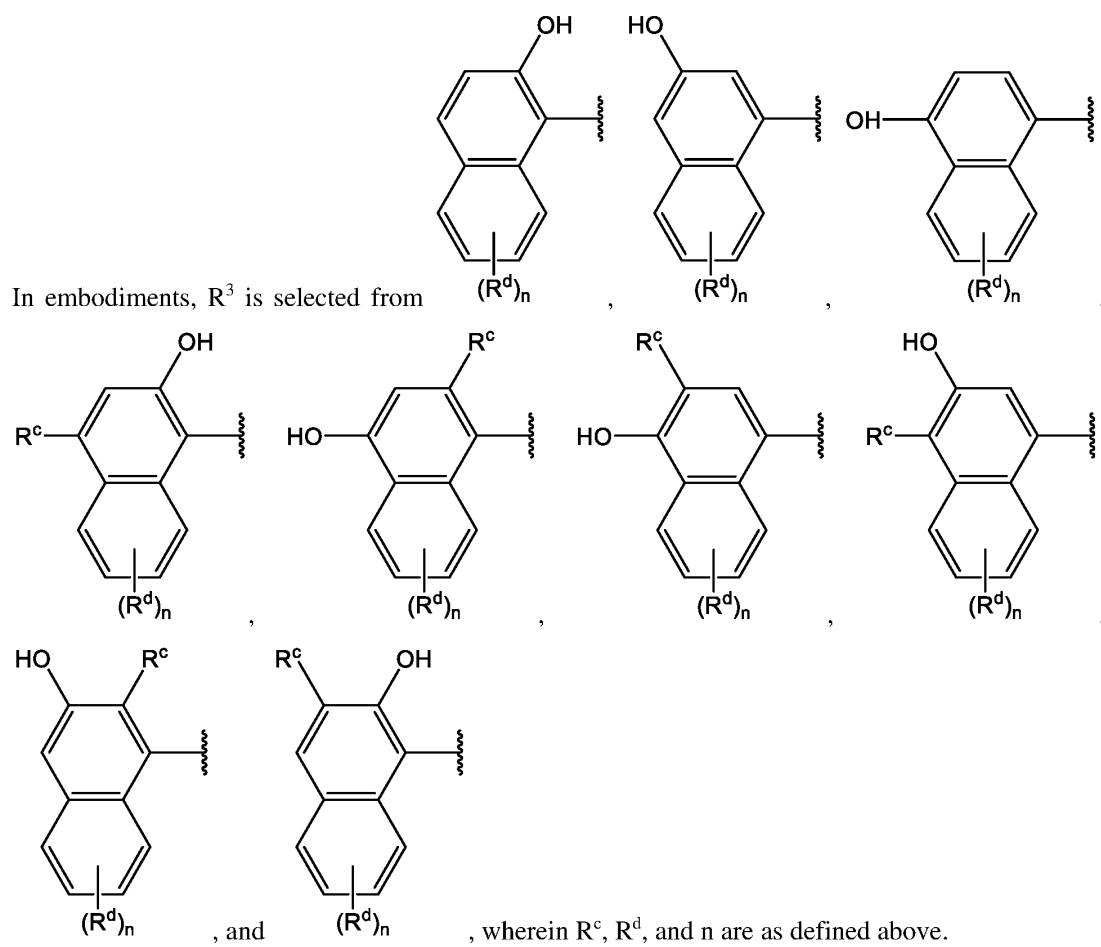
C(O)ONR*₂, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl, wherein R* is as defined above (*e.g.* in accordance with Formula (0) or in accordance with Formula (I)).



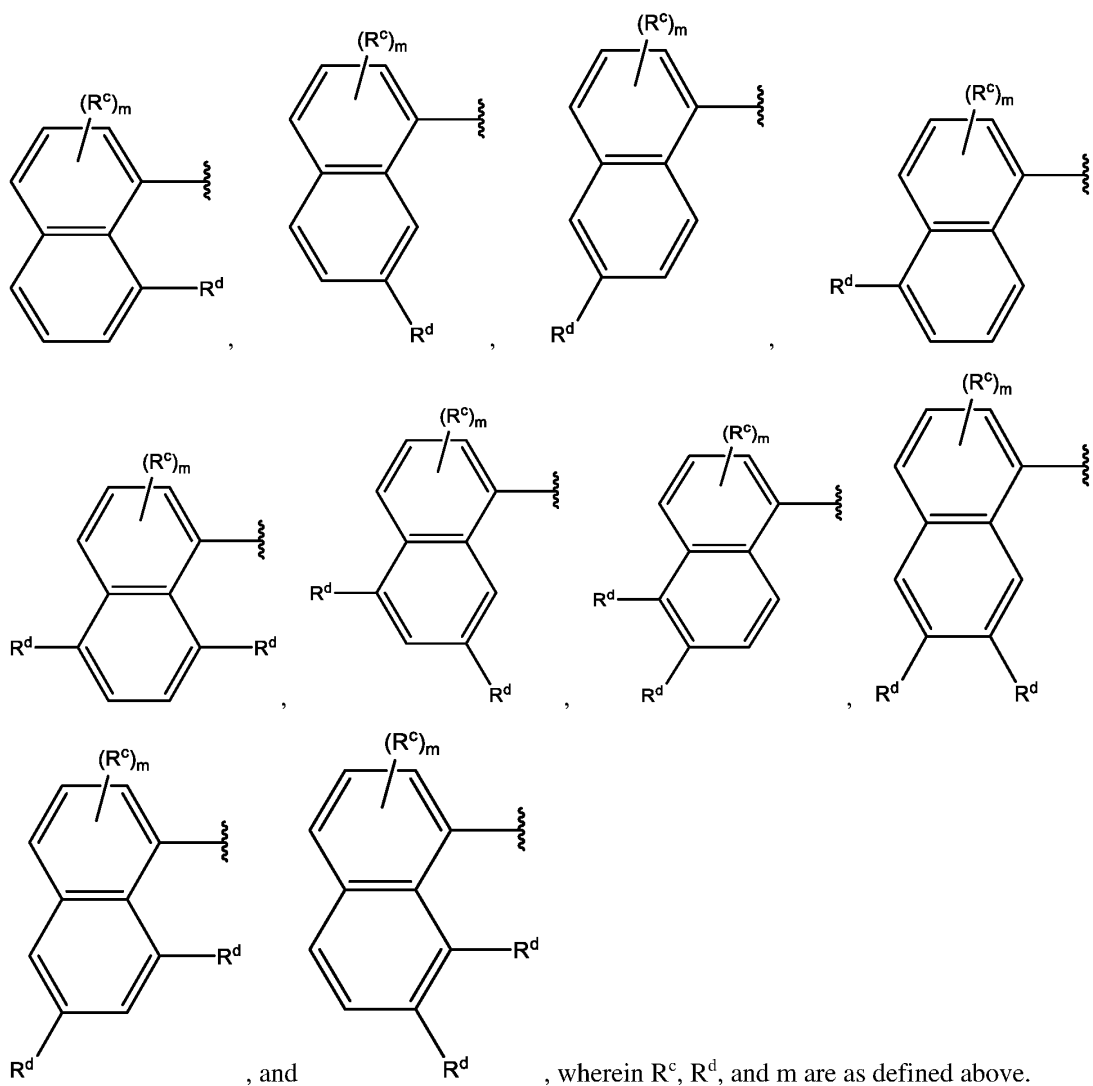
In embodiments, R³ is  wherein when m is 1, R^c is OH, and when m is 2, at least one R^c is OH and the other R^c is independently selected from F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, and (C₂-C₃)alkynyl.

In embodiments, R³ is selected from

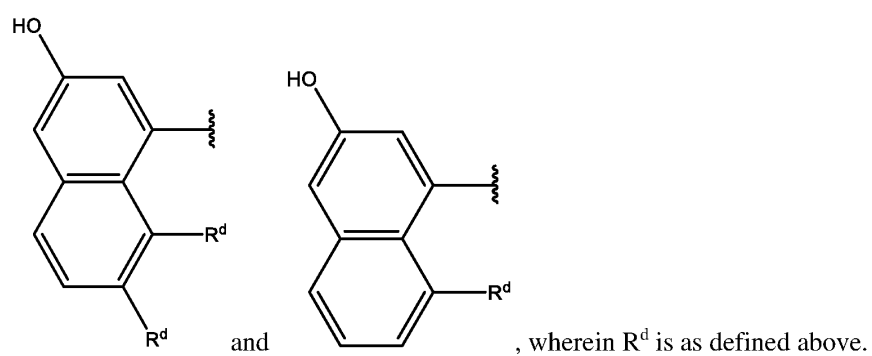




In embodiments, R^3 is selected from

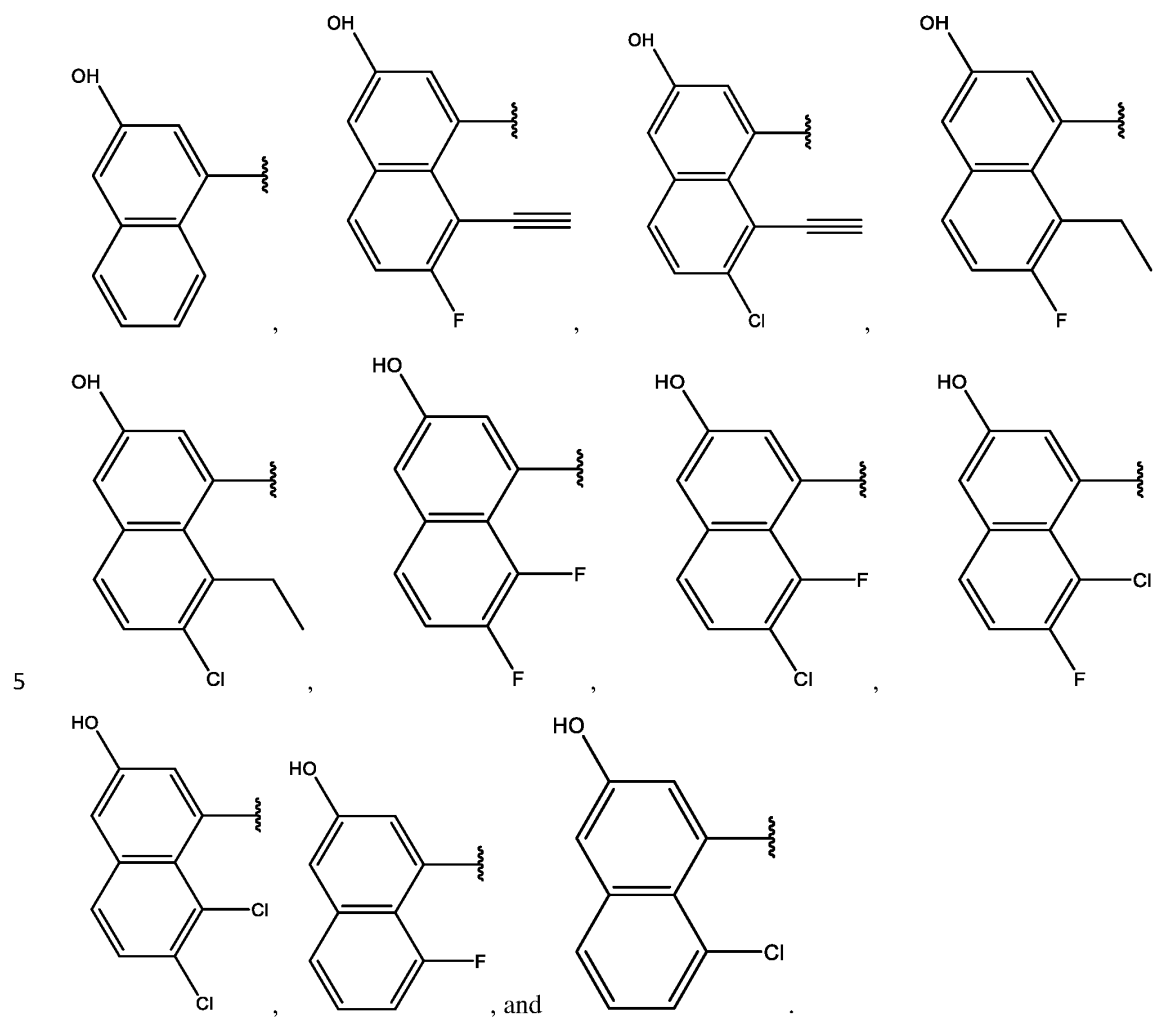


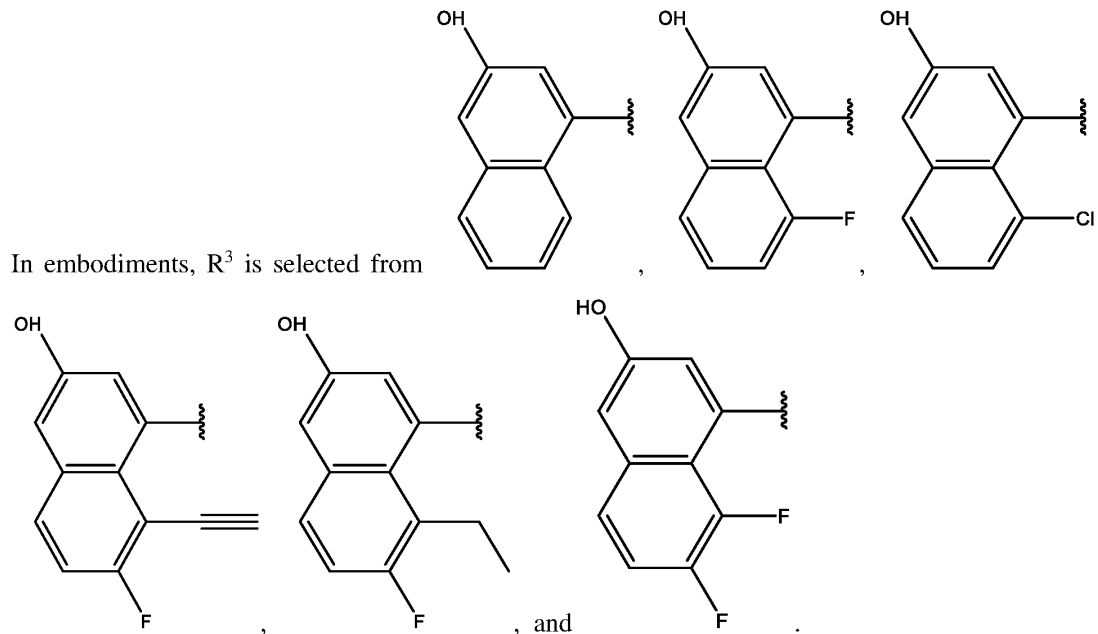
5 In embodiments, R^3 is selected from



In embodiments, each R^d is independently selected from F, Cl, $C\equiv CH$, and CH_2CH_3 .

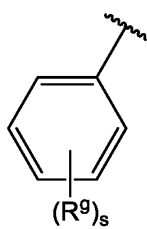
In embodiments, R^3 is selected from



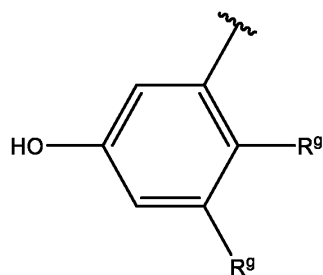


- In embodiments, R^3 is a phenyl group which is substituted by OH and optionally by one or more additional groups independently selected from CN, Cl, F, R^* , OH, OR^* , NH_2 , NHR^* , NR^{*2} , CHO, $C(O)R^*$, $C(O)OH$, $C(O)OR^*$, $C(O)NH_2$, $C(O)NHR^*$, $C(O)NR^{*2}$, $C(O)ONH_2$, $C(O)ONHR^*$, $C(O)ONR^{*2}$, (C_2-C_3) alkenyl, or (C_2-C_3) alkynyl, wherein R^* is as defined above (*e.g.* in accordance with Formula (0) or in accordance with Formula (I)).

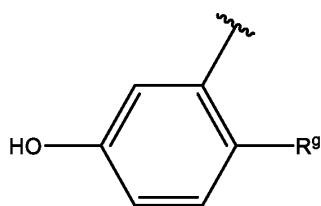
In embodiments, R^3 is



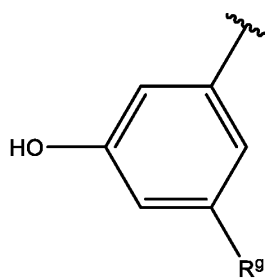
- 10 $(R^9)_s$, wherein s is 1, 2, or 3, and wherein when s is 1, R^9 is OH, and when s is 2 or 3 at least one R^9 is OH and each remaining R^9 is independently F, Cl, CN, OH, (C_1-C_3) alkyl, (C_2-C_3) alkenyl, (C_2-C_3) alkynyl, or (C_3-C_6) cycloalkyl, wherein said (C_3-C_6) cycloalkyl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, (C_1-C_3) alkyl, (C_2-C_3) alkenyl, or (C_2-C_3) alkynyl.



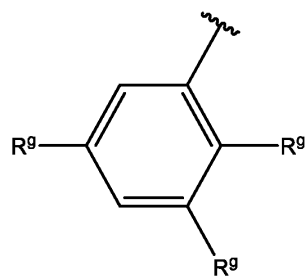
In embodiments, R^3 is , wherein each R^g is independently F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or (C₃-C₆)cycloalkyl, wherein said (C₃-C₆)cycloalkyl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl.

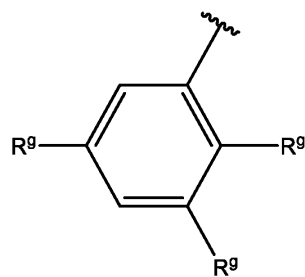


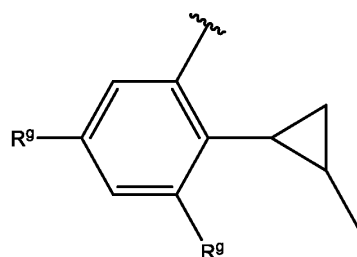
- 5 In embodiments, R^3 is , wherein R^g is F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or (C₃-C₆)cycloalkyl, wherein said (C₃-C₆)cycloalkyl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl.

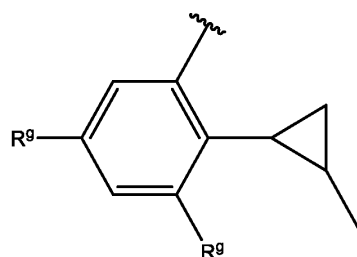


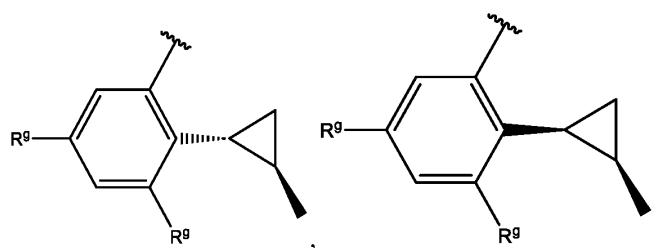
- In embodiments, R^3 is , wherein R^g is F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or (C₃-C₆)cycloalkyl, wherein said (C₃-C₆)cycloalkyl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl.
- 10



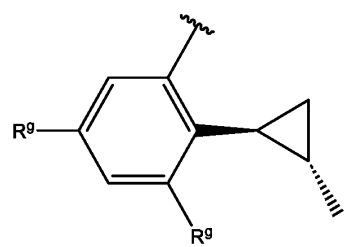
In embodiments, R^3 is , wherein each R^g is independently F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or (C₃-C₆)cycloalkyl, wherein said (C₃-C₆)cycloalkyl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl, provided that at least one R^g is OH.



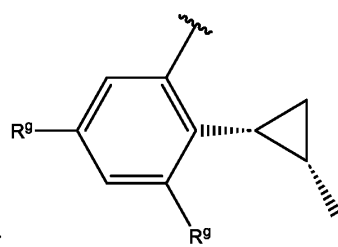
- 5 In embodiments, R^3 is , wherein each R^g is independently F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or (C₃-C₆)cycloalkyl, wherein said (C₃-C₆)cycloalkyl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl, provided that at least one R^g is OH.



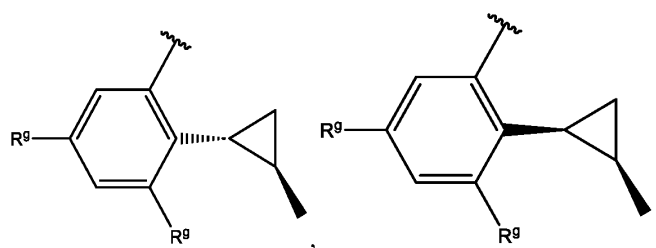
In embodiments, R^3 is

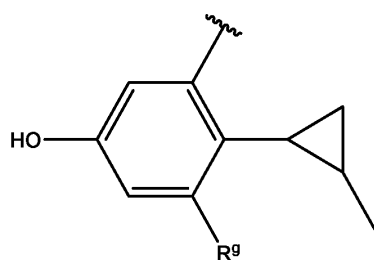


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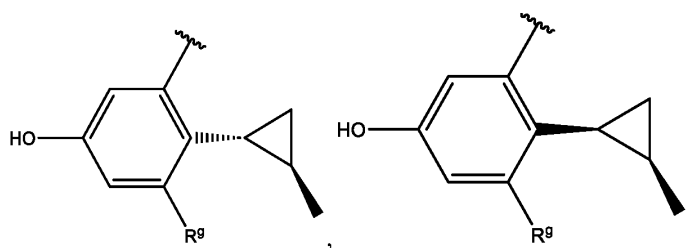
, or

, wherein each R^g is independently F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or (C₃-C₆)cycloalkyl, wherein said (C₃-C₆)cycloalkyl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl, provided that at least one R^g is OH.

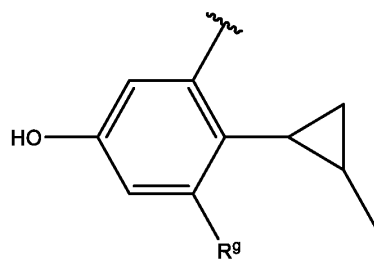


In embodiments, R^3 is , wherein R^g is F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or (C₃-C₆)cycloalkyl, wherein said (C₃-C₆)cycloalkyl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl.

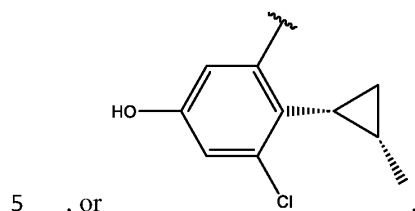
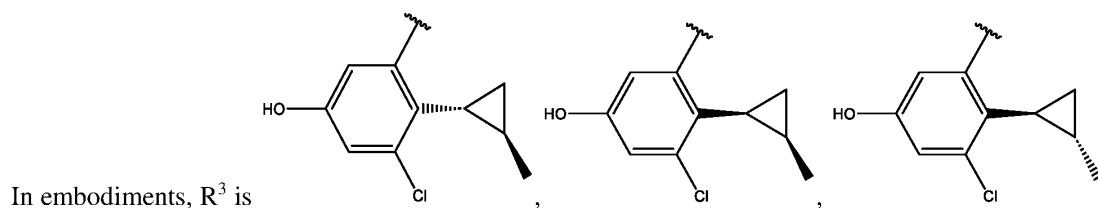
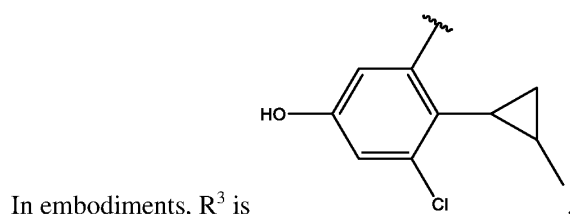
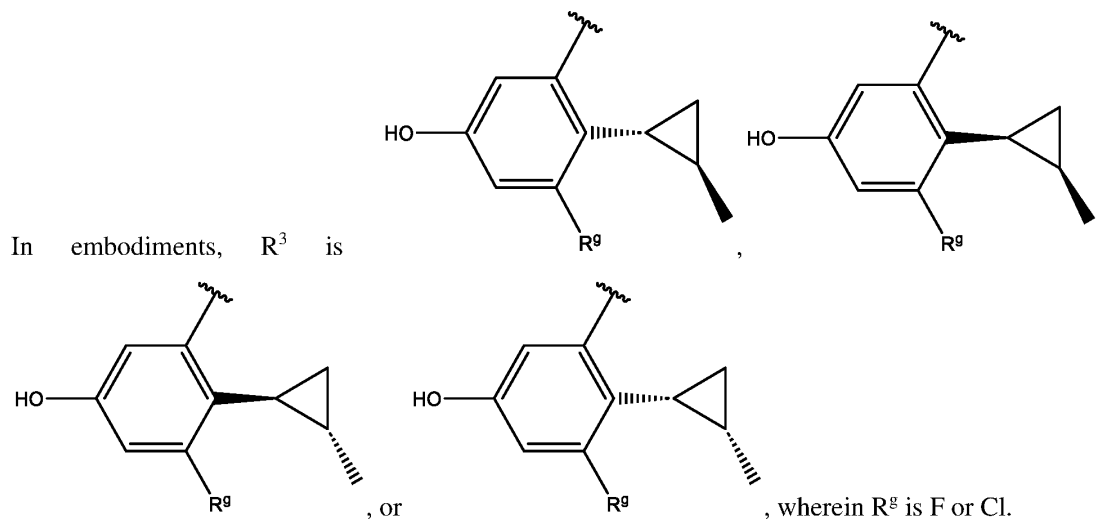
5 In embodiments, R^3 is



, or , wherein R^g is F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or (C₃-C₆)cycloalkyl, wherein said (C₃-C₆)cycloalkyl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl.



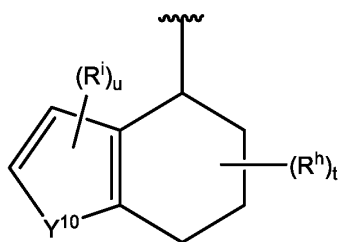
10 In embodiments, R^3 is , wherein R^g is F or Cl.



In embodiments, R^3 is a fused, 8-to-10-membered bicyclic group comprising a saturated carbocyclic ring fused to a heterocyclic ring, wherein the carbocyclic ring, the heterocyclic ring, or both, may optionally be substituted by one or more groups independently selected from CN, Cl, F, R^* , OH, OR^* , NH_2 , NHR^* , NR^{*2} , CHO, $C(O)R^*$, $C(O)OH$, $C(O)OR^*$, $C(O)NH_2$, $C(O)NHR^*$, $C(O)NR^{*2}$, $C(O)ONH_2$, $C(O)ONHR^*$, $C(O)ONR^{*2}$, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl.

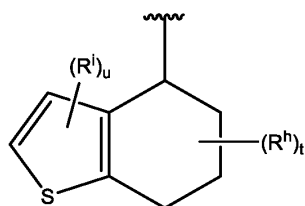
In embodiments, R^3 is a fused bicyclic group comprising a 6-membered saturated carbocyclic ring fused to a 5-membered heterocyclic ring, wherein the carbocyclic ring, the heterocyclic ring, or both, may optionally be substituted by one or more groups independently selected from CN, Cl, F, R^* , OH,

OR*, NH₂, NHR*, NR*₂, CHO, C(O)R*, C(O)OH, C(O)OR*, C(O)NH₂, C(O)NHR*, C(O)NR*₂, C(O)ONH₂, C(O)ONHR*, C(O)ONR*₂, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl. In embodiments, the heterocyclic ring comprises at least one heteroatom which is S. In embodiments, R³ is

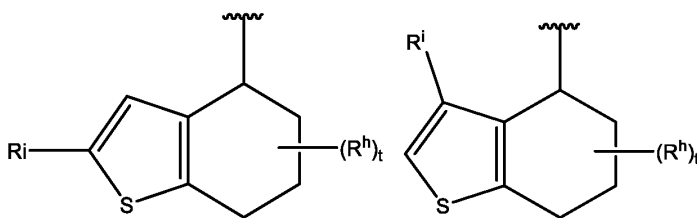


, wherein Y¹⁰ is S, O, or NR''' wherein R''' is H, OH, CN, Cl, F, or

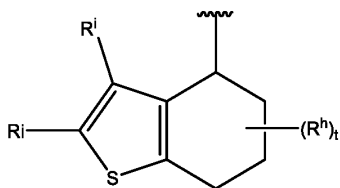
- 5 (C₁-C₃)alkyl; t is 0, 1, 2, or 3 and u is 0, 1, or 2, with the proviso that when t is zero, u is nonzero, and that when u is zero, t is nonzero; and each R^h and Rⁱ is independently selected from CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)R*, C(O)OH, C(O)OR*, C(O)NH₂, C(O)NHR*, C(O)NR*₂, C(O)ONH₂, C(O)ONHR*, C(O)ONR*₂, (C₂-C₃)alkenyl, and (C₂-C₃)alkynyl, wherein R* is as defined above (*e.g.* in accordance with Formula (0) or in accordance with Formula (I)). In embodiments, each
- 10 R^h and Rⁱ is independently selected from F, Cl, CN, OH, NH₂, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, and (C₂-C₃)alkynyl.



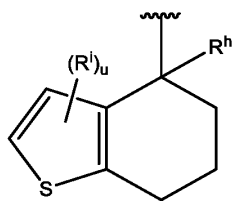
In embodiments, R³ is , wherein R^h, Rⁱ, t, and u are as defined above.



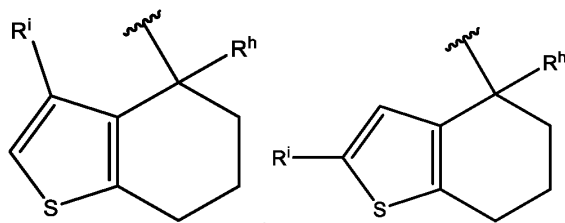
In particular embodiments, R³ is , or



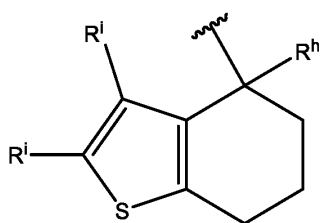
, wherein R^h, Rⁱ, t, and u are as defined above.



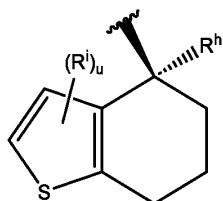
In embodiments, R^3 is , wherein R^h , R^i , and u are as defined above.



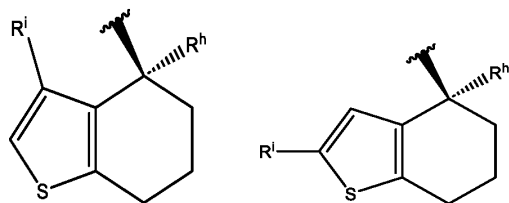
In particular embodiments, R^3 is , or



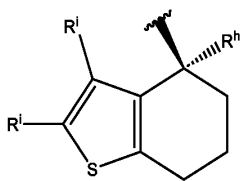
, wherein R^h and R^i are as defined above.



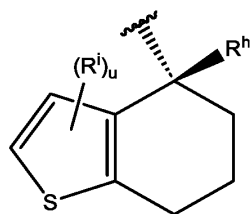
In embodiments, R^3 is wherein R^h , R^i , and u are as defined above.



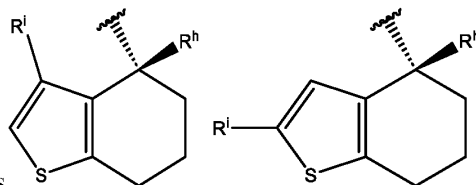
5 In particular embodiments, R^3 is , or



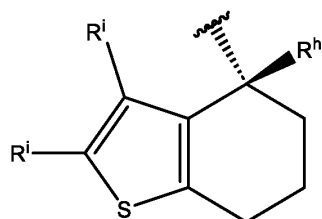
, wherein R^h and R^i are as defined above.



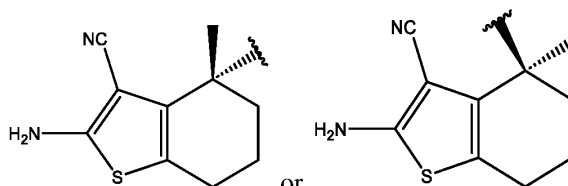
In embodiments, R^3 is , wherein R^h , R^i , and u are as defined above.



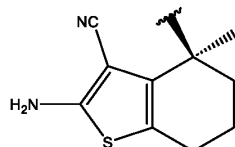
In particular embodiments, R^3 is , or



, wherein R^h and R^i are as defined above.

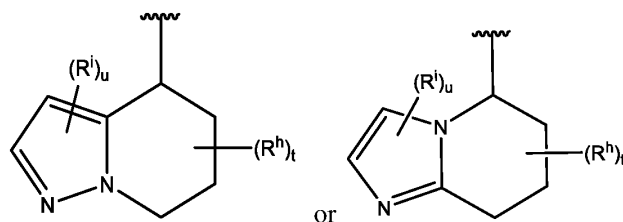


5 In more particular embodiments, R^3 is or . In even



more particular embodiments, R^3 is .

In embodiments, R^3 is a fused bicyclic group comprising a 6-membered saturated heterocyclic ring fused to a 5-membered heteroaryl ring, wherein the saturated heterocyclic ring, the heteroaryl ring, or both, may optionally be substituted by one or more groups independently selected from CN, Cl, F, R^* , OH, OR^* , NH_2 , NHR^* , NR^{*2} , CHO, $C(O)R^*$, $C(O)OH$, $C(O)OR^*$, $C(O)NH_2$, $C(O)NHR^*$, $C(O)NR^{*2}$, $C(O)ONH_2$, $C(O)ONHR^*$, $C(O)ONR^{*2}$, (C_2-C_3) alkenyl, or (C_2-C_3) alkynyl. In embodiments, the saturated heterocyclic ring comprises at least one heteroatom which is N. In embodiments, the heteroaryl ring comprises at least one heteroatom which is N.



In embodiments, R^3 is or 3 and u is 0, 1, or 2, with the proviso that when t is zero, u is nonzero, and that when u is zero, t is nonzero; and each R^h and R^i is independently selected from CN, Cl, F, R^* , OH, OR^* , NH_2 , NHR^* , NR^{*2} , CHO, $C(O)R^*$, $C(O)OH$, $C(O)OR^*$, $C(O)NH_2$, $C(O)NHR^*$, $C(O)NR^{*2}$, $C(O)ONH_2$, $C(O)ONHR^*$, $C(O)ONR^{*2}$, $(C_2-C_3)alkenyl$, and $(C_2-C_3)alkynyl$, wherein R^* is as defined above (*e.g.* in accordance with Formula (0) or in accordance with Formula (I)). In embodiments, each R^h and R^i is independently selected from F, Cl, CN, OH, NH_2 , $(C_1-C_3)alkyl$, $(C_2-C_3)alkenyl$, and $(C_2-C_3)alkynyl$.

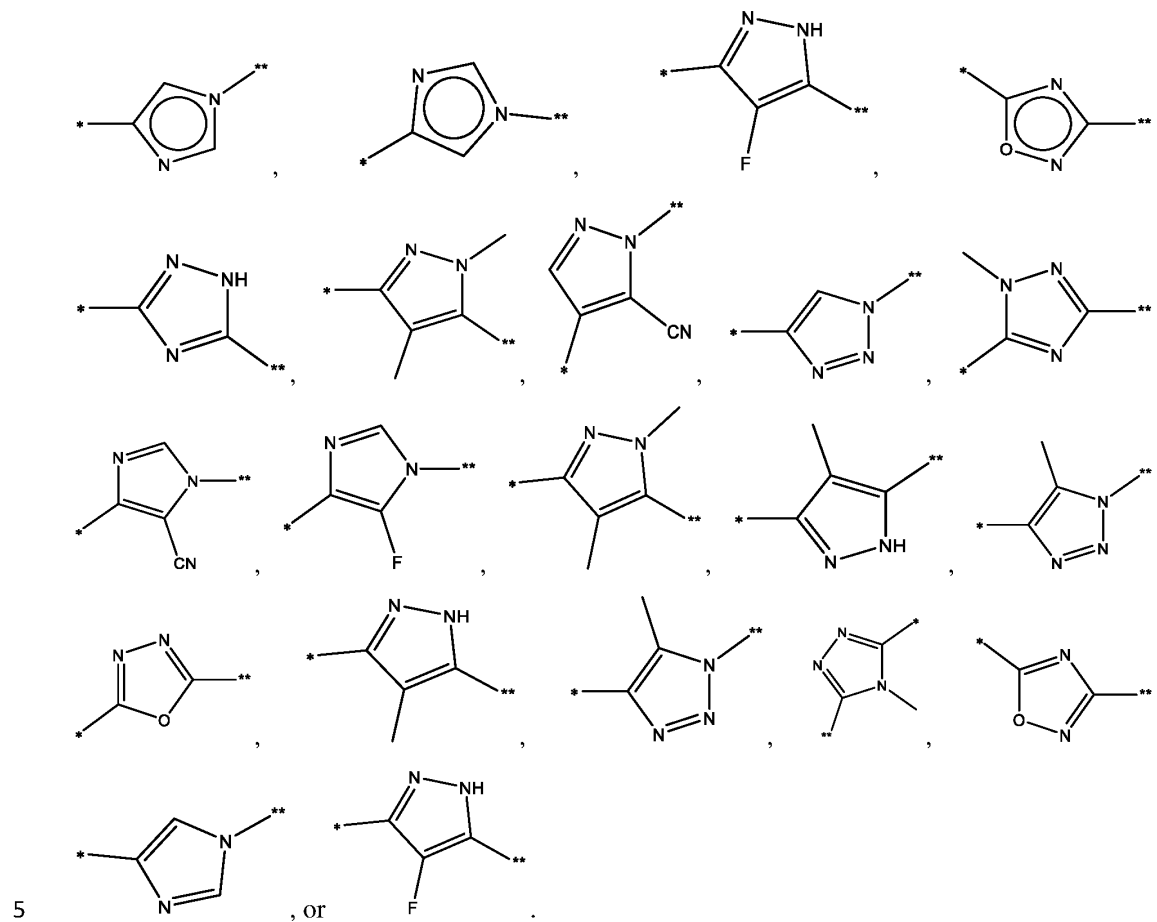
In the compounds of the present disclosure, L^2 is $-(C_1-C_3)alkyl-$, C_5 -heteroaryl optionally substituted with one or more R'' , $^*-O-(C_1-C_3)alkyl-^{**}$, $^*-(C_1-C_3)alkyl-O-^{**}$, $-(C_2-C_3)alkenyl-$, $-(C_2-C_3)alkynyl-$, $^*-(C_1-C_3)alkyl-NR''-^{**}$, $^*-NR''(C_1-C_3)alkyl-^{**}$, $^*-C(O)NR''-^{**}$, $^*-NR''C(O)-^{**}$, $^*-NR''-(C_1-C_3)alkyl-^{**}$, or $^*-(C_1-C_3)alkyl-NR''-^{**}$, wherein R'' is H, OH, CN, Cl, F, or $(C_1-C_3)alkyl$, and wherein * denotes a point of attachment to R^3 and ** denotes a point of attachment to the triazole moiety of the compound of Formula (0) (*e.g.* a compound of Formula (I)).

In embodiments, L^2 is $-(C_1-C_3)alkyl-$, C_5 -heteroaryl optionally substituted with one or more R'' and containing at least one ring atom which is N, $^*-O-(C_1-C_3)alkyl-^{**}$, $^*-(C_1-C_3)alkyl-O-^{**}$, $-(C_2-C_3)alkenyl-$, $-(C_2-C_3)alkynyl-$, $^*-(C_1-C_3)alkyl-NR''-^{**}$, $^*-NR''(C_1-C_3)alkyl-^{**}$, $^*-C(O)NR''-^{**}$, $^*-NR''C(O)-^{**}$, $^*-NR''-(C_1-C_3)alkyl-^{**}$, or $^*-(C_1-C_3)alkyl-NR''-^{**}$, wherein R'' is as defined above.

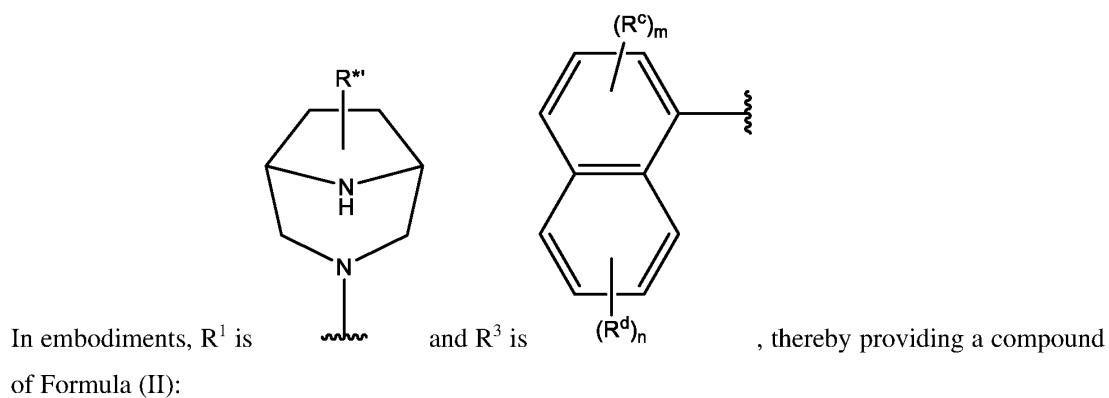
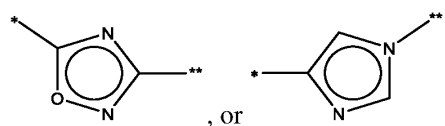
In embodiments, L^2 is $-(C_1-C_3)alkyl-$, C_5 -heteroaryl optionally substituted with one or more R'' and containing at least two ring atoms which are N, $^*-O-(C_1-C_3)alkyl-^{**}$, $^*-(C_1-C_3)alkyl-O-^{**}$, $-(C_2-C_3)alkenyl-$, $-(C_2-C_3)alkynyl-$, $^*-(C_1-C_3)alkyl-NR''-^{**}$, $^*-NR''(C_1-C_3)alkyl-^{**}$, $^*-C(O)NR''-^{**}$, $^*-NR''C(O)-^{**}$, $^*-NR''-(C_1-C_3)alkyl-^{**}$, or $^*-(C_1-C_3)alkyl-NR''-^{**}$, wherein R'' is as defined above.

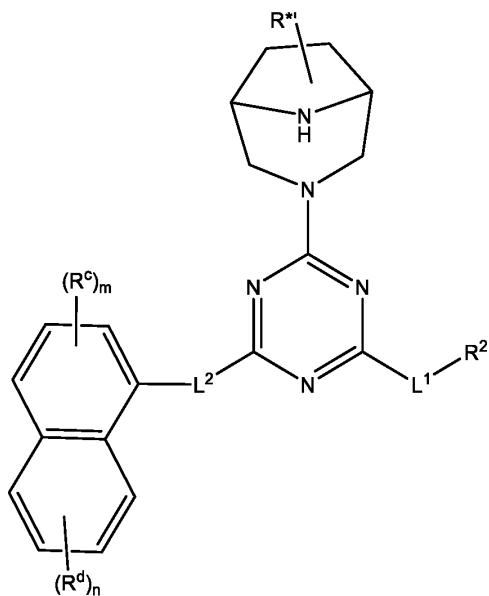
In embodiments, L^2 is $-(C_1-C_3)alkyl-$, $^*-O-(C_1-C_3)alkyl-^{**}$, $^*-(C_1-C_3)alkyl-O-^{**}$, $-(C_2-C_3)alkenyl-$, $-(C_2-C_3)alkynyl-$, $^*-(C_1-C_3)alkyl-NR''-^{**}$, $^*-NR''(C_1-C_3)alkyl-^{**}$, $^*-C(O)NR''-^{**}$, $^*-NR''C(O)-^{**}$, $^*-NR''-(C_1-C_3)alkyl-^{**}$, or $^*-(C_1-C_3)alkyl-NR''-^{**}$, or L^2 is pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, 1,3,4-oxadiazole, or 2,4-diazafuran, any of which may be optionally substituted with one or more R'' , wherein R'' is as defined above.

In embodiments L^2 is $-CH_2CH_2-$, $-CH=CH-$, $-C\equiv C-$, $^*-CH_2O-^{**}$, $^*-OCH_2-^{**}$, $^*-CH_2NH-^{**}$, $^*-NHCH_2-^{**}$, $^*-N(CH_3)C(O)-^{**}$, $^*-C(O)N(CH_3)-^{**}$, $^*-NHC(O)-^{**}$, $^*-C(O)NH-^{**}$,



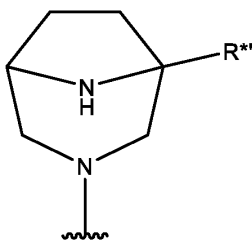
In embodiments L² is -CH₂CH₂-, -C≡C-,





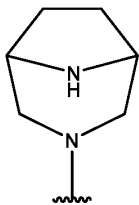
(Formula (II))

Wherein R^{*1} , L^1 , L^2 , R^2 , R^c , R^d , n , and m are as defined above.

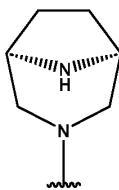


In embodiments of Formula (II), R^1 is

. In embodiments, R^{*1} is H and thus R^1

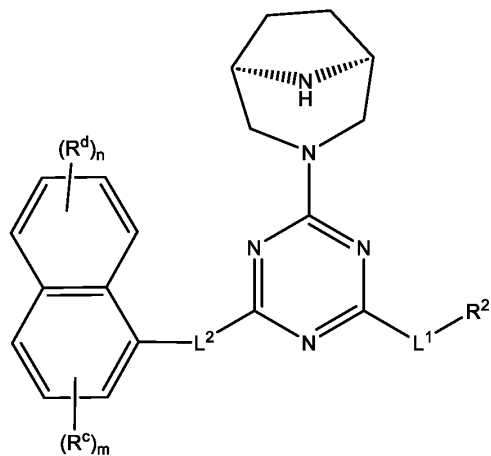


5 is .



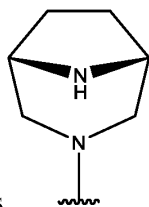
In embodiments of Formula (II), R^1 is

thereby providing a compound of Formula (IIa):

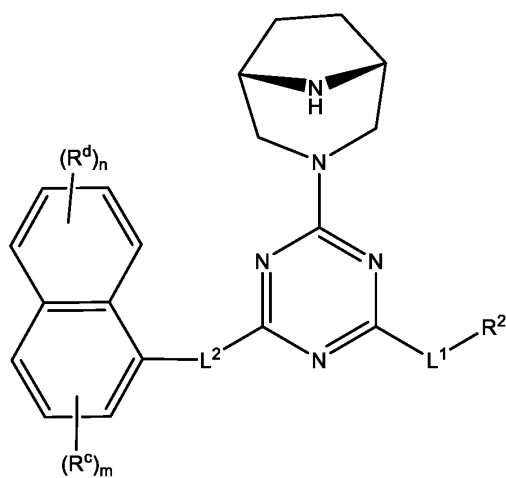


(Formula (IIa))

wherein L^1 , L^2 , R^2 , R^c , R^d , n , and m are as defined above.

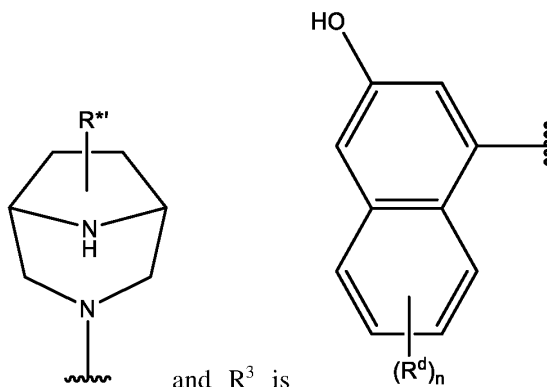


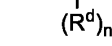
In embodiments of Formula (II), R^1 is , thereby providing a compound of Formula (IIb):

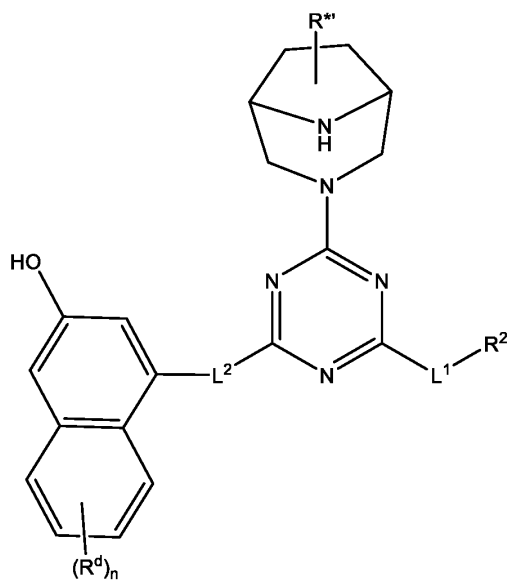


(Formula (IIb))

wherein L^1 , L^2 , R^2 , R^c , R^d , n , and m are as defined above.

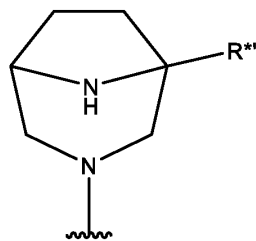


In embodiments, R^1 is  and R^3 is , thereby providing a compound of Formula (III):



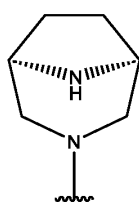
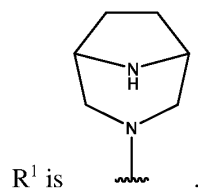
(Formula (III))

- 5 wherein R^{*1} , L^1 , L^2 , R^2 , R^c , R^d , and n are as defined above.



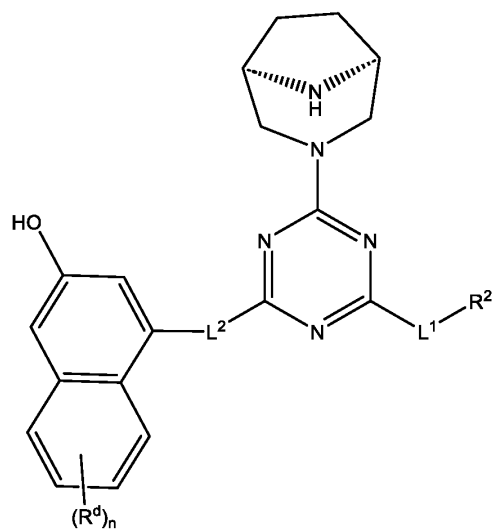
In embodiments of Formula (III), R^1 is

. In embodiments, R^{*} is H and thus



In embodiments of Formula (III), R^1 is

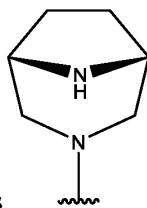
thereby providing a compound of Formula (IIIa):



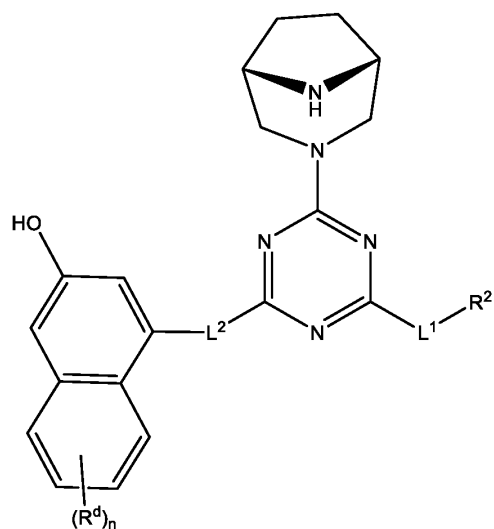
5

(Formula (IIIa))

wherein L^1 , L^2 , R^2 , R^c , R^d , and n are as defined above.



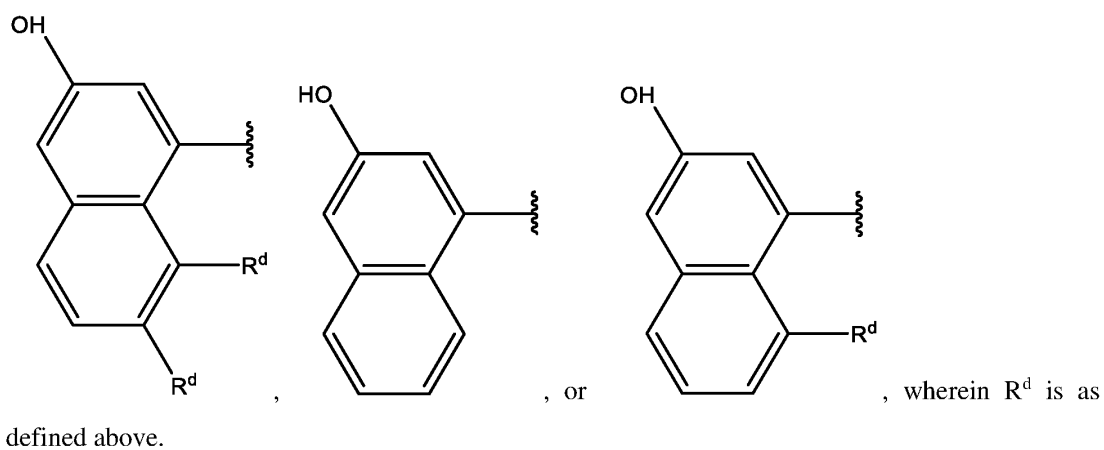
In embodiments of Formula (III), R^1 is , thereby providing a compound of Formula (IIIb):



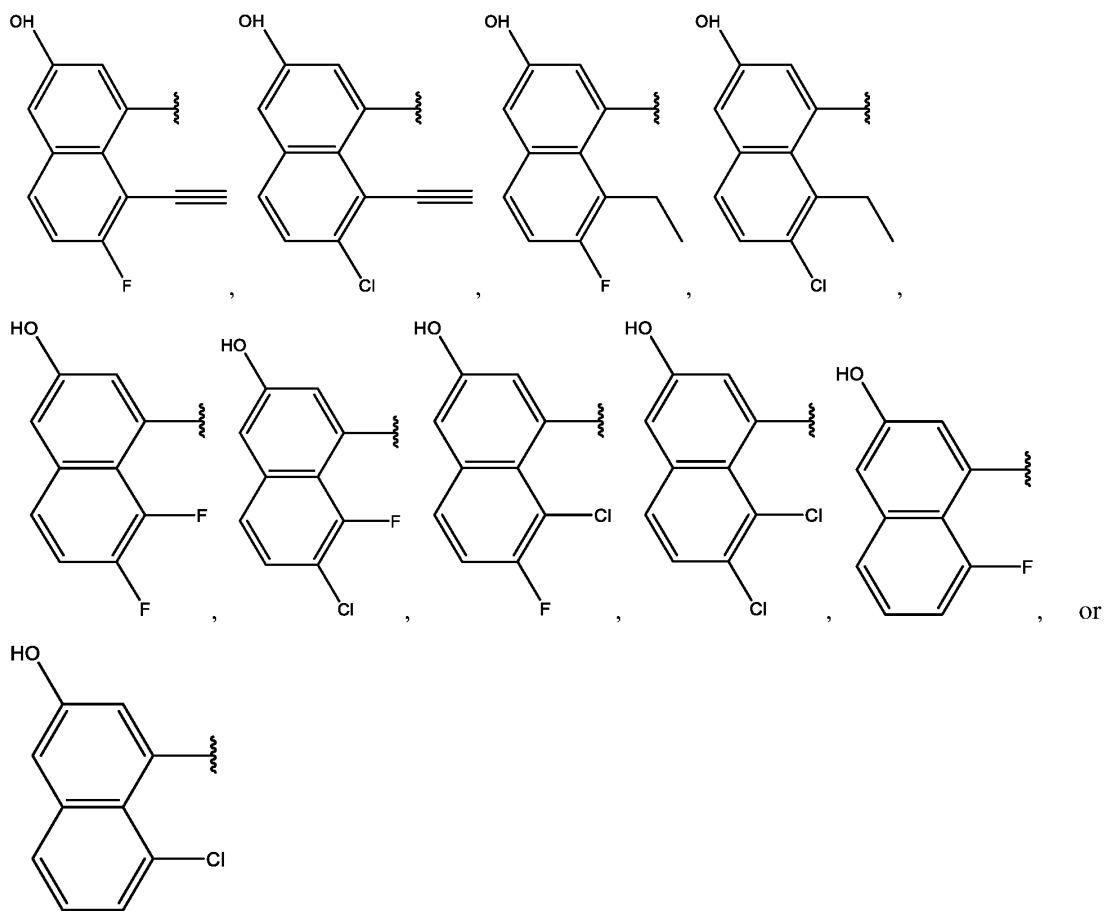
(Formula (IIIb))

5 wherein L^1 , L^2 , R^2 , R^c , R^d , and n are as defined above.

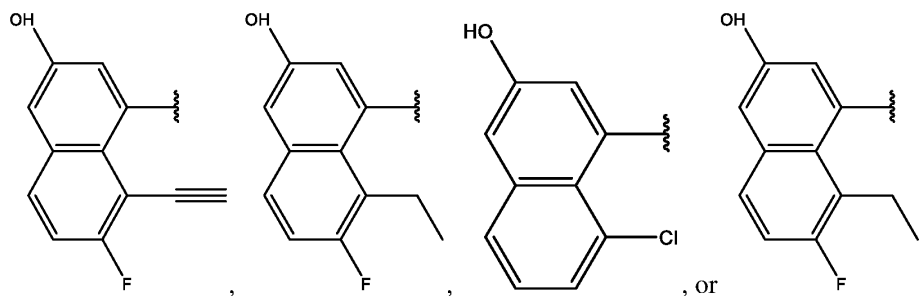
In embodiments of Formula (III), including Formula (IIIa) and Formula (IIIb), R^3 is

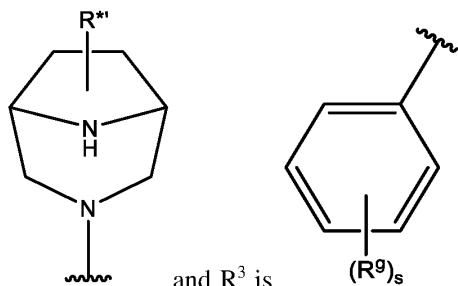


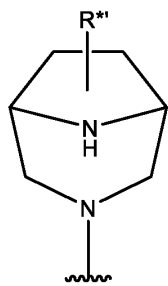
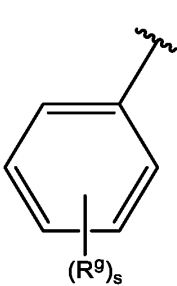
In embodiments of Formula (III), including Formula (IIIa) and Formula (IIIb), R^3 is

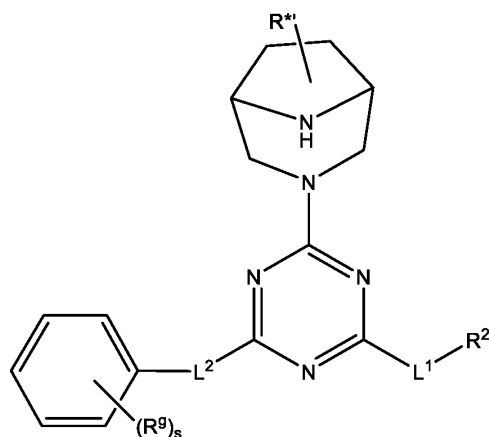


5 In embodiments of Formula (III), including Formula (IIIa) and Formula (IIIb), R^3 is



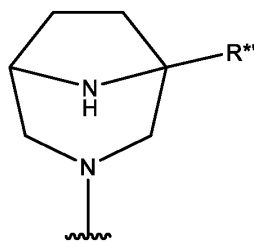


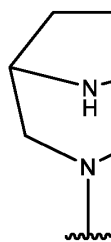
In embodiments, R^1 is  and R^3 is , thereby providing a compound of Formula (IV):

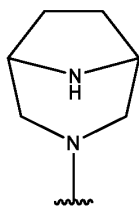


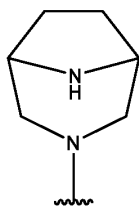
(Formula (IV))

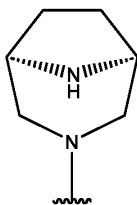
- 5 wherein R^{**} , L^1 , L^2 , R^2 , and s are as defined above, and wherein each R^g is independently F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or (C₃-C₆)cycloalkyl, wherein said (C₃-C₆)cycloalkyl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl, provided that at least one R^g is OH.



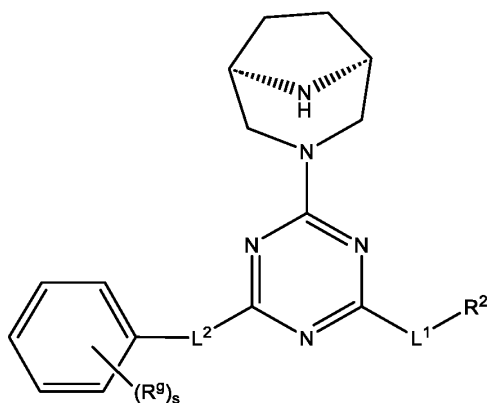
In embodiments of Formula (IV), R^1 is . In embodiments, R^{**} is H and thus



10 R^1 is .

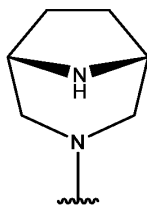


In embodiments of Formula (IV), R¹ is  thereby providing a compound of Formula (IVa):

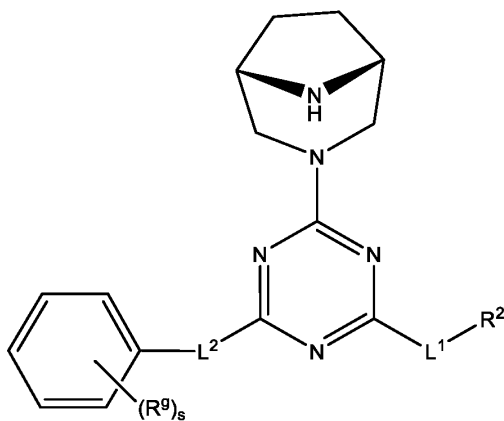


(Formula (IVa))

wherein L¹, L², R², R^g, and s are as defined above.



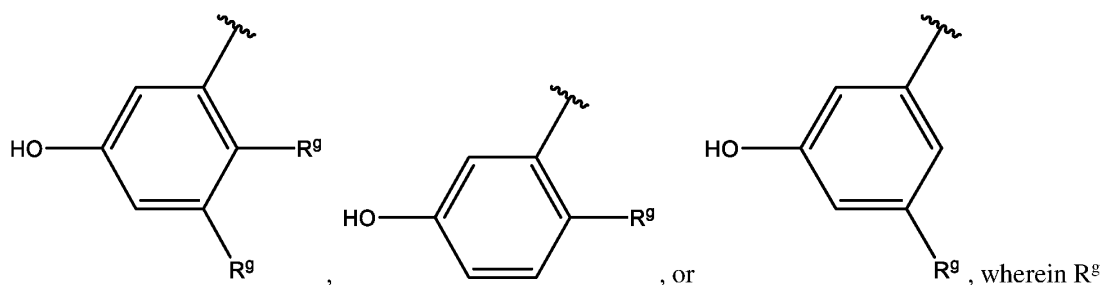
5 In embodiments of Formula (IV), R¹ is  thereby providing a compound of Formula (IVb):



(Formula (IVb))

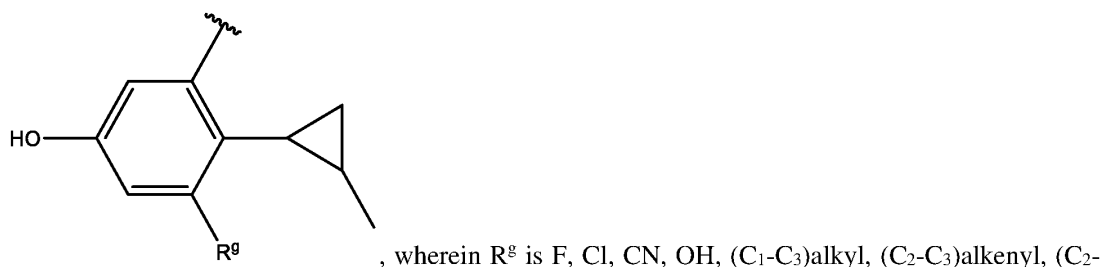
wherein L¹, L², R², R^g, and s are as defined above.

In embodiments of Formula (IV), including Formula (IVa) and Formula (IVb), R^3 is

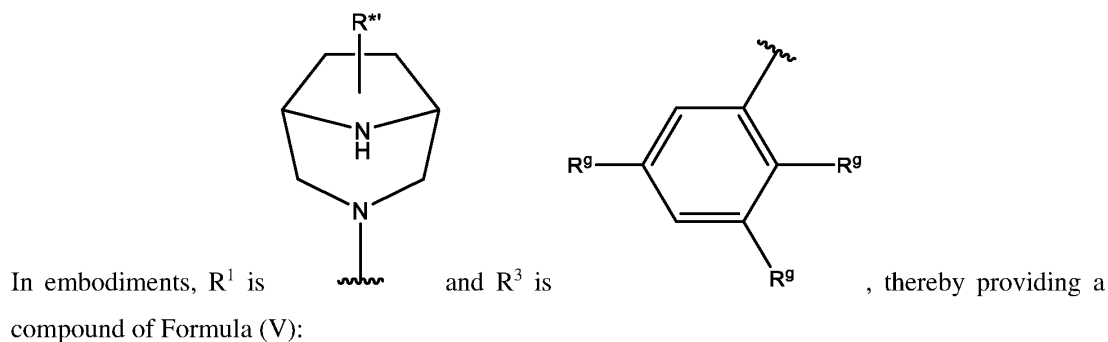


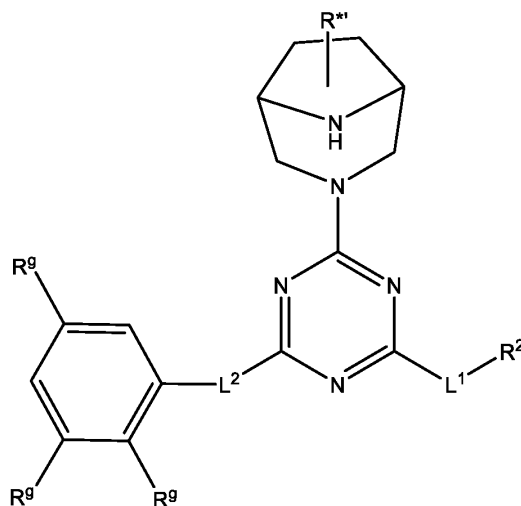
is F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or (C₃-C₆)cycloalkyl, wherein said (C₃-C₆)cycloalkyl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl.

In embodiments of Formula (IV), including Formula (IVa) and Formula (IVb), R^3 is



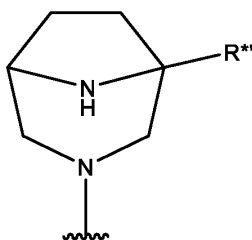
10 C₃)alkynyl.





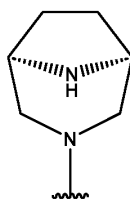
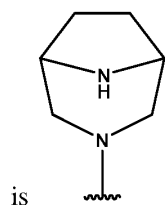
(Formula (V))

wherein L^1 , L^2 , and R^2 are as defined above, and wherein each R^g is independently F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or (C₃-C₆)cycloalkyl, wherein said (C₃-C₆)cycloalkyl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl, provided that at least one R^g is OH.



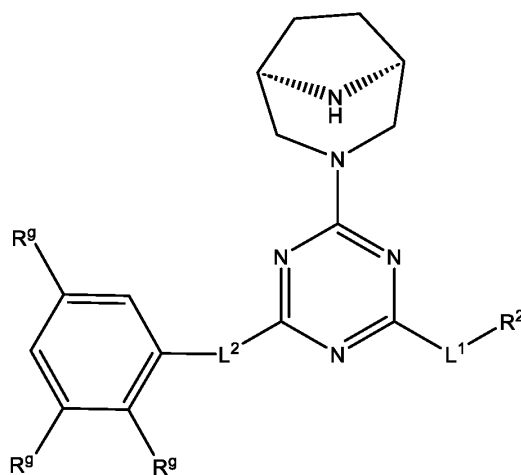
In embodiments of Formula (V), R^1 is

. In embodiments, R^{*1} is H and thus R^1



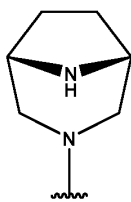
In embodiments of Formula (V), R^1 is

thereby providing a compound of Formula (Va):

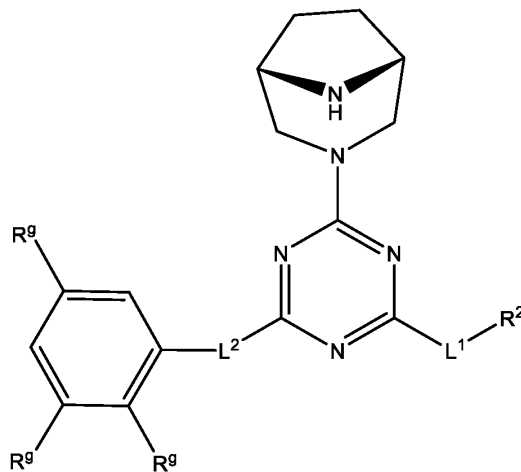


(Formula (Va))

wherein L^1 , L^2 , and R^2 are as defined above, and wherein each R^9 is independently F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or (C₃-C₆)cycloalkyl, wherein said (C₃-C₆)cycloalkyl
 5 may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl, provided that at least one R^9 is OH.



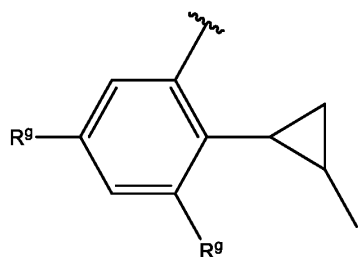
In embodiments of Formula (V), R^1 is  thereby providing a compound of Formula (Vb):



(Formula (Vb))

wherein L^1 , L^2 , and R^2 are as defined above, and wherein each R^8 is independently F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or (C₃-C₆)cycloalkyl, wherein said (C₃-C₆)cycloalkyl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl, provided that at least one R^8 is OH.

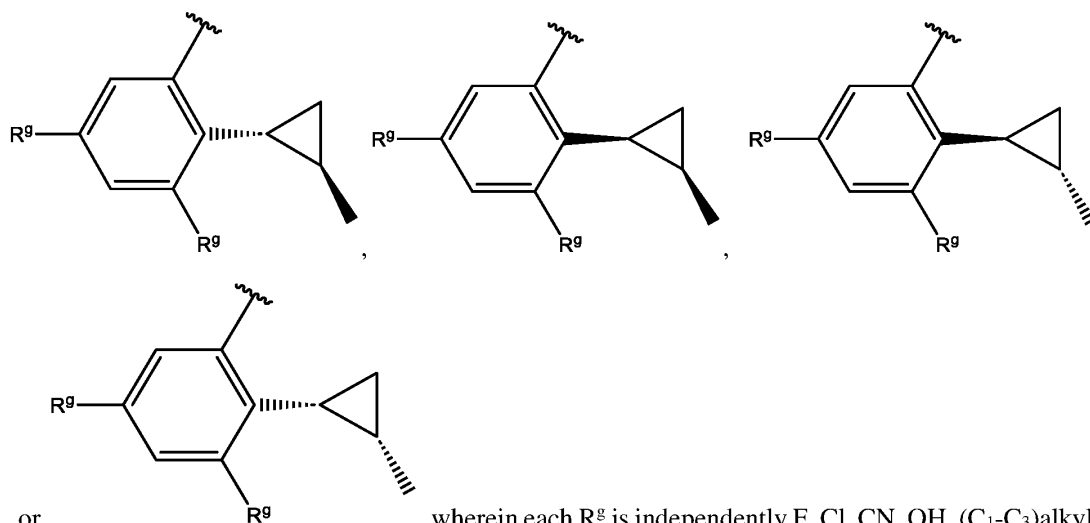
5 In embodiments of Formula (V), including Formula (Va) and Formula (Vb), R^3 is



, wherein R^8 is F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or (C₃-C₆)cycloalkyl, wherein said (C₃-C₆)cycloalkyl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl.

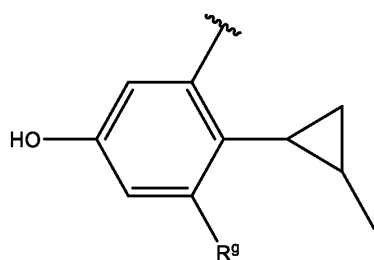
10

In embodiments of Formula (V), including Formula (Va) and Formula (Vb), R^3 is



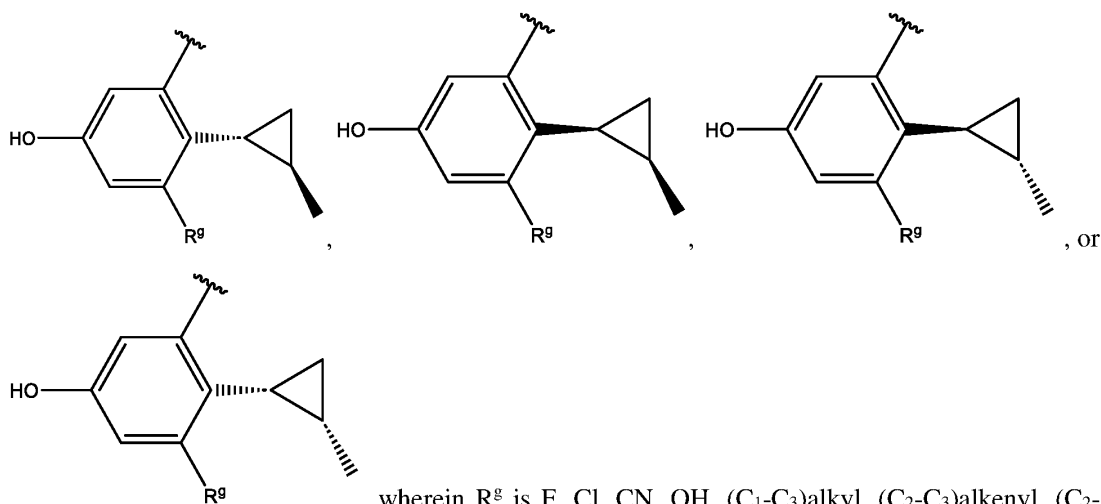
, or
 15 , wherein each R^8 is independently F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or (C₃-C₆)cycloalkyl, wherein said (C₃-C₆)cycloalkyl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl, provided that at least one R^8 is OH.

In embodiments of Formula (V), including Formula (Va) and Formula (Vb), R^3 is



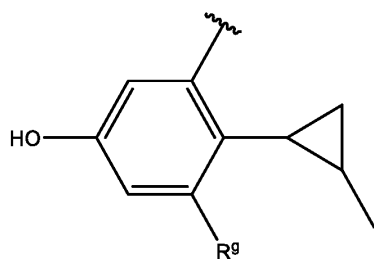
, wherein R^g is F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or (C₃-C₆)cycloalkyl, wherein said (C₃-C₆)cycloalkyl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl.

In embodiments of Formula (V), including Formula (Va) and Formula (Vb), R^3 is



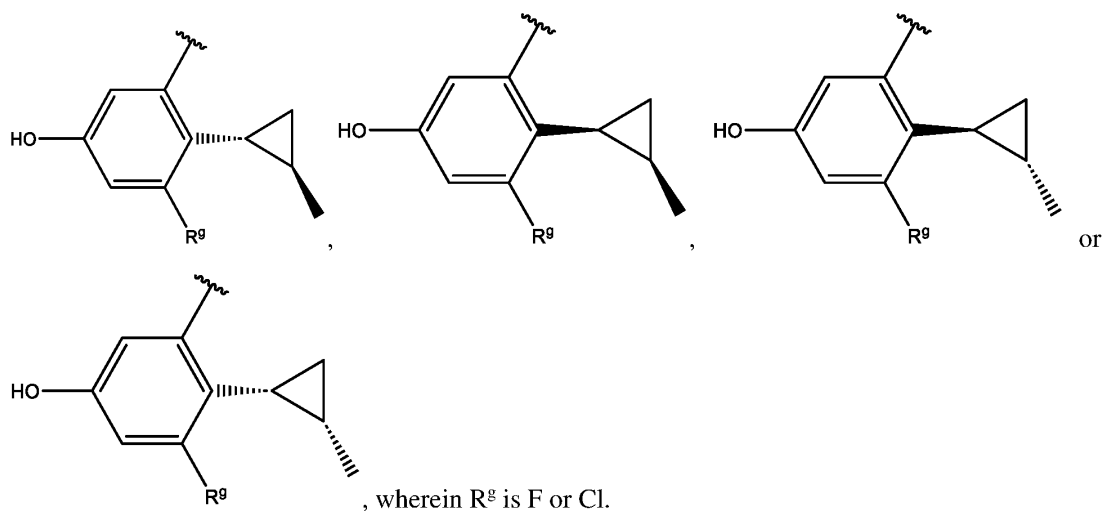
, wherein R^g is F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or (C₃-C₆)cycloalkyl, wherein said (C₃-C₆)cycloalkyl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl.

In embodiments of Formula (V), including Formula (Va) and Formula (Vb), R^3 is

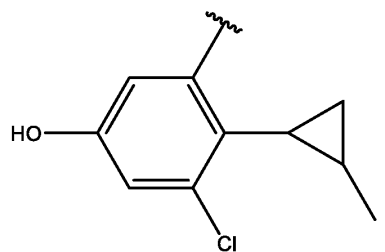


, wherein R^g is F or Cl.

In embodiments of Formula (V), including Formula (Va) and Formula (Vb), R^3 is

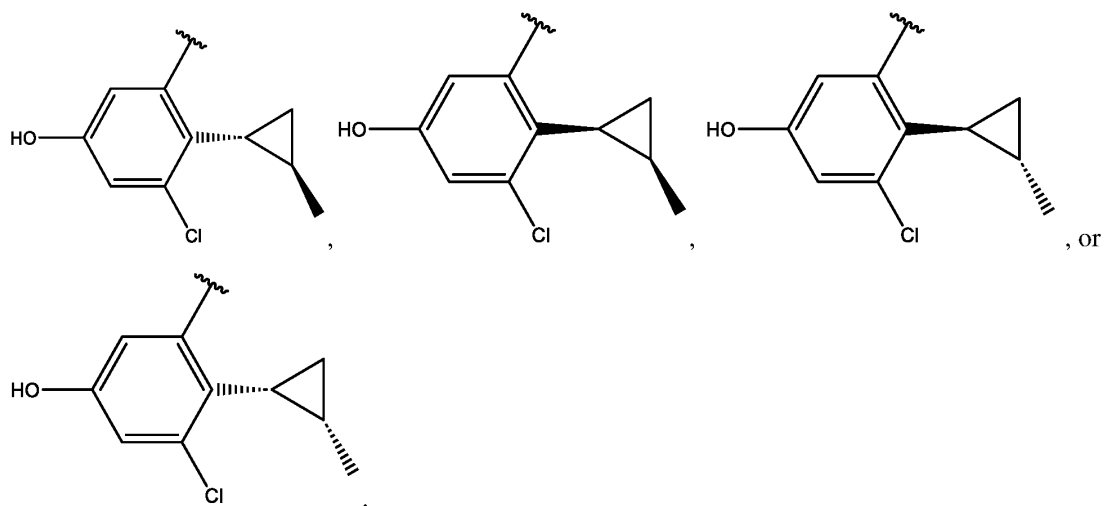


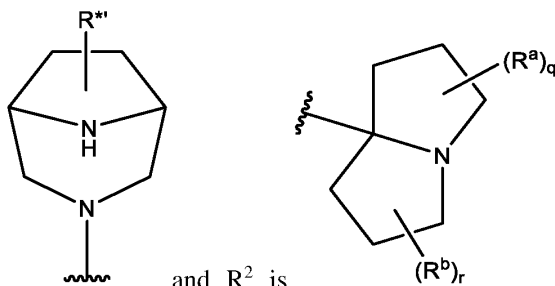
In embodiments of Formula (V), including Formula (Va) and Formula (Vb), R^3 is

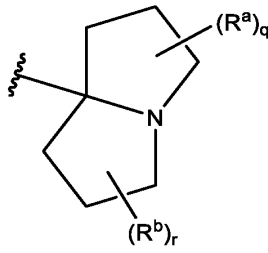


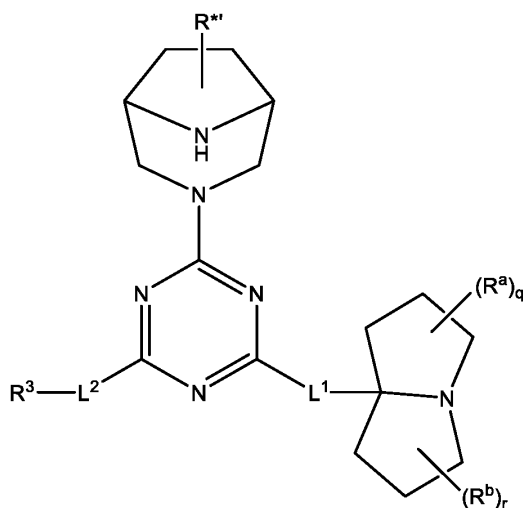
5

In embodiments of Formula (V), including Formula (Va) and Formula (Vb), R^3 is



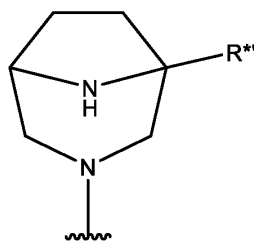


In embodiments, R^1 is  and R^2 is , thereby providing a compound of Formula (VI):

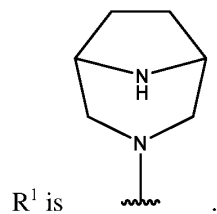


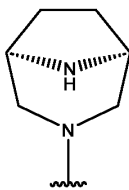
(Formula (VI))

5 wherein R^{*2} , L^1 , L^2 , R^3 , q , r , R^a , and R^b are as defined above.

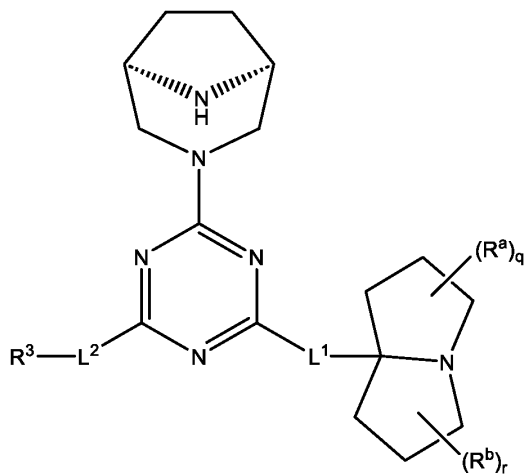


In embodiments of Formula (VI), R^1 is . In embodiments, R^{*2} is H and thus



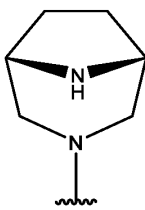


In embodiments of Formula (VI), R^1 is  thereby providing a compound of Formula (VIa):

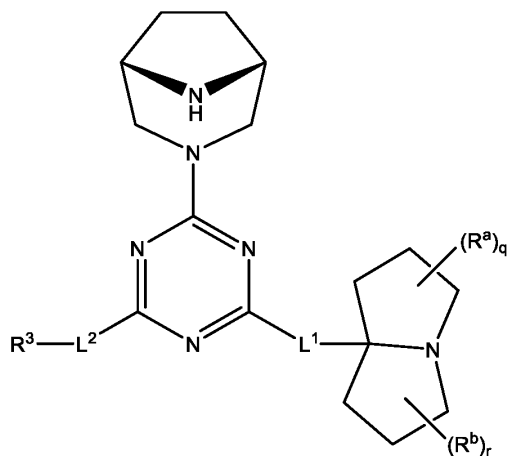


(Formula (VIa))

wherein L^1 , L^2 , R^3 , q , r , R^a , and R^b are as defined above.

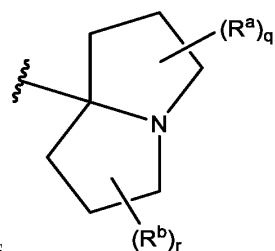
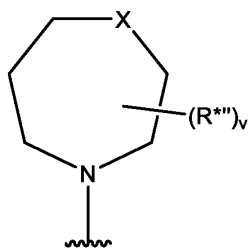


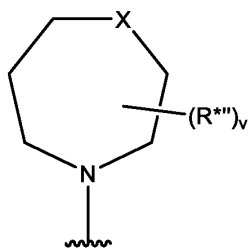
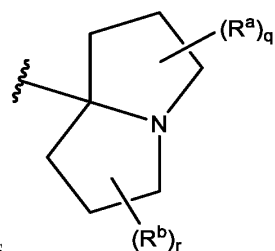
5 In embodiments of Formula (VI), R^1 is  thereby providing a compound of Formula (VIb):

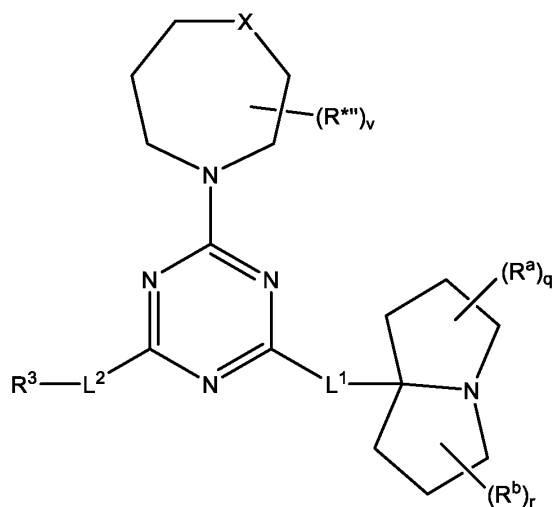


(Formula (VIb))

wherein L^1 , L^2 , R^3 , q , r , R^a , and R^b are as defined above.



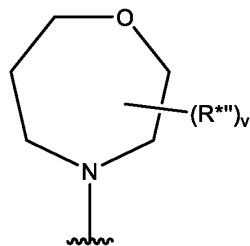
In embodiments, R^1 is  and R^2 is , thereby providing a compound of Formula (VI.I):



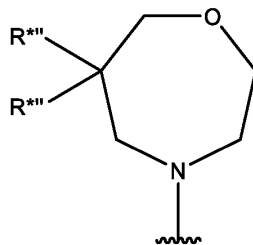
5

(Formula (VI.I))

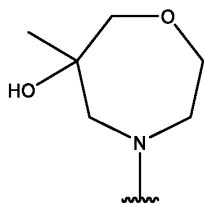
wherein $R^{*''}$, L^1 , L^2 , R^3 , X , q , r , v , R^a , and R^b are as defined above.



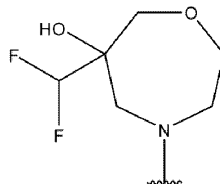
In embodiments of Formula (VI.I), X is O and thus R¹ is . In embodiments, X



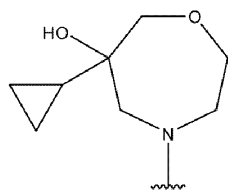
is O and v is 2. In embodiments, R¹ is . In embodiments, R¹ is



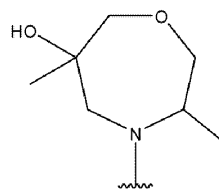
. In embodiments, R¹ is



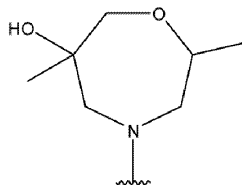
. In embodiments, R¹ is



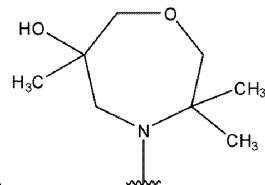
. In embodiments, R¹ is



. In embodiments, R¹ is

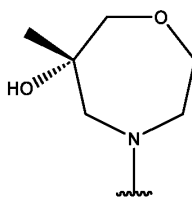


. In embodiments, R¹ is



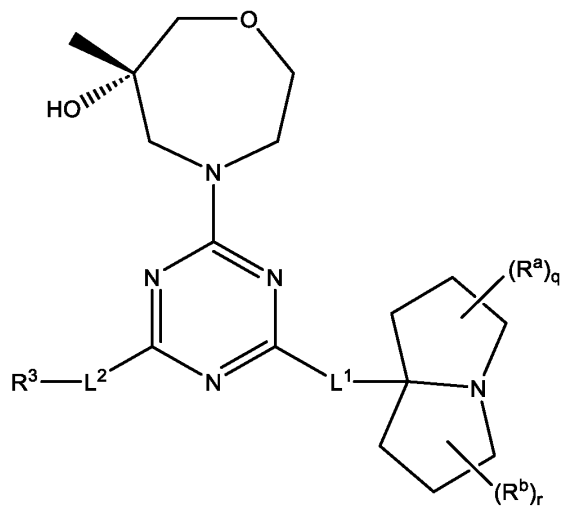
.

5



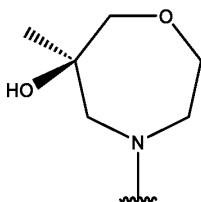
In embodiments of Formula VI.I, R¹ is (VI.Ia):

thereby providing a compound of Formula



(Formula (VI.Ia))

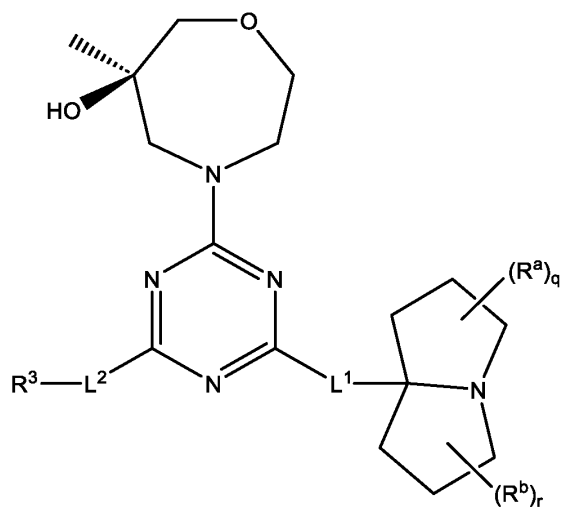
wherein L^1 , L^2 , R^3 , q , r , R^a , and R^b are as defined above.



In embodiments of Formula VI.I, R^1 is

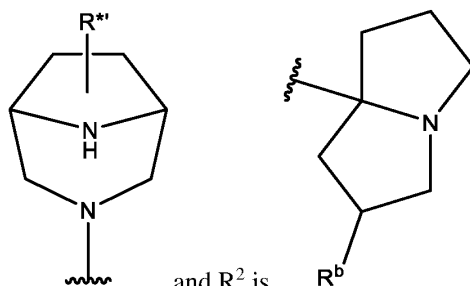
thereby providing a compound of Formula

5 (VI.Ib):

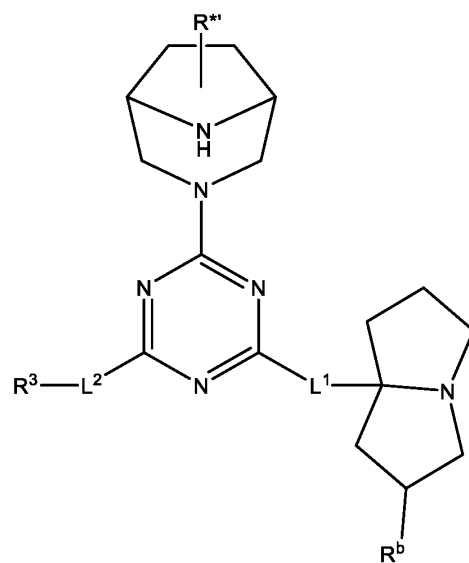


(Formula (VI.Ib))

wherein L^1 , L^2 , R^3 , q , r , R^a , and R^b are as defined above.

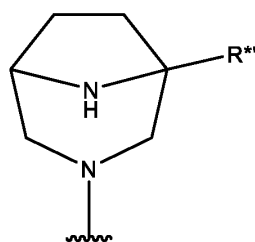


In embodiments, R^1 is  and R^2 is , thereby providing a compound of Formula (VII):

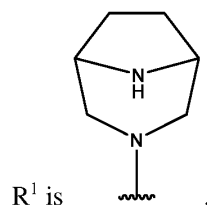


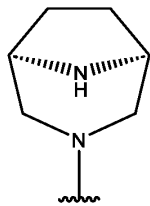
(Formula (VII))

5 wherein R^{*} , L^1 , L^2 , R^3 , and R^b are as defined above.

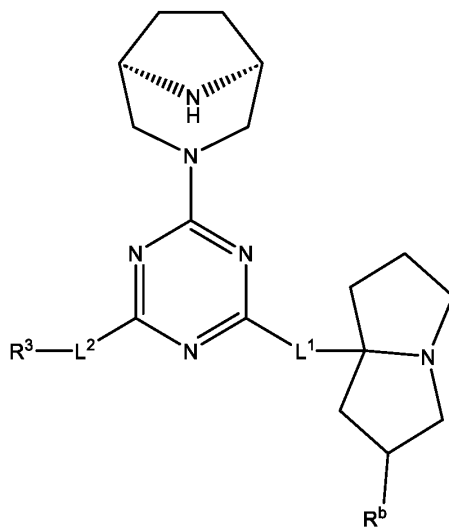


In embodiments of Formula (VII), R^1 is . In embodiments, R^{*} is H and thus



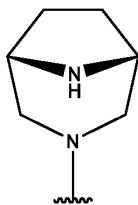


In embodiments of Formula (VII), R^1 is thereby providing a compound of Formula (VIIa):

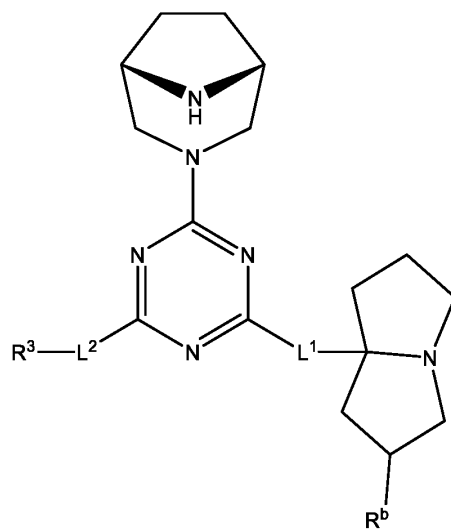


(Formula (VIIa))

5 wherein L^1 , L^2 , R^3 , and R^b are as defined above.

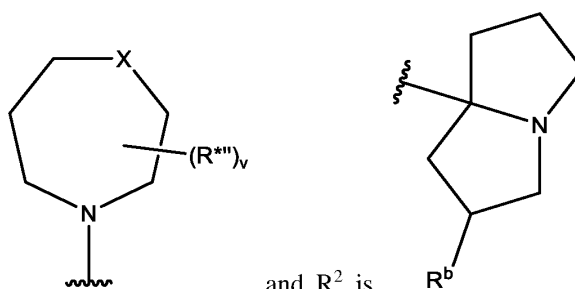


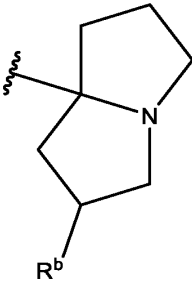
In embodiments of Formula (VII), R^1 is thereby providing a compound of Formula (VIIb):

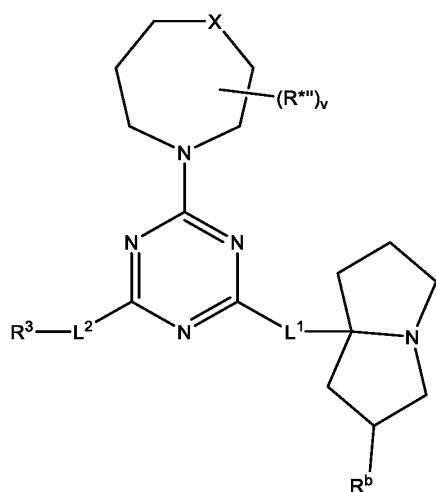


(Formula (VIIb))

wherein L^1 , L^2 , R^3 , and R^b are as defined above.

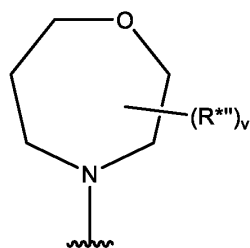


In embodiments, R^1 is  and R^2 is , thereby providing a
5 compound of Formula (VII.I):

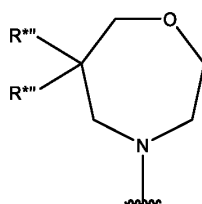


(Formula (VII.I))

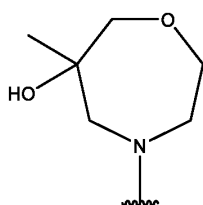
wherein R^{*v} , L^1 , L^2 , R^3 , X , v , and R^b are as defined above.



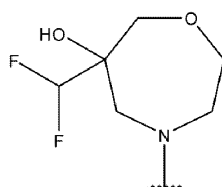
In embodiments of Formula (VII.I), X is O and thus R^1 is . In embodiments,



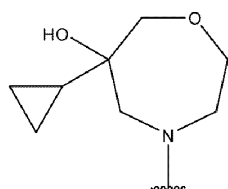
X is O and v is 2. In embodiments, R^1 is . In embodiments, R^1 is



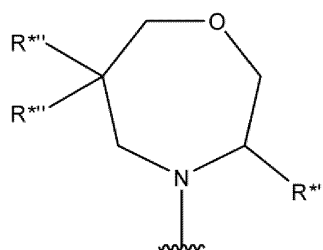
5 . In embodiments, R^1 is



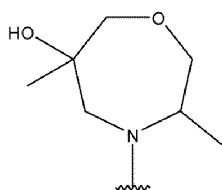
. In embodiments, R^1 is



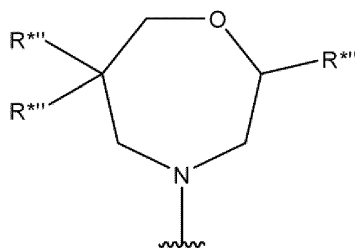
. In embodiments, R^1 is



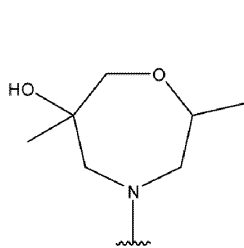
. In embodiments, R^1 is



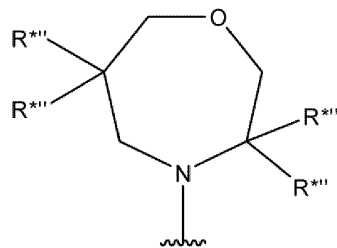
. In embodiments, R^1 is



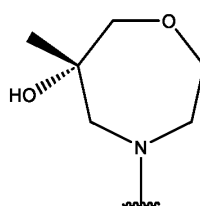
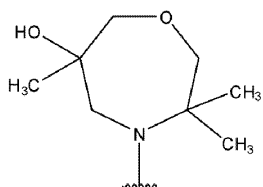
. In embodiments, R^1 is



. In embodiments, R^1 is



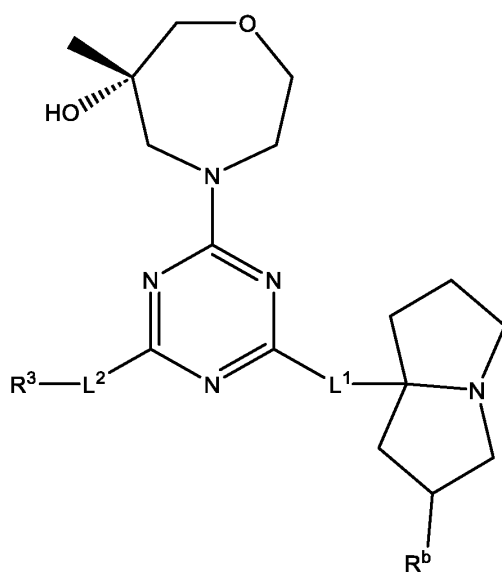
. In embodiments, R^1 is



In embodiments of Formula VII.I, R^1 is
(VII.Ia):

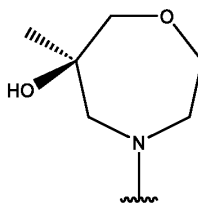
thereby providing a compound of Formula

5

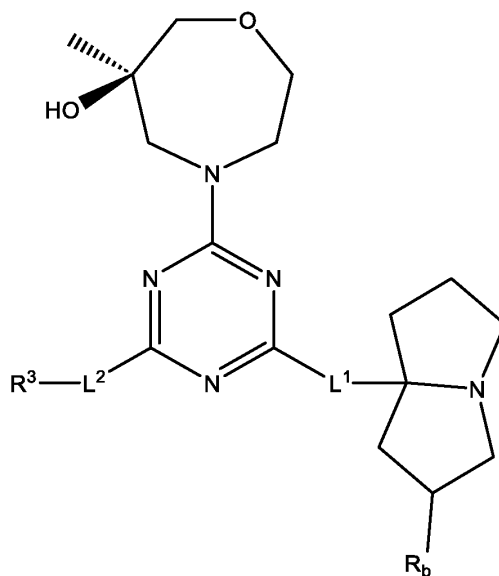


(Formula (VII.Ia))

wherein L^1 , L^2 , R^3 , and R^b are as defined above.



In embodiments of Formula VII.I, R^1 is thereby providing a compound of Formula (VII.Ib):

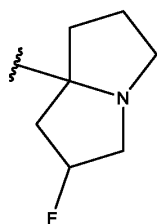


5

(Formula (VII.Ib))

wherein L^1 , L^2 , R^3 , and R^b are as defined above.

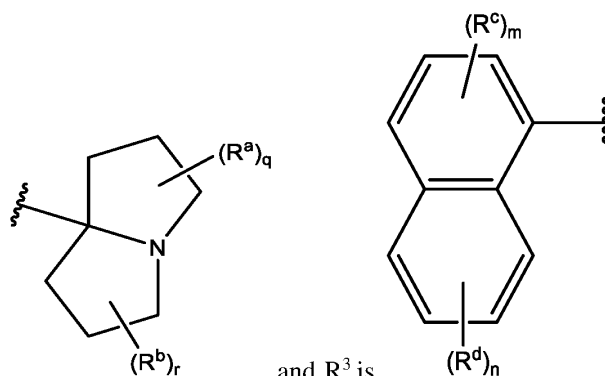
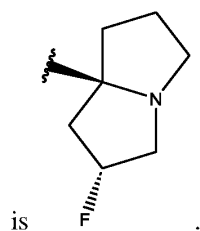
In embodiments of Formula VI (including Formula (VIa) and Formula (VIb)) and Formula VI.I (including Formula (VI.Ia) and Formula (VI.Ib)) and Formula (VII) (including Formula (VIIa) and Formula (VIIb)) and Formula (VII.I) (including Formula (VII.Ia) and Formula (VII.Ib)), R^2 is



10

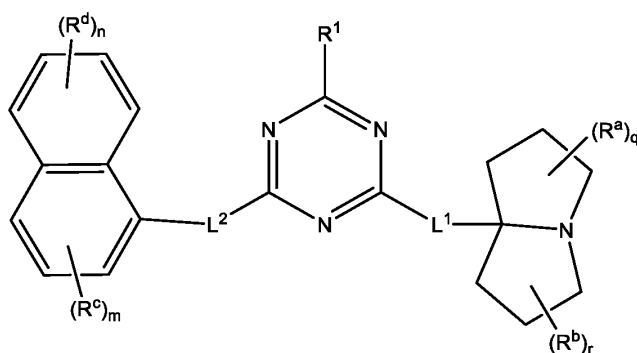
. In embodiments of Formula VI (including Formula (VIa) and Formula (VIb)) and Formula VI.I (including Formula (VI.Ia) and Formula (VI.Ib)) and Formula VII (including Formula

(VIIa) and Formula (VIIb)) and Formula VII.I (including Formula (VII.Ia) and Formula (VII.Ib)), R^2



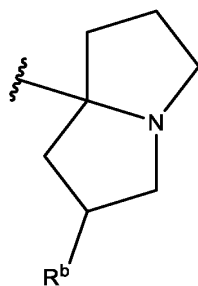
In embodiments, R^2 is and R^3 is , thereby providing a compound of Formula (VIII):

5

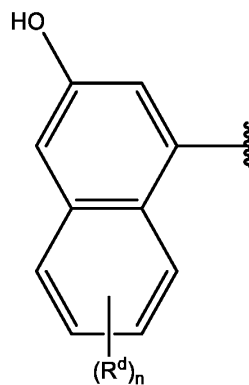


(Formula (VIII))

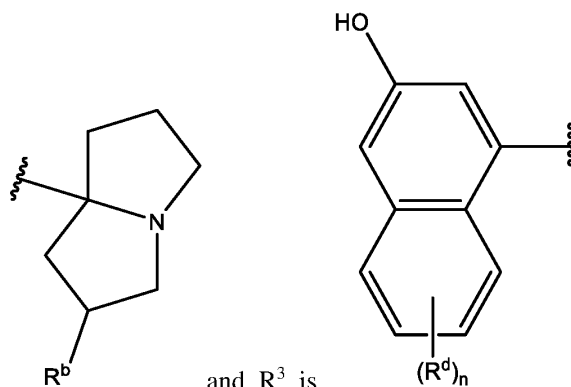
wherein L^1 , L^2 , R^1 , R^a , R^b , R^c , R^d , n , m , q , and r are as defined above.

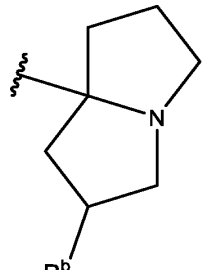
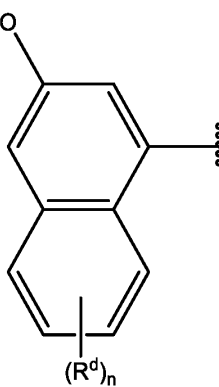


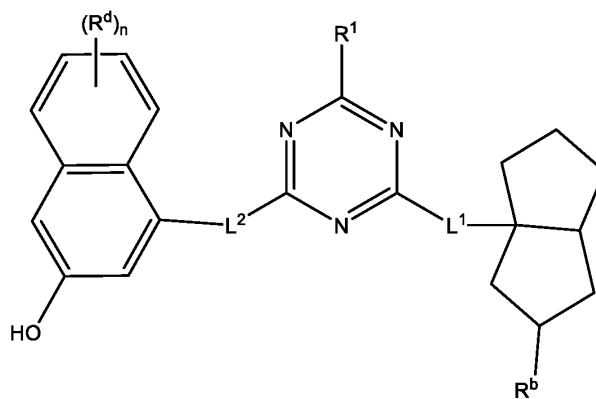
In embodiments of Formula (VIII), R^2 is , wherein R^b is as defined above.



In embodiments of Formula (VIII), R^3 is , wherein R^d and n are as defined above.



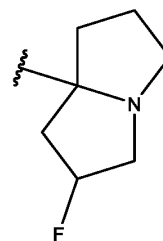
In embodiments, R^2 is  and R^3 is , thereby providing a compound of Formula (IX):



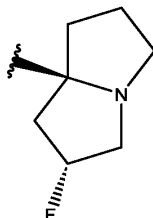
5

(Formula (IX))

wherein L^1 , L^2 , R^1 , R^b , R^d , and n are as defined above.

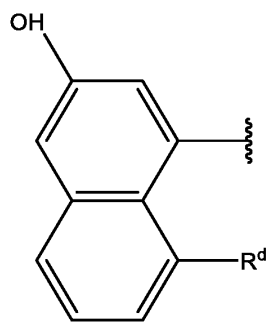
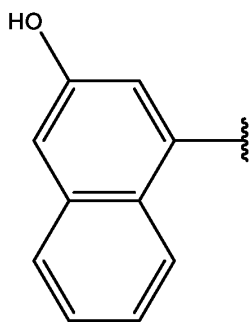
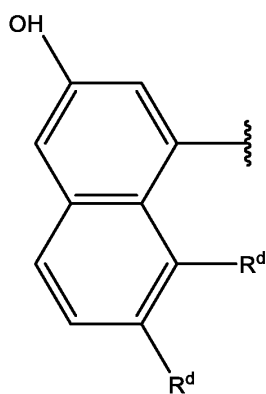


In embodiments of Formula (VIII) and Formula (IX), R^2 is . In embodiments of

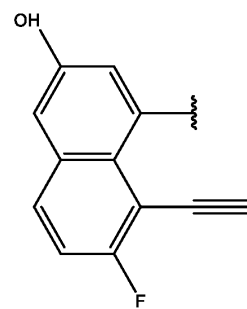


Formula (VIII) and Formula (IX), R^2 is .

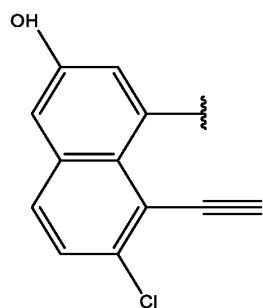
In embodiments of Formula (VIII) and Formula (IX), R^3 is



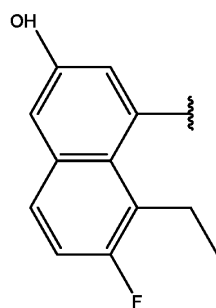
5 defined above. , or , wherein R^d is as



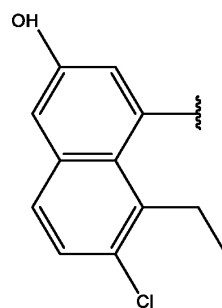
In embodiments of Formula (VIII) and Formula (IX), R^3 is



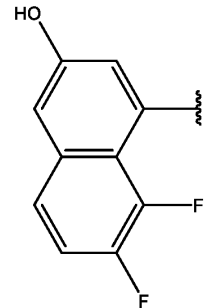
,



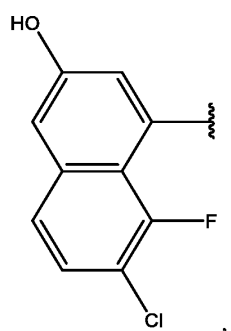
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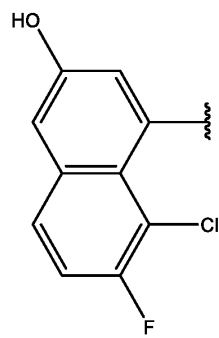
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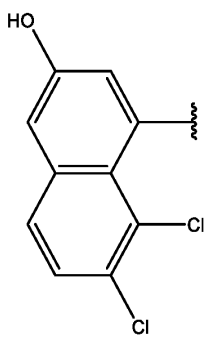
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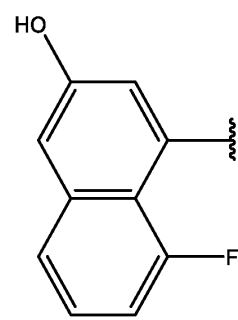
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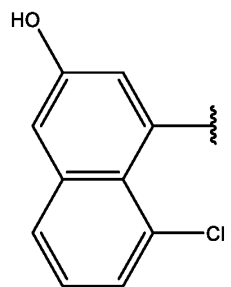


,



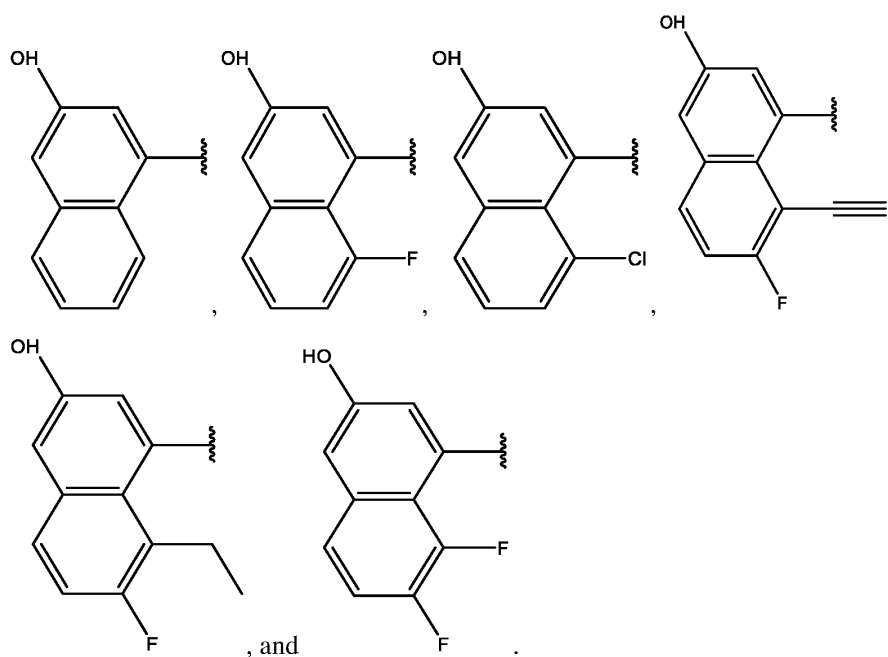
,

or

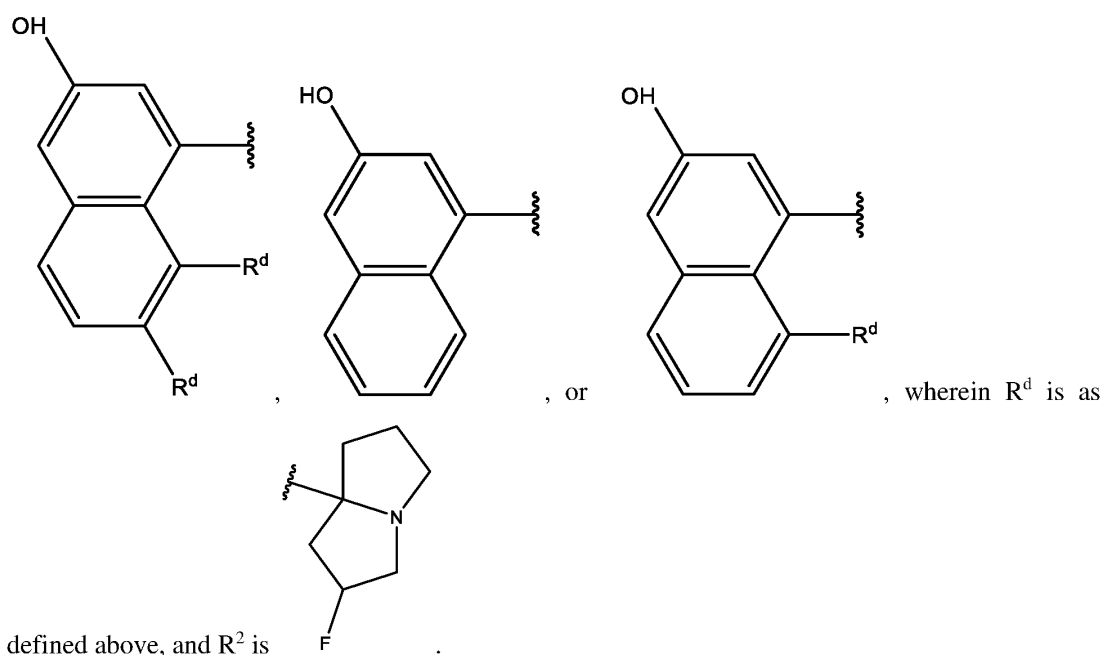


.

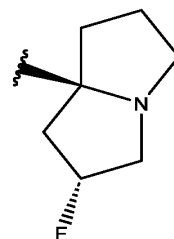
- 5 In embodiments of Formula (VIII) and Formula (IX), R^3 is selected from



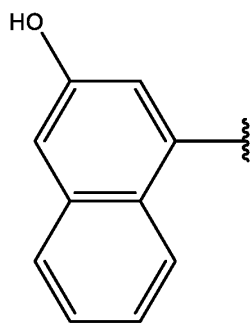
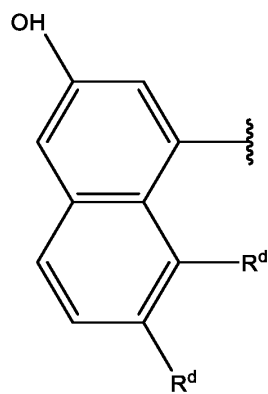
In embodiments of Formula (VIII) and Formula (IX), R^3 is



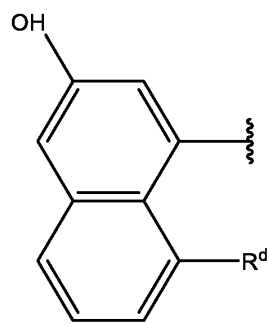
5 defined above, and R^2 is



In embodiments of Formula (VIII) and Formula (IX), R^2 is



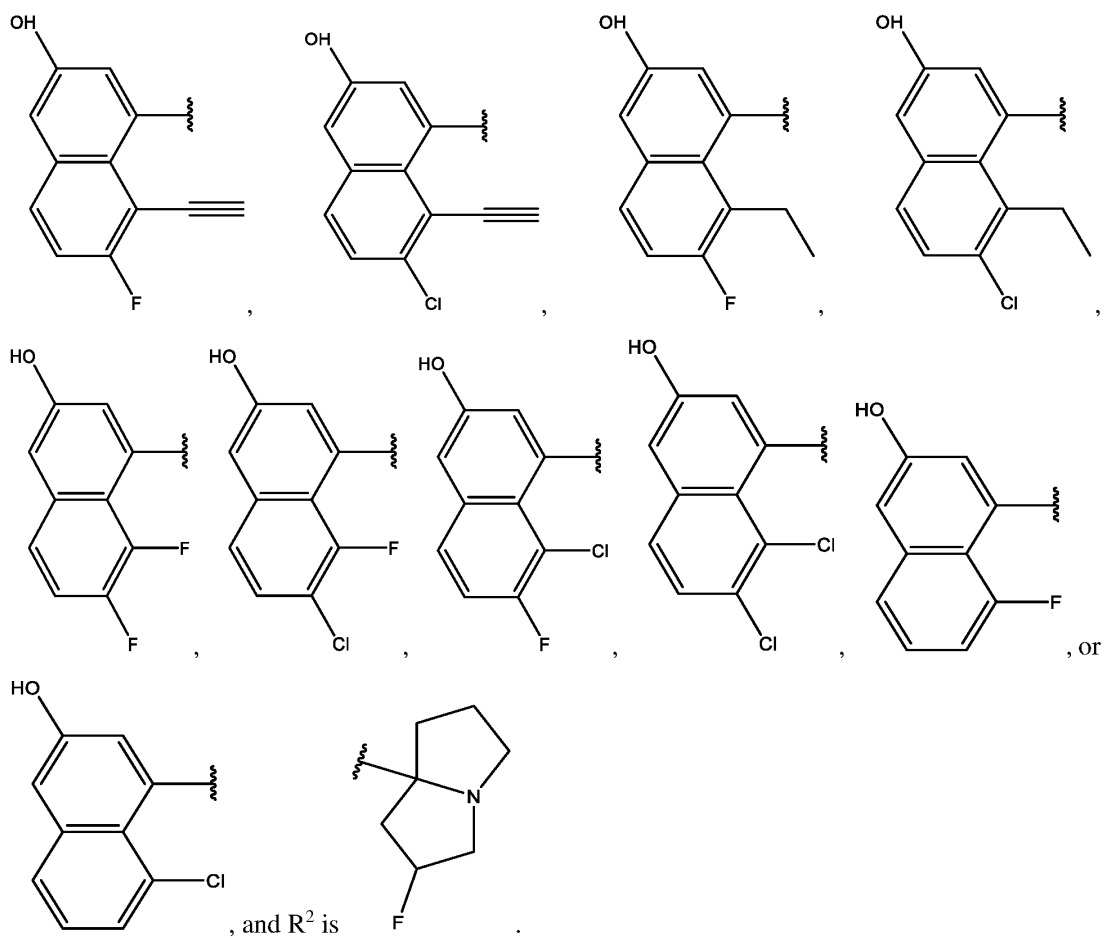
, or



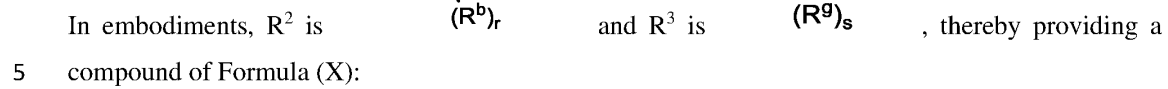
, wherein R^d is as

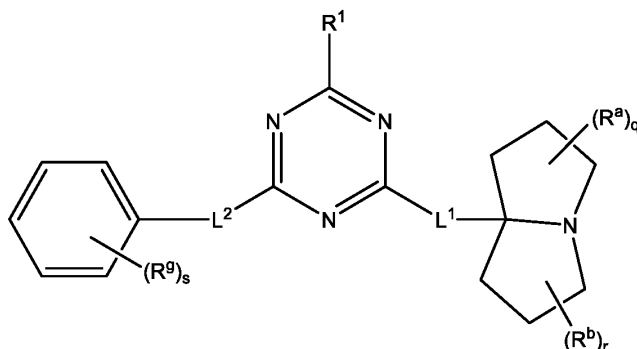
defined above.

In embodiments of Formula (VIII) and Formula (IX), R^3 is



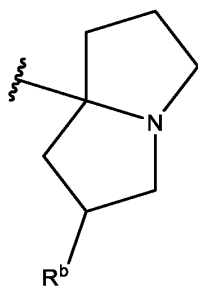
In embodiments of Formula (VIII) and Formula (IX), R³ is

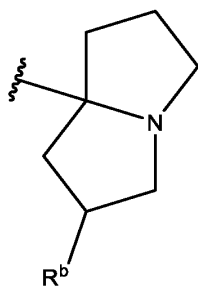


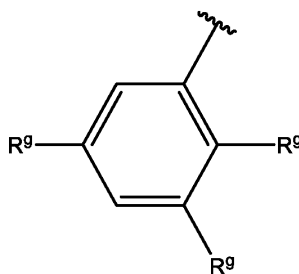


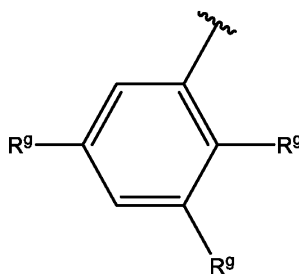
(Formula (X))

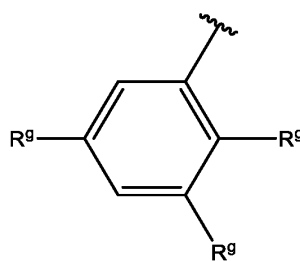
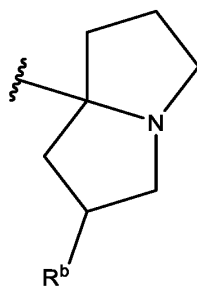
wherein R^1 , L^1 , L^2 , R^a , R^b , q , r , and s are as defined above, and wherein each R^g is independently F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or (C₃-C₆)cycloalkyl, wherein said (C₃-C₆)cycloalkyl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl, provided that at least one R^g is OH.

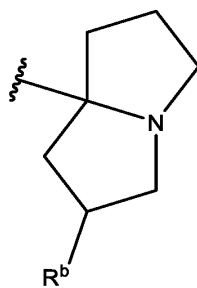
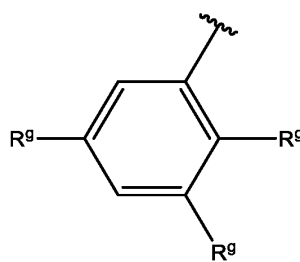


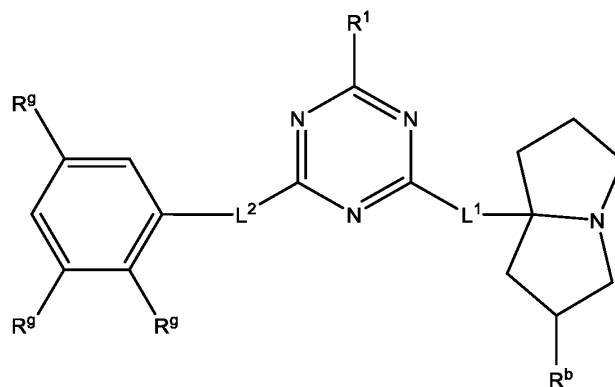
In embodiments of Formula (X), R^2 is , wherein R^b is as defined above.



In embodiments of Formula (X), R^3 is , wherein each R^g is independently F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or (C₃-C₆)cycloalkyl, wherein said (C₃-C₆)cycloalkyl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl, provided that at least one R^g is OH.

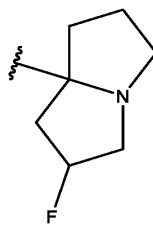


In embodiments, R^2 is  and R^3 is , thereby providing a compound of Formula (XI):

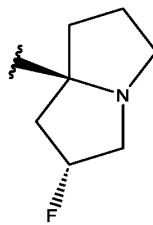


(Formula (XI))

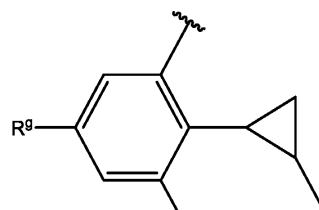
- 5 wherein R^1 , L^1 , L^2 , and R^b are as defined above, and wherein each R^g is independently F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or (C₃-C₆)cycloalkyl, wherein said (C₃-C₆)cycloalkyl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl, provided that at least one R^g is OH.



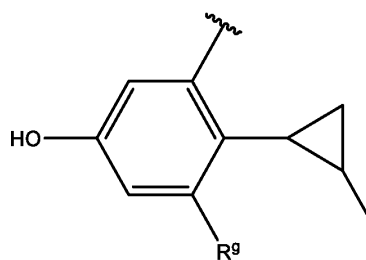
In embodiments of Formula (X) and Formula (XI), R^2 is



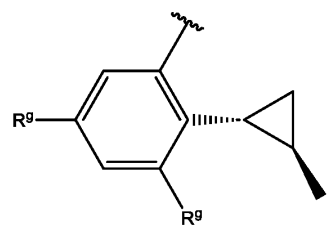
- 10 In embodiments of Formula (X) and Formula (XI), R^2 is



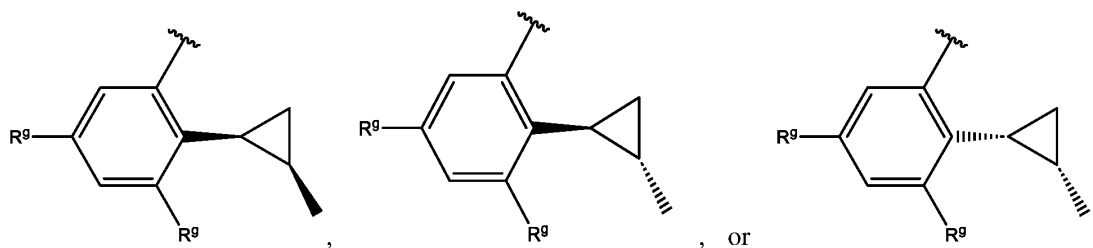
- In embodiments of Formula (X) and Formula (XI), R^3 is R^g wherein each R^g is independently F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or (C₃-C₆)cycloalkyl, wherein said (C₃-C₆)cycloalkyl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl, provided that at least one R^g is OH.



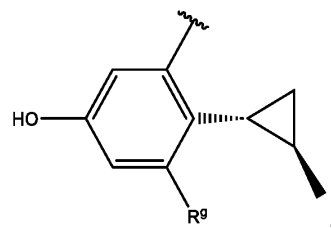
- In embodiments of Formula (X) and Formula (XI), R^3 is R^g , wherein R^g is F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or (C₃-C₆)cycloalkyl, wherein said (C₃-C₆)cycloalkyl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl.



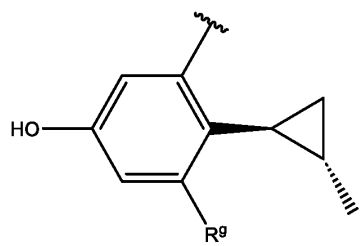
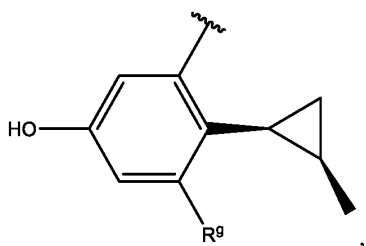
- 10 In embodiments of Formula (X) and Formula (XI), R^3 is



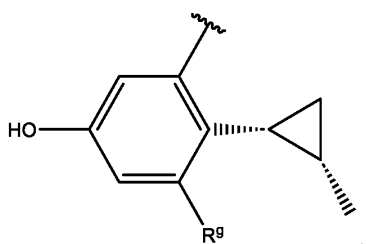
- wherein each R^g is independently F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or (C₃-C₆)cycloalkyl, wherein said (C₃-C₆)cycloalkyl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl, provided that at least one R^g is OH.



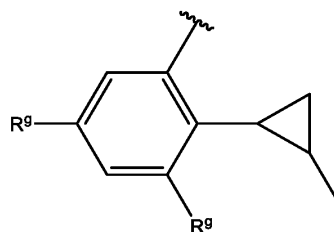
In embodiments of Formula (X) and Formula (XI), R^3 is



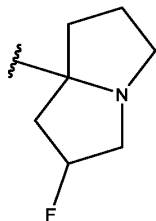
or



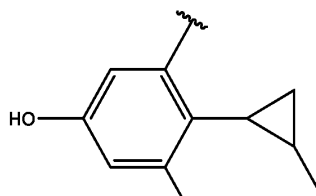
5 wherein R^8 is F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or (C₃-C₆)cycloalkyl, wherein said (C₃-C₆)cycloalkyl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl, provided that at least one R^8 is OH.



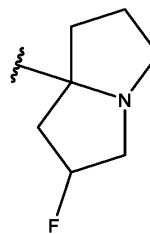
10 In embodiments of Formula (X) and Formula (XI), R^3 is R^8 is independently F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or (C₃-C₆)cycloalkyl, wherein said (C₃-C₆)cycloalkyl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl, provided



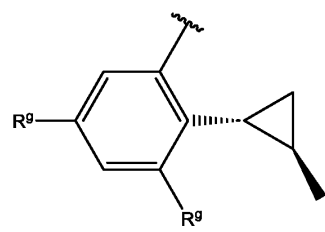
that at least one R^8 is OH, and R^2 is



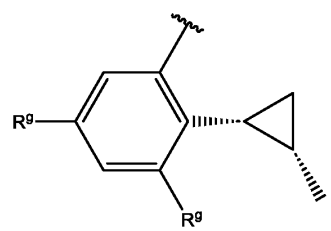
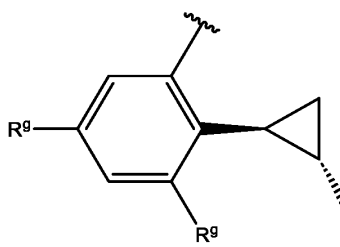
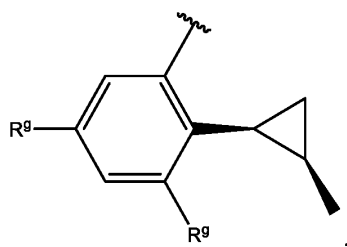
In embodiments of Formula (X) and Formula (XI), R^3 is F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or (C₃-C₆)cycloalkyl, wherein said (C₃-C₆)cycloalkyl may itself be substituted by one or more groups independently selected from F, Cl, CN,



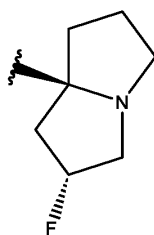
OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl, and R^2 is



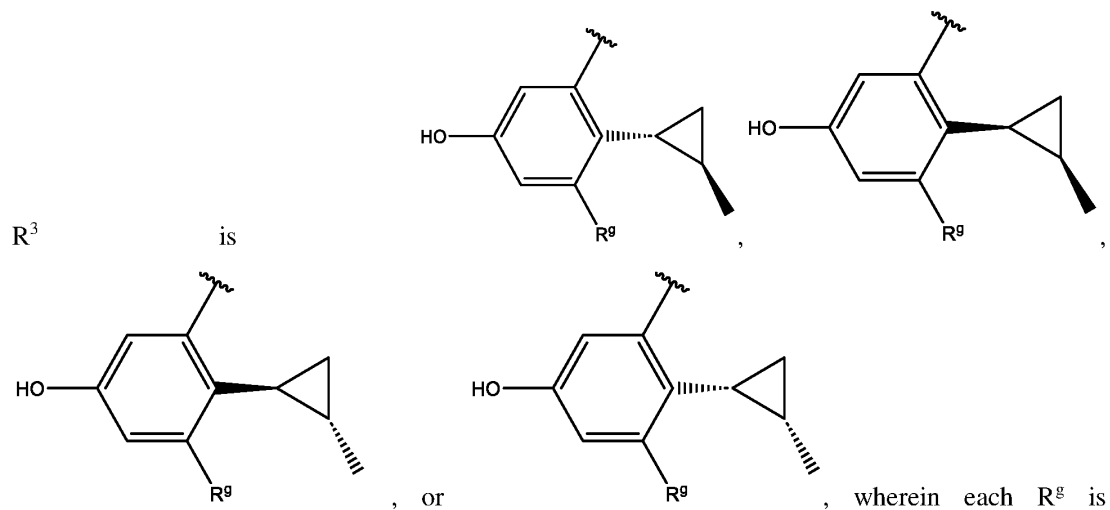
5 In embodiments of Formula (X) and Formula (XI), R^3 is



wherein each R^g is independently F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or (C₃-C₆)cycloalkyl, wherein said (C₃-C₆)cycloalkyl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl, provided

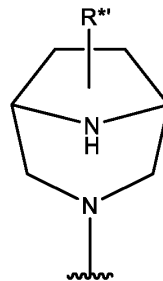
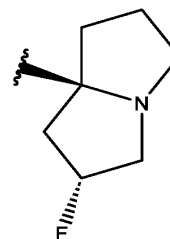


10 that at least one R^g is OH, and R^2 is . In embodiments of Formula (X) and Formula (XI),

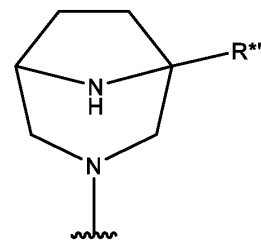


independently F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or (C₃-C₆)cycloalkyl, wherein said (C₃-C₆)cycloalkyl may itself be substituted by one or more groups independently selected

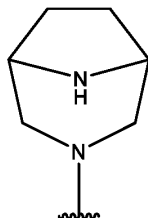
- 5 from F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl, and R^2 is



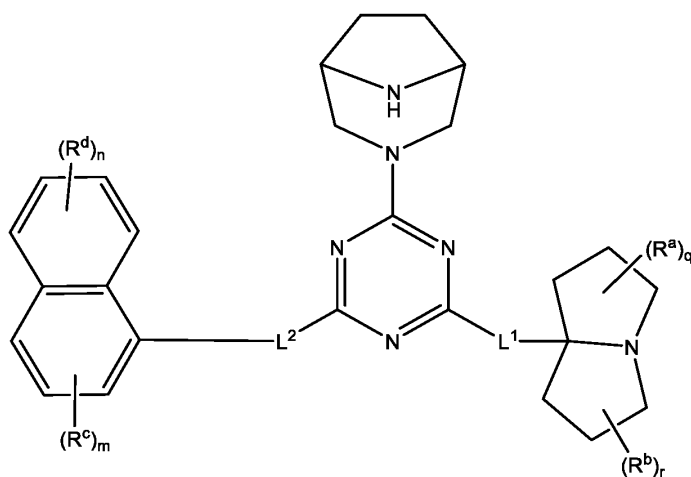
In embodiments of Formulas (VIII), (IX), (X) and (XI), R^1 is



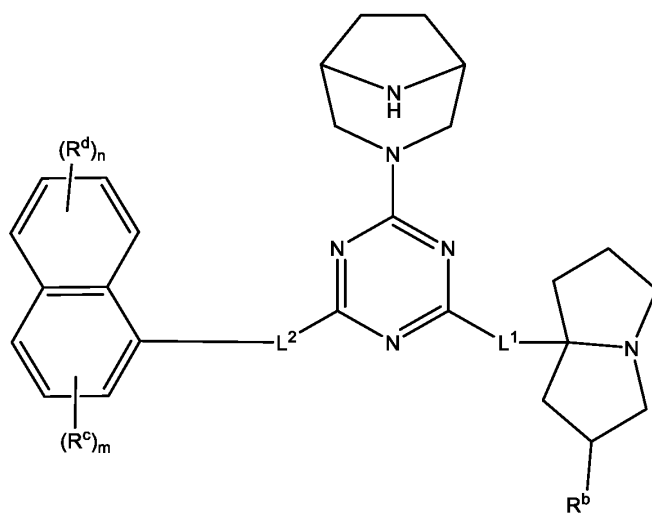
In embodiments of Formulas (VIII), (IX), (X) and (XI), R¹ is . In



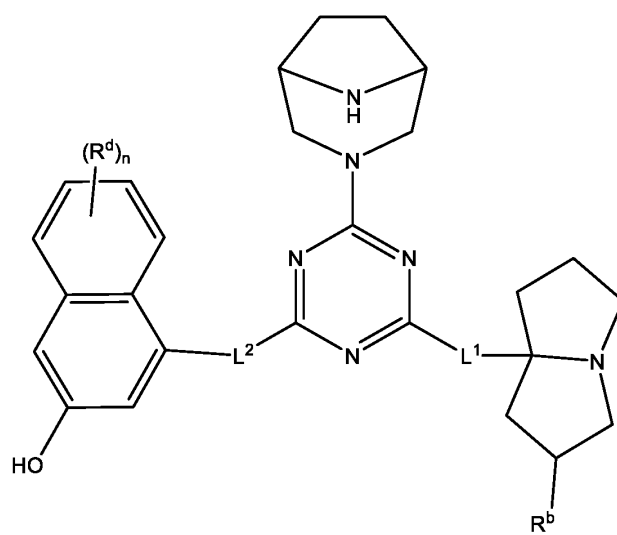
embodiments, R* is H and thus R¹ is . Thus in further embodiments there are provided compounds of Formulas (XII) – (XVIII), wherein L¹, L², R^a, R^b, R^c, R^d, R^g, n, m, q, r, and s are as defined above:



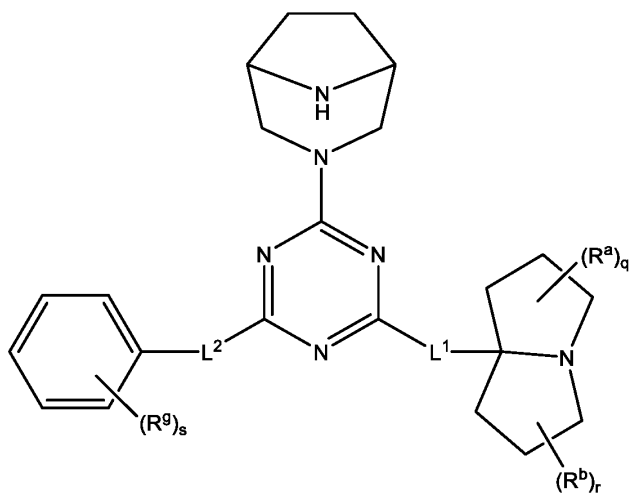
(Formula (XII))



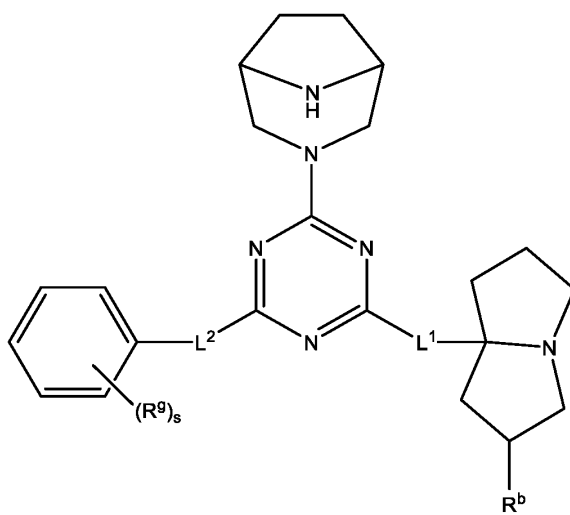
(Formula (XIII))



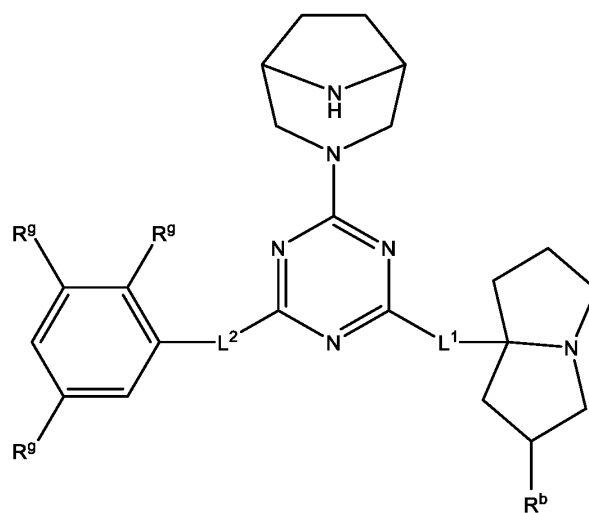
(Formula (XIV))



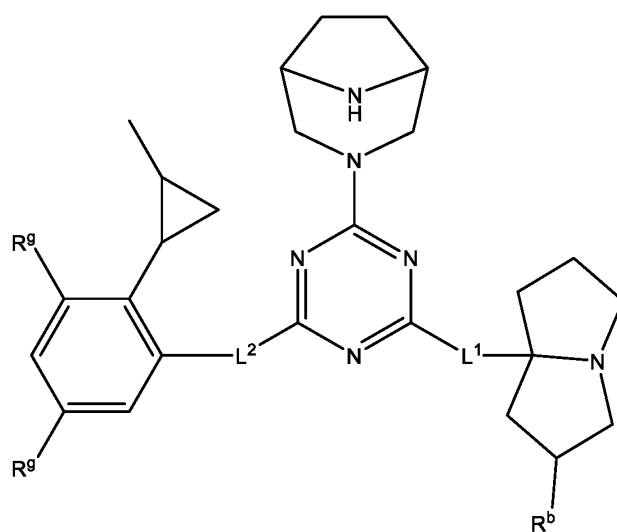
(Formula (XV))



(Formula (XVI))



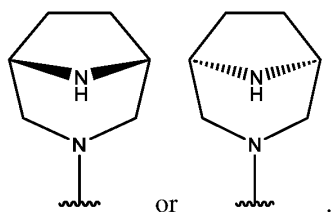
(Formula (XVII))



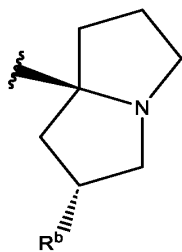
(Formula (XVIII))

5

In embodiments of Formula (XII), (XIII), (XIV), (XV), (XVI), (XVII), and (XVIII), R^1 is

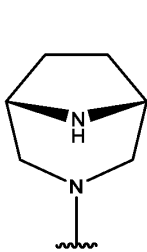


In embodiments of Formula (XII), (XIII), (XIV), (XV), (XVI), (XVII), and (XVIII), R^2 is

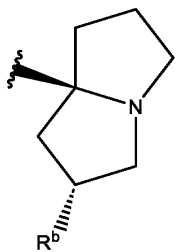


, wherein R^b is as defined above.

In embodiments of Formula (XII), (XIII), (XIV), (XV), (XVI), (XVII), and (XVIII), R^1 is



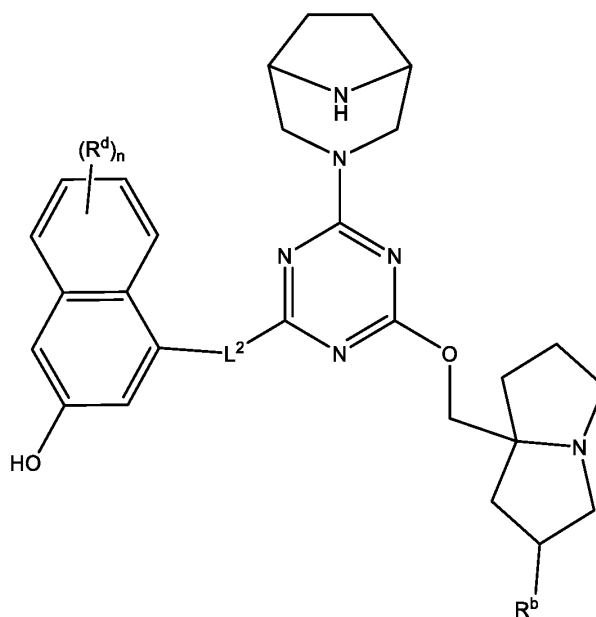
and R^2 is



, wherein R^b is as defined above.

5

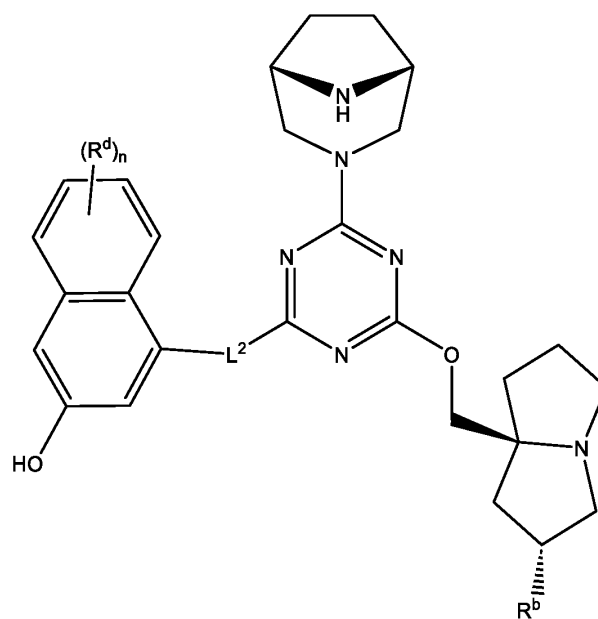
In embodiments, there are provided compounds of Formula (XIX):



(Formula (XIX))

wherein L^2 , R^b , R^d , and n are as defined above.

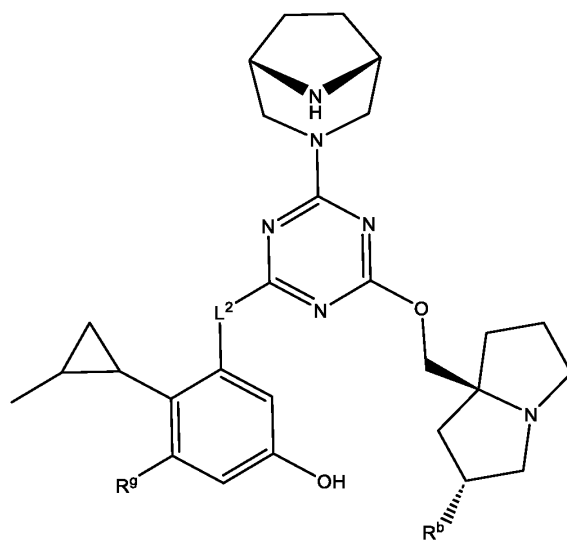
10 In embodiments, there are provided compounds of Formula (XX):



(Formula (XX))

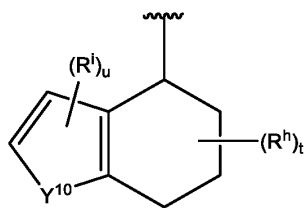
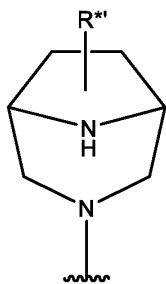
wherein L^2 , R^b , R^c , R^d , and n are as defined above.

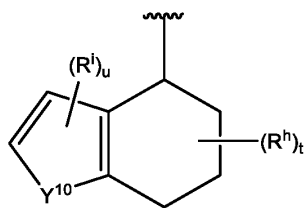
In embodiments, there are provided compounds of Formula (XXI):

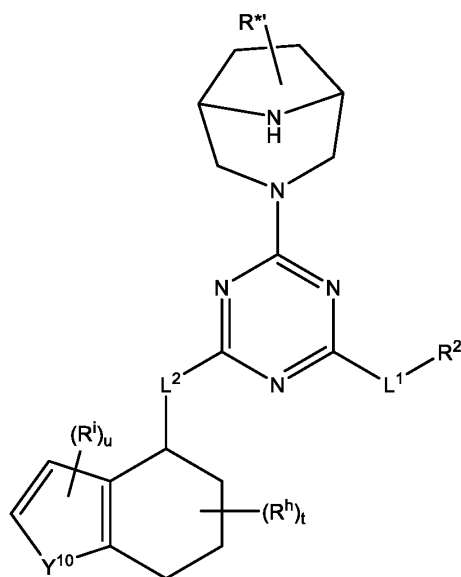


(Formula (XXI))

wherein R^g , L^2 , and R^b are as defined above.



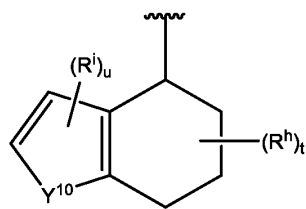
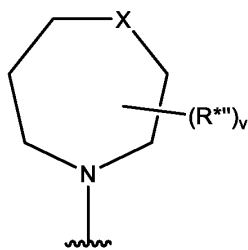
In embodiments, R^1 is  and R^3 is , thereby providing a compound of Formula (XXII):

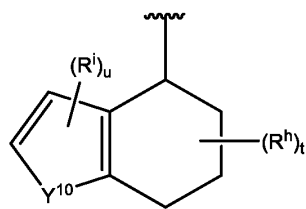


5

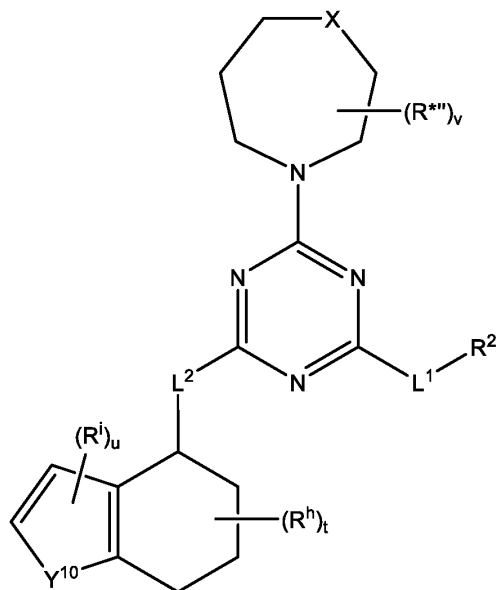
(Formula (XXII))

wherein R^{*} , L^1 , L^2 , R^2 , R^h , R^i , t , u , and Y^{10} are as defined above.



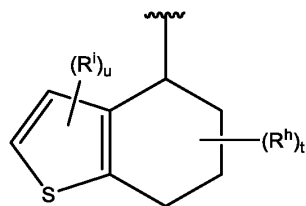
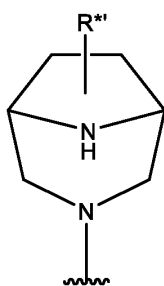
In embodiments, R^1 is  and R^3 is , thereby providing a compound of Formula (XXII.I):

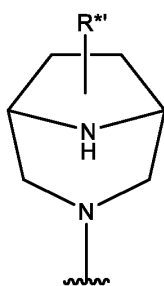
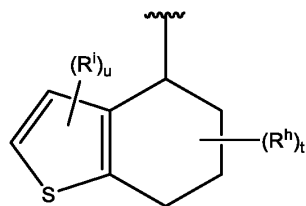
10

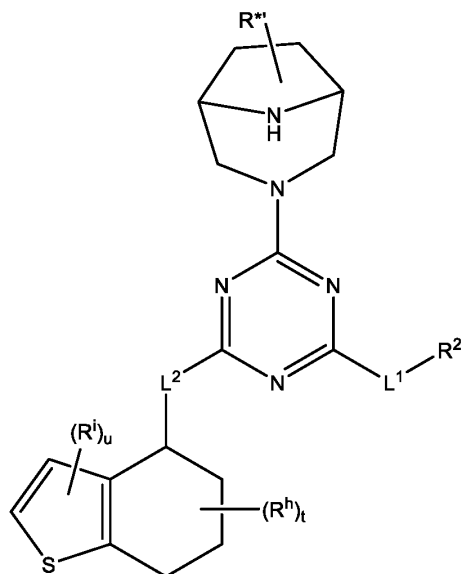


(Formula (XXII.I))

wherein R^{*v} , L^1 , L^2 , X , R^2 , R^h , R^i , t , u , v , and Y^{10} are as defined above.

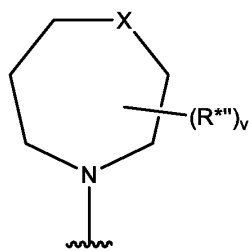


In embodiments, R^1 is  and R^3 is , thereby providing a
 5 compound of Formula (XXIII):

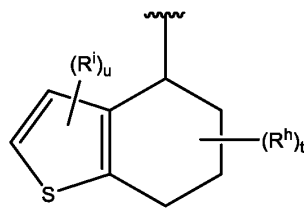


(Formula (XXIII))

wherein R^{**} , L^1 , L^2 , R^2 , R^h , R^i , t , and u are as defined above.



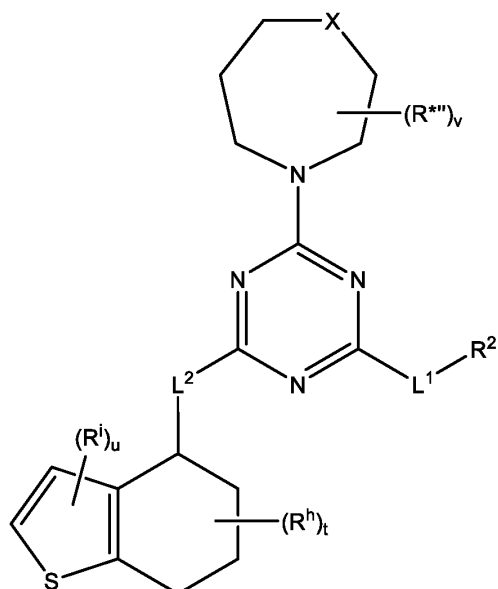
In embodiments, R^1 is



and R^3 is

, thereby providing

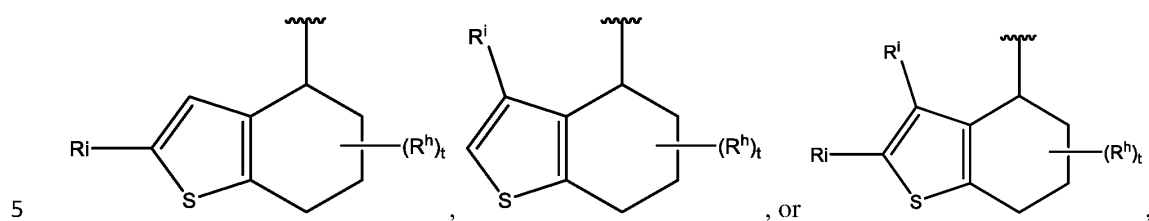
5 a compound of Formula (XXIII.I):



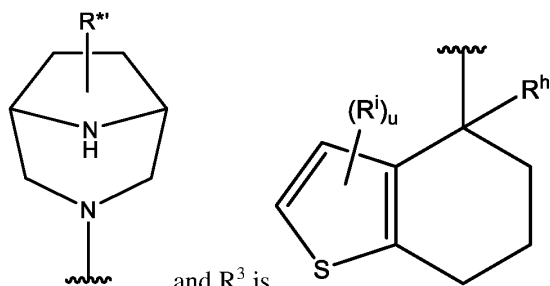
(Formula XXIII.I)

wherein $R^{*'} , L^1, L^2, X, R^2, R^h, R^i, t, u,$ and v are as defined above.

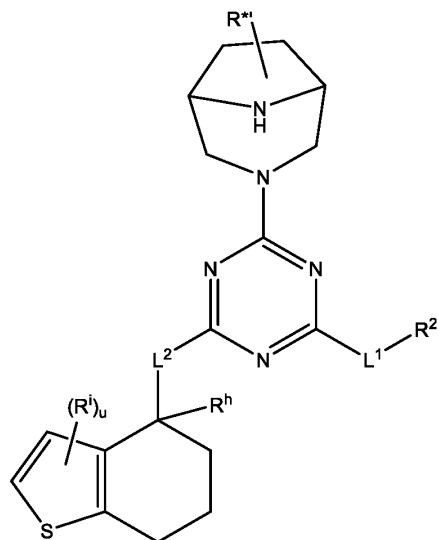
In embodiments of Formula (XXIII) and Formula (XXIII.I), R^3 is



wherein $R^h, R^i,$ and t are as defined above.

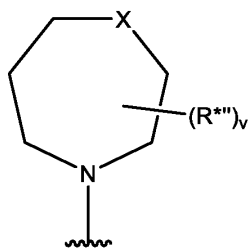


In embodiments, R^1 is and R^3 is , thereby providing a compound of Formula (XXIV):

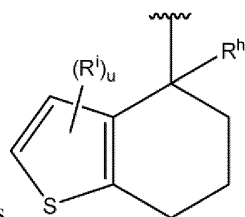


(Formula (XXIV))

wherein R^* , L^1 , L^2 , R^2 , R^h , R^i , and u are as defined above.

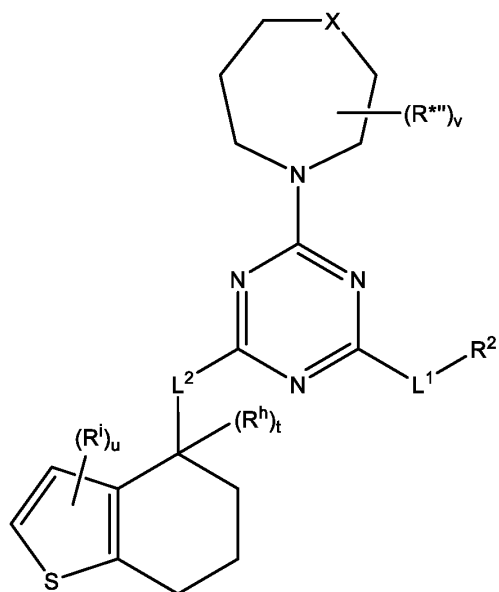


In embodiments, R^1 is



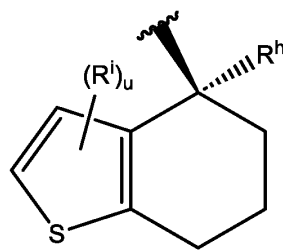
and R^3 is , thereby providing a

5 compound of Formula (XXIV.I):



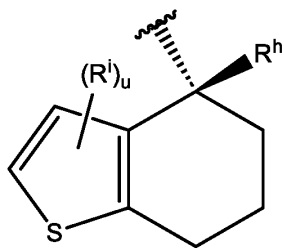
(Formula XXIV.I)

wherein R^{**} , L^1 , L^2 , X , R^2 , R^h , R^i , t , u , and v are as defined above.



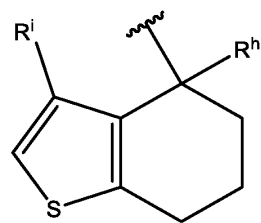
In embodiments of Formula (XXIV) and Formula (XXIV.I), R^3 is

or

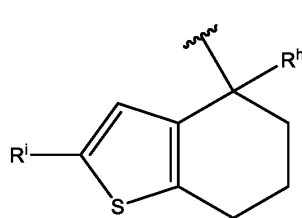


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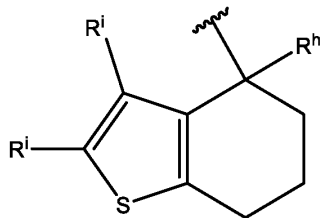
, wherein R^h , R^i , and u are as defined above.



In embodiments of Formula (XXIV) and Formula (XXIV.I), R^3 is

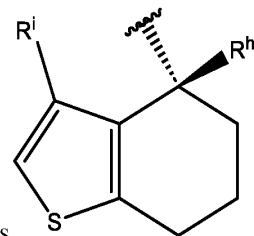


, or

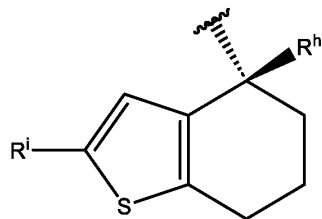


, wherein R^h and R^i are as defined

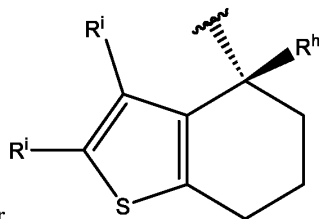
above.



In particular embodiments of Formula (XXIV) and Formula (XXIV.I), R^3 is



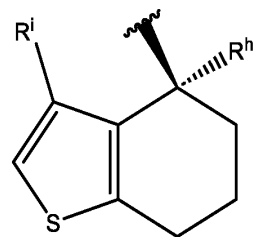
, or



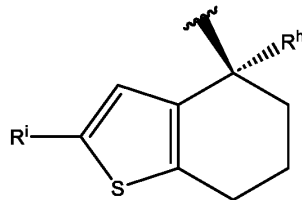
, wherein R^h and R^i are as defined

5

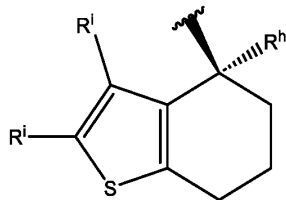
above.



In particular embodiments of Formula (XXIV) and Formula (XXIV.I), R^3 is

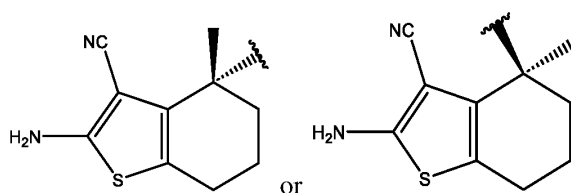


, or



, wherein R^h and R^i are as defined above.

In more particular embodiments of Formula (XXIV) and Formula (XXIV.I), R³ is



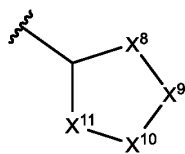
In embodiments of Formula (XXII), Formula (XXII.I), Formula (XXIII), Formula (XXIII.I), Formula (XXIV) and Formula (XXIV.I), R² is a 5- to 9-membered (*e.g.* 5- to 8-membered), monocyclic or bicyclic heterocycloalkyl or heterocycloalkenyl group comprising at least one ring atom which is N or O; a 5- or 6-membered monocyclic heteroaryl group comprising at least one ring atom which is N; a fused, 8- to 10-membered bicyclic group wherein one or both rings are aromatic, and wherein at least one ring comprises at least one ring atom which is N; and wherein R² may be substituted by one or more groups independently selected from CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)R*, C(O)OH, C(O)OR*, C(O)NH₂, C(O)NHR*, C(O)NR*₂, C(O)ONH₂, C(O)ONHR*, C(O)ONR*₂, =O, (C₂-C₃)alkenyl, and (C₂-C₃)alkynyl; and wherein each R* is independently selected from (C₁-C₄)alkyl (*e.g.* C₁-C₃)alkyl), (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkenyl, and 5- or 6-membered monocyclic heteroaryl, wherein said (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkenyl or 5- or 6-membered monocyclic heteroaryl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, NH₂, NH((C₁-C₃)alkyl), (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or O(C₁-C₃) alkyl.

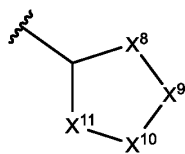
In embodiments of Formula (XXII), Formula (XXII.I), Formula (XXIII), Formula (XXIII.I), Formula (XXIV) and Formula (XXIV.I), R² is a 5- to 8-membered, monocyclic or bicyclic heterocycloalkyl or heterocycloalkenyl group comprising at least one ring atom which is N or O; a 5- or 6-membered monocyclic heteroaryl group comprising at least one ring atom which is N; or a fused, 8- to 10-membered bicyclic group wherein one or both rings are aromatic, and wherein at least one ring comprises at least one ring atom which is N; and wherein R² may be substituted by one or more groups independently selected from CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)R*, C(O)OH, C(O)OR*, C(O)NH₂, C(O)NHR*, C(O)NR*₂, C(O)ONH₂, C(O)ONHR*, C(O)ONR*₂, =O, (C₂-C₃)alkenyl, and (C₂-C₃)alkynyl; and wherein each R* is independently selected from (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, and (C₃-C₆)cycloalkenyl, wherein said (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, or (C₃-C₆)cycloalkenyl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, NH₂, NH((C₁-C₃)alkyl), (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or O(C₁-C₃) alkyl.

In embodiments of Formula (XXII), Formula (XXII.I), Formula (XXIII), Formula (XXIII.I), Formula (XXIV) and Formula (XXIV.I), R² is a 5- to 9-membered monocyclic heterocycloalkyl or

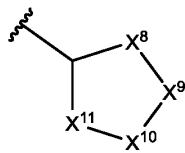
- heterocycloalkenyl group comprising at least one ring atom which is N or O, and wherein R^2 may be substituted by one or more groups independently selected from CN, Cl, F, R^* , OH, OR^* , NH_2 , NHR^* , NR^{*2} , CHO, $C(O)R^*$, $C(O)OH$, $C(O)OR^*$, $C(O)NH_2$, $C(O)NHR^*$, $C(O)NR^{*2}$, $C(O)ONH_2$, $C(O)ONHR^*$, $C(O)ONR^{*2}$, =O, (C₂-C₃)alkenyl, and (C₂-C₃)alkynyl. In embodiments, each R^* is
- 5 independently selected from (C₁-C₄)alkyl (*e.g.* C₁-C₃)alkyl), (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkenyl, and 5- or 6-membered monocyclic heteroaryl, wherein said (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkenyl or 5- or 6-membered monocyclic heteroaryl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, NH_2 , $NH((C_1-C_3)alkyl)$, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or O(C₁-C₃) alkyl. In embodiments, each R^*
- 10 is independently selected from (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, and (C₃-C₆)cycloalkenyl, wherein said (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, or (C₃-C₆)cycloalkenyl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, NH_2 , $NH((C_1-C_3)alkyl)$, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or O(C₁-C₃) alkyl

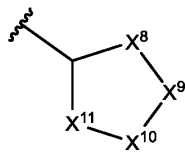
In embodiments of Formula (XXII), Formula (XXII.I), Formula (XXIII), Formula (XXIII.I), Formula



- 15 (XXIV) and Formula (XXIV.I), R^2 is , wherein X^8 , X^9 , X^{10} , and X^{11} are each independently selected from $C(R^k)_2$, C=O, $N(R^k)$, O, or S, provided that at least one of X^8 , X^9 , X^{10} , and X^{11} is $N(R^k)$; wherein each R^k is independently selected from H, CN, Cl, F, R^* , OH, OR^* , NH_2 , NHR^* , NR^{*2} , CHO, $C(O)R^*$, $C(O)OH$, $C(O)OR^*$, $C(O)NH_2$, $C(O)NHR^*$, $C(O)NR^{*2}$, $C(O)ONH_2$, $C(O)ONHR^*$, $C(O)ONR^{*2}$, (C₂-C₃)alkenyl, and (C₂-C₃)alkynyl, and wherein each R^* is
- 20 independently selected from (C₁-C₄)alkyl (*e.g.* C₁-C₃)alkyl), (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkenyl, and 5- or 6-membered monocyclic heteroaryl, wherein said (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkenyl or 5- or 6-membered monocyclic heteroaryl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, NH_2 , $NH((C_1-C_3)alkyl)$, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or O(C₁-C₃) alkyl.

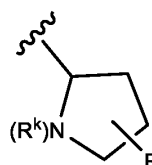
- 25 In embodiments of Formula (XXII), Formula (XXII.I), Formula (XXIII), Formula (XXIII.I), Formula



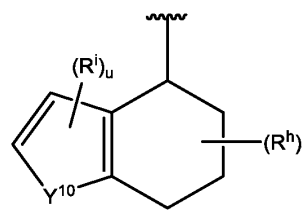
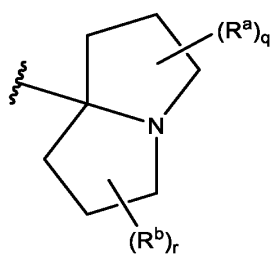
(XXIV) and Formula (XXIV.I), R^2 is , wherein X^8 , X^9 , X^{10} , and X^{11} are each independently selected from $C(R^k)_2$, C=O, $N(R^k)$, O, or S, provided that at least one of X^8 , X^9 , X^{10} , and X^{11} is $N(R^k)$; wherein each R^k is independently selected from H, CN, Cl, F, R^* , OH, OR^* , NH_2 , NHR^* , NR^{*2} , CHO, $C(O)R^*$, $C(O)OH$, $C(O)OR^*$, $C(O)NH_2$, $C(O)NHR^*$, $C(O)NR^{*2}$, $C(O)ONH_2$,

C(O)ONHR*, C(O)ONR*₂, (C₂-C₃)alkenyl, and (C₂-C₃)alkynyl, and wherein each R* is independently selected from (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, and (C₃-C₆)cycloalkenyl, wherein said (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, or (C₃-C₆)cycloalkenyl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, NH₂, NH((C₁-C₃)alkyl), (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or O(C₁-C₃) alkyl.

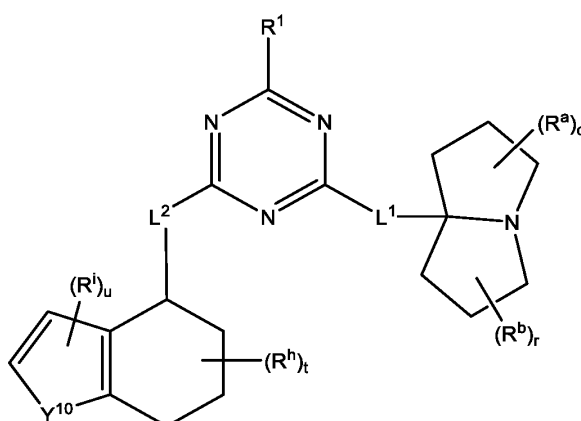
In embodiments of Formula (XXII), Formula (XXII.I), Formula (XXIII), Formula (XXIII.I), Formula



(XXIV) and Formula (XXIV.I), R² is H, CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)R*, C(O)OH, C(O)OR*, C(O)NH₂, C(O)NHR*, C(O)NR*₂, C(O)ONH₂, C(O)ONHR*, C(O)ONR*₂, (C₂-C₃)alkenyl, and (C₂-C₃)alkynyl, and wherein each R* is independently selected from (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, and (C₃-C₆)cycloalkenyl, wherein said (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, or (C₃-C₆)cycloalkenyl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, NH₂, NH((C₁-C₃)alkyl), (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or O(C₁-C₃) alkyl.

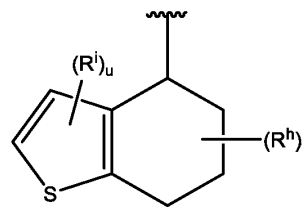
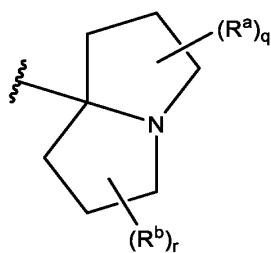


In embodiments, R² is providing a compound of Formula (XXV):



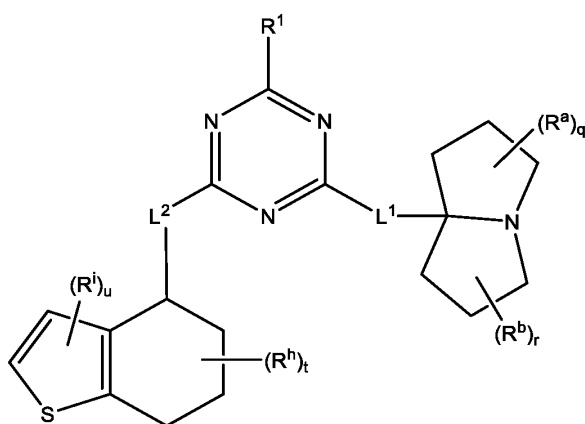
(Formula (XXV))

wherein L^1 , L^2 , R^1 , R^a , R^b , R^h , R^i , q and r , t , u , and Y^{10} are as defined above.



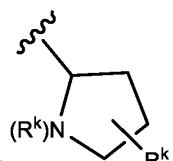
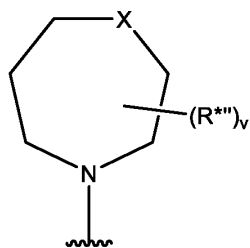
In embodiments, R^2 is and R^3 is , thereby providing a compound of Formula (XXVI):

5



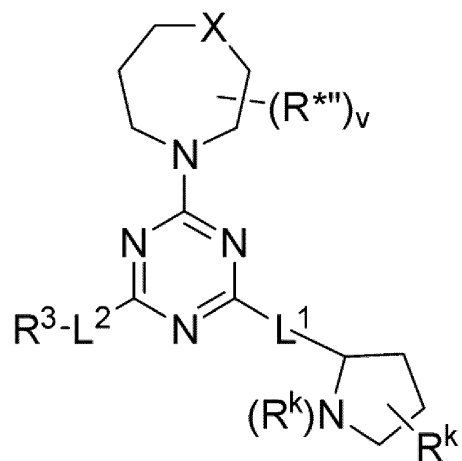
(Formula (XXVI))

Wherein L^1 , L^2 , R^1 , R^a , R^b , R^h , R^i , q and r , t , and u are as defined above.



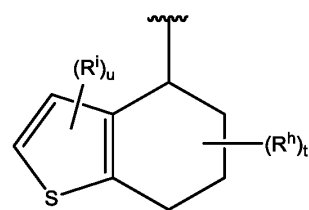
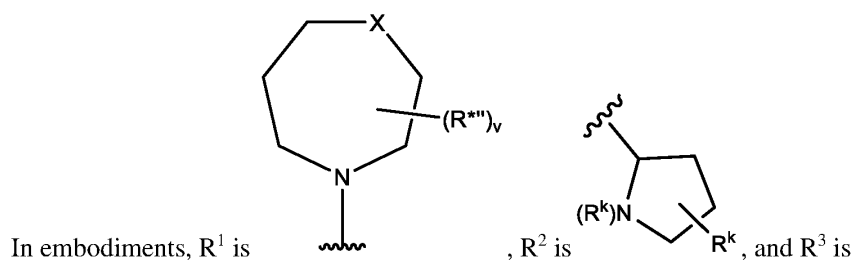
In embodiments, R^1 is and R^2 is , thereby providing a compound of Formula (XXVII):

10



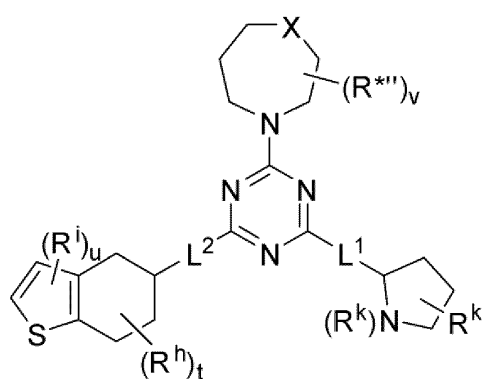
(Formula (XXVII))

wherein $R^{*''}$, L^1 , L^2 , R^3 , X , v , and R^k are as defined above.



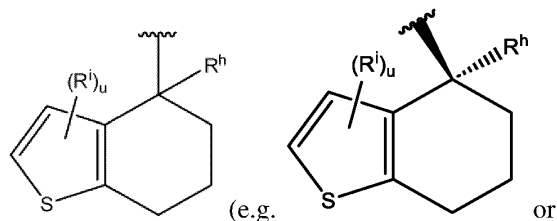
5

thereby providing a compound of Formula (XXVIII):

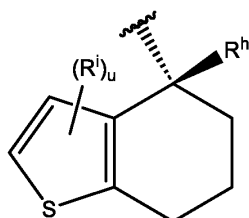


(Formula (XXVIII))

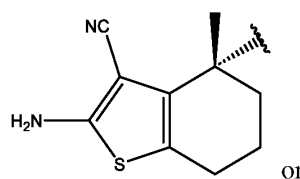
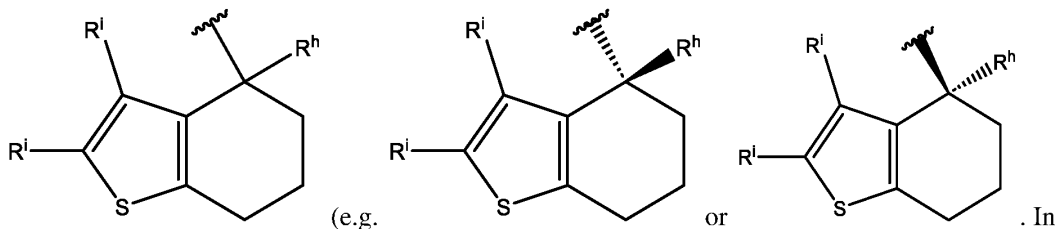
wherein $R^{*''}$, L^1 , L^2 , X , R^h , R^i , R^k , t , u and v are as defined above.



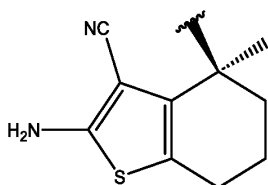
In embodiments of Formula (XXVIII), R^3 is



). In particular embodiments of Formula (XXVIII), R^3 is

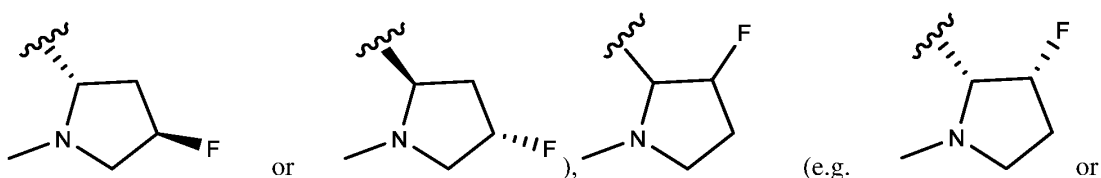


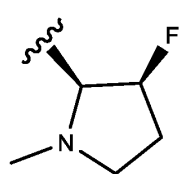
5 more particular embodiments of Formula (XXVIII), R^3 is

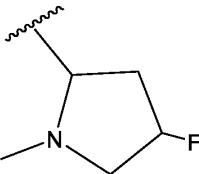


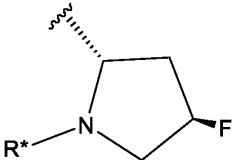
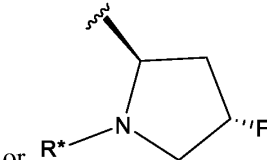
In embodiments of Formula (XXII), Formula (XXII.I), Formula (XXIII), Formula (XXIII.I), Formula

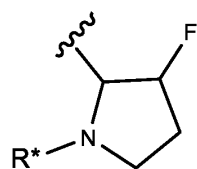
(XXIV), Formula (XXIV.I), Formula (XXVII), and Formula (XXVIII), R^2 is





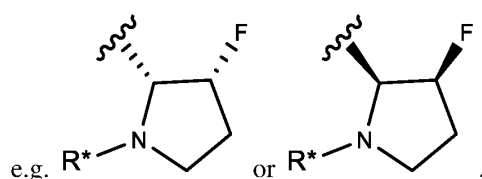
), or R^2 is  (wherein R^* is selected from (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, and (C₃-C₆)cycloalkenyl, wherein said (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, or (C₃-C₆)cycloalkenyl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, NH₂, NH((C₁-C₃)alkyl), (C₁-C₃)alkyl, (C₂-C₃)alkenyl,

5 (C₂-C₃)alkynyl, or O(C₁-C₃) alkyl)), e.g.  or , or R^2 is

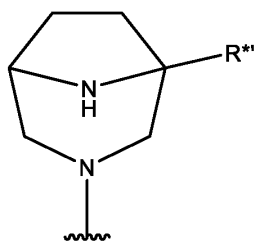


(wherein R^* is selected from (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, and (C₃-C₆)cycloalkenyl, wherein said (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, or (C₃-C₆)cycloalkenyl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, NH₂, NH((C₁-C₃)alkyl), (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or O(C₁-C₃) alkyl)),

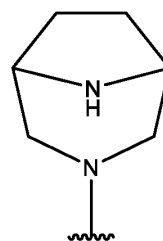
10

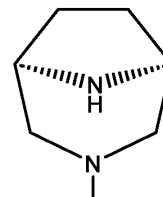


In embodiments of Formula (XXII), (XXIII), (XXIV), (XXV), and (XXVI), R^1 is

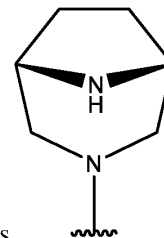


. In embodiments, R^{*2} is H and thus R^1 is



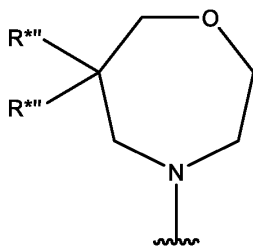


In embodiments of Formula (XXII), (XXIII), (XXIV), (XXV), and (XXVI), R¹ is . In

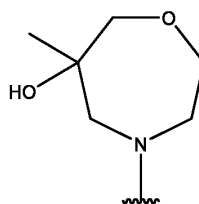


embodiments of Formula (XXII), (XXIII), (XXIV), (XXV), and (XXVI), R¹ is .

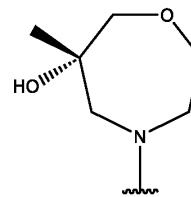
In embodiments of Formula (XXII.I), (XXIII.I), (XXIV.I), (XXV), (XXVI), (XXVII) and (XXVIII),



R¹ is . In embodiments of Formula (XXII.I), (XXIII.I), (XXIV.I), (XXV),

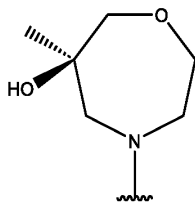


5 (XXVI), (XXVII) and (XXVIII), R¹ is . In embodiments of Formula (XXII.I),

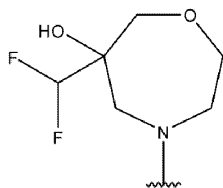


(XXIII.I), (XXIV.I), (XXV), (XXVI), (XXVII) and (XXVIII), R¹ is . In

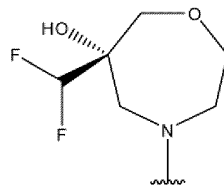
embodiments of Formula (XXII.I), (XXIII.I), (XXIV.I), (XXV), (XXVI), (XXVII) and (XXVIII), R¹



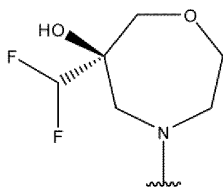
is . In embodiments of Formula (XXII.I), (XXIII.I), (XXIV.I), (XXV), (XXVI),



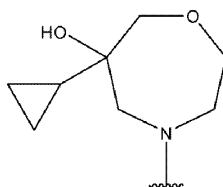
(XXVII) and (XXVIII), R¹ is . In embodiments of Formula (XXII.I), (XXIII.I),



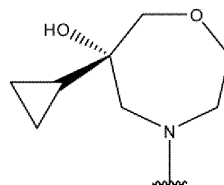
(XXIV.I), (XXV), (XXVI), (XXVII) and (XXVIII), R¹ is . In embodiments of Formula (XXII.I), (XXIII.I), (XXIV.I), (XXV), (XXVI), (XXVII) and (XXVIII), R¹ is



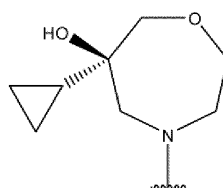
. In embodiments of Formula (XXII.I), (XXIII.I), (XXIV.I), (XXV), (XXVI),



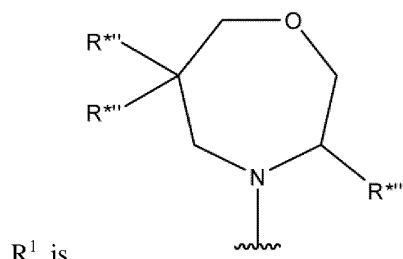
5 (XXVII) and (XXVIII), R¹ is . In embodiments of Formula (XXII.I), (XXIII.I),



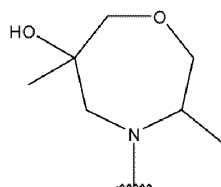
(XXIV.I), (XXV), (XXVI), (XXVII) and (XXVIII), R¹ is . In embodiments of Formula (XXII.I), (XXIII.I), (XXIV.I), (XXV), (XXVI), (XXVII) and (XXVIII), R¹ is



In embodiments of Formula (XXII.I), (XXIII.I), (XXIV.I), (XXV), (XXVI), (XXVII) and (XXVIII),

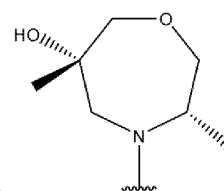


. In embodiments of Formula (XXII.I), (XXIII.I), (XXIV.I),



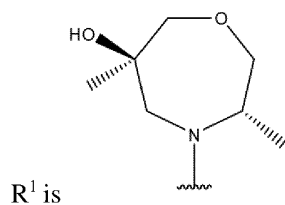
(XXV), (XXVI), (XXVII) and (XXVIII), R¹ is

. In embodiments of Formula

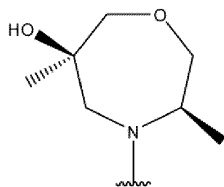


(XXII.I), (XXIII.I), (XXIV.I), (XXV), (XXVI), (XXVII) and (XXVIII), R¹ is

5 In embodiments of Formula (XXII.I), (XXIII.I), (XXIV.I), (XXV), (XXVI), (XXVII) and (XXVIII),

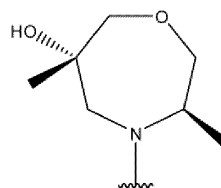


. In embodiments of Formula (XXII.I), (XXIII.I), (XXIV.I), (XXV), (XXVI)



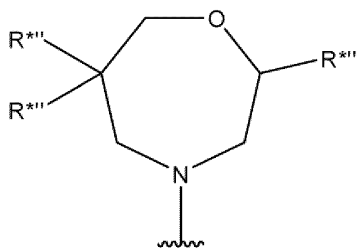
, (XXVII) and (XXVIII), R¹ is

. In embodiments of Formula (XXII.I), (XXIII.I),



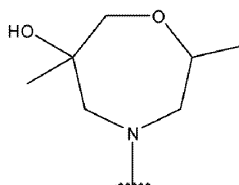
(XXIV.I), (XXV), (XXVI), (XXVII) and (XXVIII), R¹ is

In embodiments of Formula (XXII.I), (XXIII.I), (XXIV.I), (XXV), (XXVI), (XXVII) and (XXVIII),



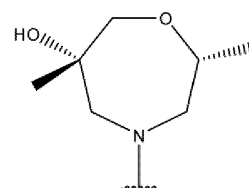
R¹ is

. In embodiments of Formula (XXII.I), (XXIII.I), (XXIV.I),



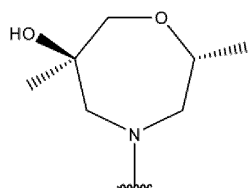
(XXV), (XXVI), (XXVII) and (XXVIII), R¹ is

. In embodiments of Formula



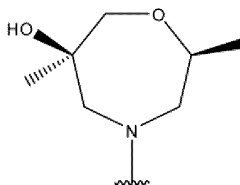
(XXII.I), (XXIII.I), (XXIV.I), (XXV), (XXVI), (XXVII) and (XXVIII), R¹ is

5 . In embodiments of Formula (XXII.I), (XXIII.I), (XXIV.I), (XXV), (XXVI), (XXVII) and (XXVIII),



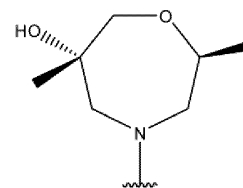
R¹ is

. In embodiments of Formula (XXII.I), (XXIII.I), (XXIV.I), (XXV),



(XXVI), (XXVII) and (XXVIII), R¹ is

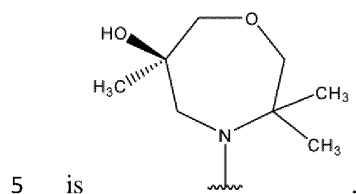
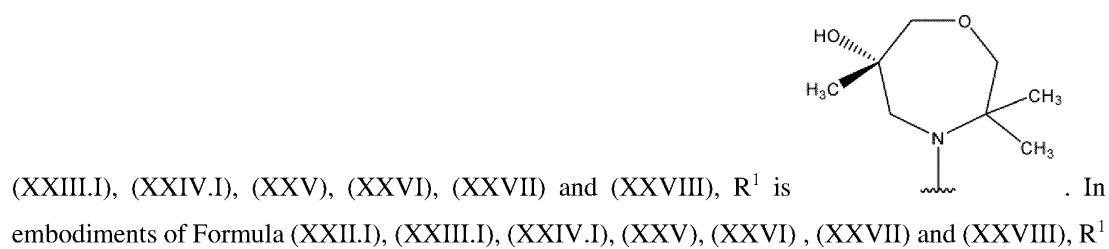
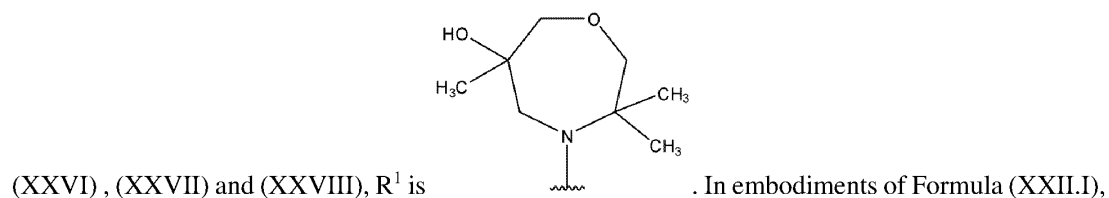
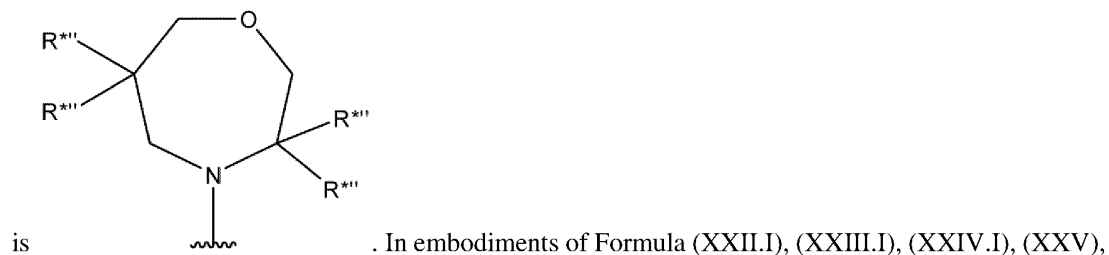
. In embodiments of Formula (XXII.I),



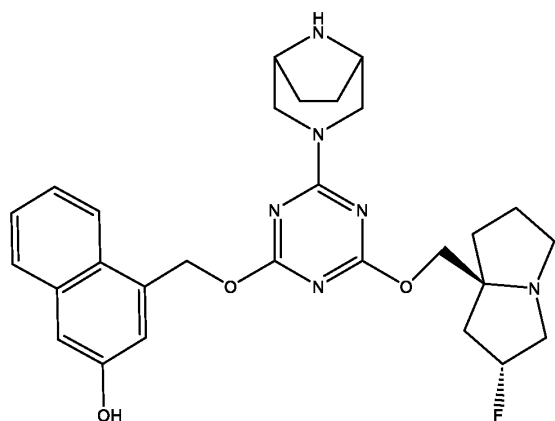
(XXIII.I), (XXIV.I), (XXV), (XXVI), (XXVII) and (XXVIII), R¹ is

. In

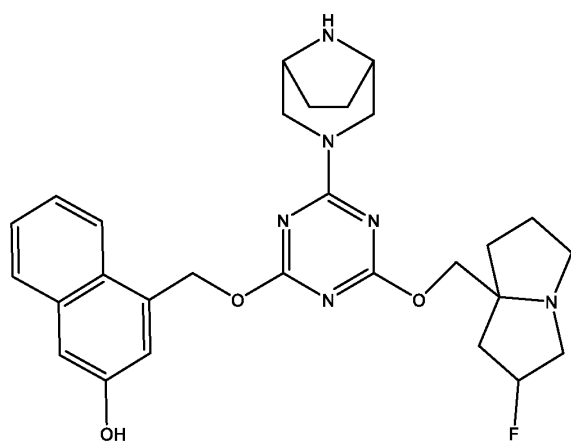
embodiments of Formula (XXII.I), (XXIII.I), (XXIV.I), (XXV), (XXVI), (XXVII) and (XXVIII), R¹



In embodiments, the compound of Formula (0) or Formula (I) is not:

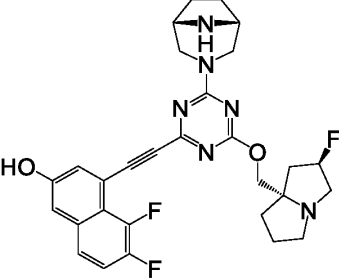
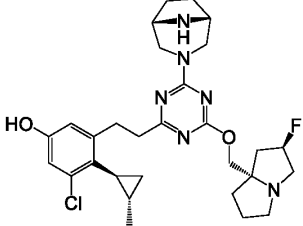
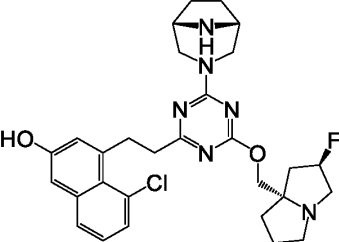
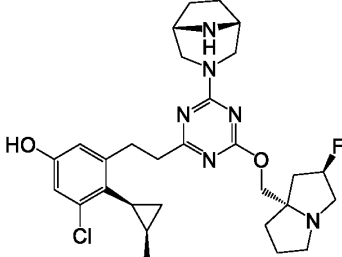
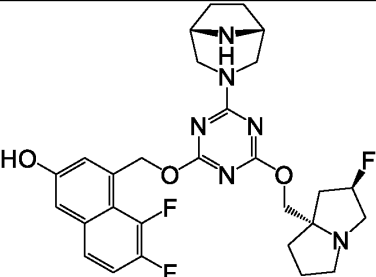
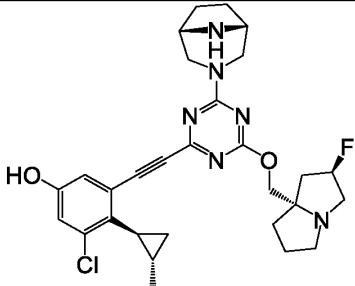
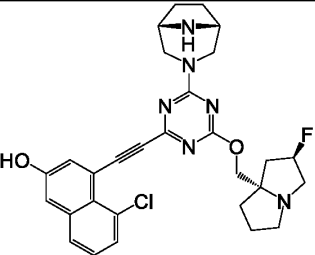
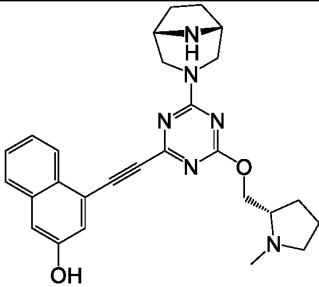


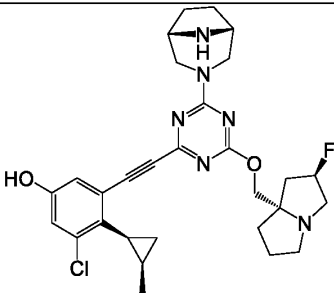
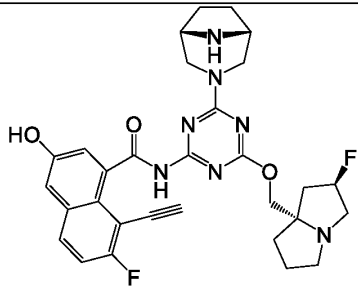
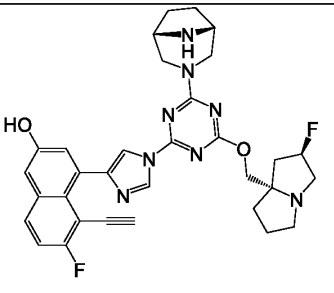
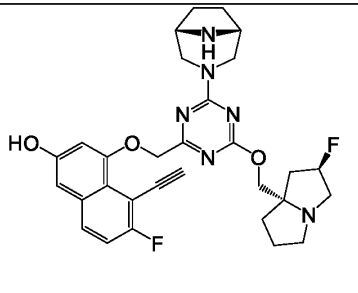
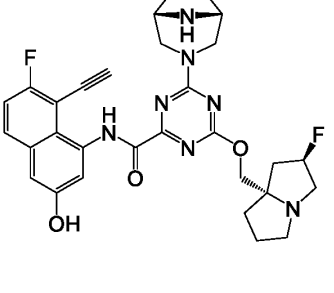
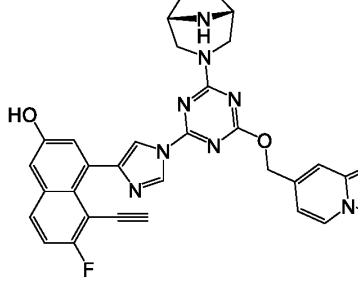
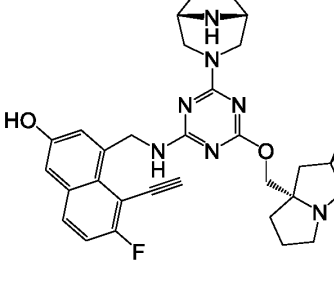
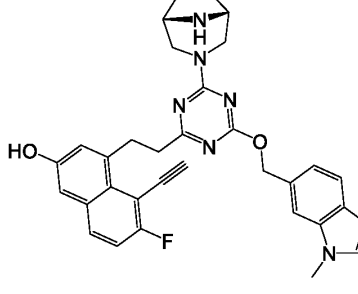
In embodiments, the compound of Formula (0) or Formula (I) is not:



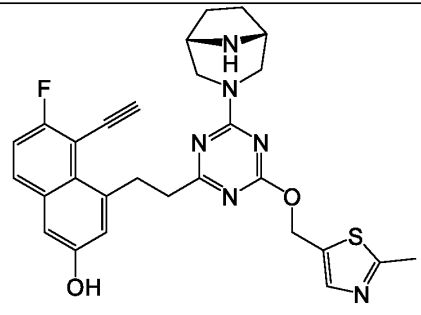
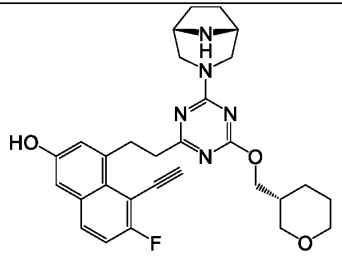
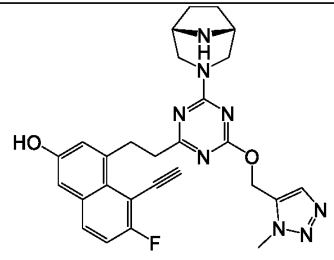
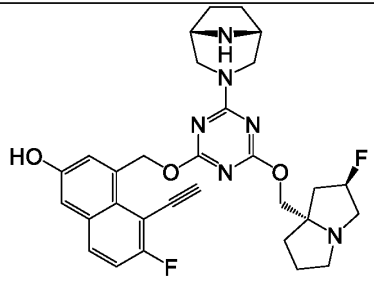
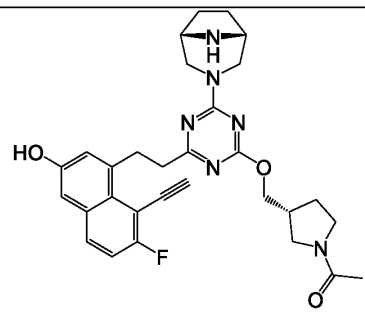
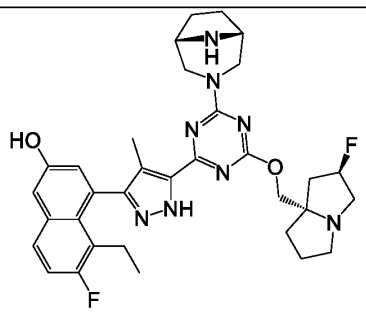
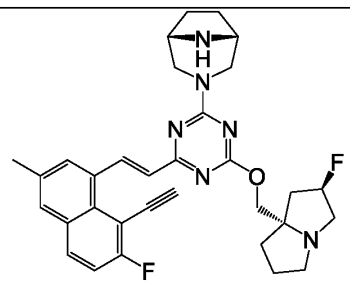
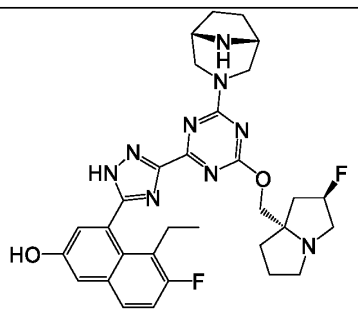
In embodiments, the compound is selected from the group consisting of the compounds in Table 1 below and their stereoisomers (including enantiomers and diastereomers thereof, and mixtures of stereoisomers thereof, such as mixtures of enantiomers or mixtures of diastereomers of the compounds of Table 1) wherein “#” denotes “Compound number”:

Table 1

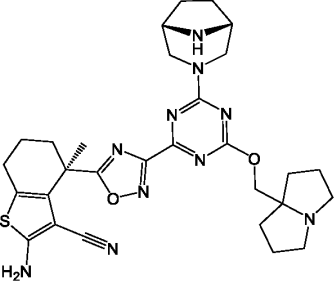
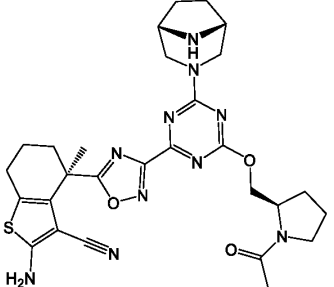
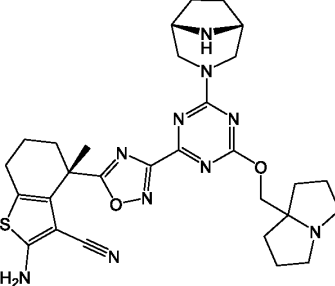
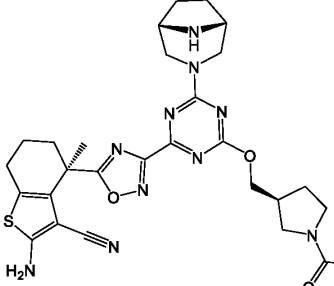
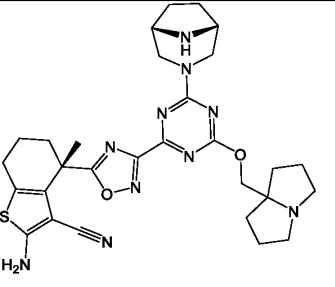
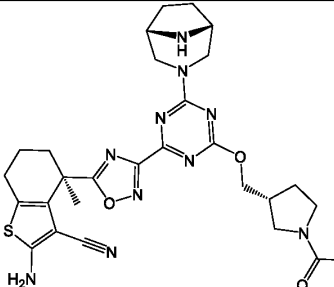
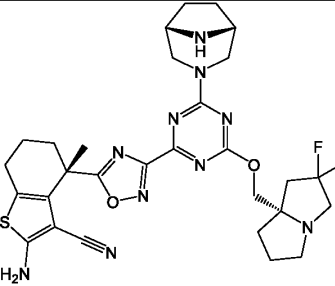
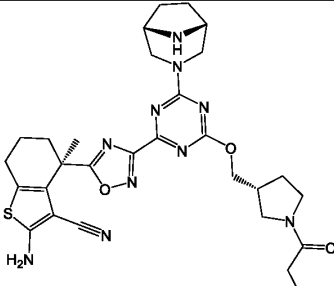
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(2)		(6)	
(3)		(7)	
(4)		(8)	

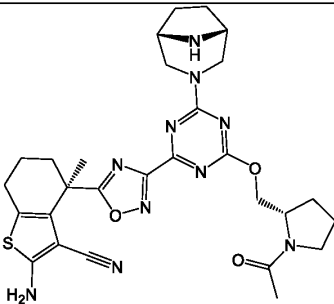
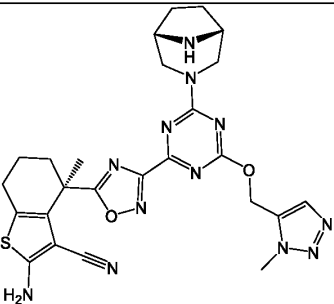
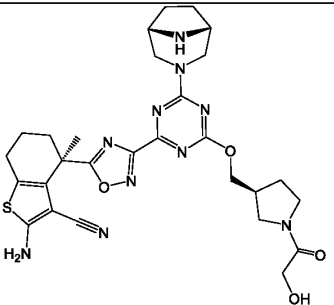
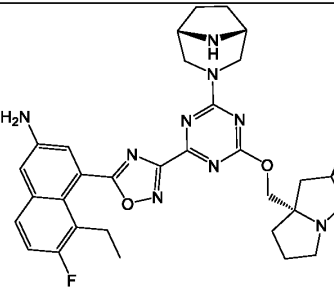
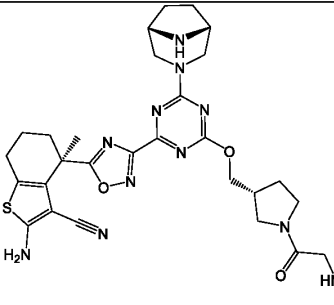
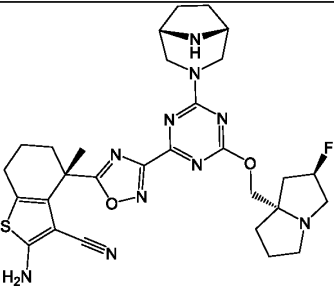
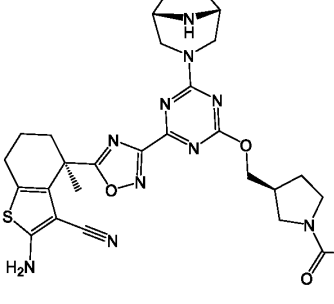
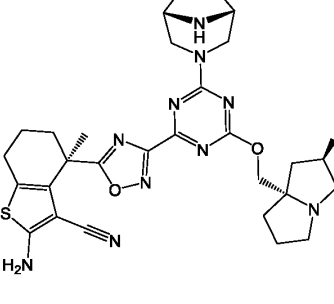
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(10)		(14)	
(11)		(15)	
(12)		(16)	

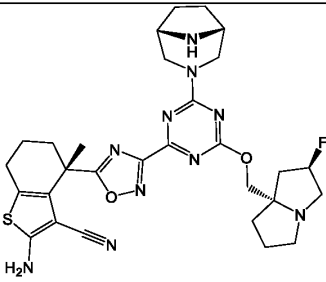
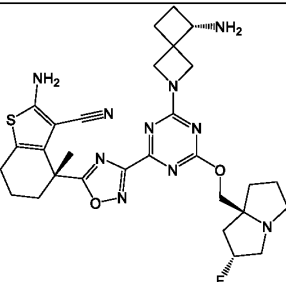
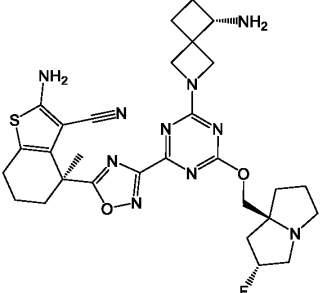
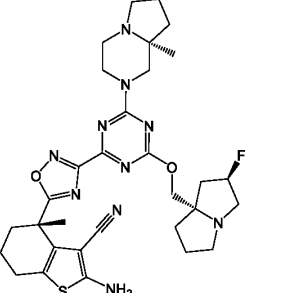
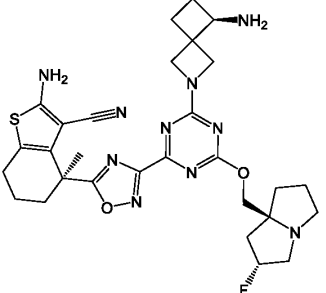
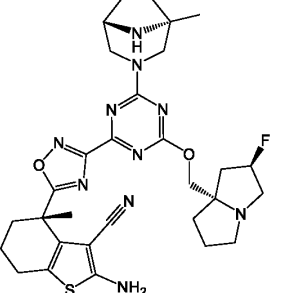
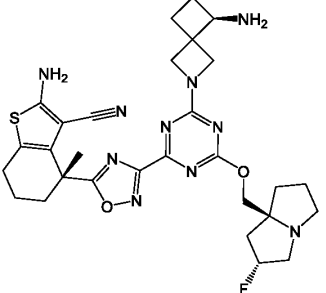
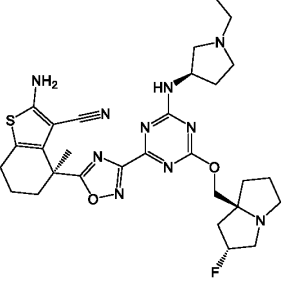
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(18)		(22)	
(19)		(23)	
(20)		(24)	

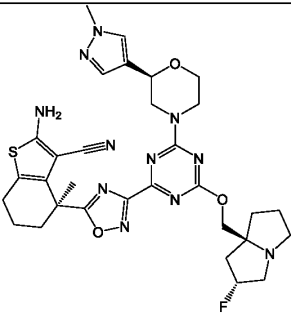
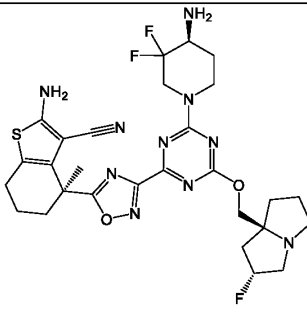
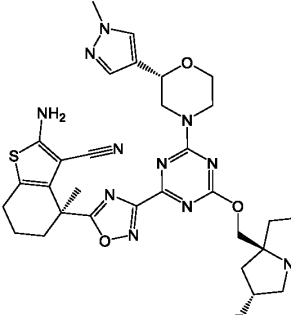
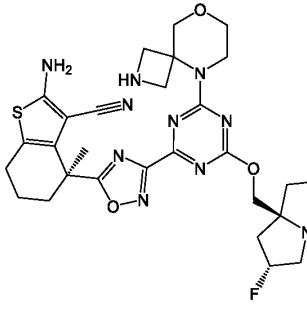
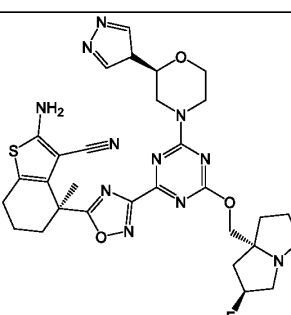
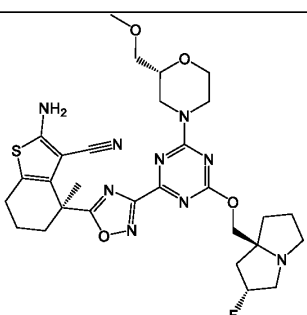
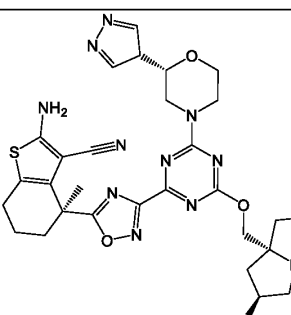
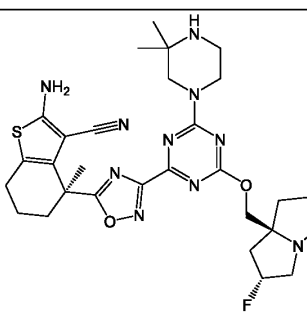
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(26)		(30)	
(27)		(31)	
(28)		(32)	

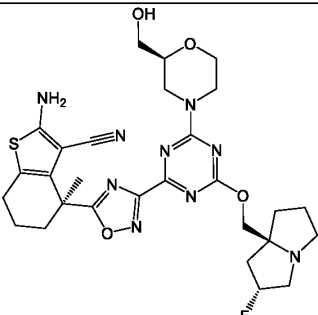
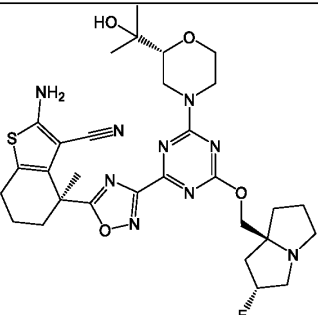
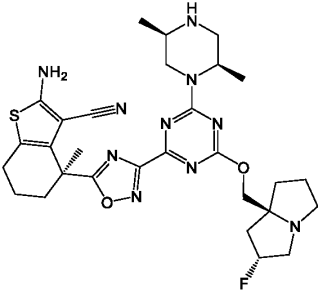
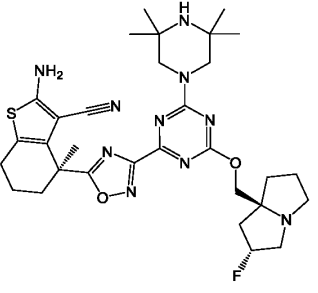
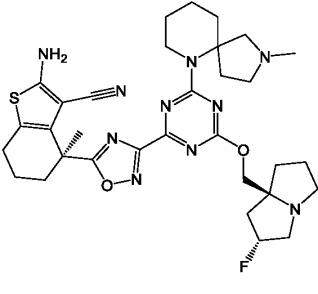
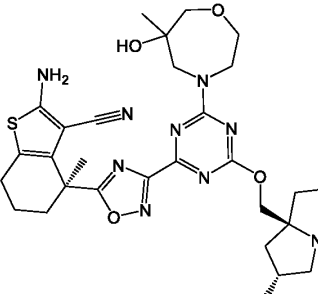
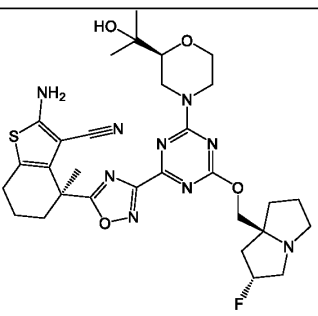
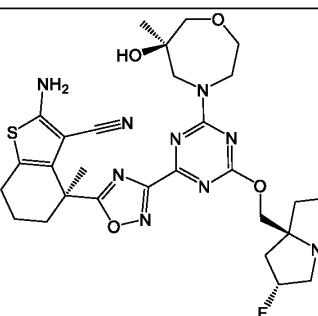
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(34)		(38)	
(35)		(39)	
(36)		(40)	

#	Structural formula	#	Structural formula
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(42)		(46)	
(43)		(47)	
(44)		(48)	

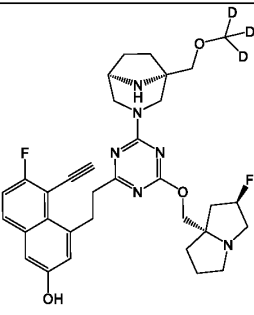
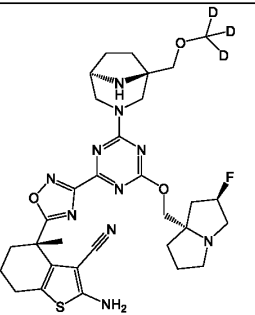
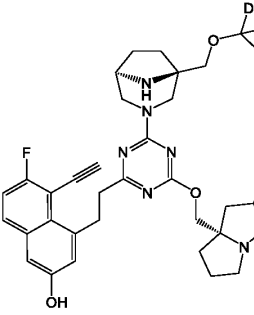
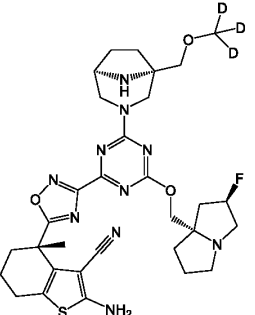
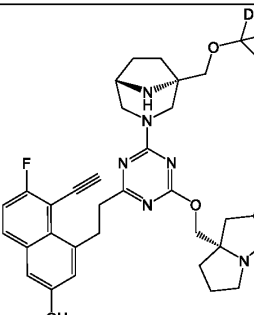
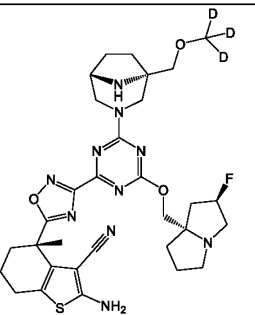
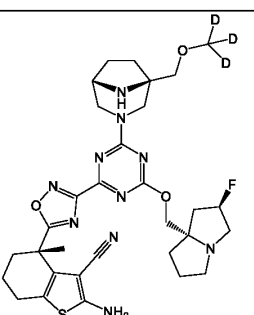
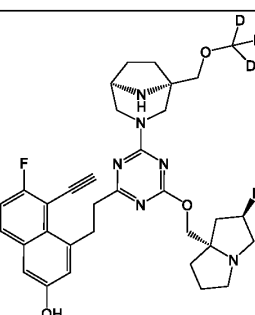
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(50)		(54)	
(51)		(55)	
(52)		(56)	

#	Structural formula	#	Structural formula
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(58)		(59)	
(58a)		(60)	
(58b)		(61)	

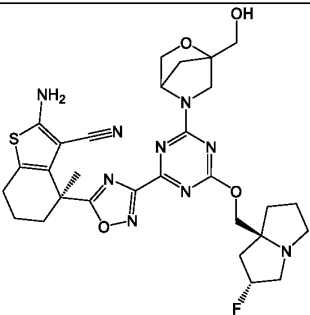
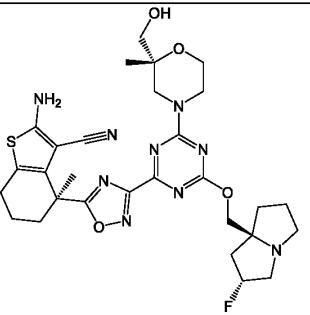
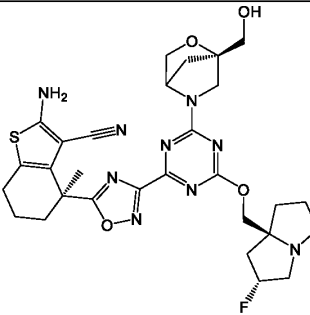
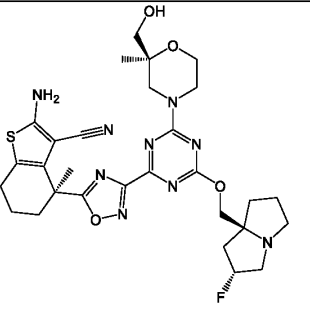
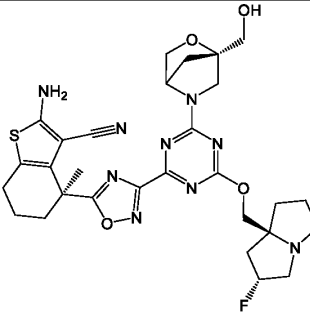
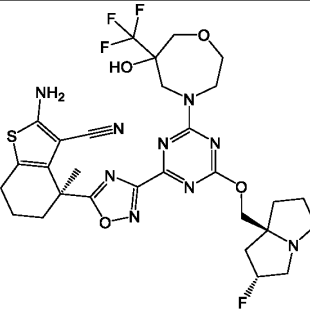
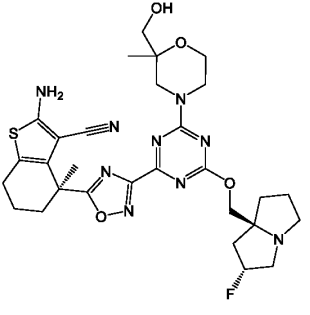
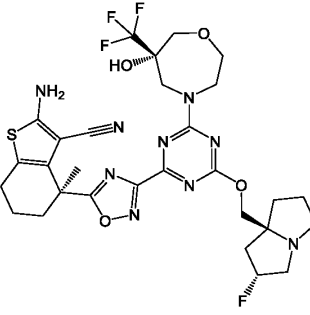
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(62a)		(65)	
(63)		(66)	
(63a)		(67)	

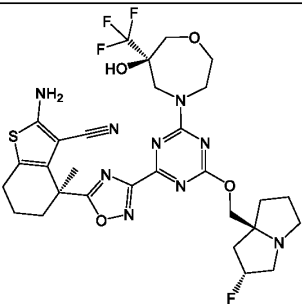
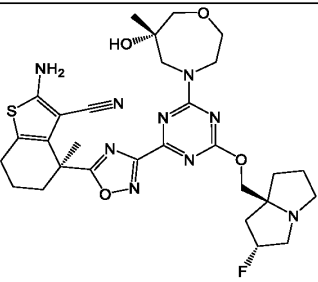
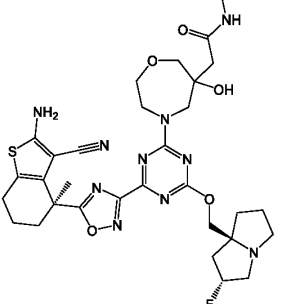
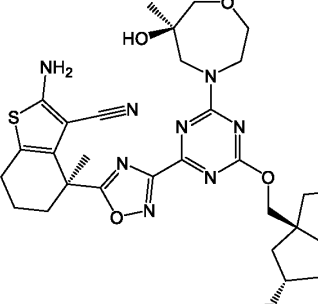
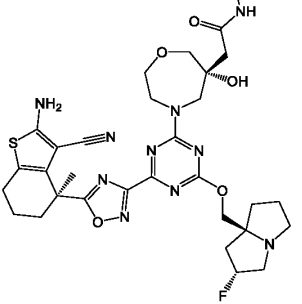
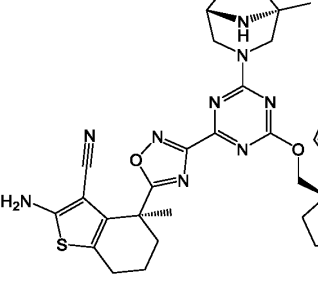
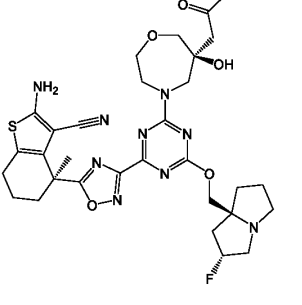
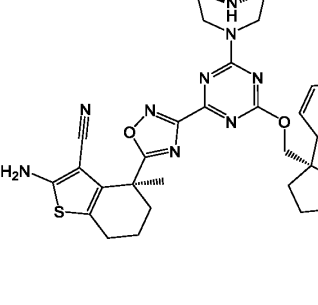
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(69)		(72)	
(70)		(73)	
(71)		(73a)	

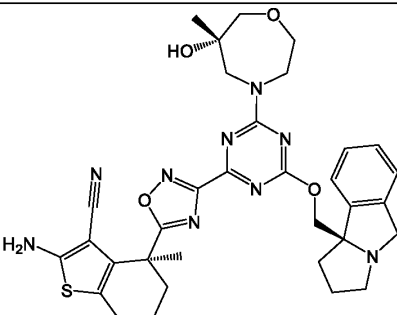
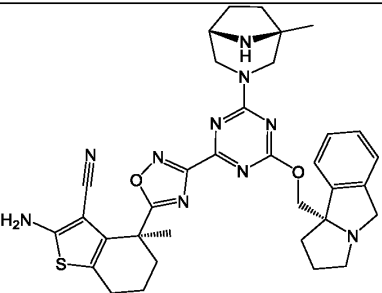
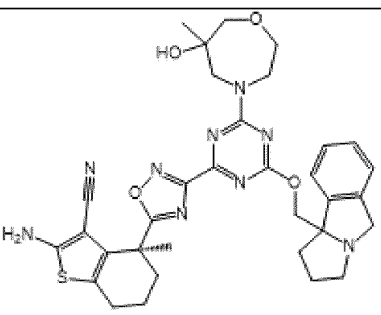
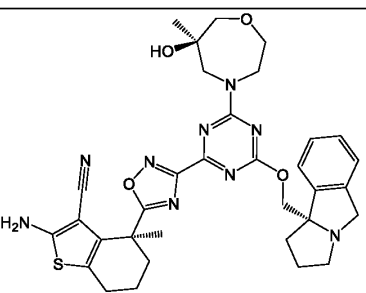
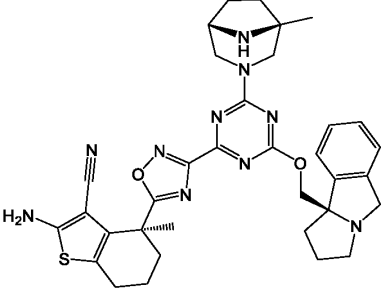
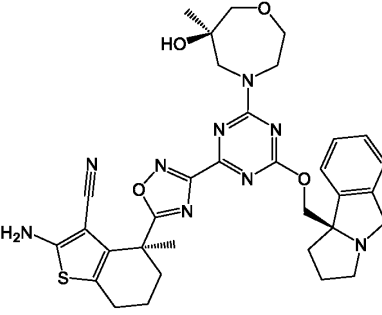
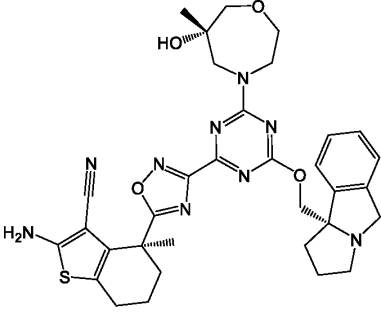
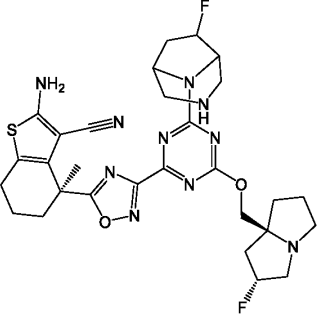
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(74)		(77)	
(75)		(77a)	
(75a)		(78)	

#	Structural formula	#	Structural formula
(78a)		(79a)	
(78b)		(80)	
(78c)		(80a)	
(79)		(81)	

#	Structural formula	#	Structural formula
(81a)		(82a)	
(81b)		(83)	
(81c)		(84)	
(82)		(84a)	

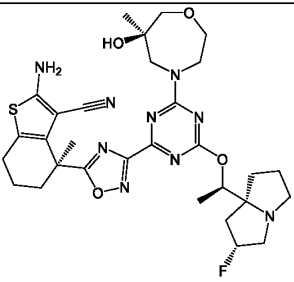
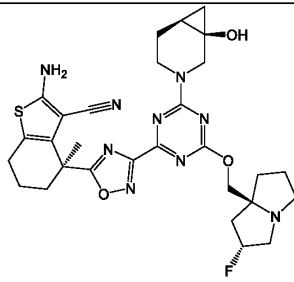
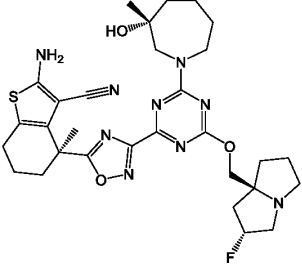
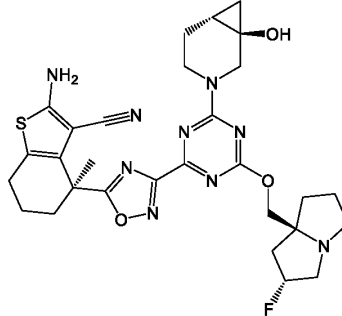
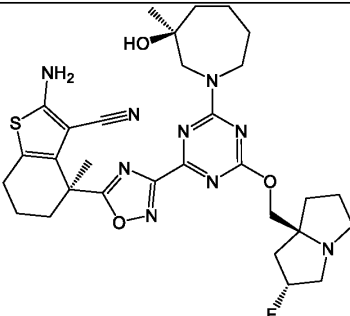
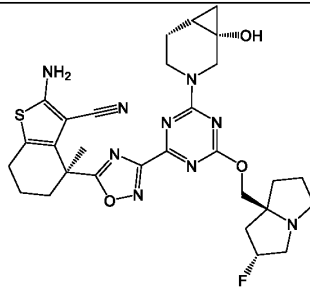
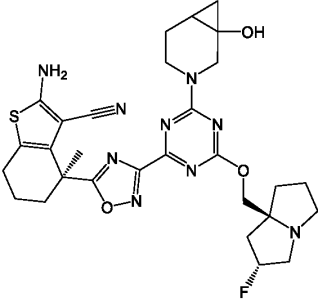
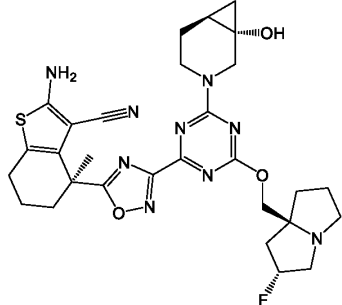
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(85)		(86a)	
(85a)		(86b)	
(85b)		(87)	
(86)		(87a)	

#	Structural formula	#	Structural formula
(87b)		(89)	
(88)		(90)	
(88a)		(91)	
(88b)		(92)	

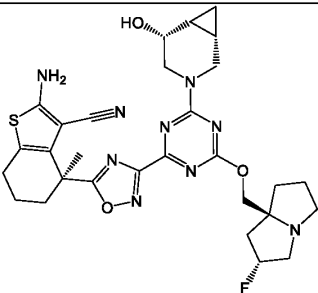
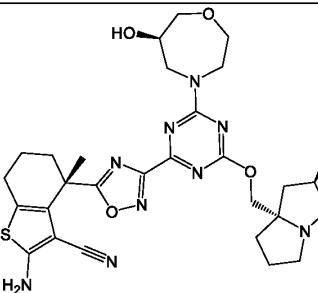
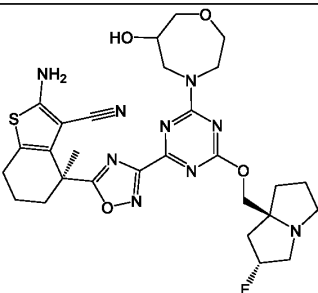
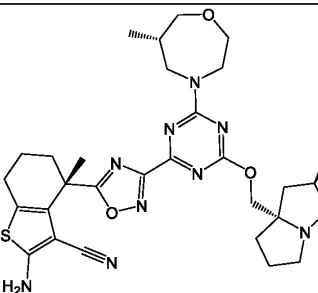
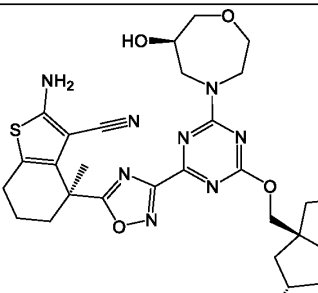
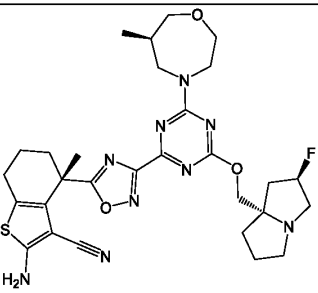
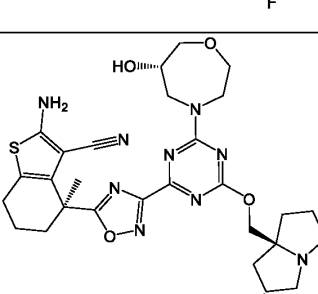
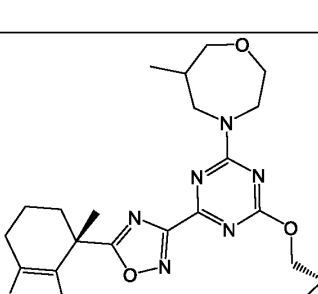
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(93a)		(97)	
(94)		(98)	
(95)		(99)	

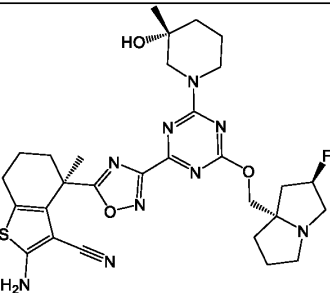
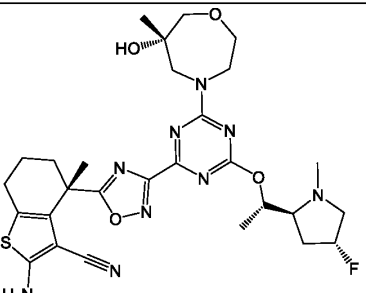
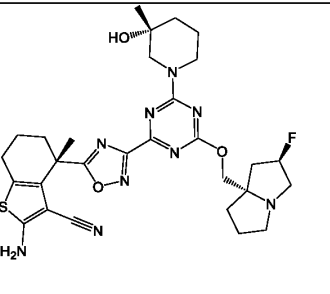
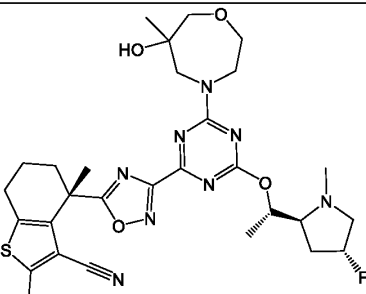
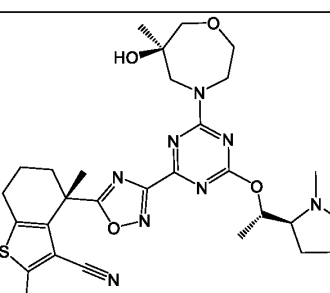
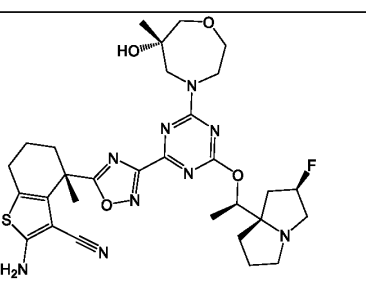
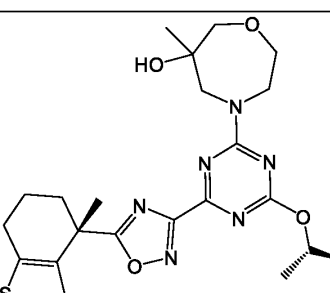
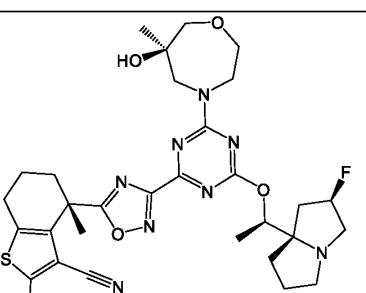
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(99b)		(99f)	
(99c)		(99g)	
(99d)		(99h)	

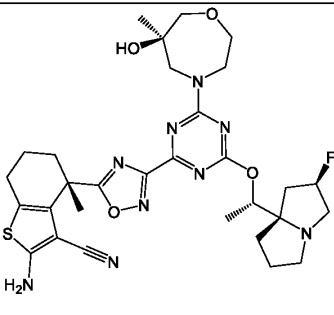
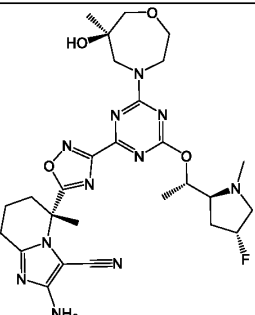
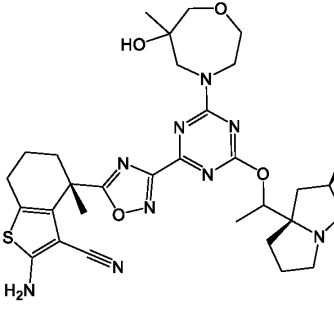
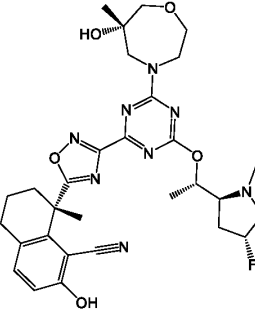
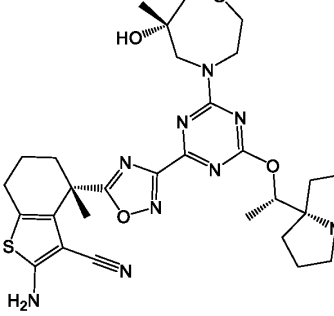
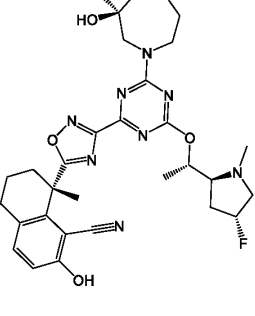
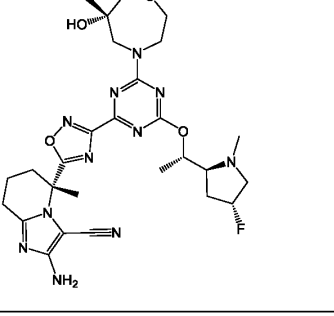
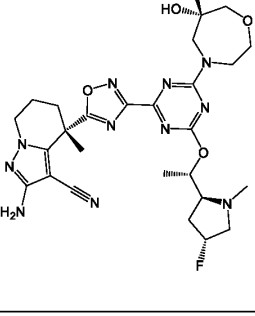
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(101)		(104)	
(102)		(105)	
(102a)		(106)	

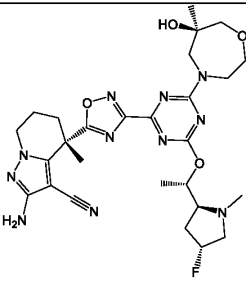
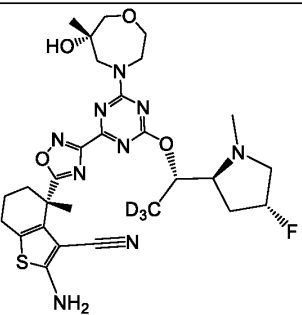
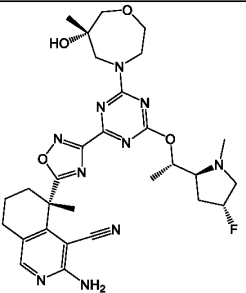
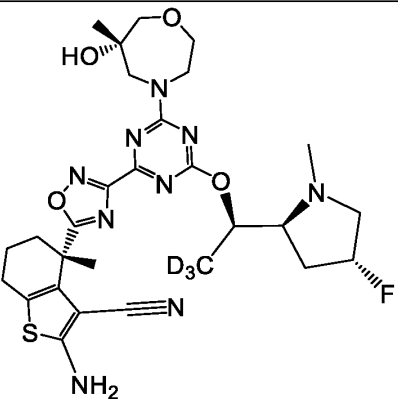
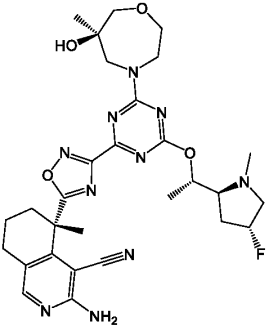
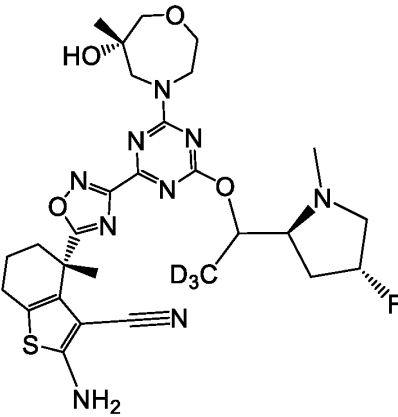
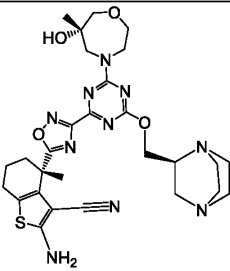
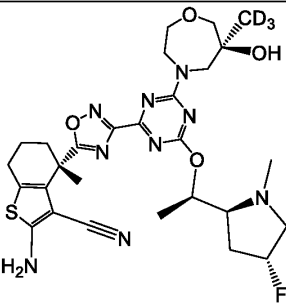
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(107)		(109b)	
(108)		(109c)	
(109)		(109d)	

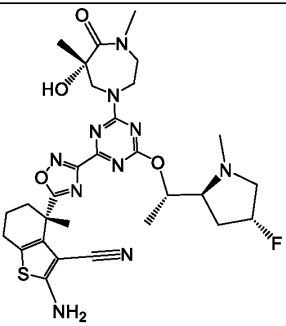
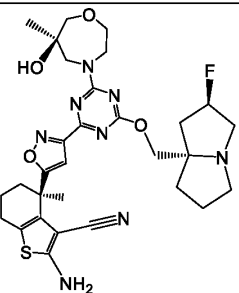
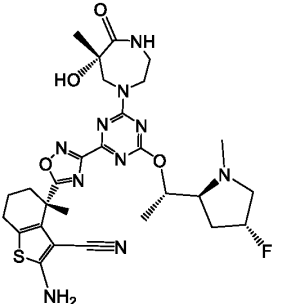
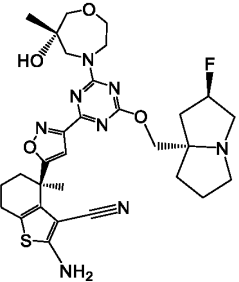
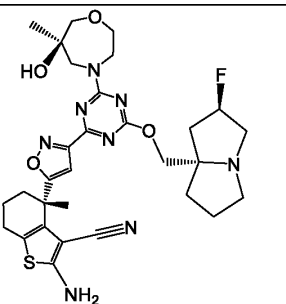
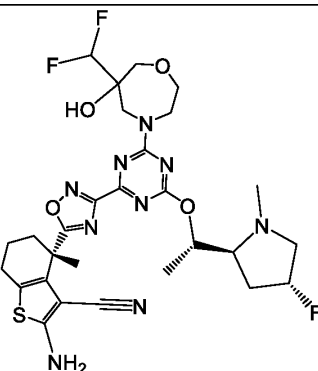
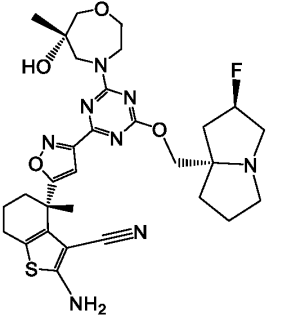
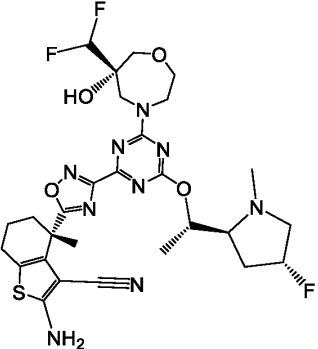
#	Structural formula	#	Structural formula
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(110a)		(110e)	
(110b)		(110f)	
(110c)		(110g)	

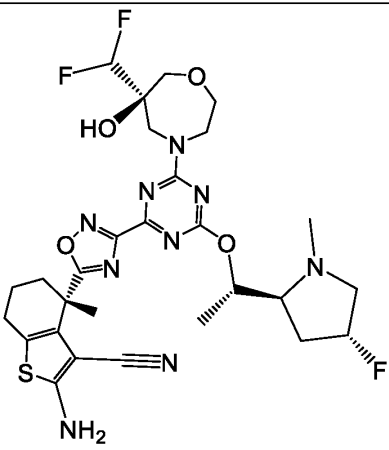
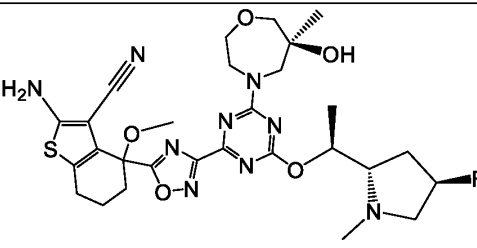
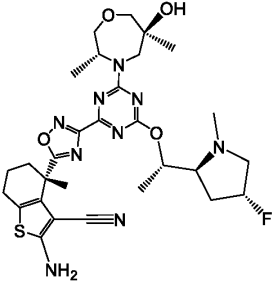
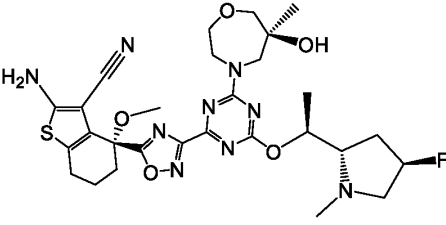
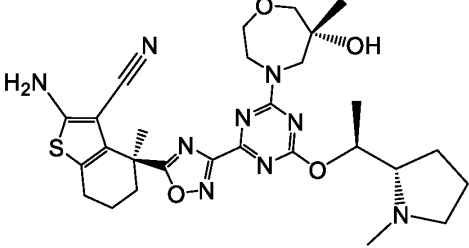
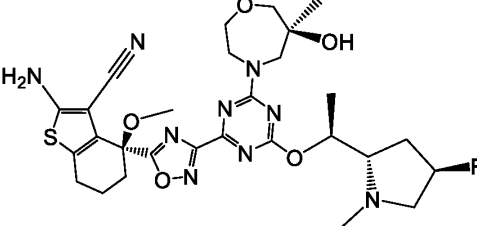
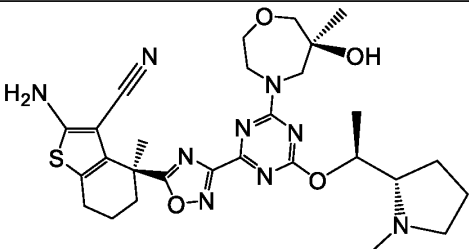
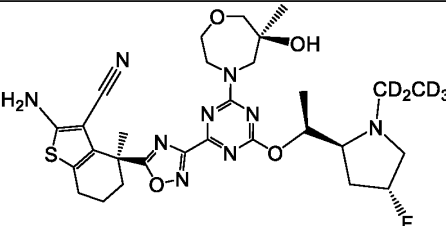
#	Structural formula	#	Structural formula
(110h)		(112)	
(111)		(113)	
(111a)		(113a)	
(111b)		(113b)	

#	Structural formula	#	Structural formula
(114)		(116)	
(114a)		(116a)	
(115)		(117)	
(115a)		(118)	

#	Structural formula	#	Structural formula
(119)		(121a)	
(119a)		(122)	
(120)		(122a)	
(121)		(123)	

#	Structural formula	#	Structural formula
(123a)		(126)	
(124)		(126a)	
(124a)		(126b)	
(125)		(127)	

#	Structural formula	#	Structural formula
(128)		(131)	
(129)		(131a)	
(130)		(132)	
(130a)		(132a)	

#	Structural formula	#	Structural formula
(132b)		(135)	
(133)		(135a)	
(134)		(135b)	
(134a)		(136)	

#	Structural formula	#	Structural formula
(137)		(138)	
(137a)		(138a)	
(137b)		(138b)	
(137c)		(139)	

#	Structural formula	#	Structural formula
(139a)		(140b)	
(139b)		(140c)	
(140)		(140d)	
(140a)		(141)	

#	Structural formula	#	Structural formula
(141a)		(142b)	
(141b)		(143)	
(142)		(143a)	
(142a)		(143b)	

#	Structural formula	#	Structural formula
(143c)			
(143d)			

In embodiments, the compounds of the disclosure are characterised according to their binding and/or inhibitory activity against KRAS G12D, e.g., as measured according to the assays described in the examples below.

- 5 In embodiments, the compounds of the disclosure are characterised according to their dissociation constants K_D in relation to KRAS G12D, e.g. when measured according to SPR, such as when measured according to an SPR assay as described in the examples below.

In embodiments the compounds have a K_D of $\leq 10 \mu\text{M}$ with respect to KRAS G12D. In embodiments, the compounds have a K_D of less than about $5 \mu\text{M}$, less than about $1 \mu\text{M}$, less than about $0.5 \mu\text{M}$, less than about $0.4 \mu\text{M}$, less than about $0.3 \mu\text{M}$, less than about $0.2 \mu\text{M}$ or less than about $0.1 \mu\text{M}$. In

10 In embodiments, the compounds have a K_D of less than about 50 nM , e.g. less than about 40 nM , less than about 35 nM , less than about 30 nM , less than about 25 nM , less than about 20 nM , less than about 15 nM , less than about 10 nM , or less than about 5 nM with respect to KRAS G12D.

In embodiments, the compounds of the disclosure are characterised according to their binding and/or

15 inhibitory activity against GDP-bound KRAS G12D, e.g., as measured according to the assays described in the examples below.

In embodiments, the compounds have an IC₅₀ for binding GDP-bound KRAS G12D of less than about 50 nM, *e.g.* less than about 40 nM, less than about 35 nM, less than about 30 nM, less than about 25 nM, less than about 20 nM, less than about 15 nM, less than about 10 nM, or less than about 5 nM. In embodiments, the compounds have an IC₅₀ for binding GDP-bound KRAS G12D of less than about 2 nM, *e.g.* less than about 1.5 nM, less than about 1.25 nM, less than about 1 nM, less than about 0.75 nM, or less than about 0.5 nM.

In embodiments the compounds have greater affinity for KRAS G12D than for wild-type (WT) KRAS. Thus, in embodiments the compounds have a higher K_D with respect to WT KRAS than with respect to KRAS G12D, *e.g.*, when measured according to SPR, such as when measured according to an SPR assay as described in the examples below. In embodiments, the compound has at least 5-fold selectivity for binding to KRAS G12D in preference to WT KRAS (*e.g.*, as defined by the ratio of K_D (WT KRAS) to K_D (KRAS G12D), *e.g.*, when measured according to SPR, such as when measured according to an SPR assay as described in the examples below). In embodiments, the compound has at least about 10-fold, 15-fold, 20-fold, 25-fold, or 30-fold selectivity for KRAS G12D over WT KRAS (*e.g.*, as defined by the ratio of K_D (WT KRAS) to K_D (KRAS G12D), *e.g.*, when measured according to SPR, such as when measured according to an SPR assay as described in the examples below). In embodiments, the compounds show significant improvements in cellular potency as compared to compounds known in the art.

In embodiments, the compounds have multi-mutant RAS cellular inhibition whilst sparing WT KRAS, NRAS and HRAS; thus, the compounds act as pan-KRAS inhibitors which not only spare other RAS isoforms but also spare wild-type KRAS while exhibiting multi-mutant KRAS inhibition. This has the beneficial effect of significantly expanding the patient population by approximately three-fold as compared to compounds known in the art. In embodiments, the compounds exhibit cellular inhibition of KRAS mutant G12D and at least one of KRAS mutants G12A, G12C, G12V, Q61H, G13D, or other KRAS mutants, or a combination thereof (*e.g.* cellular inhibition of a combination of KRAS G12D and at least two, at least three, at least four, or at least five thereof, such as a combination of KRAS G12D and any two, any three, any four, or any five thereof), whilst sparing WT KRAS. In embodiments, the compounds exhibit cellular inhibition of KRAS mutant G12D and at least one of KRAS mutants G12A, G12C, G12V, Q61H, G13D, or a combination thereof (*e.g.* cellular inhibition of a combination of KRAS G12D and at least two, at least three, at least four, or all five thereof, such as a combination of any two, any three, any four, or all five thereof), whilst sparing WT KRAS. In embodiments, the compounds exhibit cellular inhibition of each of KRAS mutants G12D, G12A, G12C, G12V, Q61H, and G13D, whilst sparing WT KRAS.

In embodiments, the compounds of the disclosure are characterised according to their cellular inhibition of KRAS cell lines, e.g., as measured by inhibition of KRAS mediated phosphorylation of ERK as described in the examples below. In embodiments, the compounds exhibit IC₅₀ for inhibition of ERK phosphorylation for WT KRAS cell lines of greater than about 10 µM, and inhibition of ERK phosphorylation for KRAS mutant G12D and optionally at least one of KRAS mutants G12A, G12C, G12V, Q61H, or G13D, or a combination thereof (e.g. inhibition of ERK phosphorylation of a combination of KRAS G12D and at least two, at least three, at least four, or all five thereof, such as a combination of KRAS G12D and any two, any three, any four, or all five thereof), of less than about 500 nM, e.g., less than about 250 nM, less than about 100 nM, less than about 50 nM, less than about 25 nM, less than about 10 nM, less than about 5 nM, less than about 2.5 nM, or less than about 1 nM.

In embodiments, the compounds exhibit increased permeability and/or improved oral bioavailability compared to compounds known in the art.

Pharmaceutical Compositions

In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound described herein (e.g., a compound of Formula (I) or a pharmaceutically acceptable salt thereof, or a compound of Formula (0) or a pharmaceutically acceptable salt thereof) and at least one pharmaceutically acceptable excipient or carrier.

In embodiments, the pharmaceutical composition comprises a compound of Formula (0) or a pharmaceutically acceptable salt thereof.

In embodiments, the pharmaceutical composition comprises a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

In embodiments, the pharmaceutical composition comprises a compound of Formula (II) or a pharmaceutically acceptable salt thereof. In embodiments, the pharmaceutical composition comprises a compound of Formula (IIa) or a pharmaceutically acceptable salt thereof. In embodiments, the pharmaceutical composition comprises a compound of Formula (IIb) or a pharmaceutically acceptable salt thereof.

In embodiments, the pharmaceutical composition comprises a compound of Formula (III) or a pharmaceutically acceptable salt thereof. In embodiments, the pharmaceutical composition comprises a compound of Formula (IIIa) or a pharmaceutically acceptable salt thereof. In embodiments, the pharmaceutical composition comprises a compound of Formula (IIIb) or a pharmaceutically acceptable salt thereof.

In embodiments, the pharmaceutical composition comprises a compound of Formula (IV) or a pharmaceutically acceptable salt thereof. In embodiments, the pharmaceutical composition comprises a compound of Formula (Iva) or a pharmaceutically acceptable salt thereof. In embodiments, the pharmaceutical composition comprises a compound of Formula (IVb) or a pharmaceutically acceptable salt thereof.

In embodiments, the pharmaceutical composition comprises a compound of Formula (V) or a pharmaceutically acceptable salt thereof. In embodiments, the pharmaceutical composition comprises a compound of Formula (Va) or a pharmaceutically acceptable salt thereof. In embodiments, the pharmaceutical composition comprises a compound of Formula (Vb) or a pharmaceutically acceptable salt thereof.

In embodiments, the pharmaceutical composition comprises a compound of Formula (VI) or a pharmaceutically acceptable salt thereof. In embodiments, the pharmaceutical composition comprises a compound of Formula (Via) or a pharmaceutically acceptable salt thereof. In embodiments, the pharmaceutical composition comprises a compound of Formula (VIb) or a pharmaceutically acceptable salt thereof.

In embodiments, the pharmaceutical composition comprises a compound of Formula (VI.I) or a pharmaceutically acceptable salt thereof. In embodiments, the pharmaceutical composition comprises a compound of Formula (VI.Ia) or a pharmaceutically acceptable salt thereof. In embodiments, the pharmaceutical composition comprises a compound of Formula (VI.Ib) or a pharmaceutically acceptable salt thereof.

In embodiments, the pharmaceutical composition comprises a compound of Formula (VII) or a pharmaceutically acceptable salt thereof. In embodiments, the pharmaceutical composition comprises a compound of Formula (VIIa) or a pharmaceutically acceptable salt thereof. In embodiments, the pharmaceutical composition comprises a compound of Formula (VIIb) or a pharmaceutically acceptable salt thereof.

In embodiments, the pharmaceutical composition comprises a compound of Formula (VII.I) or a pharmaceutically acceptable salt thereof. In embodiments, the pharmaceutical composition comprises a compound of Formula (VII.Ia) or a pharmaceutically acceptable salt thereof. In embodiments, the pharmaceutical composition comprises a compound of Formula (VII.Ib) or a pharmaceutically acceptable salt thereof.

In embodiments, the pharmaceutical composition comprises a compound of Formula (VIII) or a pharmaceutically acceptable salt thereof.

In embodiments, the pharmaceutical composition comprises a compound of Formula (IX) or a pharmaceutically acceptable salt thereof.

In embodiments, the pharmaceutical composition comprises a compound of Formula (X) or a pharmaceutically acceptable salt thereof.

- 5 In embodiments, the pharmaceutical composition comprises a compound of Formula (XI) or a pharmaceutically acceptable salt thereof.

In embodiments, the pharmaceutical composition comprises a compound of Formula (XII) or a pharmaceutically acceptable salt thereof.

- 10 In embodiments, the pharmaceutical composition comprises a compound of Formula (XIII) or a pharmaceutically acceptable salt thereof.

In embodiments, the pharmaceutical composition comprises a compound of Formula (XIV) or a pharmaceutically acceptable salt thereof.

In embodiments, the pharmaceutical composition comprises a compound of Formula (XV) or a pharmaceutically acceptable salt thereof.

- 15 In embodiments, the pharmaceutical composition comprises a compound of Formula (XVI) or a pharmaceutically acceptable salt thereof.

In embodiments, the pharmaceutical composition comprises a compound of Formula (XVII) or a pharmaceutically acceptable salt thereof.

- 20 In embodiments, the pharmaceutical composition comprises a compound of Formula (XVIII) or a pharmaceutically acceptable salt thereof.

In embodiments, the pharmaceutical composition comprises a compound of Formula (XIX) or a pharmaceutically acceptable salt thereof.

In embodiments, the pharmaceutical composition comprises a compound of Formula (XX) or a pharmaceutically acceptable salt thereof.

- 25 In embodiments, the pharmaceutical composition comprises a compound of Formula (XXI) or a pharmaceutically acceptable salt thereof.

In embodiments, the pharmaceutical composition comprises a compound of Formula (XXII) or a pharmaceutically acceptable salt thereof.

- 30 In embodiments, the pharmaceutical composition comprises a compound of Formula (XXII.I) or a pharmaceutically acceptable salt thereof.

In embodiments, the pharmaceutical composition comprises a compound of Formula (XXIII) or a pharmaceutically acceptable salt thereof.

In embodiments, the pharmaceutical composition comprises a compound of Formula (XXIII.I) or a pharmaceutically acceptable salt thereof.

- 5 In embodiments, the pharmaceutical composition comprises a compound of Formula (XXIV) or a pharmaceutically acceptable salt thereof.

In embodiments, the pharmaceutical composition comprises a compound of Formula (XXIV.I) or a pharmaceutically acceptable salt thereof.

- 10 In embodiments, the pharmaceutical composition comprises a compound of Formula (XXV) or a pharmaceutically acceptable salt thereof.

In embodiments, the pharmaceutical composition comprises a compound of Formula (XXVI) or a pharmaceutically acceptable salt thereof.

In embodiments, the pharmaceutical composition comprises a compound of Formula (XXVII) or a pharmaceutically acceptable salt thereof.

- 15 In embodiments, the pharmaceutical composition comprises a compound of Formula (XXVIII) or a pharmaceutically acceptable salt thereof.

- The pharmaceutical compositions disclosed herein may be formulated for administration in solid or liquid form, e.g., using conventional carriers or excipients. Compositions may be adapted for, e.g., oral administration (e.g., as a solution, suspension, tablet, or capsule), parenteral administration (e.g., as a solution, dispersion, suspension, or emulsion, or as a dry powder for reconstitution), or topical application (e.g., as a cream, ointment, patch, or spray to be applied to the skin) using techniques known in the art.
- 20

- In embodiments, the compounds have good permeability and oral bioavailability (*e.g.* improved permeability and/or improved oral bioavailability as compared to compounds known in the art). These properties are particularly beneficial as they reduce or avoid altogether the need to employ lipid/liposome formulations for dosing of the compounds. Thus, in embodiments, the pharmaceutical compositions disclosed herein are not formulated as lipid formulations or as liposome formulations.
- 25

Medical uses

- Compounds of the present disclosure act as inhibitors of KRAS G12D, which gives them utility in the treatment of KRAS G12D-associated disorders and conditions. In particular, compounds of the disclosure are useful in the treatment of cancers, especially KRAS G12D-associated cancers.
- 30

Viewed from this aspect, the disclosure provides a method of treatment comprising administering to a subject in need thereof a therapeutically effective amount of a compound of the disclosure (e.g., a compound of Formula (I) or a pharmaceutically acceptable salt thereof, or a compound of Formula (0) or a pharmaceutically acceptable salt thereof). In a related aspect, the disclosure provides the use of a compound of the disclosure (e.g. a compound of Formula (I) or a pharmaceutically acceptable salt thereof, or a compound of Formula (0) or a pharmaceutically acceptable salt thereof) in the manufacture of a medicament. In a further related aspect, the disclosure provides a compound of the disclosure (e.g., a compound of Formula (I) or a pharmaceutically acceptable salt thereof, or a compound of Formula (0) or a pharmaceutically acceptable salt thereof) for use in therapy.

- 10 Compounds of the present disclosure are useful in treating or preventing diseases or disorders in which KRAS G12D is known to play a role; diseases or disorders associated with increased KRAS G12D activity; and diseases or disorders in which inhibition or antagonism of KRAS G12D activity is beneficial.

In one aspect, the present disclosure provides a method of treating or preventing a disease or disorder mediated by KRAS G12D, or a disease or disorder in which KRAS G12D is implicated, in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound of the disclosure (e.g., a compound of Formula (I) or a pharmaceutically acceptable salt thereof, or a compound of Formula (0) or a pharmaceutically acceptable salt thereof). In a related aspect, the disclosure provides the use of a compound of the disclosure (e.g., a compound of Formula (I) or a pharmaceutically acceptable salt thereof, or a compound of Formula (0) or a pharmaceutically acceptable salt thereof) in the manufacture of a medicament for the treatment or prevention of a disease or disorder mediated by KRAS G12D, or a disease or disorder in which KRAS G12D is implicated. In a further related aspect, the disclosure provides a compound of the disclosure (e.g., a compound of Formula (I) or a pharmaceutically acceptable salt thereof, or a compound of Formula (0) or a pharmaceutically acceptable salt thereof) for use in the treatment or prevention of a disease or disorder mediated by KRAS G12D, or a disease or disorder in which KRAS G12D is implicated.

In another aspect, the present disclosure provides a method of treating or preventing a disease or disorder associated with KRAS G12D (e.g., cancer, such as a KRAS G12D-associated cancer) in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound of the disclosure (e.g., a compound of Formula (I) or a pharmaceutically acceptable salt thereof, or a compound of Formula (0) or a pharmaceutically acceptable salt thereof). In a related aspect, the disclosure provides the use of a compound of the disclosure (e.g., a compound of Formula (I) or a pharmaceutically acceptable salt thereof, or a compound of Formula (0) or a pharmaceutically acceptable salt thereof) in the manufacture of a medicament for the treatment or prevention of a disease

or disorder associated with KRAS G12D (e.g., cancer, such as a KRAS G12D-associated cancer). In a further related aspect, the disclosure provides a compound of the disclosure (e.g., a compound of Formula (I) or a pharmaceutically acceptable salt thereof, or a compound of Formula (0) or a pharmaceutically acceptable salt thereof) for use in the treatment or prevention of a disease or disorder associated with KRAS G12D (e.g., cancer, such as a KRAS G12D-associated cancer).

In another aspect, the present disclosure provides a method of treating or preventing cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound of the disclosure (e.g., a compound of Formula (I) or a pharmaceutically acceptable salt thereof, or a compound of Formula (0) or a pharmaceutically acceptable salt thereof). In a related aspect, the disclosure provides the use of a compound of the disclosure (e.g., a compound of Formula (I) or a pharmaceutically acceptable salt thereof, or a compound of Formula (0) or a pharmaceutically acceptable salt thereof) in the manufacture of a medicament for the treatment or prevention of cancer. In a further related aspect, the disclosure provides a compound of the disclosure (e.g., a compound of Formula (I) or a pharmaceutically acceptable salt thereof, or a compound of Formula (0) or a pharmaceutically acceptable salt thereof) for use in the treatment or prevention of cancer (e.g., a KRAS G12D-associated cancer).

In embodiments, the compound reduces angiogenesis, reduces, or prevents metastasis, reduces inflammation, blocks tumorigenesis (e.g., in part or completely), reduces evasion of growth suppression, reduces, or inhibits growth of cancerous or pre-cancerous cells, suppresses proliferation of cancerous or pre-cancerous cells, and/or reduces the survival of cancerous or pre-cancerous cells.

In embodiments, the cancer is a KRAS G12D-associated cancer. In embodiments, the cancer is characterized by increased KRAS G12D expression. In embodiments, the cancer has elevated KRAS G12D activity. In embodiments, one or more cancer cells express KRAS G12D.

In embodiments, the cancer is a solid tumour (e.g., a melanoma, carcinoma, or blastoma). In other embodiments, the cancer is leukaemia (e.g., chronic lymphocytic leukaemia, CLL; acute myelogenous leukaemia, AML; or chronic myelogenous leukaemia, CML).

In embodiments, the cancer is a primary tumour. In other embodiments, the cancer is a secondary tumour (e.g., a metastatic tumour).

In embodiments, the cancer is selected from colorectal cancer (CRC) (e.g., rectal cancer), small bowel cancer, lung cancer (e.g., non-small cell lung cancer, NSCLC; small cell lung cancer; lung adenocarcinoma; or lung squamous cell carcinoma), pancreatic cancer (e.g., adenocarcinoma), breast cancer (e.g., ductal breast carcinoma or breast adenocarcinoma), liver cancer, kidney cancer (e.g., hepatocellular carcinoma), prostate cancer, ovarian cancer, brain cancer (e.g., glioblastoma), cervical

cancer (e.g., adenocarcinoma), gastric cancer, skin cancer, bile duct cancer (e.g., cholangiocarcinoma), nervous system cancer (e.g., neuroblastoma), and melanoma.

In embodiments, the cancer is selected from colorectal cancer (CRC) (e.g., rectal cancer), lung cancer (e.g., non-small cell lung cancer, NSCLC; small cell lung cancer; lung adenocarcinoma; or lung squamous cell carcinoma), and pancreatic cancer (e.g., adenocarcinoma).

In another aspect, the disclosure provides a method of inhibiting KRAS G12D activity, the method comprising contacting KRAS G12D (e.g., a cell comprising KRAS G12D) with a compound of the present disclosure (e.g., a compound of Formula (I) or a pharmaceutically acceptable salt thereof, or a compound of Formula (0) or a pharmaceutically acceptable salt thereof). In embodiments, the method is an *in vitro* or *ex vivo* method. In other embodiments the method is an *in vivo* method. In a related aspect, the disclosure provides an *in vitro* method of inhibiting KRAS G12D activity in a cell, the method comprising contacting the cell with a compound of the present disclosure (e.g., a compound of Formula (I) or a pharmaceutically acceptable salt thereof, or a compound of Formula (0) or a pharmaceutically acceptable salt thereof).

Compounds of the present disclosure (e.g., compounds of Formula (I), or compounds of Formula (0)) and the pharmaceutically acceptable salts thereof may be administered as pharmaceutical compositions, which may optionally comprise one or more pharmaceutically acceptable excipients.

It will be appreciated that the methods and treatments of the various aspects of this disclosure may be effected by administering to a subject an effective amount of a compound of the disclosure (e.g., a compound of Formula (I) or a pharmaceutically acceptable salt thereof, or a compound of Formula (0) or a pharmaceutically acceptable salt thereof), in the form of a pharmaceutical composition, which may optionally comprise one or more pharmaceutically acceptable excipients, as described herein.

The compounds disclosed herein may be used alone (e.g., as a monotherapy) or in combination with one or more cancer therapies.

Having been generally disclosed herein, the following non-limiting examples are provided to further illustrate this disclosure.

EXAMPLES

The preparation of exemplary compounds according to the present disclosure is described below. Other compounds within the scope of the disclosure may be made according to analogous methods and procedures to those described in detail below, in accordance with techniques known to those of skill in the art.

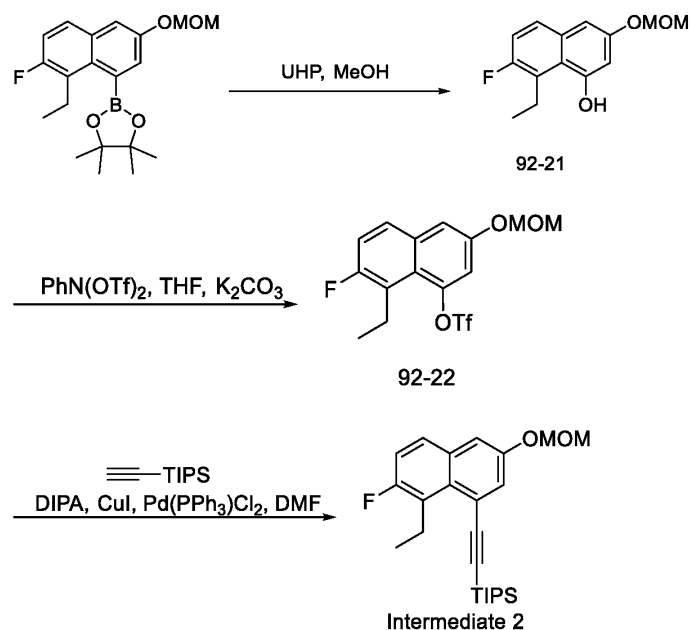
Example 1: General synthetic schemes

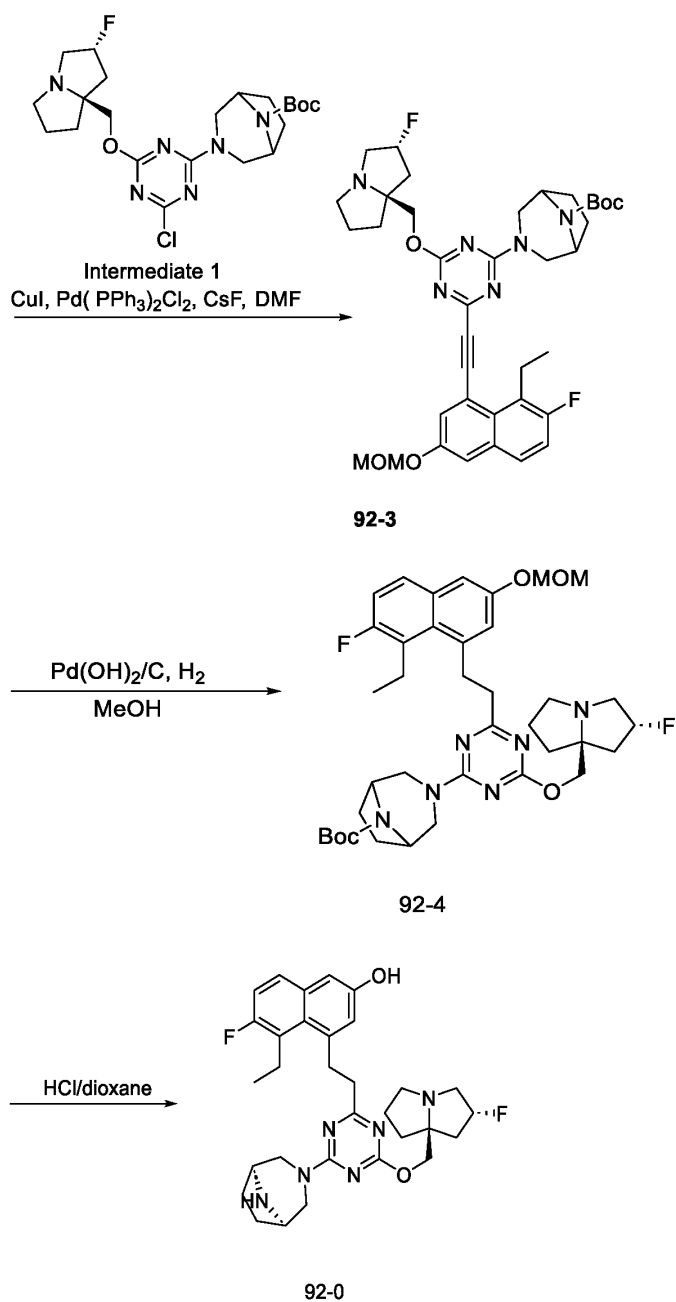
A number of synthetic protocols were used to produce the compounds described herein. These synthetic protocols have common intersections and can be used alternatively for synthesis of the compounds described herein.

5 **Scheme 1**

The following scheme, Scheme 1, illustrates an exemplary way of preparing compounds in accordance with the present disclosure and examples.

2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane is reacted with UHP to provide (92-21). (92-21) is reacted with $\text{PhN}(\text{OTf})_2$ and K_2CO_3 to provide (92-22). (92-22) is coupled with ethynyltriisopropylsilane in the presence of palladium catalyst to provide Intermediate 2. Intermediate 2 is coupled with Intermediate 1 in the presence of palladium catalyst to provide Intermediate (92-3). The triple bond of (92-3) is reduced by adding hydrogen and $\text{Pd}(\text{OH})_2/\text{C}$ to provide (92-4), and the BOC protecting group of (92-4) is removed to provide (92-0).



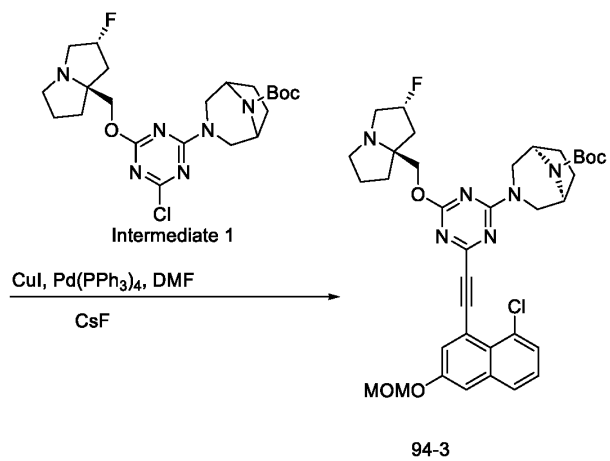
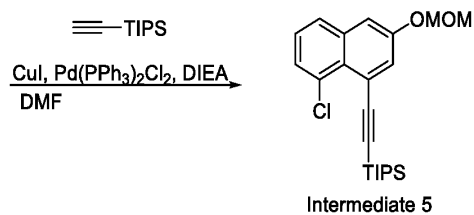
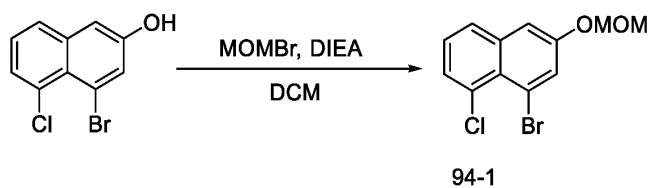


Scheme 2

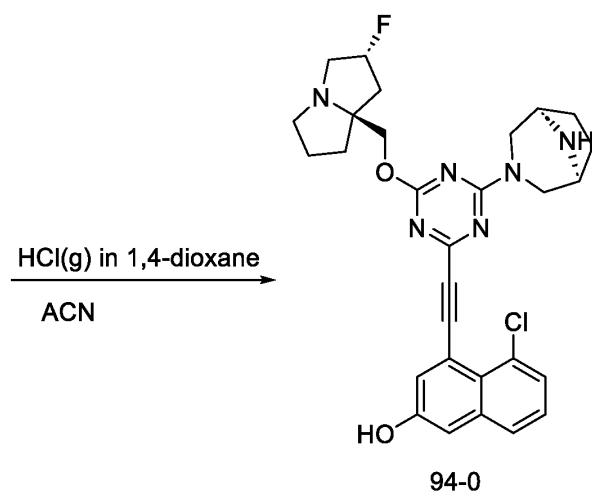
- 5 The following scheme, Scheme 2, illustrates an exemplary way of preparing compounds in accordance with the present disclosure and examples.

4-bromo-5-chloronaphthalen-2-ol is reacted with MOMBr to provide (94-1). (94-1) is coupled with ethynyltriisopropylsilane in the presence of palladium catalyst to provide Intermediate 5. Intermediate

5 is coupled with Intermediate 1 in the presence of palladium catalyst to provide Intermediate (94-3), and the BOC protecting group of (94-3) is removed to provide (94-0).



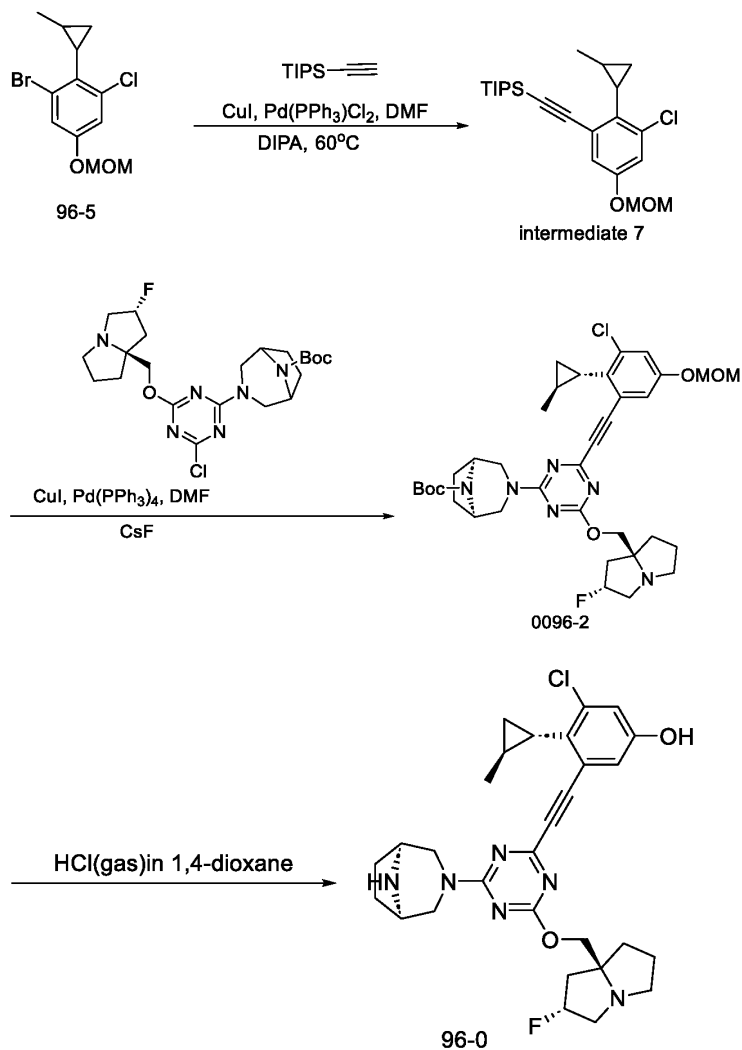
5



Scheme 3

The following scheme, Scheme 3, illustrates an exemplary way of preparing compounds in accordance with the present disclosure and examples.

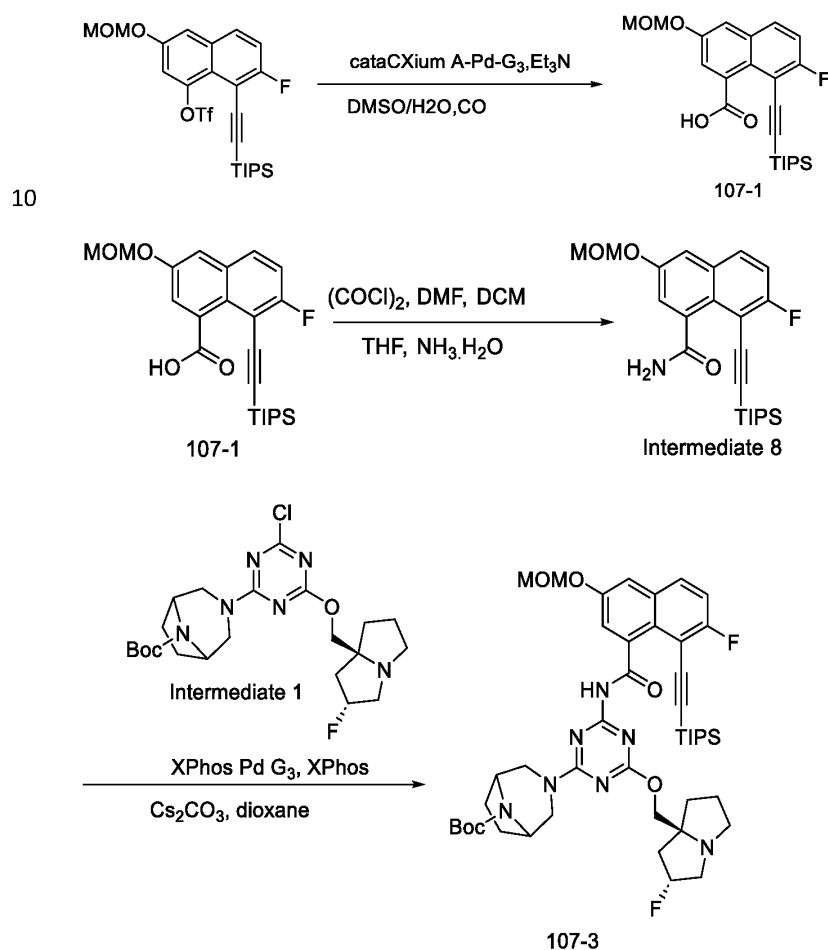
- (96-5) is coupled with ethynyltriisopropylsilane in the presence of palladium catalyst to provide Intermediate 7. Intermediate 7 is coupled with Intermediate 1 in the presence of palladium catalyst to provide Intermediate (96-2). The BOC protecting group of (96-2) is removed to provide (96-0).

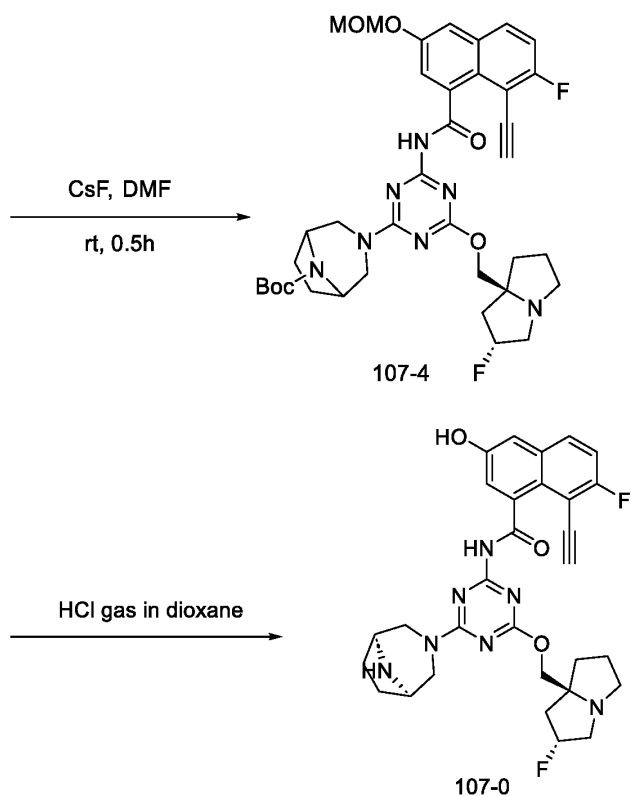


Scheme 4

The following scheme, Scheme 4, illustrates an exemplary way of preparing compounds in accordance with the present disclosure and examples.

- Commercial product 7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl trifluoromethanesulfonate is coupled with CO in the presence of palladium catalyst to provide Intermediate (107-1). (107-1) is reacted with oxalyl chloride and ammonium hydroxide to provide Intermediate 8. Intermediate 8 is coupled with Intermediate 1 in the presence of palladium catalyst to provide (107-3). The TIPS protecting group of (107-3) is removed to provide (107-4). The BOC protecting group of (96-2) is removed to provide (107-0).

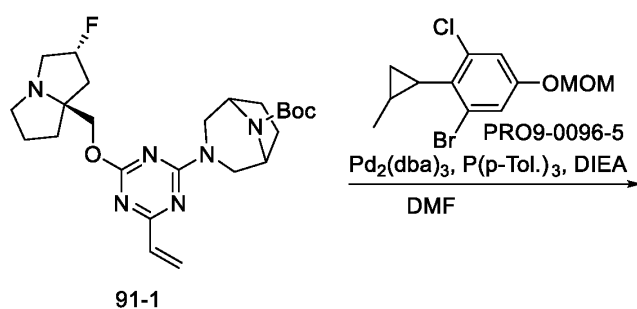


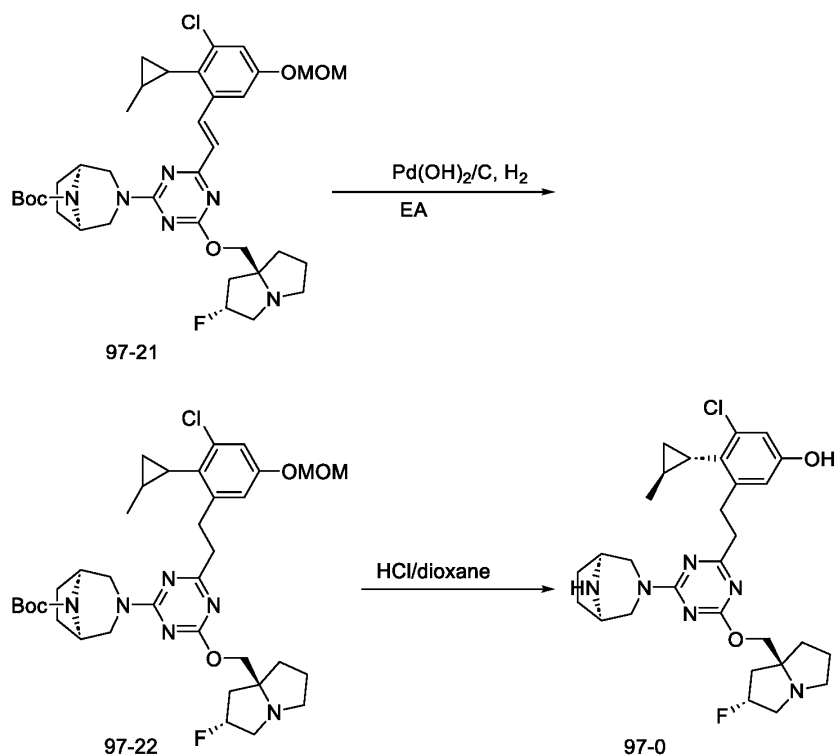


Scheme 5

The following scheme, Scheme 5, illustrates an exemplary way of preparing compounds in accordance with the present disclosure and examples.

(91-1) is coupled with (96-5) in the presence of palladium catalyst to provide (97-21). The double bond of (97-21) is reduced by adding hydrogen and Pd(OH)₂/C to provide (97-22). The BOC protecting group of (97-22) is removed to provide (97-0).



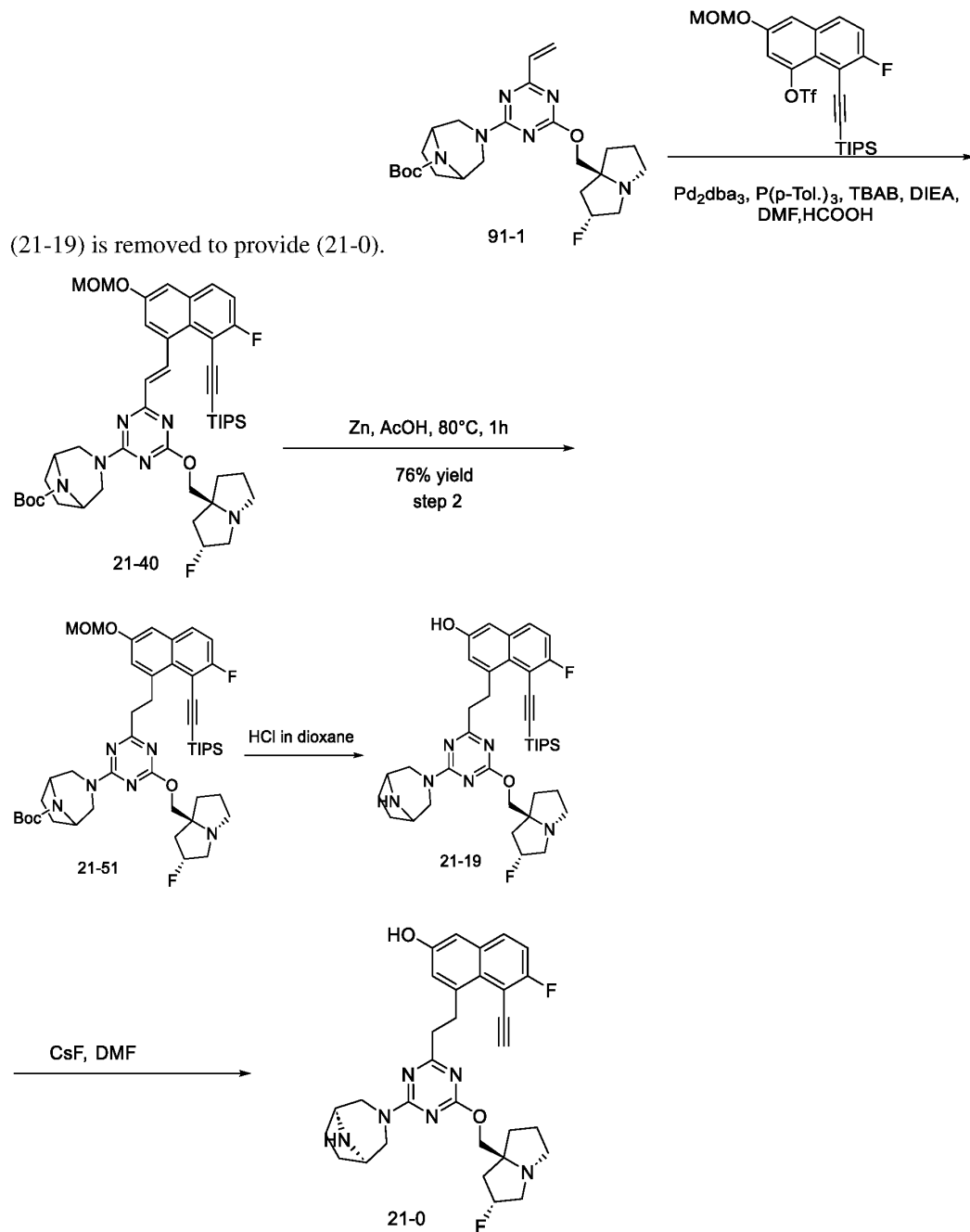


Scheme 6

- 5 The following scheme, Scheme 6, illustrates an exemplary way of preparing compounds in accordance with the present disclosure and examples.

Commercial product 7-fluoro-3-(methoxymethoxy)-8-(((triisopropylsilyl)ethynyl)naphthalen-1-yl trifluoromethanesulfonate is coupled with (91-1) in the presence of palladium catalyst to provide Intermediate (21-40). The double bond of (21-40) is reduced by Zn and AcOH to provide (21-51).

- 10 The BOC protecting group of (21-51) is removed to provide (21-19). The TIPS protecting group of

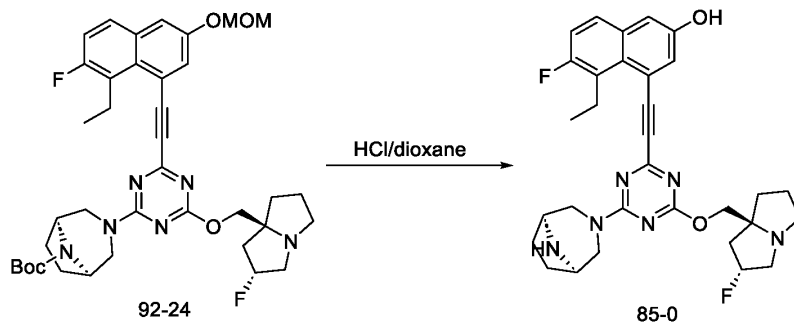


5

Scheme 7

The following scheme, Scheme 7, illustrates an exemplary way of preparing compounds in accordance with the present disclosure and examples.

The BOC protecting group of (92-24) is removed to provide (85-0).



Examples 2 - 45: Synthetic examples

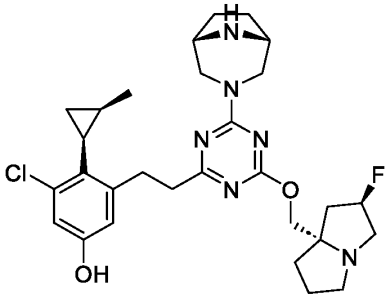
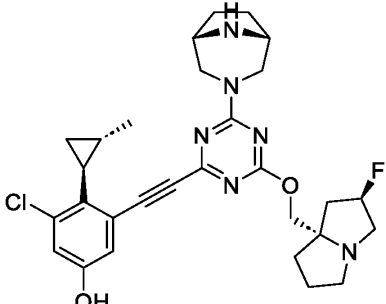
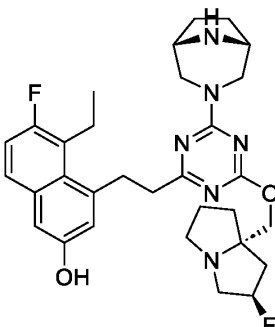
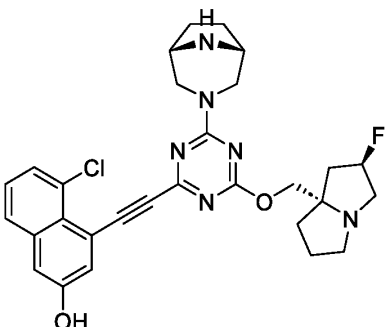
Examples 2 to 45 describe synthetic protocols which were employed in order to arrive at illustrative compounds disclosed herein. As would be understood by the skilled person, further compounds of the disclosure may be synthesized analogously.

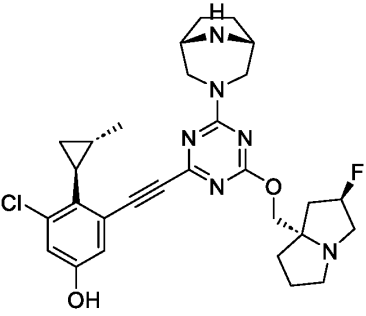
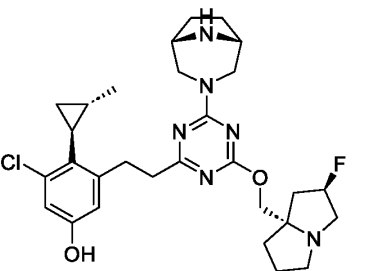
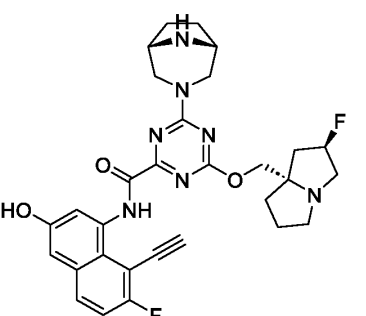
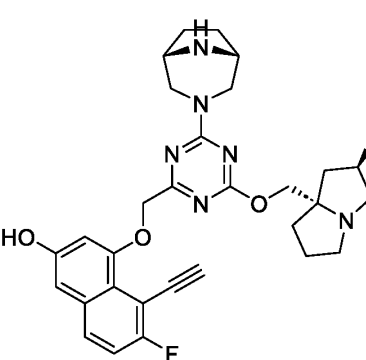
In the synthetic protocols which follow, R and S (or R* and S*) notation is employed to indicate the stereochemistry at particular chiral centres; thus, unless expressly stated otherwise, the use of the index R, R, R*, or R* in the specific examples below should not be understood as referring to a substituent group R or R* as defined in relation to the Markush formulae provided in the preceding disclosure.

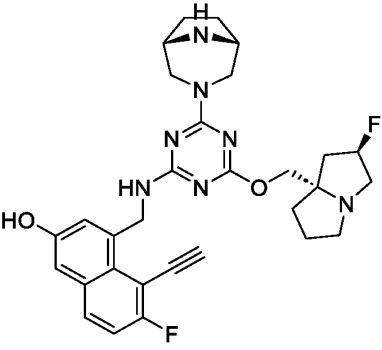
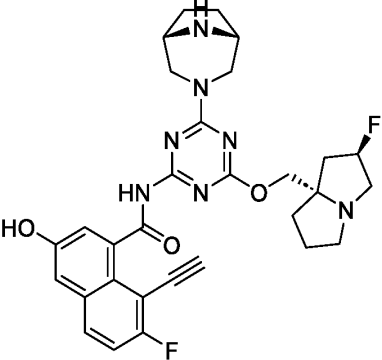
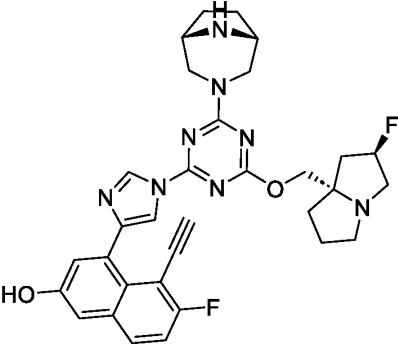
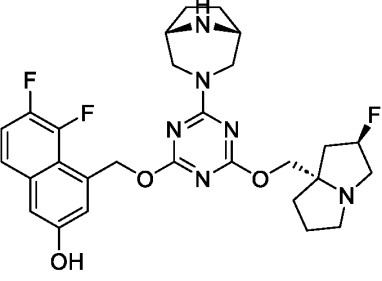
Table 2 below lists the compounds synthesized in the following synthetic examples, identified according to the relevant Example No. as well as (where appropriate) the compound numbers allocated to such compounds in Table 1:

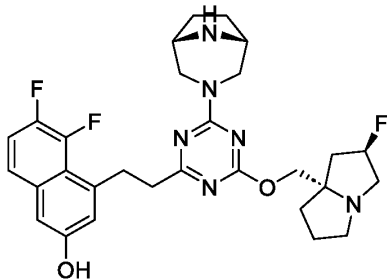
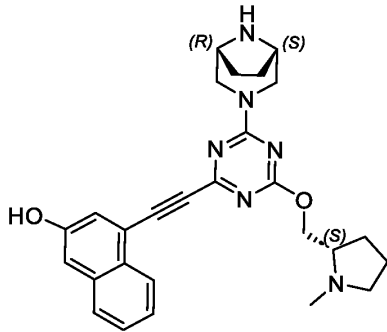
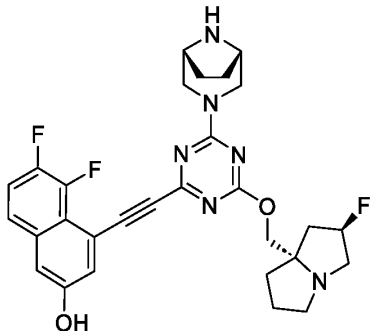
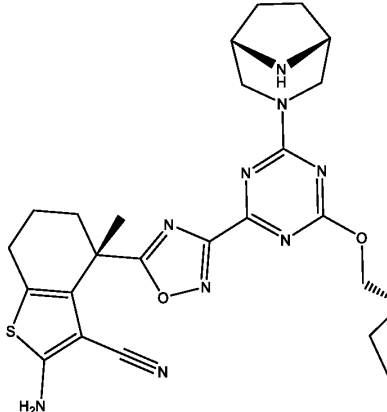
Table 2

Example	Compound No.	Structure
2	(19)	
3	(30)	
4	(2)	
5	(38)	

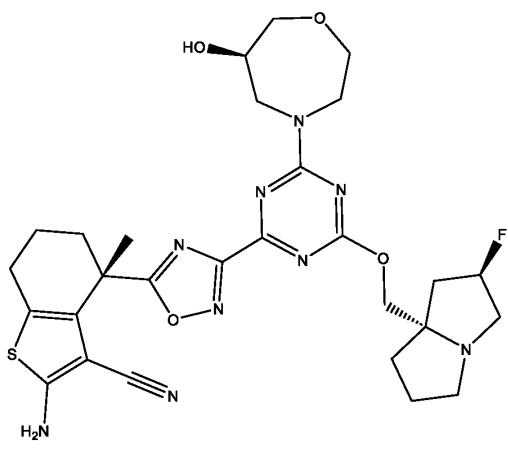
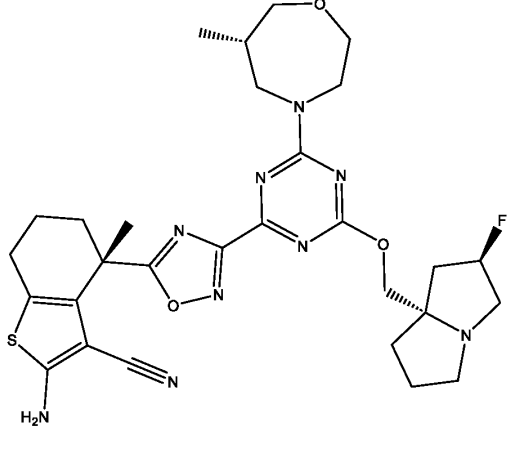
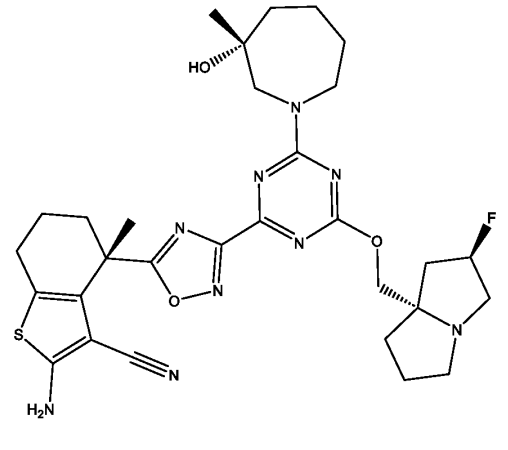
Example	Compound No.	Structure
6	(6)	
7	(7)	
8	(35)	
9	(4)	

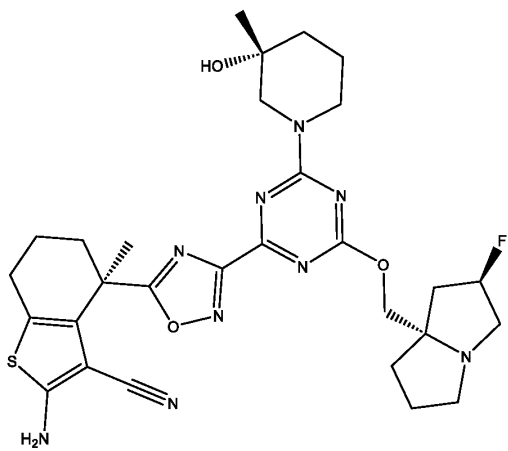
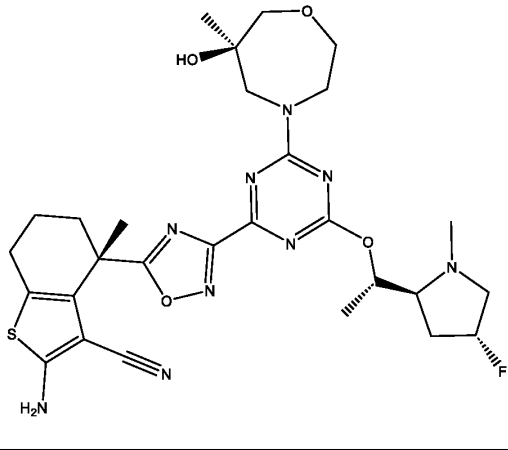
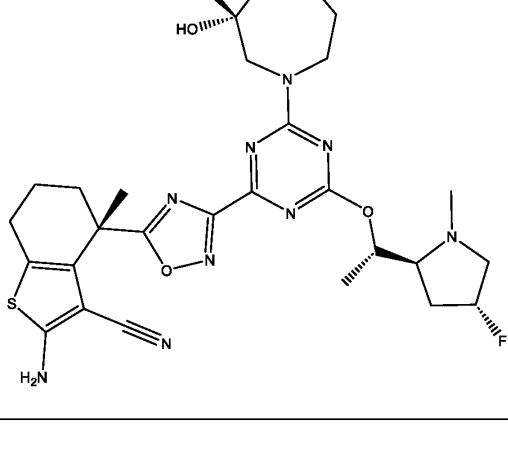
Example	Compound No.	Structure
10	(9)	
11	(5)	
12	(11)	
13	(14)	

Example	Compound No.	Structure
14	(12)	
15	(13)	
16	(10)	
17	(3)	

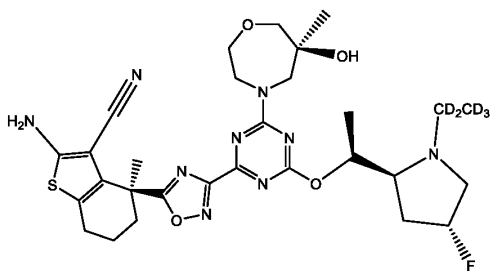
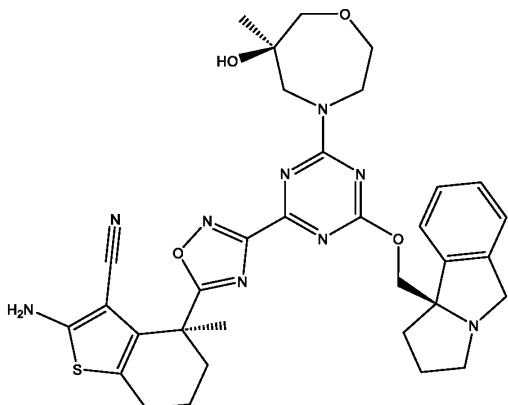
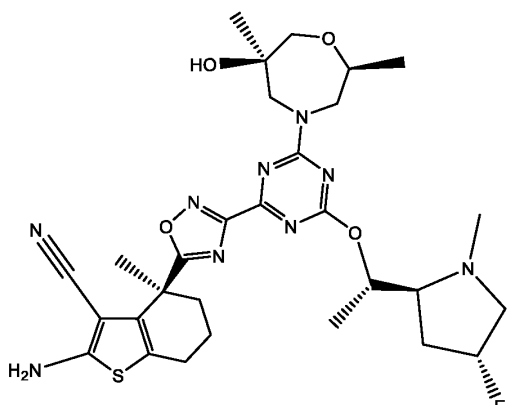
Example	Compound No.	Structure
18	(40)	
19	(8)	
20	(1)	
21	(55)	

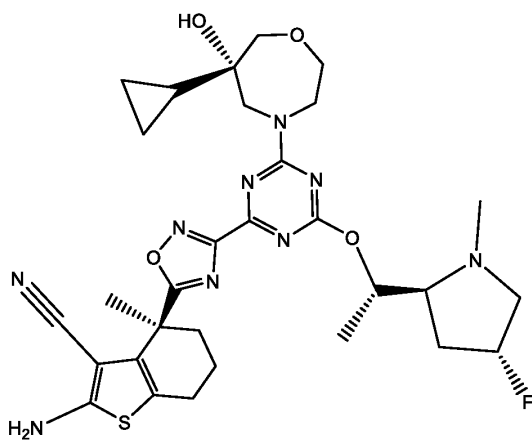
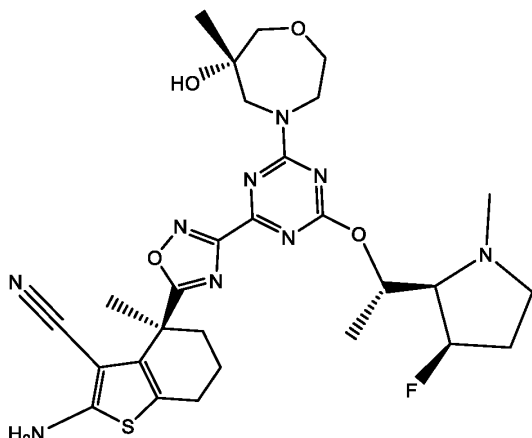
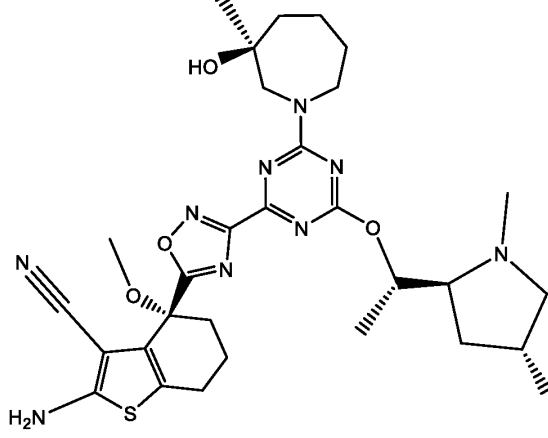
Example	Compound No.	Structure
22	(56)	
23	(89)	
23	(90)	

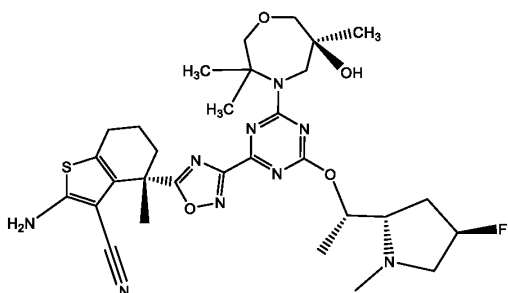
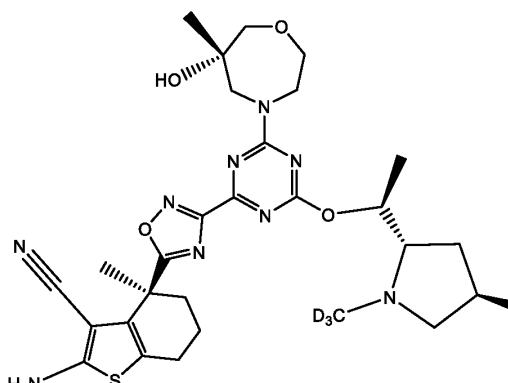
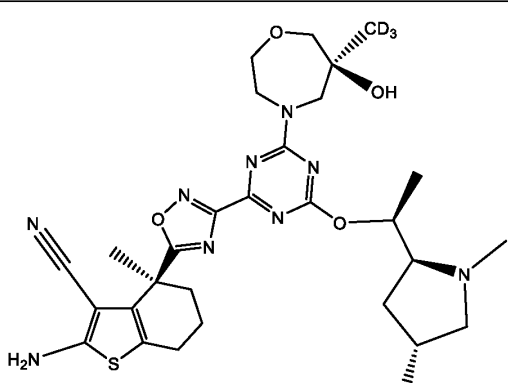
Example	Compound No.	Structure
24	(112)	
25	(113)	
26	(107)	

Example	Compound No.	Structure
27	(114)	
28	(115)	
28	(116)	

Example	Compound No.	Structure
29	(132a)	
30	(120)	
30	(106)	

Example	Compound No.	Structure
34	(136)	
35	(98)	
36	(137a)	

Example	Compound No.	Structure
37	(138a)	
38	(139a)	
39	(140a)	

Example	Compound No.	Structure
40	(141a)	
41	(143b)	
42	(142b)	

Example	Compound No.	Structure
43	(126)	
44	(119)	
45	(19)	

Experimental techniques

The following analytical techniques were employed in Examples 2-45 below, unless otherwise specified.

400 MHz Liquid-state NMR experiments were recorded on 400 MHz(9.4 Tesla) AVANCE NEO 400MHz (400 MHz for ^1H , 100 MHz for ^{13}C) using a 5mm PI HR-BBO400S1-BBF/H/D-5.0-Z SP probe (Bruker BioSpin AG, Switzerland).

300 MHz Liquid-state NMR experiments were recorded on 300 MHz(7.04 Tesla) AVANCE III HD 300MHz (300 MHz for ^1H , 75 MHz for ^{13}C) using a 5mm PABBO BB-1H/D Z-GRD probe (Bruker BioSpin AG, Switzerland).

All the experiments used for the resonance assignment procedure and the elucidation of the products structure ($1\text{D}^1\text{H}$, $2\text{D}^1\text{H}-^1\text{H}$ -COSY, $2\text{D}^1\text{H}-^1\text{H}$ -ROESY, $2\text{D}^1\text{H}-^{13}\text{C}$ -HSQC, $2\text{D}^1\text{H}-^{13}\text{C}$ -HMBC) were recorded at 300K. ^1H chemical shifts are reported in ppm as s (singlet), d (doublet), t (triplet), q (quartet), dd (double doublet), m (multiplet), or br s (broad singlet). Chemical shift values (δ) are indicated in parts per million (ppm) with reference to tetramethylsilane (TMS) as the internal standard.

LCMS chromatography analysis were recorded using the following apparatus: Agilent 1260 (UV: Acquity PDA MS: QDa, ELSD)

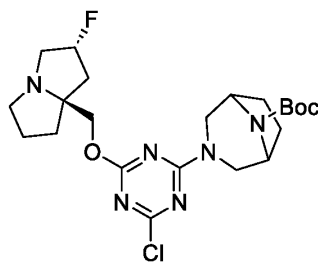
The apparatus was tested using a Ascentis Express C18 (100*4.6mm). All of them used a combination of the following eluents: Water/0.1%FA and Acetonitrile/0.1%FA and a positive electrospray ES+ as ionization mode, The UV detection was set up at 220 and 254 nm.

Temperatures are given in degrees Celsius ($^{\circ}\text{C}$). The reactants used in the examples below may be obtained from commercial sources or they may be prepared from commercially available starting materials as described herein or by methods known in the art. The progress of the reactions described herein were followed as appropriate by LC or TLC, and as the skilled person will readily realise, reaction times and temperatures may be adjusted accordingly.

Preparation of Intermediates

Intermediates were prepared for use in Examples 2-22 below according to the following methods.

Intermediate 1: *tert*-Butyl 3-(4-chloro-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

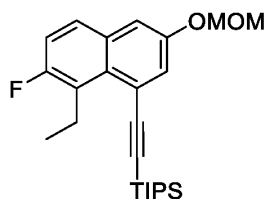


Step 1: To a stirred solution of cyanuric chloride (10.00 g, 54.2 mmol, 1.0 equiv) and DIEA (10.51 g, 81.3 mmol, 1.5 equiv) in DCM (250 mL) was added tert-butyl 3,8-diazabicyclo[3.2.1]octane-8-carboxylate (9.21 g, 43.4 mmol, 0.8 equiv) in portions at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 2h at 20 °C under nitrogen atmosphere. The resulting mixture was diluted with water (250 mL). The resulting mixture was extracted with DCM (3 x 250 mL). The combined organic layers were washed with brine (3x200 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to give a residue which was purified by silica gel column chromatography, eluting with PE/EtOAc (30:1) to afford tert-butyl (1R,5S)-3-(4,6-dichloro-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8 carboxylate (13.70 g, 63% yield) as a white solid.

Step 2: tert-Butyl 3-(4-chloro-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

To a stirred mixture of tert-butyl (1R,5S)-3-(4,6-dichloro-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8 carboxylate (5.00 g, 13.9 mmol, 1.0 equiv) and Cs₂CO₃ (27.13 g, 83.3 mmol, 3 equiv) in MeCN (200 mL) was added [(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methanol (6.63 g, 41.6 mmol, 1.5 equiv) in portions at 25 °C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 25 °C under nitrogen atmosphere. The resulting mixture was diluted with water (200 mL). The resulting mixture was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (3x200 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to give a residue which was purified by silica gel column chromatography, eluting with PE/EtOAc (5:1) to afford tert-butyl (1R,5S)-3-(4-([(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy)-6-chloro-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (5.30 g, 79% yield) as a white solid.

Intermediate 2: ((8-ethyl-7-fluoro-3-(methoxymethoxy) naphthalen-1-yl)ethynyl)triisopropylsilane



Step 1: 8-Ethyl-7-fluoro-3-(methoxymethoxy) naphthalen-1-ol

A solution of 2-[8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.00 g, 11.1 mmol, 1.0 equiv) and UHP (4.17 g, 44.4 mmol, 4.0 equiv) in MeOH (40 mL) was stirred for 6 h at 40 °C under nitrogen atmosphere. The resulting mixture was cooled down to room temperature and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (6:1) to afford 8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-ol (2.00 g, 74% yield) as a light yellow oil. ESI-MS m/z = 249.10 $[M-H]^-$; Calculated MW: 250.01

Step 2: 8-ethyl-7-fluoro-3-(methoxymethoxy) naphthalen-1-yl trifluoromethanesulfonate

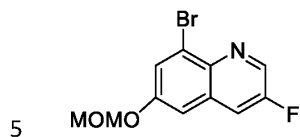
A mixture of 8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-ol (1.00 g, 3.99 mmol, 1.0 equiv), K_2CO_3 (1.10 g, 7.99 mmol, 2.0 equiv) and 1,1,1-trifluoro-N-phenyl-N-trifluoromethanesulfonylmethanesulfonamide (1.71g, 4.79mmol, 1.2equiv) in THF (10 mL) was stirred for 5h at 40°C under nitrogen atmosphere. The resulting mixture was cooled down to room temperature and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (10:1) to afford 8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl trifluoromethanesulfonate (1.50g, 98% yield) as a light yellow oil. ESI-MS m/z = 381.00 $[M-H]^-$; Calculated MW: 382.05

Step 3: ((8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)ethynyl)triisopropylsilane

A mixture of 8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl trifluoromethanesulfonate (1.00 g, 2.61 mmol, 1.0 equiv), CuI (50.0 mg, 0.26 mmol, 0.1 equiv), ethynyltriisopropylsilane (0.57 g, 3.13 mmol, 1.2 equiv) and $Pd(PPh_3)_2Cl_2$ (90.0 mg, 0.13 mmol, 0.05 equiv) in DMF (10 mL) was stirred for 5h at 80 °C under argon atmosphere. The resulting mixture was cooled down to room temperature and diluted with EtOAc. The resulting mixture was washed with brine and dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (8:1) to afford ((8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)ethynyl)triisopropylsilane (800.0 mg, 74% yield) as a light yellow oil.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.82 (dd, J = 9.0, 6.0 Hz, 1H), 7.61 (d, J = 2.7 Hz, 1H), 7.47 (d, J = 2.7 Hz, 1H), 7.42 (t, J = 9.3 Hz, 1H), 5.31 (s, 2H), 3.64 (qd, J = 7.3, 3.0 Hz, 2H), 3.42 (s, 3H), 1.26 (m, J = 7.3, 3.0 Hz, 3H), 1.2-1.11 (m, 21H).

Intermediate 3: 8-bromo-3-fluoro-6-(methoxymethoxy)quinoline



Step 1: 6, 8-Dibromo-3-fluoroquinolin-5-amine

To a stirred solution of 3-fluoroquinolin-5-amine (2.00 g, 12.3 mmol, 1.0 equiv) in DMF (30 mL) was added a solution of NBS (4.50 g, 25.2 mmol, 2.0 equiv) in DMF (10 mL) dropwise at -15 °C under nitrogen atmosphere. The resulting mixture was stirred for 1h at -15 °C under nitrogen atmosphere. The reaction was quenched by the addition of water at -15 °C. The precipitated solids were collected by filtration and washed with water. This resulted in 6, 8-dibromo-3-fluoroquinolin-5-amine (4.00 g, 95% yield) as a yellow solid.

10

ESI-MS *m/z* = 318.9 [M+H]⁺; Calculated MW: 317.9

Step 2: 5-Bromo-8-fluoro-[1,2,3]oxadiazolo[4,5-f]quinoline

To a mixture of 6,8-dibromo-3-fluoroquinolin-5-amine (4.00 g, 12.6 mmol, 1.0 equiv) and NaNO₂ (1.62 g, 23.4 mmol, 2.5 equiv) in CH₃COOH (50 mL) were added propanoic acid (50 mL) at 0 °C. The resulting mixture was stirred for 1 h at 0 °C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (1:1) to afford 5-bromo-8-fluoro-[1,2,3]oxadiazolo[4,5-f]quinoline (2.20 g, 64% yield) as a yellow solid.

ESI-MS m/z = 267.9 [M+H]⁺; Calculated MW: 266.9

Step 3: 8-Bromo-3-fluoroquinolin-6-ol

To a stirred solution of 5-bromo-8-fluoro-[1,2,3]oxadiazolo[4,5-f]quinoline (2.20 g, 8.20 mmol, 1.0 equiv) in EtOH (50 mL) and THF (50 mL) was added NaBH₄ (776.2 mg, 20.5 mmol, 2.5 equiv) at 0 °C. The resulting mixture was stirred for 1 h at 0 °C under nitrogen atmosphere. The resulting mixture was diluted with water at 0 °C. The mixture was acidified to pH 7 with 1M HCl (aq.). The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (1:1) to afford 8-bromo-3-fluoroquinolin-6-ol (1.23 g, 53.2% yield) as a brown solid.

ESI-MS m/z = 242.0 [M+H]⁺; Calculated MW: 241.0

¹H NMR (300 MHz, DMSO-d₆) δ 10.69 (s, 1H), 8.77 (d, J = 2.7 Hz, 1H), 8.14 (dd, J = 9.9, 2.8 Hz, 1H), 7.68 (d, J = 2.8 Hz, 1H), 7.22 (d, J = 2.5 Hz, 1H).

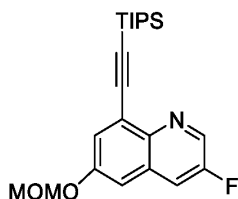
Step 4: 8-Bromo-3-fluoro-6-(methoxymethoxy)quinoline

To a stirred solution of 8-bromo-3-fluoroquinolin-6-ol (500.0 mg, 2.06 mmol, 1.0 equiv) and DIEA (533.9 mg, 4.13 mmol, 2.0 equiv) in DCM (10 mL) was added bromo(methoxy)methane (309.7 mg, 2.47 mmol, 1.2 equiv) dropwise at 0 °C under argon atmosphere. The resulting mixture was stirred for 2 h at room temperature under argon atmosphere. The reaction was diluted with water at 0 °C. The resulting mixture was extracted with DCM. The combined organic layers were dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EtOAc 2:1) to afford 8-bromo-3-fluoro-6-(methoxymethoxy)quinoline (433.0 mg, 73% yield) as a brown solid.

ESI-MS m/z = 286.0 [M+H]⁺; Calculated MW: 285.0

¹H NMR (400 MHz, Chloroform-d) δ 8.70 (d, J = 2.7 Hz, 1H), 7.71 (d, J = 2.6 Hz, 1H), 7.62 (dd, J = 8.8, 2.7 Hz, 1H), 7.23 (d, J = 2.6 Hz, 1H), 5.22 (s, 2H), 3.45 (s, 3H).

Intermediate 4: 3-Fluoro-6-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)quinolone



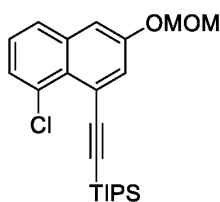
Step 1: 3-Fluoro-6-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)quinolone

Into a 40 mL vial were added 8-bromo-3-fluoro-6-(methoxymethoxy)quinoline (300.0 mg, 1.04 mmol, 1.0 equiv), ethynyltriisopropylsilane (1.34 g, 7.34 mmol, 7.0 equiv), CuI (39.9 mg, 0.21 mmol, 0.2 equiv), Pd(PPh₃)₂Cl₂ (73.6 mg, 0.10 mmol, 0.1 equiv), DIEA (406.5 mg, 3.14 mmol, 3.0 equiv) and DMF (15 mL) at room temperature. The resulting mixture was stirred for 2h at 100 °C under argon atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was filtered, and the filter cake was washed with EtOAc. The reaction was diluted with water at room temperature. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EtOAc 4:1) to afford 3-fluoro-6-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)quinolone (322.0 mg, 79% yield) as a black oil.

ESI-MS m/z = 388.2 [M+H]⁺; Calculated MW: 387.2

¹H NMR (400 MHz, Chloroform-d) δ 8.73 (d, J = 2.8 Hz, 1H), 7.67 – 7.56 (m, 2H), 7.28 (d, J = 2.7 Hz, 1H), 5.28 (s, 2H), 3.51 (s, 3H), 1.21-1.18 (m, 21H).

Intermediate 5: ((8-chloro-3-(methoxymethoxy)naphthalen-1-yl)ethynyl)triisopropylsilane



Step 1: 1-Bromo-8-chloro-3-(methoxymethoxy)naphthalene

To a stirred solution of 4-bromo-5-chloronaphthalen-2-ol (2.00 g, 7.76 mmol, 1.0 equiv) and DIEA (2.01 g, 15.5 mmol, 2.0 equiv) in DCM (20 mL) was added bromo(methoxy)methane (1.94 g, 15.5 mmol, 2.0 equiv) dropwise at 0 °C under argon atmosphere. The resulting mixture was stirred for 2h at room temperature under argon atmosphere. The reaction was quenched by the addition of water at 0°C. The resulting mixture was extracted with DCM. The combined organic layers were washed with brine and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under

reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE / EtOAc (4:1) to afford 1-bromo-8-chloro-3-(methoxymethoxy)naphthalene (2.16 g, 93% yield) as a reddish solid.

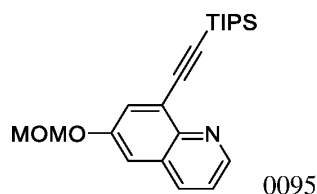
¹H NMR (300 MHz, Chloroform-d) δ 7.70 – 7.62 (m, 2H), 7.50 (dd, J = 7.5, 1.3 Hz, 1H), 7.37 (d, J = 2.6 Hz, 1H), 7.34 – 7.24 (m, 1H), 5.27 (s, 2H), 3.51 (s, 3H).

Step 2: ((8-Chloro-3-(methoxymethoxy)naphthalen-1-yl)ethynyl)triisopropylsilane

To a stirred mixture of 1-bromo-8-chloro-3-(methoxymethoxy)naphthalene (1.00 g, 3.31 mmol, 1.0 equiv), CuI (130.0 mg, 0.66 mmol, 0.2 equiv), Pd(PPh₃)₂Cl₂ (230.0 mg, 0.33 mmol, 0.1 equiv) and DIEA (1.29 g, 9.94 mmol, 3.0 equiv) in DMF (20 mL) was added ethynyltriisopropylsilane (3.02 g, 16.5 mmol, 5.0 equiv) at room temperature under argon atmosphere. The resulting mixture was stirred for 16h at 100 °C under argon atmosphere. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EtOAc 3:1) to afford ((8-chloro-3-(methoxymethoxy)naphthalen-1-yl)ethynyl)triisopropylsilane (1.30 g, 97% yield) as a black liquid.

¹H NMR (300 MHz, DMSO-d₆) δ 7.87 (dd, J = 8.1, 1.5 Hz, 1H), 7.63 (d, J = 2.6 Hz, 1H), 7.56 – 7.39 (m, 3H), 5.35 (s, 2H), 3.43 (s, 3H), 1.13 (d, J = 2.8 Hz, 21H).

Intermediate 6: 6-(Methoxymethoxy)-8-((triisopropylsilyl)ethynyl)quinoline



Step 1: 6, 8-Dibromoquinolin-5-amine

To a stirred solution of 5-aminoquinoline (5.00 g, 34.7 mmol, 1.0 equiv) in DMF (30 mL) was added NBS (12.34 g, 69.4 mmol, 2.0 equiv) (dissolved in 30 mL DMF) dropwise at -10 °C. The resulting mixture was stirred for 1h at -10 °C. The resulting mixture was diluted with water. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with water and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography and eluted with PE/EtOAc (3:1) to afford 6,8-dibromoquinolin-5-amine (9.00 g, 81%) as a brown solid. ESI-MS m/z = 300.8 [M+H]⁺; Calculated MW: 299.9.

¹H NMR (400 MHz, DMSO-d₆) δ 8.94 (dd, J = 4.2, 1.5 Hz, 1H), 8.74 (dd, J = 8.6, 1.6 Hz, 1H), 8.04 (s, 1H), 7.56 (dd, J = 8.6, 4.1 Hz, 1H), 6.35 (s, 2H).

Step 2: 5-Bromo-[1,2,3]oxadiazolo[4,5-f]quinoline

To a stirred mixture of 6,8-dibromoquinolin-5-amine (8.80 g, 29.1 mmol, 1.0 equiv) in AcOH (60 mL) and propanoic acid (20 mL) was added NaNO₂ (3.02 g, 43.7 mmol, 1.5 equiv) in portions at 0 °C. The resulting mixture was stirred for 1 h at 0 °C. The resulting mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (4:1) to afford 5-bromo-[1,2,3]oxadiazolo[4,5-f]quinoline (7.20 g, 96% yield) as a brown solid.

ESI-MS m/z = 249.8 [M+H]⁺; Calculated MW: 249.0

Step 3: 8-Bromoquinolin-6-ol

To a stirred mixture of 5-bromo-[1,2,3]oxadiazolo[4,5-f]quinoline (7.00 g, 27.9 mmol, 1.0 equiv) in EtOH (40 mL) and THF (40 mL) was added NaBH₄ (2.44 g, 64.5 mmol, 2.3 equiv) in portions at 0 °C. The resulting mixture was stirred for 4 h at 0 °C under nitrogen atmosphere. The resulting mixture was diluted with water. The mixture was neutralized to pH 7 with 1M HCl (aq.) and extracted with EtOAc. The combined organic layers were washed with brine. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 8-bromoquinolin-6-ol (6.20 g, 44% yield) as a brown solid. The crude product mixture was used in the next step directly without further purification. ESI-MS m/z = 223.8 [M+H]⁺; Calculated MW: 223.0

Step 4: 8-Bromo-6-(methoxymethoxy)quinoline

To a stirred mixture of 8-bromoquinolin-6-ol (6.10 g, 27.2 mmol, 1.0 equiv) and DIEA (7.04 g, 54.5 mmol, 2.0 equiv) in DCM (50 mL) was added methane, bromo(methoxy)methane (4.42 g, 35.4 mmol, 1.3 equiv) dropwise at 0 °C. The resulting mixture was stirred for 1.5 h at 25 °C under nitrogen atmosphere. The resulting mixture was quenched with water and extracted with DCM. The combined organic layers were concentrated under reduced pressure to afford 8-bromo-6-(methoxymethoxy)quinoline (3.20 g, 43% yield) as a brown oil. ESI-MS m/z = 205.0 [M+H]⁺; Calculated MW: 204.1.

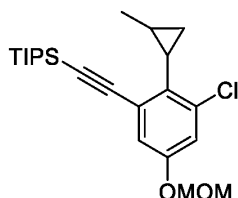
¹H NMR (400 MHz, DMSO-d₆) δ 8.88 (dd, J = 4.2, 1.6 Hz, 1H), 8.34 (dd, J = 8.4, 1.7 Hz, 1H), 7.91 (d, J = 2.6 Hz, 1H), 7.58 (m, 2H), 5.37 (s, 2H), 3.45 (s, 3H).

Step 5: 6-(Methoxymethoxy)-8-[2-(triisopropylsilyl)ethynyl]quinoline

To a stirred mixture of 8-bromo-6-(methoxymethoxy)quinoline (1.60 g, 5.9 mmol, 1.0 equiv) and ethynyltriisopropylsilane (5.44 g, 29.8 mmol, 5.0 equiv) in DMF (15 mL) were added DIEA (2.31 g, 17.9 mmol, 3.0 equiv), CuI (14.2 mg, 0.07 mmol, 0.2 equiv) and Pd(PPh₃)₂Cl₂ (418.9 mg, 0.59 mmol, 0.1 equiv). The resulting mixture was stirred for 2 h at 100 °C under nitrogen atmosphere. The resulting mixture was cooled down to room temperature, diluted with water (50 mL), and filtered. The filter cake was washed with EtOAc. The filtrate was extracted with EtOAc. The combined organic layers were washed with water and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE / EtOAc 5:1) to afford 6-(methoxymethoxy)-8-[2-(triisopropylsilyl)ethynyl]quinoline (1.60 g, 72% yield) as a green solid. ESI-MS m/z = 370.2 [M+H]⁺; Calculated MW: 369.2

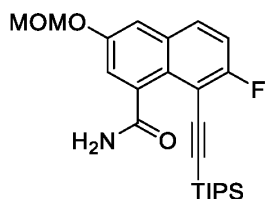
Intermediate 7:

((3-chloro-5-(methoxymethoxy)-2-(2-methylcyclopropyl)phenyl)ethynyl)triisopropylsilane

**Step 1: ((3-Chloro-5-(methoxymethoxy)-2-(2-methylcyclopropyl) phenyl)ethynyl)triisopropylsilane**

To a stirred mixture of 1-bromo-3-chloro-5-(methoxymethoxy)-2-(2-methylcyclopropyl)benzene (420.0 mg, 1.37 mmol, 1.0 equiv), DIPA (1.39 g, 13.7 mmol, 10 equiv) and ethynyltriisopropylsilane (300.7 mg, 1.64 mmol, 1.2 equiv) in DMF (10 mL) were added CuI (26.1 mg, 0.13 mmol, 0.1 equiv) and Pd(PPh₃)₂Cl₂ (48.2 mg, 0.06 mmol, 0.05 equiv) at 25 °C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 60 °C under nitrogen atmosphere. The mixture was allowed to cool down to 30 °C. The resulting mixture was diluted with water (10 mL) then extracted with EtOAc. The combined organic layers were washed with brine and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EtOAc 10:1) to afford {2-[3-chloro-5-(methoxymethoxy)-2-(2-methylcyclopropyl)phenyl]ethynyl}triisopropylsilane (459.1 mg, 78% yield) as a yellow solid. Calculated MW: 406.2. ¹HNMR (400 MHz, Chloroform-d) δ 6.97 (d, J = 3.2 Hz, 1H), 6.95 (d, J = 3.4 Hz, 1H), 5.04 (d, J = 3.2 Hz, 2H), 3.39 (s, J = 1.0 Hz, 3H), 1.44 – 1.38 (m, 1H), 1.25 – 1.14 (m, 6H), 1.11 – 1.01 (m, 21H).

Intermediate 8: 7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)-1-naphthamide



Step 1: 7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)-1-naphthoic acid

A mixture of 7-fluoro-3-(methoxymethoxy)-8-[2-(triisopropylsilyl)ethynyl]naphthalen-1-yl trifluoromethanesulfonate (5.00 g, 9.53 mmol, 1.0 equiv) and Et₃N (2.84 g, 28.05 mmol, 3.0 equiv) and butyl[(3R,5S,7s)-adamantan-1-yl][(1s,3R,5S,7s)-adamantan-1-yl]phosphane {2'-amino-[1,1'-biphenyl]-2-yl}palladiumylium methanesulfonate (3.41 g, 4.67 mmol, 0.5 equiv) in DMSO:H₂O(100ml:10ml) was stirred for 16h at 80 °C under carbon monoxide (20 atm) atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (200 mL). The resulting mixture was extracted with EtOAc (3 x 100mL). The combined organic layers were washed with brine (3x100 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.1% FA), 0% to 100% gradient in 30 min; detector, UV 254 nm to afford 7-fluoro-3-(methoxymethoxy)-8-[2-(triisopropylsilyl)ethynyl]naphthalene-1-carboxylic acid (1.50 g, 22%) as a brown oil.

ESI-MS m/z = 431.30 [M+H]⁺; Calculated MW: 430.20

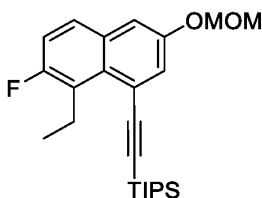
Step 2: 7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)-1-naphthamide

To a mixture of 7-fluoro-3-(methoxymethoxy)-8-[2-(triisopropylsilyl)ethynyl]naphthalene-1-carboxylic acid (1.50 g, 3.48 mmol, 1.0 equiv) and DMF (127.3 mg, 1.742 mmol, 0.5 equiv) in DCM was added (COCl)₂ (663.2 mg, 5.22 mmol, 1.5 equiv) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for additional 1h at 0 °C. The resulting mixture was concentrated under vacuum. To the above mixture was added THF (10 mL) at 0 °C, then added NH₃.H₂O (5 mL, 128.40 mmol, 36.8 equiv) at 0 °C. The resulting mixture was stirred for additional 1h at 0 °C. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.1% FA), 0% to 100% gradient in 30 min; detector, UV 254 nm to afford 7-fluoro-3-(methoxymethoxy)-8-[2-(triisopropylsilyl)ethynyl]naphthalene-1-carboxamide (540.0 mg, 34% yield) as a dark red solid. ESI-MS m/z = 430.17 [M+H]⁺; Calculated MW: 429.21

^1H NMR (400 MHz, DMSO- d_6) δ 8.03 – 7.92 (m, 2H), 7.58 (d, J = 2.6 Hz, 1H), 7.50 (t, J = 8.9 Hz, 1H), 7.23 (d, J = 2.6 Hz, 1H), 7.01 (s, 1H), 5.33 (s, 2H), 3.43 (s, 3H), 1.13 (d, J = 4.8 Hz, 21H).

Intermediate 9:

((8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)ethynyl)triisopropylsilane



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Step 1: 8-Ethyl-7-fluoro-3-(methoxymethoxy) naphthalen-1-ol

A solution of 2-[8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.00 g, 11.1 mmol, 1.0 equiv) and UHP (4.17 g, 44.4 mmol, 4.0 equiv) in MeOH (40 mL) was stirred for 6 h at 40 °C under nitrogen atmosphere. The resulting mixture was cooled down to room temperature and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc(6:1) to afford 8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-ol (2.00 g, 74% yield) as a light yellow oil. ESI-MS m/z = 249.10 $[\text{M-H}]^-$; Calculated MW: 250.10

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Step 2: 8-Ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl trifluoromethanesulfonate

A mixture of 8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-ol (1.00 g, 3.99 mmol, 1.0 equiv), K_2CO_3 (1.10 g, 7.99 mmol, 2.0 equiv) and 1,1,1-trifluoro-N-phenyl-N-trifluoromethanesulfonylmethanesulfonamide (1.71g, 4.79mmol, 1.2equiv) in THF (10 mL) was stirred for 5h at 40 °C under nitrogen atmosphere. The resulting mixture was cooled down to room temperature and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (10:1) to afford 8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl trifluoromethanesulfonate (1.50g, 98% yield) as a light yellow oil.

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ESI-MS m/z = 381.00 $[\text{M-H}]^-$; Calculated MW: 382.05

Step 3: ((8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)ethynyl)triisopropylsilane

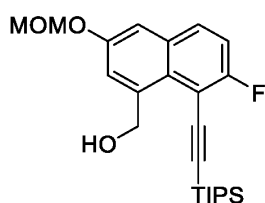
A mixture of 8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl trifluoromethanesulfonate (1.00 g, 2.61 mmol, 1.0 equiv), CuI (50.0 mg, 0.26 mmol, 0.1 equiv) and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (90.0 mg, 0.13 mmol, 0.05 equiv) in DMF (10 mL) was stirred for 5h at 80 °C under argon atmosphere. The resulting mixture was cooled down to room temperature and diluted with EtOAc. The resulting mixture was washed with brine and dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated

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under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (8:1) to afford ((8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)ethynyl)triisopropylsilane (800.0 mg, 74% yield) as a light yellow oil. Calculated MW: 414.24

¹H NMR (400 MHz, DMSO-d₆) δ 7.82 (dd, J = 9.0, 6.0 Hz, 1H), 7.61 (d, J = 2.7 Hz, 1H), 7.47 (d, J = 2.7 Hz, 1H), 7.42 (t, J = 9.3 Hz, 1H), 5.31 (s, 2H), 3.64 (qd, J = 7.3, 3.0 Hz, 2H), 3.42 (s, 3H), 1.26 (m, J = 7.3, 3.0 Hz, 3H), 1.2-1.11 (m, 21H).

Intermediate 10: (7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl) ethynyl)naphthalen-1-yl)methanol



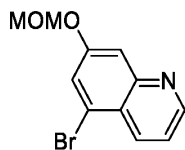
10 Step 1: 8-Ethyl-7-fluoro-3-(methoxymethoxy) naphthalen-1-ol

A solution of 2-[8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.00 g, 11.1 mmol, 1.0 equiv) and UHP (4.17 g, 44.4 mmol, 4.0 equiv) in MeOH (40 mL) was stirred for 6 h at 40 °C under argon atmosphere. The resulting mixture was cooled down to 20 °C and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, and eluted with PE/EtOAc (6:1) to afford 8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-ol (2.00 g, 74%) as a light yellow oil. ESI-MS m/z = 249.10 [M-H]⁻; Calculated MW: 250.01

Step 2: 8-ethyl-7-fluoro-3-(methoxymethoxy) naphthalen-1-yl trifluoromethanesulfonate

A mixture of 8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-ol (1.00 g, 3.99 mmol, 1.0 equiv), K₂CO₃ (1.10 g, 7.99 mmol, 2.0 equiv) and 1,1,1-trifluoro-N-phenyl-N-trifluoromethanesulfonylmethanesulfonamide (1.71g, 4.79mmol, 1.2equiv) in THF (10 mL) was stirred for 5h at 40 °C under argon atmosphere. The resulting mixture was cooled down to 20 °C and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (10:1) to afford 8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl trifluoromethanesulfonate (1.50g, 98%) as a light yellow oil. ESI-MS m/z = 381.00 [M-H]⁻; Calculated MW: 382.05

Intermediate 11: 5-bromo-7-(methoxymethoxy)quinoline

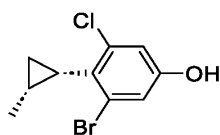


Step 1: To a stirred mixture of 5-bromo-7-methoxyquinoline (1.00 g, 4.20 mmol, 1.0 equiv) in toluene (10 mL) was added AlCl_3 (1.68 g, 12.6 mmol, 3.0 equiv) in portions at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 3 h at 100 °C under nitrogen atmosphere. The mixture was allowed to cool down to 20 °C. The reaction was quenched with water at 0 °C. The aqueous layer was extracted with $\text{CHCl}_3/i\text{-PrOH}$ (3/1). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure to afford 5-bromoquinolin-7-ol (600.0 mg, 64% yield) as an orange solid.

ESI-MS m/z = 224.0/226.0 $[\text{M}+\text{H}]^+$; Calculated MW: 223.1/225.1. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 10.58 (s, 1H), 8.81 (dd, J = 4.3, 1.6 Hz, 1H), 8.33 (ddd, J = 8.5, 1.7, 0.9 Hz, 1H), 7.54 (d, J = 2.3 Hz, 1H), 7.45 – 7.41 (m, 1H), 7.30 (dd, J = 2.3, 0.9 Hz, 1H).

Step 2: To a stirred mixture of 5-bromoquinolin-7-ol (440.0 mg, 4.46 mmol, 1.0 equiv) and DIEA (1.73 g, 13.4 mmol, 3.0 equiv) in DCM (20 mL) was added bromo(methoxy)methane (1.45 g, 11.6 mmol, 2.6 equiv) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 20 °C under nitrogen atmosphere. The reaction was poured into the ice/water and the resulting mixture was extracted with DCM (3 x 20 mL). The combined organic layers were washed with brine (2 x 20 mL) and dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure to give a residue which was purified by silica gel column chromatography, eluting with DCM/MeOH (100%~10:1). The pure fractions were concentrated to afford 5-bromo-7-(methoxymethoxy)quinolone (410.0 mg, 99.% yield) as a yellow solid. ESI-MS m/z = 268.0/270.0 $[\text{M}+\text{H}]^+$; Calculated MW: 267.1/269.1. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.91 (dd, J = 4.3, 1.6 Hz, 1H), 8.42 (ddd, J = 8.5, 1.6, 0.8 Hz, 1H), 7.76 (d, J = 2.4 Hz, 1H), 7.64 – 7.51 (m, 2H), 5.41 (s, 2H), 3.44 (s, 3H).

Intermediate 12: 1-bromo-3-chloro-5-(methoxymethoxy)-2-(2-methylcyclopropyl) benzene



Step 1: (3-bromo-5-chlorophenoxy)(tert-butyl)dimethylsilane

To a stirred mixture of 3-bromo-5-chlorophenol (20.00 g, 96.4 mmol, 1.0 equiv) and imidazole (32.82 g, 482.0 mmol, 5.0 equiv) in DCM (400 mL) was added TBSCl (21.80 g, 144.6 mmol, 1.5 equiv) in portions at 0 °C under argon atmosphere. The resulting mixture was stirred for 2h at 20 °C under argon atmosphere. The resulting mixture was diluted with water (400 mL). The resulting mixture was extracted with DCM (3 x 400 mL). The combined organic layers were washed with brine (2x300 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc(10:1) to afford 3-bromo-5-chlorophenoxy(tert-butyl)dimethylsilane (27.00 g, 87% yield) as a yellow oil.

10 Calculated MW: 320.0

Step 2: 2-bromo-6-chloro-4-hydroxybenzaldehyde

To a stirred solution of (3-bromo-5-chlorophenoxy) (tert-butyl) dimethylsilane (18.00 g, 55.9 mmol, 1.0 equiv) in THF (200 mL) was added LDA (56 mL, 111.9 mmol, 2.0 equiv, 2M in THF) dropwise at -78 °C under argon atmosphere. The resulting mixture was stirred for 1h at -65 °C under argon atmosphere. To the above mixture was added DMF (20.45 g, 279.8 mmol, 5.0 equiv) dropwise over 1 h at -78 °C. The resulting mixture was stirred for additional 2 h at -65 °C. The mixture was warmed up to 0 °C. The reaction was quenched by the addition of sat. NH₄Cl (aq.) (200 mL) at 0 °C. The resulting mixture was diluted with water (200 mL). The resulting mixture was extracted with EtOAc (3x300 mL). The combined organic layers were washed with brine (2x300 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The crude product 2-bromo-6-chloro-4-hydroxybenzaldehyde was used in the next step directly without further purification. ¹H NMR (400 MHz, CD₃OD-*d*₄) δ 10.2 (s, 1H), 7.10 (s, 1H), 6.92 (s, 1H).

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Step 3: 2-bromo-6-chloro-4-(methoxymethoxy)benzaldehyde

To a stirred mixture of 2-bromo-6-chloro-4-hydroxybenzaldehyde (22.00 g, 93.4 mmol, 1.0 equiv) and DIEA (36.23 g, 280.3 mmol, 3.0 equiv) in DCM was added MOM-Cl (12.42 g, 186.8 mmol, 2.0 equiv) dropwise at 0 °C under argon atmosphere. The resulting mixture was stirred for 2 h at 0 °C under argon atmosphere. The resulting mixture was diluted with water (300 mL). The resulting mixture was extracted with DCM (3 x 300 mL). The combined organic layers were washed with brine (2x300 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (10:1) to afford 2-bromo-6-chloro-4-(methoxymethoxy) benzaldehyde (18.00 g, 69% yield) as a brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.98 (s, 1H), 7.24 (s, 1H), 7.10 (s, 1H), 5.16 (s, 2H), 3.20 (s, 3H).

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Step 4: (Z/E)-1-bromo-3-chloro-5-(methoxymethoxy)-2-(prop-1-en-1-yl) benzene

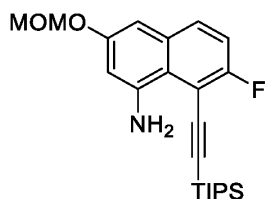
To a stirred mixture of ethyltriphenylphosphonium bromide (39.85 g, 107.3 mmol, 1.5 equiv) in THF (300 mL) at 0°C was added potassium tert-butoxide (107.3 mL, 107.3 mmol, 1.5 equiv, 1M in THF) under argon atmosphere. The resulting mixture was stirred for 1 h at 0 °C under argon atmosphere.

- 5 To the above mixture was added 2-bromo-6-chloro-4-(methoxymethoxy) benzaldehyde (20.00 g, 71.5 mmol, 1.0 equiv) in THF (100 mL) dropwise over 30min at 0 °C. The resulting mixture was stirred for additional 1h at 20 °C. The resulting mixture was diluted with water (400 mL). The resulting mixture was extracted with EtOAc (3 x 400 mL). The combined organic layers were washed with brine (2x300 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was
- 10 concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE / EtOAc (6:1) to afford (Z/E)-1-bromo-3-chloro-5-(methoxymethoxy)-2-(prop-1-en-1-yl) benzene (15.00 g, 72% yield) as a colorless oil. Calculated MW: 290.0

Step 5: 1-bromo-3-chloro-5-(methoxymethoxy)-2-(2-methylcyclopropyl) benzene

- To a stirred mixture of diethylzinc (21.18 g, 171.4 mmol, 10 equiv) and TFA (19.55 g, 171.4 mmol, 10 equiv) in DCM (200 mL) at -40 °C under argon atmosphere. The resulting mixture was stirred for
- 15 1h at -40 °C under argon atmosphere. To the above mixture was added diiodomethane (45.93 g, 171.4 mmol, 10 equiv) dropwise over 10 min at -40 °C. The resulting mixture was stirred for additional 1h at -40°C. To the above mixture was added (E/Z)-1-bromo-3-chloro-5-(methoxymethoxy)-2-(prop-1-en-1-yl)benzene (5.00 g, 17.1 mmol, 1.0 equiv) dropwise over 10 min at -40°C. The resulting mixture
- 20 was stirred for additional 20 h at 20°C. The mixture was allowed to cool down to 0°C. The resulting mixture was diluted with water (200 mL). The resulting mixture was extracted with DCM (3 x 300 mL). The combined organic layers were washed with brine (2x300 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was
- 25 purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.1% FA), 10% to 100% gradient in 2 h; detector, UV 254 nm to afford 1-bromo-3-chloro-5-(methoxymethoxy)-2-(2-methylcyclopropyl)benzene (1.00 g, 19% yield) as a colorless oil. Calculated MW: 304. ¹H NMR (400 MHz, CDCl₃) δ 7.25 (s, 1H), 7.01 (s, 1H), 5.11 (s, 2H), 3.50 (s, 3H), 1.37-1.31 (m, 1H), 1.28-1.25 (m, 3H), 1.04-1.01 (m, 1H), 0.98-0.86 (m, 2H).

Intermediate 13: 7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-amine



Step 1: *N*-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-1,1-diphenylmethanimine

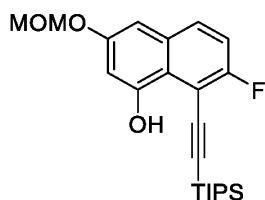
- 5 To a stirred mixture of 7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl trifluoromethanesulfonate (6.00 g, 11.0 mmol, 1.0 equiv), Pd₂(dba)₃CHCl₃ (1.16 g, 1.10 mmol, 0.1 equiv) and Cs₂CO₃ (7.31 g, 22.4 mmol, 2.0 equiv) was added diphenylmethanimine (4.06 g, 22.4 mmol, 2.0 equiv) in toluene (100 mL) at room temperature under argon atmosphere. The resulting mixture was stirred for 2 h at 110 °C under argon atmosphere. The resulting mixture was cooled down
- 10 to room temperature. The resulting mixture was filtered, and the filter cake was washed with DCM (3x100 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (5:1) to afford *N*-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-1,1-diphenylmethanimine (3.55 g, 56% yield) as a black oil.
- 15 ESI-MS *m/z* = 566.3 [M+H]⁺; Calculated MW: 565.3

Step 2: 7-Fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-amine

- To a stirred mixture of *N*-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-1,1-diphenylmethanimine (3.55 g, 6.27 mmol, 1.0 equiv) in THF (20 mL) was added HCl (4 mL, 1 M) dropwise at room temperature under air atmosphere. The resulting mixture was stirred for 30 min
- 20 at room temperature under air atmosphere. The resulting mixture was concentrated under vacuum. The crude product was purified by reverse phase flash with the following conditions (Column: Xselect CSH Prep C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH₄HCO₃), Mobile Phase B: MeCN; Flow rate: 70 mL/min; Gradient: 60% B to 100% B in 30 min, 100% B; wavelength: 220/254 nm; RT1(min): 10.88; to afford 7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-amine (1.65 g, 66% yield) as a black oil.
- 25

ESI-MS *m/z* = 402.2 [M+H]⁺; Calculated MW: 401.2. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.75 (dd, *J* = 9.2, 6.1 Hz, 1H), 7.32 (t, *J* = 8.9 Hz, 1H), 6.77 (d, *J* = 2.5 Hz, 1H), 6.56 (s, 2H), 6.53 (d, *J* = 2.4 Hz, 1H), 5.23 (s, 2H), 3.42 (s, 3H), 1.12 (d, *J* = 3.9 Hz, 21H).

Intermediate 14: 7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-ol



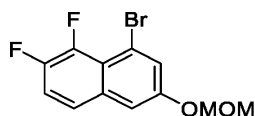
Step 1: 7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalene-1,3-diol

To a mixture of 7-fluoronaphthalene-1,3-diol (20.00 g, 112.3 mmol, 1.0 equiv), [RuCl₂(Binap)₂]Dichloro[(R)-(+)-2,2-bis(diphenylphosphino)-1,1-binaphthyl]ruthenium (II) (8.92 g, 11.2 mmol, 0.1 equiv) and AcOK (22.03 g, 224.5 mmol, 2.0 equiv) in toluene were added (2-bromoethynyl)triisopropylsilane (29.33 g, 112.2 mmol, 1.0 equiv) at 0 °C. The resulting mixture was stirred for additional 2 h at 110 °C. The mixture was allowed to cool down to 20 °C. The resulting mixture was filtered with diatomite, the filter cake was washed with EtOAc (3x300 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc to afford 7-fluoro-8-[2-(triisopropylsilyl)ethynyl]naphthalene-1,3-diol (40.00 g, 91% yield) as a dark yellow oil. ESI-MS m/z = 359.2 [M+H]⁺; Calculated MW: 358.2

Step 2: 7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl) naphthalen-1-ol

To a stirred mixture of 7-fluoro-8-[2-(triisopropylsilyl)ethynyl]naphthalene-1,3-diol (50.00 g, 139.4 mmol, 1.0 equiv) and DIEA (54.07 g, 418.3 mmol, 3.0 equiv) in DCM (500 mL) was added bromomethoxy-methane (26.14 g, 209.2 mmol, 1.5 equiv) dropwise at 0 °C under argon atmosphere. The resulting mixture was stirred for 1h at 20 °C under argon atmosphere. The resulting mixture was diluted with water (500 mL). The resulting mixture was extracted with DCM (3 x 500 mL). The combined organic layers were washed with brine (2x500 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc to afford 7-fluoro-3-(methoxymethoxy)-8-[2-(triisopropylsilyl)ethynyl]naphthalen-1-ol (30.00 g, 54% yield) as a brown oil. ESI-MS m/z = 403.0 [M+H]⁺; Calculated MW: 402.0

Intermediate 15: 8-bromo-1,2-difluoro-6-(methoxymethoxy)naphthalene



Step 1: (3E)-4-(2,3-difluorophenyl)but-3-enoic acid

To a stirred mixture of 2,3-difluorobenzaldehyde (50.00 g, 351.8 mmol, 1.0 equiv) and 3-(bromotriphenyl-lambda-5-phosphanyl) propanoic acid (160.70 g, 387.0 mmol, 1.1 equiv) in THF (500 mL) was added t-BuOK (703.7 mL, 703.7 mmol, 2.0 equiv, 1M in THF) dropwise at -70 °C under nitrogen atmosphere. The resulting mixture was stirred for 1h at -70 °C under nitrogen atmosphere. The mixture was warmed up to 20 °C and stirred for 1 h at 20 °C under nitrogen atmosphere. The resulting mixture was diluted with water (500 mL) and concentrated under reduced pressure. The resulting mixture was filtered and the filtrate was acidified to pH 2 with HCl (1M aq.). The resulting mixture was extracted with EtOAc (3 x 500 mL). The combined organic layers were washed with water (500x2 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (10:1-2:1), and the pure fraction was concentrated under reduced pressure to afford (3E)-4-(2,3-difluorophenyl)but-3-enoic acid (52.00 g, 75% yield) as a yellow oil. ¹H NMR (400 MHz, Chloroform) δ 7.10 – 6.98 (m, 3H), 6.44 (d, *J* = 11.5, 1.7 Hz, 1H), 5.82 (td, *J* = 11.6, 7.2 Hz, 1H), 2.43 (dd, *J* = 7.3 Hz, 2H).

Step 2: 4-(2,3-Difluorophenyl) butanoic acid

To a stirred solution of (3E)-4-(2,3-difluorophenyl)but-3-enoic acid (52.00 g, 262.4 mmol, 1.0 equiv) in EtOAc (1.5 L) was added 10% Pd/C (11.17g, 104.9 mmol, 0.4 equiv) at 20 °C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 20 °C under hydrogen atmosphere. The resulting mixture was filtered, and the filter cake was washed with EtOAc (3 x 200 mL). The filtrate was concentrated under reduced pressure to afford 4-(2,3-difluorophenyl) butanoic acid (50.00 g, 95% yield) as a colorless oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.32 – 7.08 (m, 3H), 2.74 – 2.63 (m, 2H), 2.25 (t, *J* = 7.3 Hz, 2H), 1.81 (m, 2H).

Steps 3-4: 5,6-Difluoro-3,4-dihydro-2H-naphthalen-1-one

To a stirred solution of 4-(2,3-difluorophenyl)butanoic acid (50.00 g, 249.7 mmol, 1.0 equiv) and DMF (912.8 mg, 12.4 mmol, 0.05 equiv) in DCM (1 L) was added oxalyl chloride (63.40 g, 499.5 mmol, 2.0 equiv) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 0.5 h at 20 °C under nitrogen atmosphere. The resulting mixture was concentrated under vacuum to afford the residue (50.00 g, yellow solid). To a stirred solution of the residue (50.00 g, yellow solid) in DCM (1 L) was added AlCl₃ (50.31 g, 377.3 mmol, 1.5 equiv) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 40 °C under nitrogen atmosphere. The reaction was quenched by the addition of water/ice (1 L) at 0 °C. The resulting mixture was extracted with DCM (3 x 500 mL). The combined organic layers were washed with brine (3 x 500 mL) and dried over anhydrous Na₂SO₄.

After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (100:1~2:1), and the pure fraction was concentrated under reduced pressure to afford 5,6-difluoro-3,4-dihydro-2H-naphthalen-1-one (43.00 g, 95% yield two steps) as a yellow oil. ESI-MS m/z = 183.1 $[M+H]^+$; Calculated MW: 182.0

5 Steps 5-6: 3-Ethyl-7-(hydroxymethyl)-1,5-naphthyridin-2(1H)-one

To a stirred solution of 5,6-difluoro-3,4-dihydro-2H-naphthalen-1-one (41.00 g, 225.0 mmol, 1.0 equiv) and HBr/AcOH (2.0 mL, 22.5 mmol, 0.1 equiv, 33%) in AcOH (900 mL) was added Br₂ (11.5 mL, 225.0 mmol, 1.0 equiv) in AcOH (50 mL) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 20 °C under nitrogen atmosphere. The resulting mixture was diluted with DCM (500 mL). The resulting mixture was washed with water (3 x 500 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to afford the residue. To a stirred solution of the residue in DMF (1 L) was added LiBr (23.75 g, 273.4 mmol, 1.7 equiv) and Li₂CO₃ (20.21 g, 273.5 mmol, 1.7 equiv) at 20 °C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 160 °C under nitrogen atmosphere. The mixture was allowed to cool down to 20 °C. The resulting mixture was diluted with EtOAc (2 L). The resulting mixture was washed with water (3 x 1 L). The combined organic layers were washed with brine (3 x 1 L) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (100:1~10:1) and the pure fraction was concentrated under reduced pressure to afford 5,6-difluoronaphthalen-1-ol (26.00 g, 64% yield two steps) as a brown solid. ESI-MS m/z = 179.1 $[M-H]^-$; Calculated MW: 180.0.

¹H NMR (400 MHz, DMSO-*d*₆) δ 10.59 (s, 1H), 8.06 – 7.95 (m, 1H), 7.54 – 7.41 (m, 3H), 7.01 – 6.91 (m, 1H).

Step 7: 5,6-Difluoronaphthalen-1-yl trifluoromethanesulfonate

To a stirred mixture of 5,6-difluoronaphthalen-1-ol (26.00 g, 144.3 mmol, 1.0 equiv) in DCM (300 mL) was added DIEA (46.63 g, 360.8 mmol, 2.5 equiv) and Tf₂O (52.93 g, 187.6 mmol, 1.3 equiv) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 20 °C under nitrogen atmosphere. The resulting mixture was diluted with water (200 mL). The resulting mixture was extracted with DCM (3 x 200 mL). The combined organic layers were washed with brine (3 x 200 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (20:1~5:1) and the pure fraction was concentrated under reduced pressure to afford 5,6-difluoronaphthalen-1-yl trifluoromethanesulfonate (36.00 g, 80% yield) as a yellow oil.

ESI-MS $m/z = 310.9$ $[M-H]^-$; Calculated MW: 311.9. 1H NMR (400 MHz, DMSO- d_6) δ 8.20 (d, $J = 7.3$ Hz, 1H), 8.01 – 7.70 (m, 4H).

Step 8: *N*-(5,6-difluoronaphthalen-1-yl)-1,1-diphenylmethanimine

To a stirred mixture of 5, 6-difluoronaphthalen-1-yl trifluoromethanesulfonate (36.00 g, 115.3 mmol, 1.0 equiv) and α -phenyl-benzenemethanimine (62.69 g, 345.9 mmol, 3.0 equiv) in toluene (500 mL) were added $Pd_2(dba)_3$ (10.56 g, 11.5 mmol, 0.1 equiv), XantPhos (13.34 g, 23.1 mmol, 0.2 equiv) and Cs_2CO_3 (112.71 g, 345.9 mmol, 3.0 equiv) at 20 °C under nitrogen atmosphere. The resulting mixture was stirred for 12 h at 90 °C under nitrogen atmosphere. The mixture was allowed to cool down to 20 °C. The resulting mixture was diluted with water (500 mL). The resulting mixture was extracted with EtOAc (3 x 500 mL). The combined organic layers were washed with brine (3 x 500 mL) and dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (100:1~5:1), and the pure fraction was concentrated under reduced pressure to afford *N*-(5,6-difluoronaphthalen-1-yl)-1,1-diphenylmethanimine (34.00 g, 86% yield) as a yellow solid. ESI-MS $m/z = 344.0$ $[M+H]^+$; Calculated MW: 343.1

Step 9: 5,6-Difluoronaphthalen-1-amine

A solution of *N*-(5,6-difluoronaphthalen-1-yl)-1,1-diphenylmethanimine (34.00 g, 99.0 mmol, 1.0 equiv) in 4 M HCl(g) in MeOH (500 mL) was stirred for 4 h at 10 °C under air atmosphere. The resulting mixture was concentrated under vacuum. The residue was neutralized to pH 8 with saturated $NaHCO_3$ (aq.). The resulting mixture was extracted with EtOAc (3 x 500 mL). The combined organic layers were washed with brine (3 x 500 mL) and dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (50:1~3:1), and the pure fraction was concentrated under reduced pressure to afford 5,6-difluoronaphthalen-1-amine (16.00 g, 90% yield) as a yellow solid. ESI-MS $m/z = 180.0$ $[M+H]^+$; Calculated MW: 179.0

Step 10: 2,4-Dibromo-5,6-difluoronaphthalen-1-amine

To a stirred solution of 5,6-difluoronaphthalen-1-amine (16.00 g, 89.3 mmol, 1.0 equiv) in AcOH (550 mL) was added a solution of Br_2 (31.11 g, 194.7 mmol, 2.2 equiv) in AcOH (550 mL) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 70 °C under nitrogen atmosphere. The mixture was allowed to cool down to 20 °C. The precipitated solids were collected by filtration and washed with AcOH (550 mL). The residue was diluted with 15% aqueous of NaOH (200 mL). The resulting mixture was stirred for 20 min at 20 °C under air atmosphere. The precipitated

solids were collected by filtration and washed with water (3 x 100 mL). The resulting mixture was concentrated under vacuum to afford 2,4-dibromo-5,6-difluoronaphthalen-1-amine (25.00 g, 83% yield) as an off-white solid. ESI-MS $m/z = 337.9$ $[M+H]^+$; Calculated MW: 336.9

Step 11: 5-Bromo-6,7-difluoronaphtho[1,2-d][1,2,3]oxadiazol

- 5 To a stirred solution of 2,4-dibromo-5,6-difluoronaphthalen-1-amine (25.00 g, 74.1 mmol, 1.0 equiv) in AcOH (450 mL) was added propanoic acid (41.66 g, 562.3 mmol, 7.5 equiv) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 0.5 h at 0 °C under nitrogen atmosphere. To the above mixture was added NaNO₂ (7.68 g, 111.3 mmol, 1.5 equiv) at 0 °C. The resulting mixture was stirred for additional 1 h at 20 °C. The precipitated solids were collected by filtration and washed
- 10 with water (3 x 200 mL). The residue was concentrated under vacuum to afford 5-bromo-6,7-difluoronaphtho[1,2-d][1,2,3]oxadiazole (17.40 g, 82% yield) as a yellow solid. ESI-MS $m/z = 284.9$ $[M+H]^+$; Calculated MW: 283.9

Step 12: 4-Bromo-5,6-difluoronaphthalen-2-ol

- To a stirred solution of 5-bromo-6,7-difluoronaphtho[1,2-d][1,2,3]oxadiazole (17.40 g, 61.0 mmol, 1.0 equiv) in THF (70 mL) and EtOH (210 mL) was added NaBH₄ (5.38 g, 142.2 mmol, 2.3 equiv) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 0.5 h at 0 °C under nitrogen atmosphere. The reaction was quenched by the addition of water (70 mL) at 20 °C. The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (2 x 100 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under
- 20 reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (20:1~3:1), and the pure fraction was concentrated under reduced pressure to afford 4-bromo-5,6-difluoronaphthalen-2-ol (8.90 g, 56% yield) as a yellow solid. ESI-MS $m/z = 256.9$ $[M+H]^+$; Calculated MW: 257.9

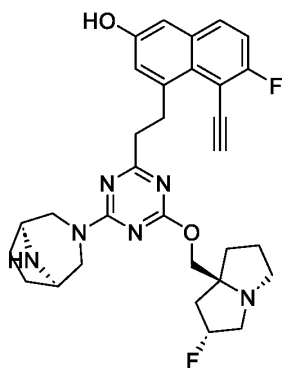
Step 13: 8-Bromo-1,2-difluoro-6-(methoxymethoxy)naphthalene

- 25 To a stirred solution of 4-bromo-5,6-difluoronaphthalen-2-ol (8.90 g, 34.3 mmol, 1.0 equiv) and DIEA (11.10 g, 85.8 mmol, 2.5 equiv) in DCM (100 mL) was added bromomethoxy-methane (7.56 g, 60.4 mmol, 1.7 equiv) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 0.5 h at 0 °C under nitrogen atmosphere. The resulting mixture was diluted with water (100 mL). The resulting mixture was extracted with DCM (3 x 100 mL). The combined organic layers were washed
- 30 with brine (2 x 100 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (20:1-5:1). The pure fraction was concentrated under reduced pressure to

afford 8-bromo-1,2-difluoro-6-(methoxymethoxy)naphthalene (8.90 g, 85% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.89 – 7.56 (m, 4H), 5.36 (s, 2H), 3.45 (s, 3H).

Preparation of Compounds

Example 2: 4-(2-(4-(((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)ethyl)-5-ethynyl-6-fluoronaphthalen-2-ol



Step 1: tert-butyl 3-(4,6-dichloro-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

To a stirred solution of 2,4,6-trichloro-1,3,5-triazine (5.00 g, 27.1 mmol, 1.0 equiv) in DCM (50 mL) was added DIEA (3.50 g, 27.1 mmol, 1.0 equiv) and tert-butyl 3,8-diazabicyclo[3.2.1]octane-8-carboxylate (5.76 g, 27.1 mmol, 1.0 equiv) at 0 °C. The resulting mixture was warmed to room temperature and stirred for 2h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc (100mL) and washed with water (50mL). The resulting mixture was concentrated under vacuum to afford tert-butyl 3-(4,6-dichloro-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (8.00 g, 82% yield) as an off-white solid. ESI-MS *m/z* = 360.15 [M+H]⁺; Calculated MW: 359.09.

Step 2: tert-butyl 3-(4-chloro-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

To a stirred solution of tert-butyl 3-(4,6-dichloro-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (8.00 g, 22.2 mmol, 1.0 equiv), ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (3.54 g, 22.2 mmol, 1.0 equiv), DCM (60 mL) and DIEA (2.87 g, 22.2 mmol, 1.0 equiv). The resulting mixture was stirred 16h at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluting with DCM:MeOH (10:1) to afford tert-butyl 3-(4-chloro-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (10.00 g, 93% yield) as a white solid. ESI-MS *m/z* = 483.45 [M+H]⁺; Calculated MW: 482.22.

¹H NMR (300 MHz, Chloroform-d) δ 5.41 – 5.13 (m, 1H), 4.53 – 4.41 (m, 2H), 4.41 – 4.20 (m, 2H), 4.20 – 4.02 (m, 2H), 3.23 (dd, J = 29.3, 13.5 Hz, 5H), 3.04 – 2.90 (m, 1H), 2.35 – 2.03 (m, 3H), 1.92 (d, J = 17.3 Hz, 5H), 1.73 – 1.56 (m, 2H), 1.50 (s, 9H).

- 5 Step 3: *tert*-butyl 3-(4-((*E*)-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)vinyl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

To a stirred solution of *tert*-butyl 3-(4-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-6-vinyl-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (2.20 g, 4.63 mmol, 1.0 equiv), 7-fluoro-3-(methoxymethoxy)-8-[2-(triisopropylsilyl)ethynyl]naphthalen-1-yl trifluoromethanesulfonate (2.48 g, 4.63 mmol, 1.0 equiv), Pd₂(dba)₃ (850.0 mg, 0.93 mmol, 0.2 equiv), P(*p*-Tol)₃ (710.0 mg, 2.32 mmol, 0.5 equiv), DIEA (3.00 g, 23.2 mmol, 5.0 equiv), HCOOH (320.0 mg, 6.95 mmol, 1.5 equiv), TBAB (2.24 g, 6.95 mmol, 1.5 equiv) and DMF (15 mL). The resulting mixture was stirred for 1.5h at 120 °C under nitrogen atmosphere. The mixture was allowed to cool
15 down to room temperature. The resulting mixture was added water (50mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (100mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EtOAc = 1:2) to afford *tert*-butyl 3-(4-((*E*)-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)vinyl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.3 g, 33%
20 yield) as a yellow solid. ESI-MS m/z = 859.45 [M+H]⁺; Calculated MW: 858.47.

Step 4: *tert*-butyl 3-(4-(2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)ethyl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

25 To a stirred solution of *tert*-butyl 3-(4-((*E*)-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)vinyl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.30 g, 1.51 mmol, 1.0 equiv), Zn (990.0 mg, 15.1 mmol, 10 equiv) and AcOH (15 mL). The resulting mixture was stirred for 1 h at 80 °C under nitrogen atmosphere. The mixture was allowed to cool down to room
30 temperature. The resulting mixture was filtered and the filter cake was washed with EtOAc (3x10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 10:1) to afford *tert*-butyl 3-(4-(2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)ethyl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-

7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.00 g, 76% yield) as a yellow oil.

ESI-MS m/z = 861.35 $[M+H]^+$; Calculated MW: 860.48.

Step 5: 4-(2-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)ethyl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol

Into a 40 mL vial were added tert-butyl 3-(4-(2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)ethyl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.00 g, 1.16 mmol, 1.0 equiv), dioxane (2 mL) and HCl(gas) in dioxane (6 mL) dropwise. The resulting mixture was stirred for 1 h at 25 °C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure to afford 4-(2-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)ethyl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol (740.0 mg, 88% yield) as a yellow solid. ESI-MS m/z = 717.50 $[M+H]^+$; Calculated MW: 716.40.

Step 6: 4-(2-(4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)ethyl)-5-ethynyl-6-fluoronaphthalen-2-ol

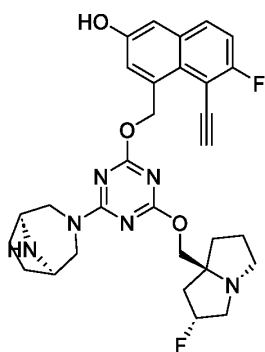
To a stirred solution of 4-(2-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)ethyl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol (730.0 mg, 1.02 mmol, 1.0 equiv), CsF (7.73 g, 50.9 mmol, 50 equiv) and DMF (15 mL). The resulting mixture was stirred for 1 h at 25 °C under nitrogen atmosphere. The resulting mixture was added water (20mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (3x10 mL) and dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH= 5:1) to afford the crude product (150 mg) as an off-white solid. The crude product was repurified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18 ExRS 30*150 mm, 5m; Mobile Phase A: Water(10mmol/L NH_4HCO_3), Mobile Phase B: MeCN; Flow rate: 60 mL/min mL/min; Gradient: 30% B to 57% B in 7 min; wavelength: 254nm/220nm nm; RT1(min): 6.8) to afford 4-(2-(4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)ethyl)-5-ethynyl-6-fluoronaphthalen-2-ol (41.7 mg, 7% yield, LCMS purity: 95.6% @254nm, 96.2% @220nm) as a white solid.

ESI-MS m/z = 561.25 $[M+H]^+$; Calculated MW: 560.27.

¹H NMR (400 MHz, DMSO-d₆) δ 9.75 (s, 1H), 7.83 (dd, J = 9.1, 6.1 Hz, 1H), 7.39 (t, J = 8.9 Hz, 1H), 7.07 (d, J = 2.6 Hz, 1H), 7.01 (d, J = 2.6 Hz, 1H), 5.25 (d, J = 54.4 Hz, 1H), 4.63 (d, J = 1.2 Hz, 1H), 4.28 (d, J = 12.4 Hz, 1H), 4.19 (d, J = 12.5 Hz, 1H), 4.00 (t, J = 10.6 Hz, 1H), 3.94 – 3.78 (m, 3H), 3.50 – 3.39 (m, 2H), 3.12 – 3.02 (m, 2H), 3.03 – 2.85 (m, 5H), 2.84 – 2.74 (m, 1H), 2.45 – 2.36 (m, 1H), 2.10 – 2.04 (m, 1H), 2.03 – 1.97 (m, 1H), 1.97 – 1.87 (m, 1H), 1.86 – 1.79 (m, 1H), 1.78 – 1.67 (m, 2H), 1.65 – 1.54 (m, 2H), 1.54 – 1.38 (m, 2H).

¹⁹F NMR (377 MHz, DMSO-d₆) δ -110.33, -172.13 (d, J = 4.3 Hz).

Example 3: 4-(((4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)oxy)methyl)-5-ethynyl-6-fluoronaphthalen-2-ol



Step 1: Tert-butyl (1R,5S)-3-(4-((7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)methoxy)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

To a stirred solution of [7-fluoro-3-(methoxymethoxy)-8-[2-(triisopropylsilyl)ethynyl]naphthalen-1-yl]methanol (258.8 mg, 0.62 mmol, 1.0 equiv) in THF (5 mL) was added NaH (74.5 mg, 3.10 mmol, 5.0 equiv) in portions at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 30 min at 20°C under nitrogen atmosphere. To the above mixture was added tert-butyl (1R,5S)-3-(4-chloro-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (300.0 mg, 0.62 mmol, 1 equiv) at 20°C. The resulting mixture was stirred for additional 2 h at 20°C. The reaction was quenched by the addition of water (10 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (1x30 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column

chromatography, eluting with PE/EtOAc (10:1~5:1) and the pure fraction was concentrated under reduced pressure to afford tert-butyl (1R,5S)-3-(4-((7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)methoxy)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (420.0 mg, 78%)
5 as a yellow solid. ESI-MS m/z = 863.4 $[M+H]^+$; Calculated MW: 862.5

Step 2: Tert-butyl (1R,5S)-3-(4-((8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)methoxy)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate.

To a stirred solution of tert-butyl (1R,5S)-3-(4-((7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)methoxy)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (400.0 mg, 0.46 mmol, 1.0 equiv) in DMF (10 mL) was added CsF (704.0 mg, 4.63 mmol, 10 equiv) at 20°C under nitrogen atmosphere. The resulting mixture was stirred for 16 h at 20 °C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel
10 column chromatography, eluted with PE/EtOAc (10:1~5:1) and the pure fraction was concentrated under reduced pressure to afford tert-butyl (1R,5S)-3-(4-((8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)methoxy)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (280.0 mg, crude) as an off-white solid. ESI-MS m/z = 707.2 $[M+H]^+$; Calculated MW: 706.3
15

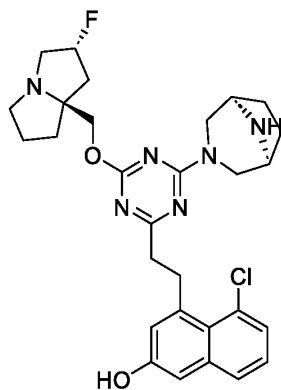
20 Step 3: 1-Bromo-3-chloro-5-(methoxymethoxy)-2-(2-methylcyclopropyl) benzene

A solution of tert-butyl (1R,5S)-3-(4-{[(2R,7S)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-{[(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl]methoxy}-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (100.0 mg, 0.14 mmol, 1.0 equiv) in HCOOH (2 mL) was stirred for 4 h at 20 °C under nitrogen atmosphere. The residue was purified by reversed combi-flash
25 chromatography with the following conditions: YMC-Actus Triart C18 ExRS Column, 30*150 mm, 5 μ m; Mobile Phase A: Water (10mmol/L NH₄HCO₃), Mobile Phase B: MeCN; Flow rate: 60 mL/min mL/min; Gradient: 39% B to 59% B in 8 min; wavelength: 254nm/220nm nm; RT1(min): 6.08. The pure fraction was concentrated and then lyophilized to afford 4-{[(4-{[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-1,3,5-triazin-2-yl)oxy]methyl}-5-ethynyl-6-fluoronaphthalen-2-ol (14.1 mg, 17% yield, 97.3% @254 nm; 96.8%
30 @220 nm) as a white solid.

ESI-MS m/z = 563.2 $[M+H]^+$; Calculated MW: 562.3

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.90 (dd, *J* = 9.2, 6.1 Hz, 1H), 7.44 (t, *J* = 9.0 Hz, 1H), 7.34 (d, *J* = 2.6 Hz, 1H), 7.23 (d, *J* = 2.6 Hz, 1H), 6.07 (q, *J* = 13.1 Hz, 2H), 5.24 (d, *J* = 54.3 Hz, 1H), 4.60 (d, *J* = 1.1 Hz, 1H), 4.30 – 4.14 (m, 2H), 4.05 – 3.84 (m, 2H), 3.43 (s, 3H), 3.04 (s, 2H), 3.01 – 2.90 (m, 3H), 2.80 (q, *J* = 8.5 Hz, 1H), 2.06 (d, *J* = 3.7 Hz, 1H), 1.98 (s, 1H), 1.90 (d, *J* = 15.3 Hz, 1H), 1.82 (s, 1H), 1.74 (dd, *J* = 13.1, 7.9 Hz, 2H), 1.61 (s, 2H), 1.53 – 1.36 (m, 2H).

Example 4: 4-(2-(4-(((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)ethyl)-5-chloronaphthalen-2-ol



Step 1: Tert-butyl (1R,5S)-3-(4-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-vinyl-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

To a stirred solution of tert-butyl (1R,5S)-3-(4-chloro-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (2.00 g, 4.14 mmol, 1.0 equiv) and 2-ethenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (960.0 mg, 6.21 mmol, 1.5 equiv) in dioxane/water (24 mL, 5:1) were added Pd(DtBPF)Cl₂ (270.0 mg, 0.41 mmol, 0.1 equiv) and K₂CO₃ (1.72 g, 12.4 mmol, 3.0 equiv) in portions at 20 °C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 80 °C under nitrogen atmosphere. The mixture was allowed to cool down to 20 °C. The resulting mixture was diluted with water (100 mL). The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (3 x 50 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (1:9). The pure fraction was concentrated under reduced pressure to afford tert-butyl (1R,5S)-3-(4-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-vinyl-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.98 g, 83%, yield) as a yellow solid. ESI-MS *m/z* = 475.5 [M+H]⁺; Calculated MW: 474.3

Step 2: Tert-butyl (1R,5S)-3-(4-((E)-2-(8-chloro-3-(methoxymethoxy)naphthalen-1-yl)vinyl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

To a stirred solution of tert-butyl (1R,5S)-3-(4-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-vinyl-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (900.0 mg, 1.89 mmol, 1.0 equiv) and 1-bromo-8-chloro-3-(methoxymethoxy)naphthalene (629.0 mg, 2.08 mmol, 1.1 equiv) in dioxane (10 mL) were added 1,2,2,6,6-pentamethylpiperidine (883.4 mg, 5.68 mmol, 3.0 equiv), tris(2-methylphenyl)phosphane (115.4 mg, 0.37 mmol, 0.2 equiv) and Pd(OAc)₂ (42.58 mg, 0.190 mmol, 0.1 equiv) in portions at 20 °C under nitrogen atmosphere. The resulting mixture was stirred 16 h at 80 °C under nitrogen atmosphere. The mixture was allowed to cool down to 20 °C. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (1:3). The pure fraction was concentrated under reduced pressure to afford tert-butyl (1R,5S)-3-(4-((E)-2-(8-chloro-3-(methoxymethoxy)naphthalen-1-yl)vinyl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (720.0 mg, 54.61%, yield) as a brown solid. ESI-MS m/z = 695.4 [M+H]⁺; Calculated MW: 694.3

Step 3: Tert-butyl (1R,5S)-3-(4-(2-(8-chloro-3-(methoxymethoxy)naphthalen-1-yl)ethyl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

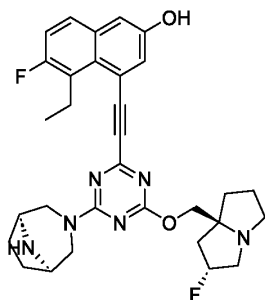
To a stirred mixture of tert-butyl (1R,5S)-3-(4-((E)-2-(8-chloro-3-(methoxymethoxy)naphthalen-1-yl)vinyl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (500.0 mg, 0.71 mmol, 1.0 equiv) in DCM (100 mL) was added Pt/C (841.8 mg, 4.31 mmol, 6.0 equiv) at 20 °C under nitrogen atmosphere. The resulting mixture was stirred for 4 h at 20 °C under hydrogen atmosphere. The resulting mixture was filtered and the filter cake was washed with DCM (2 x 50 mL). The filtrate was concentrated under reduced pressure. The residue was purified by reversed combi-flash chromatography with the following conditions: column, C18; mobile phase, MeCN in water (0.1% FA), 70% to 80% gradient in 10 min; detector, UV 254 nm. The pure fraction was concentrated under reduced pressure to afford tert-butyl (1R,5S)-3-(4-(2-(8-chloro-3-(methoxymethoxy)naphthalen-1-yl)ethyl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (150.0 mg, 30% yield) as a yellow solid. ESI-MS m/z = 697.2 [M+H]⁺; Calculated MW: 696.3

Step 4: 4-(2-(4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)ethyl)-5-chloronaphthalen-2-ol

To a stirred solution of tert-butyl (1*R*,5*S*)-3-(4-(2-(8-chloro-3-(methoxymethoxy)naphthalen-1-yl)ethyl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (150.0 mg, 0.21 mmol, 1.0 equiv) in MeCN (1.5 mL) was added HCl(gas) in dioxane (0.3 mL) at 20 °C under air atmosphere. The resulting mixture was stirred for 1 h at 20 °C under air atmosphere. The resulting mixture was purified by Prep-HPLC with the following conditions (Column: Kinetex EVO C18 Column, 30*150 mm, 5µm; Mobile Phase A: water (10mmol/L NH₄HCO₃), Mobile Phase B: MeCN; Flow rate: 60 mL/min mL/min; Gradient: 35% B to 41% B in 10 min; wavelength: 254nm/220nm nm; RT1(min): 9.6). The pure fraction was lyophilized to afford 4-(2-(4-((1*R*,5*S*)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)ethyl)-5-chloronaphthalen-2-ol (13.6 mg, 11%, yield) as a white solid. ESI-MS *m/z* = 553.2 [M+H]⁺; Calculated MW: 552.2.

¹H NMR (400 MHz, DMSO-*d*₆) δ 9.91 (s, 1H), 7.67 (d, 1H), 7.43 – 7.23 (m, 2H), 7.12 – 6.96 (m, 2H), 5.24 (d, *J* = 54.3 Hz, 1H), 4.25 (dd, *J* = 37.1, 12.5 Hz, 2H), 4.03 – 3.81 (m, 2H), 3.81 – 3.66 (m, 2H), 3.44 (s, 2H), 3.13 – 3.02 (m, 2H), 3.02 – 2.83 (m, 5H), 2.83 – 2.71 (m, 1H), 2.09 – 1.97 (m, 2H), 1.95 – 1.78 (m, 2H), 1.78 – 1.64 (m, 2H), 1.64 – 1.55 (m, 2H), 1.48 – 1.34 (m, 2H).

Example 5: 4-[2-(4-(((2*R*,7*aS*)-2-fluoro-hexahydropyrrolizin-7*a*-yl)methoxy)-6-((1*R*,5*S*)-3,8-diazabicyclo[3.2.1]octan-3-yl)-1,3,5-triazin-2-yl)ethynyl]-5-ethyl-6-fluoronaphthalen-2-ol



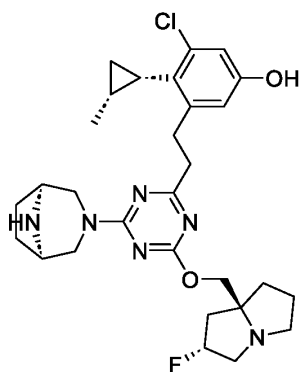
Step 1: 4-[2-(4-(((2*R*,7*aS*)-2-fluoro-hexahydropyrrolizin-7*a*-yl)methoxy)-6-((1*R*,5*S*)-3,8-diazabicyclo[3.2.1]octan-3-yl)-1,3,5-triazin-2-yl)ethynyl]-5-ethyl-6-fluoronaphthalen-2-ol

To a stirred solution of tert-butyl (1*R*,5*S*)-3-(4-(((2*R*,7*aS*)-2-fluoro-hexahydropyrrolizin-7*a*-yl)methoxy)-6-([2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)ethynyl]-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (120.0 mg, 0.17 mmol, 1.0 equiv) in dioxane (2 mL) was added HCl(gas) in dioxane (3 mL) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 2h at 0°C. The mixture was concentrated under reduced pressure. The residue was dissolved in MeOH (2 mL). The residue was purified by prep-HPLC with the following conditions: Column: XBridge Shield RP18 OBD Column 30*150 mm, 5m; Mobile Phase A: Water(0.1% FA), Mobile Phase B: MeCN; Flow rate: 60 mL/min mL/min; Gradient: 2% B to 2% B

in 1 min, 2% B to 7% B in 1.5 min, 7% to 30% B in 10 min; wavelength: 254nm/220nm nm; RT1(min): 7.73 This resulted in 4-((4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)ethynyl)-5-ethyl-6-fluoronaphthalen-2-ol (70.1 mg, 73% yield) as a light brown solid.

- 5 ¹H NMR (400 MHz, DMSO-d₆) δ 8.27-8.15 (m, 2H), 7.75 (dd, J = 9.1, 5.9 Hz, 1H), 7.49 (d, J = 2.6 Hz, 1H), 7.44 – 7.34 (m, 2H), 5.27 (d, J = 54 Hz, 1H), 4.44 – 4.22 (m, 2H), 4.13 – 3.95 (m, 2H), 3.77 – 3.48 (m, 5H), 3.09-3.07 (m, 3H), 3.02-2.98 (m, 1H), 2.87 – 2.79 (m, 1H), 2.12-2.10 (m, 1H), 2.03-2.01 (m, 1H), 2.00 – 1.92 (m, 1H), 1.89 – 1.68 (m, 5H), 1.56-1.54 (m, 2H), 1.32 (t, J = 7.3 Hz, 3H).

- Example 6:** 3-[2-(4-[[[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy]-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-1,3,5-triazin-2-yl)ethyl]-5-chloro-4-[(1RS,2SR)-2-methylcyclopropyl]phenol



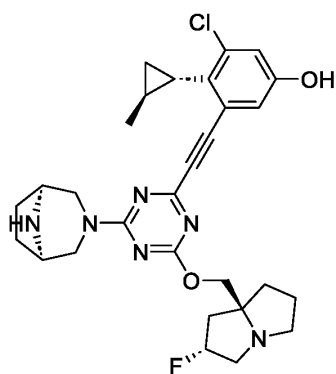
- Steps 1-2:** 3-[2-(4-[[[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy]-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-1,3,5-triazin-2-yl)ethyl]-5-chloro-4-[(1RS,2SR)-2-methylcyclopropyl]phenol

- To a stirred solution of tert-butyl (1R,5S)-3-(4-[[[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy]-6-(2-{3-chloro-5-hydroxy-2-[(1RS,2RS&)-2-methylcyclopropyl]phenyl}ethynyl)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (350.0 mg, 0.53 mmol, 1.0 equiv) in MeOH (6 mL) was added Pd(OH)₂/C (150.4 mg, 1.07 mmol, 2.0 equiv) at 20 °C under nitrogen atmosphere. The resulting mixture was stirred for 3 h at 20 °C under hydrogen atmosphere. The resulting mixture was filtered and the filter cake was washed with MeOH (3 x 10 mL). The filtrate was concentrated under reduced pressure to afford tert-butyl (1R,5S)-3-(4-[[[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy]-6-(2-{3-chloro-5-hydroxy-2-[(1RS,2RS&)-2-methylcyclopropyl]phenyl}ethyl)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (300.0 mg, 85% yield) as a brown solid.

To a stirred mixture of tert-butyl (1R,5S)-3-(4-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy)-6-(2-{3-chloro-5-hydroxy-2-[(1R,2R&)-2-methylcyclopropyl]phenyl}ethyl)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (200.0 mg, 0.28 mmol, 1.0 equiv) in MeCN (2 mL) was added HCl(gas) indioxane (2 mL, 4M) at 20°C under nitrogen atmosphere. The resulting mixture was stirred for 0.5 h at 20 °C under air atmosphere. The mixture was concentrated to give the crude product (200.0 mg) which was purified by prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5µm; Mobile Phase A: Water(10mmol/L NH₄HCO₃, Mobile Phase B: MeCN; Flow rate: 60 mL/min mL/min; Gradient: 42% B to 57% B in 8 min; wavelength: 254nm/220nm nm; RT1(min): 8.38). The pure fraction was lyophilized to afford 3-[2-(4-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy)-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-1,3,5-triazin-2-yl)ethyl]-5-chloro-4-[(1R,2SR)-2-methylcyclopropyl]phenol (40.0 mg, 21% yield 96.3% purity @254nm; 96.1%@220nm) as a white solid. ESI-MS m/z = 557.3 [M+H]⁺; Calculated MW: 556.2

¹H NMR (400 MHz, DMSO-*d*₆) δ 9.58 (s, 1H), 6.59 (dd, J = 23.3, 2.5 Hz, 2H), 5.24 (d, J = 54.4 Hz 1H), 4.25 (dd, J = 45.1, 12.5 Hz, 2H), 4.07 – 3.79 (m, 2H), 3.43 (s, 2H), 3.17 – 3.01 (m, 4H), 3.00 – 2.91 (m, 3H), 2.85 – 2.72 (m, 3H), 2.15 – 1.87 (m, 3H), 1.85 – 1.66 (m, 3H), 1.65-1.55 (m, 2H), 1.49-1.36 (m, 2H), 1.31-1.24 (m, 1H), 1.22 (d, J = 5.8 Hz, 3H), 0.92 – 0.67 (m, 3H).

Example 7: 3-[2-(4-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy)-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-1,3,5-triazin-2-yl)ethynyl]-5-chloro-4-[(1S,2S)-2-methylcyclopropyl]phenol



Step 1: {2-[3-Chloro-5-(methoxymethoxy)-2-[(1R,2RS&)-2-methylcyclopropyl]phenyl]ethynyl} triisopropylsilane

To a stirred mixture of 1-bromo-3-chloro-5-(methoxymethoxy)-2-[(1R,2RS&)-2-methylcyclopropyl]benzene (1.00 g, 3.27 mmol, 1.0 equiv) and ethynyltris(propan-2-yl)silane (1.19 g, 6.54 mmol, 2.0 equiv) in DMF (10 mL) were added DIEA (1.27 g, 9.81 mmol, 3.0 equiv), Pd(PPh₃)₂Cl₂

(229.6 mg, 0.32 mmol, 0.1 equiv) and CuI (124.6 mg, 0.65 mmol, 0.2 equiv) at 20 °C under nitrogen atmosphere. The resulting mixture was stirred for 16 h at 100°C under nitrogen atmosphere. The mixture was allowed to cool down to 20 °C. The resulting mixture was diluted with water (20 mL). The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (3 x 30 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed combi-flash chromatography with the following conditions: column, C18; mobile phase, A: FA (0.1%) in water, B: MeCN, 60% to 100% gradient in 20 min; detector, UV 254 nm. The pure fraction was concentrated under vacuum to afford {2-[3-chloro-5-(methoxymethoxy)-2-[(1R,2R&)-2-methylcyclopropyl]phenyl]ethynyl}triisopropylsilane (1.16 g, 87% yield) as a brown solid. ESI-MS m/z = no Ms signal; Calculated MW: 406.2

Step 2: Tert-butyl (1R,5S)-3-(4-{[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-{2-[3-chloro-5-(methoxymethoxy)-2-[(1S,2S)-2-methylcyclopropyl]phenyl]ethynyl}-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

To a stirred mixture of tert-butyl (1R,5S)-3-(4-{[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-chloro-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.57 g, 3.24 mmol, 1.2 equiv) and {2-[3-chloro-5-(methoxymethoxy)-2-[(1R,2R&)-2-methylcyclopropyl]phenyl]ethynyl}triisopropylsilane (1.16 g, 2.85 mmol, 1.0 equiv) in DMF (20 mL) were added CuI (108.5 mg, 0.57 mmol, 0.2 equiv) and Pd(PPh₃)₄ (329.3 mg, 0.28 mmol, 0.1 equiv) at 20°C under nitrogen atmosphere. The resulting mixture was stirred for 0.5 h at 0°C under nitrogen atmosphere. To the above mixture was added CsF (1.30 g, 8.55 mmol, 3.0 equiv) at 0°C. The resulting mixture was stirred for additional 16 h at 40°C. The resulting mixture was diluted with water (20 mL). The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (3 x 20 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (50:1~ 2:1) and the pure fraction was concentrated under reduced pressure to afford tert-butyl (1R,5S)-3-(4-{[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-{2-[3-chloro-5-(methoxymethoxy)-2-[(1S,2S)-2-methylcyclopropyl]phenyl]ethynyl}-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.20 g, 66% yield) as a brown solid. ESI-MS m/z = 697.3 [M+H]⁺; Calculated MW: 696.3

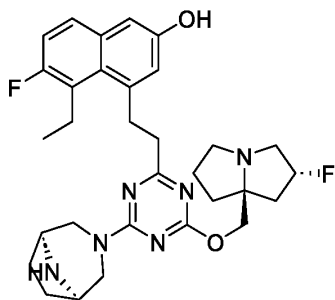
Step 3: 3-[2-(4-{[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-1,3,5-triazin-2-yl)ethynyl]-5-chloro-4-[(1S,2S)-2-methylcyclopropyl]phenol

To a stirred mixture of tert-butyl (1R,5S)-3-(4-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy)-6-{2-[3-chloro-5-(methoxymethoxy)-2-[(1S,2S)-2-methylcyclopropyl]phenyl]ethynyl}-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (200.0 mg, 0.28 mmol, 1.0 equiv) in MeCN (1 mL) was added HCl (gas) in dioxane (1 mL, 4M) at 20 °C under air atmosphere. The resulting mixture was stirred for 0.5 h at 20°C under air atmosphere. The resulting mixture was concentrated under vacuum. The residue was purified by reversed combi-flash chromatography with the following conditions: Column: Xbridge Phenyl OBD Column, 19*150 mm, 5m; Mobile Phase A: water (10mmol/L NH₄HCO₃+0.05%NH₃H₂O), Mobile Phase B: MeCN; Flow rate: 60 mL/min mL/min; Gradient: 40% B to 55% B in 8 min; wavelength: 254nm/220nm nm; RT1(min): 6.9. The pure fraction was concentrated under vacuum to afford 3-[2-(4-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy)-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-1,3,5-triazin-2-yl)ethynyl]-5-chloro-4-[(1S,2S)-2-methylcyclopropyl]phenol (28.0 mg, 17% yield, 95.7% purity @254nm, 95.5% @220nm) as a white solid.

ESI-MS m/z = 553.2 [M+H]⁺; Calculated MW: 552.2

¹H NMR (300 MHz, DMSO-*d*₆) δ 6.94 (d, *J* = 2.5 Hz, 1H), 6.89 (d, *J* = 2.5 Hz, 1H), 5.26 (d, *J* = 54.4 Hz, 1H), 4.23 (t, *J* = 12.4 Hz, 2H), 4.10-3.88 (m, 2H), 3.50-3.44(m, 3H), 3.10 – 2.96 (m, 5H), 2.81 (q, *J* = 9.0, 8.3 Hz, 1H), 2.10 (d, *J* = 4.8 Hz, 1H), 2.03 – 1.90 (m, 2H), 1.88 – 1.70 (m, 3H), 1.64 (s, 2H), 1.53-1.38 (m, 3H), 1.28 (d, *J* = 5.9 Hz, 3H), 1.08 (s, 1H), 0.92-0.75 (m, 2H).

Example 8: 4-(2-(4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)ethyl)-5-ethyl-6-fluoronaphthalen-2-ol



Step 1: Tert-butyl 3-(4-((8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)ethynyl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

To a stirred mixture of {2-[8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl]ethynyl}triisopropylsilane (800.0 mg, 1.92 mmol, 1.0 equiv), tert-butyl 3-(4-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy)-6-chloro-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-

carboxylate (1.11 g, 2.31 mmol, 1.2 equiv), CuI (73.4 mg, 0.38 mmol, 0.2 equiv) and Pd(PPh₃)₂Cl₂ (135.4 mg, 0.19 mmol, 0.1 equiv) in DMF (8 mL) was added CsF (1.46 g, 9.64 mmol, 5.0 equiv) in portions at 0°C under argon atmosphere. The resulting mixture was stirred for 0.5h at 0°C under argon atmosphere. The resulting mixture was stirred for 5h at 40°C under argon atmosphere. The resulting mixture was cooled down to room temperature and diluted with EtOAc. The resulting mixture was washed with brine and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE / EtOAc (1:1) to afford tert-butyl 3-(4-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy)-6-{2-[8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl]ethynyl}-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (800.0 mg, 59% yield) as a brown yellow oil. ESI-MS m/z = 705.45[M+H]⁺; Calculated MW: 704.35.

¹H NMR (400 MHz, DMSO-d₆) δ 7.88 (dd, J = 9.1, 5.9 Hz, 1H), 7.74 (d, J = 2.7 Hz, 1H), 7.70 (d, J = 2.7 Hz, 1H), 7.48 (t, J = 9.3 Hz, 1H), 5.36 (s, 2H), 4.48 – 4.34 (m, 2H), 4.26 (s, 2H), 4.09 (t, J = 10.9 Hz, 1H), 4.01 (t, J = 10.1 Hz, 1H), 3.58 (d, J = 8.1 Hz, 2H), 3.43 (s, 3H), 3.28-3.20(m, 1H), 3.18 – 2.92 (m, 5H), 2.83 (d, J = 7.2 Hz, 1H), 2.10 (s, 1H), 2.03 (s, 1H), 1.98 (d, J = 10.2 Hz, 1H), 1.88 – 1.70 (m, 4H), 1.56 (d, J = 9.4 Hz, 2H), 1.44 (s, 9H), 1.35 – 1.31 (m, 3H).

Step 2: Tert-butyl 3-(4-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy)-6-{2-[8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl]ethyl}-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

A mixture of tert-butyl 3-(4-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy)-6-{2-[8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl]ethynyl}-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (400.0 mg, 0.56 mmol, 1.0 equiv) and Pd(OH)₂/C (400.0 mg, 2.84 mmol, 5.0 equiv) in MeOH (20 mL) was stirred for 1h at room temperature under hydrogen atmosphere. The resulting mixture was filtered and the filter cake was washed with EtOAc. The filtrate was concentrated under reduced pressure. This resulted in tert-butyl 3-(4-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy)-6-{2-[8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl]ethyl}-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (300.0 mg, 75% yield) as a light yellow solid. ESI-MS m/z = 709.35[M+H]⁺; Calculated MW: 708.38

¹H NMR (400 MHz, DMSO-d₆) δ 7.74 (dd, J = 9.0, 6.2 Hz, 1H), 7.39 – 7.29 (m, 2H), 7.18 (d, J = 2.7 Hz, 1H), 5.26 (s, 2H), 4.44 (d, J = 12.8 Hz, 1H), 4.37 (d, J = 12.9 Hz, 1H), 4.21 (s, 2H), 4.07 – 3.99 (m, 1H), 3.97 – 3.87 (m, 1H), 3.54 (dd, J = 9.3, 6.3 Hz, 2H), 3.39 (s, 3H), 3.28 – 3.18 (m, 2H), 3.09 – 2.96 (m, 6H), 2.88 (t, J = 7.9 Hz, 2H), 2.81 (q, J = 8.7 Hz, 1H), 2.06 (d, J = 3.1 Hz, 1H), 2.00 – 1.96 (m, 1H), 1.96 – 1.89 (m, 1H), 1.82 (d, J = 7.2 Hz, 3H), 1.76 – 1.68 (m, 2H), 1.53 – 1.45 (m, 2H), 1.43 (d, J = 2.5 Hz, 9H), 1.24 (t, J = 7.4 Hz, 3H).

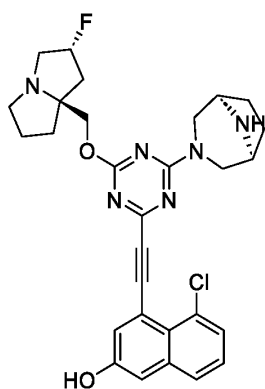
Step 3: 4-(2-(4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)ethyl)-5-ethyl-6-fluoronaphthalen-2-ol

To a stirred solution of tert-butyl 3-(4-{[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-{2-[8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl]ethyl}-1,3,5-triazin-2-yl)-3,8-

- 5 diazabicyclo[3.2.1]octane-8-carboxylate (280.0 mg, 0.39 mmol, 1.0 equiv) in dioxane (2 mL) was added HCl(gas) in dioxane (9 mL) dropwise at 0°C under argon atmosphere. The resulting mixture was stirred for 2h at room temperature under argon atmosphere. The resulting mixture was concentrated under reduced pressure. The crude product was purified by prep-HPLC with the following conditions (Column: YMC-Actus Triart C18 ExRS 30*150 mm, 5m; Mobile Phase A: Water(10mmol/L NH₄HCO₃), Mobile Phase B: MeCN; Flow rate: 60 mL/min mL/min; Gradient: 5% B to 20% B in 7 min; wavelength: 254nm/220nm nm; RT1(min): 6.35) to afford 4-[2-(4-{[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-1,3,5-triazin-2-yl)ethyl]-5-ethyl-6-fluoronaphthalen-2-ol (33.0 mg, 15% yield) as a light yellow solid. ESI-MS m/z = 565.25[M+H]⁺; Calculated MW: 564.30

- 15 ¹H NMR (400 MHz, DMSO-d₆) δ9.59 (s, 1H), 8.24-8.18 (m, 1H), 7.61 (dd, J = 9.0, 6.2 Hz, 1H), 7.25 (t, J = 9.4 Hz, 1H), 7.02 (t, J = 2.3 Hz, 2H), 5.25 (d, J = 54.3 Hz, 1H), 4.35 (d, J = 12.7 Hz, 1H), 4.25 (d, J = 12.9 Hz, 1H), 4.12-3.17 (m, 3H), 3.55-3.53 (m, 2H), 3.50-3.42 (m, 1H), 3.25 – 3.18 (m, 2H), 3.13 – 2.94 (m, 5H), 2.91 – 2.75 (m, 3H), 2.08-2.06 (m, 1H), 2.00-1.98 (m, 1H), 1.97-1.88 (m, 1H), 1.87-1.78 (m, 1H), 1.78 – 1.70 (m, 2H), 1.67-1.65 (m, 2H), 1.49-1.46 (m, 2H), 1.23 (t, J = 7.3 Hz, 3H).

- 20 **Example 9:** 4-((4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)ethynyl)-5-chloronaphthalen-2-ol



- Step 1: Tert-butyl (1R,5S)-3-(4-((8-chloro-3-(methoxymethoxy)naphthalen-1-yl)ethynyl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-
- 25 diazabicyclo[3.2.1]octane-8-carboxylate

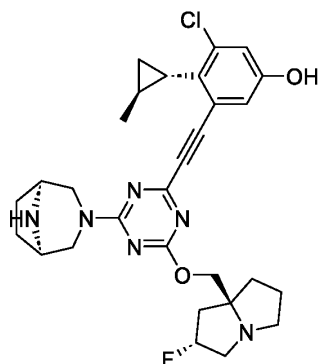
Into a 40 mL vial were added ((8-chloro-3-(methoxymethoxy)naphthalen-1-yl)ethynyl)triisopropylsilane (300.0 mg, 0.74 mmol, 1.0 equiv), tert-butyl 3-(4-chloro-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (431.4 mg, 0.89 mmol, 1.2 equiv), CuI (28.3 mg, 0.14 mmol, 0.2 equiv), Pd(PPh₃)₄ (86.0 mg, 0.07 mmol, 0.1 equiv) and DMF (10 mL) at 0 °C. The resulting mixture was stirred for 30 min at 0°C under argon atmosphere. To the above mixture was added CsF (565.3 mg, 3.72 mmol, 5.0 equiv) at 0°C under argon atmosphere. The resulting mixture was stirred for 16h at 40°C under argon atmosphere. The resulting mixture was filtered and the filter cake was washed with EtOAc. The reaction was diluted with water. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by prep-TLC (DCM / MeOH 10:1) to afford tert-butyl (1*R*,5*S*)-3-(4-((8-chloro-3-(methoxymethoxy)naphthalen-1-yl)ethynyl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (425.0 mg, 82% yield) as a black solid. ESI-MS *m/z* = 693.3 [M+H]⁺; Calculated MW: 692.3

Step 2: 4-((4-((1*R*,5*S*)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)ethynyl)-5-chloronaphthalen-2-ol

To a stirred solution of tert-butyl (1*R*,5*S*)-3-(4-((8-chloro-3-(methoxymethoxy)naphthalen-1-yl)ethynyl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (250.0 mg, 0.36 mmol, 1.0 equiv) in MeCN (6 mL) was added HCl (gas) in dioxane (6 mL) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 30 min at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The crude product was purified by prep-HPLC with the following conditions (Column: XBridge Prep Phenyl OBD Column 19*250 mm, 5 m; Mobile Phase A: 10 mmol/L NH₄HCO₃ + 0.05% NH₃H₂O, Mobile Phase B: MeCN; Flow rate: 60 mL/min; Gradient: 5% B to 5% B in 1 min, 5% B to 31% B in 2 min, 31% to 50% B in 10 min; wavelength: 254 nm/220 nm; RT1(min): 9.32) to afford 4-((4-((1*R*,5*S*)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)ethynyl)-5-chloronaphthalen-2-ol (31.0 mg, 15% yield, 96.5% @ 254 nm, 96.7% @ 220nm) as a yellow solid.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.59 (t, *J* = 3.1 Hz, 1H), 7.47 (d, *J* = 8.2 Hz, 1H), 7.31 – 7.27 (m, 1H), 7.22 – 7.15 (m, 2H), 5.29 (d, *J* = 53.4 Hz, 1H), 4.43-4.40 (m, 2H), 4.19 – 4.02 (m, 2H), 3.60 (s, 2H), 3.34 – 3.19 (m, 3H), 3.13 – 2.99 (m, 3H), 2.31 – 2.16 (m, 2H), 2.08-2.06 (m, 1H), 1.93-1.91 (m, 3H), 1.80 – 1.60 (m, 4H).

Example 10: 3-((4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)ethynyl)-5-chloro-4-((1S,2S)-2-methylcyclopropyl)phenol



- 5 Step 1: Tert-butyl (1R,5S)-3-(4-((3-chloro-5-(methoxymethoxy)-2-((1S,2S)-2-methylcyclopropyl)phenyl)ethynyl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate.

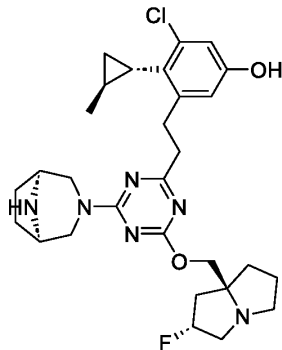
To a stirred mixture of {2-[3-chloro-5-(methoxymethoxy)-2-(2-methylcyclopropyl)phenyl]ethynyl}triisopropylsilane (460.0 mg, 1.13 mmol, 1.0 equiv) and tert-butyl
 10 3-(4-[[[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy]-6-chloro-1,3,5-triazin-2-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (654.9 mg, 1.35 mmol, 1.2 equiv) in DMF (10 mL) were added CuI (21.5 mg, 0.11 mmol, 0.1 equiv) and Pd(PPh₃)₄ (65.2 mg, 0.05 mmol, 0.05 equiv) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 30 min at 0 °C under nitrogen atmosphere. To the above mixture was added CsF (858.2 mg, 5.65 mmol, 5.0 equiv) at 0 °C. The
 15 resulting mixture was stirred for additional 2 h at 40 °C. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with water and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by prep-TLC (PE/EtOAc 3:1) to afford tert-butyl (1R,5S)-3-(4-[[[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy]-6-{2-[3-chloro-5-(methoxymethoxy)-2-[(1R*,2S*)-2-methylcyclopropyl]phenyl]ethynyl}-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate
 20 (55 mg, 30.50% yield) as a light yellow solid. ESI-MS m/z =697.3 [M+H]⁺; Calculated MW: 696.3

Step 2: 3-((4-((1R,5S)-3,8-Diazabicyclo[3.2.1]octan-3-yl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)ethynyl)-5-chloro-4-((1S,2S)-2-methylcyclopropyl)phenol

- 25 Into a 40 mL vial were added tert-butyl (1R,5S)-3-(4-[[[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy]-6-{2-[3-chloro-5-(methoxymethoxy)-2-[(1R*,2S*)-2-

- methylcyclopropyl]phenyl]ethynyl)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (70.0 mg, 0.10 mmol, 1.0 equiv) and HCl(gas) in dioxane at 0 °C. The resulting mixture was stirred for 1 h at 0 °C under nitrogen atmosphere. The resulting mixture was concentrated under vacuum. The crude product was purified by prep-HPLC with the following conditions (Column: XBridge Prep
- 5 Phenyl OBD Column 19*250 mm, 5m; Mobile Phase A: 10mmol/L NH₄HCO₃+0.05%NH₃H₂O, Mobile Phase B: MeCN; Flow rate: 60 mL/min mL/min; Gradient: 5% B to 5% B in 1 min, 5% B to 38% B in 2 min, 38% to 55% B in 10 min; wavelength: 254nm/220nm nm; RT1(min): 9.23) to afford 3-[2-(4-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy)-6-[(1R,5S)-3,8-
- 10 diazabicyclo[3.2.1]octan-3-yl]-1,3,5-triazin-2-yl)ethynyl]-5-chloro-4-[(1R*,2S*)-2-methylcyclopropyl]phenol (18.0 mg, 32% yield, 98.8% purity @254nm; 98.9% purity @220nm) as an off-white solid. ESI-MS m/z =553.2. [M+H]⁺; Calculated MW: 552.2.
- ¹H NMR (400 MHz, DMSO-d₆) δ 10.14 (s, 1H), 6.92 (dd, J = 23.3, 2.6 Hz, 2H), 5.26 (d, J = 54.3 Hz, 1H), 4.24 (t, J = 14.1 Hz, 2H), 4.12 – 3.91 (m, 2H), 3.50 (s, 2H), 3.12 – 2.97 (m, 5H), 2.86 – 2.77 (m, 1H), 2.16 – 1.89 (m, 3H), 1.88 – 1.70 (m, 3H), 1.65 (s, 2H), 1.53 – 1.41 (m, 3H), 1.28 (d, J = 5.9 Hz,
- 15 3H), 1.15 – 1.01 (m, 1H), 0.91 – 0.76 (m, 2H).

Example 11: 3-[2-(4-[(2R,7aS)-2-Fluoro-hexahydropyrrolizin-7a-yl]methoxy)-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-1,3,5-triazin-2-yl)ethyl]-5-chloro-4-[(1R,2R)-2-methylcyclopropyl]phenol



- 20 **Step 1:** Tert-butyl (1R,5S)-3-(4-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy)-6-[(E)-2-[3-chloro-5-(methoxymethoxy)-2-[(1R,2R)-2-methylcyclopropyl]phenyl]ethenyl]-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate
- To a stirred mixture of tert-butyl 3-(4-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy)-6-ethenyl-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.31 g, 2.75 mmol, 1.2
- 25 equiv) and rel-1-bromo-3-chloro-5-(methoxymethoxy)-2-[(1R,2R)-2-methylcyclopropyl]benzene (700.3 mg, 2.29 mmol, 1.0 equiv) in DMF (8 mL) were added DIEA (1.18 g, 9.17 mmol, 4.0 equiv)

at room temperature under nitrogen atmosphere. To the above mixture was added Pd₂(dba)₃ (209.8 mg, 0.23 mmol, 0.1 equiv) and P(p-Tol.)₃ (139.5 mg, 0.46 mmol, 0.2 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for additional 2 h at 100°C. The resulting mixture was cooled down to room temperature and filtered, the filter cake was washed with EtOAc.

- 5 The filtrate was washed with brine and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with EtOAc/PE (2:1) to afford tert-butyl (1R,5S)-3-(4-[[[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-[(E)-2-[3-chloro-5-(methoxymethoxy)-2-[(1R,2R)-2-methylcyclopropyl]phenyl]ethenyl]-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate
10 (1.30 g, 81% yield) as a light yellow solid. ESI-MS m/z = 699.3 [M+H]⁺; Calculated MW: 698.3

Step 2: Tert-butyl (1R,5S)-3-(4-[[[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-{2-[3-chloro-5-(methoxymethoxy)-2-[(1R,2R)-2-methylcyclopropyl]phenyl]ethyl]-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

- To a stirred mixture of tert-butyl (1R,5S)-3-(4-[[[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-[(E)-2-[3-chloro-5-(methoxymethoxy)-2-[(1R,2R)-2-methylcyclopropyl]phenyl]ethenyl]-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate
15 (300.0 mg, 0.43 mmol, 1.0 equiv) in EtOAc (10 mL) was added Pd(OH)₂/C (300.0 mg, 2.14 mmol, 5.0 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for additional 30 min at room temperature under hydrogen atmosphere. The resulting mixture was filtered
20 and the filter cake was washed with EtOAc. The filtrate was concentrated under reduced pressure. The residue was purified by prep-TLC (EtOAc) to afford tert-butyl (1R,5S)-3-(4-[[[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-{2-[3-chloro-5-(methoxymethoxy)-2-[(1R,2R)-2-methylcyclopropyl]phenyl]ethyl]-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate
(220.0 mg, 73% yield) as a white solid. ESI-MS m/z = 701.3 [M+H]⁺; Calculated MW: 700.4

- 25 Step 3: 3-[2-(4-[[[(2R,7aS)-2-Fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-1,3,5-triazin-2-yl)ethyl]-5-chloro-4-[(1R,2R)-2-methylcyclopropyl]phenol

- To a stirred mixture of tert-butyl (1R,5S)-3-(4-[[[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-{2-[3-chloro-5-(methoxymethoxy)-2-[(1R,2R)-2-methylcyclopropyl]phenyl]ethyl]-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate
30 (210.0 mg, 0.30 mmol, 1.0 equiv) in dioxane (2 mL) was added HCl(gas) (4M in dioxane) (6 mL) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for additional 30 min at 0°C. The resulting mixture was concentrated under reduced pressure. The crude product was purified by prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column 30*150 mm, 5m;

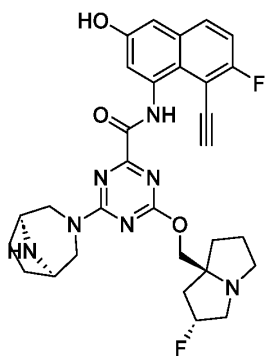
Mobile Phase A: Water(0.1% FA), Mobile Phase B: MeCN; Flow rate: 60 mL/min mL/min;
 Gradient: 0% B to 27% B in 10 min; wavelength: 254nm/220nm nm; RT1(min): 7.08/8.49). This
 resulted in 3-[2-(4-[[[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-[(1R,5S)-3,8-

- 5 methylcyclopropyl]phenol (37.0 mg, 22% yield, 96.0%purity @254nm; 96.8% purity @220nm) as a
 white
 solid.

ESI-MS m/z = 557.3 $[M+H]^+$; Calculated MW: 556.3

- 1H NMR (400 MHz, DMSO- d_6) δ 9.55 (s, 1H), 8.16 (d, J = 15.0 Hz, 1H), 6.62 (d, J = 2.5 Hz, 2H),
 10 5.25 (d, J = 56.0 Hz, 1H), 4.60-4.25 (m, 2H), 4.21-3.98 (m, 3H), 3.80-3.70 (m, 2H), 3.20-3.17 (m, 3H),
 3.15-3.05 (m, 5H), 2.99-2.97 (m, 1H), 2.84-2.81 (m, 2H), 2.07-2.04 (m, 1H), 1.99-1.96 (m, 1H), 1.89-
 1.62 (m, 5H), 1.53-1.51 (m, 1H), 1.31-1.21 (m, 4H), 0.87-0.70 (m, 3H).

- Example 12:** 4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-N-(8-ethynyl-7-fluoro-3-
 hydroxynaphthalen-1-yl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-
 15 triazine-2-carboxamide



Step 1: 4-((1R,5S)-8-(tert-butoxycarbonyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-(((2R,7aS)-2-
 fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazine-2-carboxylic acid

- To a stirred solution of tert-butyl (1R,5S)-3-(4-[[[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-
 20 yl]methoxy}-6-chloro-1,3,5-triazin-2-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (2.00 g, 4.14
 mmol, 1.0 equiv) and DIEA (2.68 g, 20.7 mmol, 5.0 equiv) in dioxane (20 mL) and water (2 mL) were
 added Pd(OAc)₂ (139.45 mg, 0.62 mmol, 0.15 equiv) and DPPP (256.19 mg, 0.62 mmol, 0.15 equiv)
 in portions at 20 °C under nitrogen atmosphere. The resulting mixture was stirred for 16 h at 100 °C
 under carbon monoxide atmosphere. The mixture was allowed to cool down to 20°C. The resulting
 25 mixture was concentrated under reduced pressure. The residue was purified by silica gel column
 chromatography, eluting with DCM/MeOH (1:0 to 5:1) and the pure fraction was concentrated to

afford 4-[[[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy]-6-[(1R,5S)-8-(tert-butoxycarbonyl)-3,8-diazabicyclo[3.2.1]octan-3-yl]-1,3,5-triazine-2-carboxylic acid (450.0 mg, 22% yield) as an off-white solid. ESI-MS m/z = 493.3 $[M+H]^+$; Calculated MW: 492.2

Step 2: Tert-butyl (1R,5S)-3-(4-((7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)carbamoyl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

To a stirred solution of 4-[[[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy]-6-[(1R,5S)-8-(tert-butoxycarbonyl)-3,8-diazabicyclo[3.2.1]octan-3-yl]-1,3,5-triazine-2-carboxylic acid (200.0 mg, 0.41 mmol, 1.0 equiv) and TEA (164.4 mg, 1.62 mmol, 4.0 equiv) in DCM (5 mL) was added (COCl)₂ (103.1 mg, 0.81 mmol, 2.0 equiv) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 30min at 20 °C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. A solution of 7-fluoro-3-(methoxymethoxy)-8-[2-(triisopropylsilyl)ethynyl]naphthalen-1-amine (163.1 mg, 0.41 mmol, 1.0 equiv) and TEA (123.3 mg, 1.22 mmol, 3.0 equiv) in DCM (2 mL) at 0 °C was added the above mixture in DCM (2 mL) dropwise at 20°C. The resulting mixture was stirred for additional 3h at 20°C. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (10:1 to 1:1) and the pure fraction was concentrated under vacuum to afford tert-butyl (1R,5S)-3-(4-[[[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy]-6-[[7-fluoro-3-(methoxymethoxy)-8-[2-(triisopropylsilyl)ethynyl]naphthalen-1-yl]carbamoyl]-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (70.0 mg, 20% yield) as a brown solid. ESI-MS m/z = 876.4 $[M+H]^+$; Calculated MW: 875.5

Step 3: 4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-N-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazine-2-carboxamide

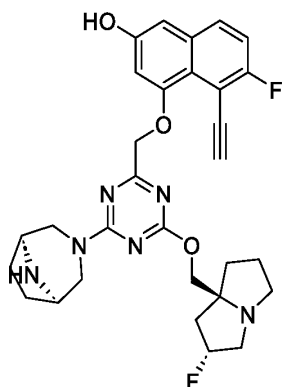
To a stirred solution of tert-butyl (1R,5S)-3-(4-[[[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy]-6-[[7-fluoro-3-(methoxymethoxy)-8-[2-(triisopropylsilyl)ethynyl]naphthalen-1-yl]carbamoyl]-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (70.0 mg, 0.08 mmol, 1.0 equiv) in MeCN (1 mL) was added HCl (gas) in dioxane (0.2 mL, 4M) at 20 °C under nitrogen atmosphere. The resulting mixture was stirred for 2h at 20°C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The crude product was used in the next step directly without further purification.

To the above mixture was added DMF (1mL) and CsF (124.5 mg, 0.80 mmol, 10 equiv) at 20°C. The resulting mixture was stirred for additional 1 h at 50°C. The mixture was allowed to cool down to 20°C. The resulting mixture was filtered and the filter cake was washed with DMF (2x0.5 mL). The

filtrate was concentrated under reduced pressure. The crude product (40.0 mg) was purified by prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μ m; Mobile Phase A: water (10mmol/L NH₄HCO₃+0.05%NH₃H₂O, Mobile Phase B: MeCN; Flow rate: 60 mL/min mL/min; Gradient: 30% B to 45% B in10 min; wavelength: 254nm/220nm nm; RT1(min): 8.18). The pure fraction was concentrated and then lyophilized to afford 4-[[[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-N-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-1,3,5-triazine-2-carboxamide (7.2 mg, 16% yield, 96.38% @254nm, 95.99% @220nm) as a yellow solid. ESI-MS *m/z* = 576.35 [M+H]⁺; Calculated MW: 575.25.

¹H NMR (400 MHz, DMSO-*d*₆) δ 11.00 (s, 1H), 10.64 – 9.33 (m, 1H), 7.82 (dd, *J* = 9.2, 6.0 Hz, 1H), 7.58 (d, *J* = 2.5 Hz, 1H), 7.36 (t, *J* = 9.0 Hz, 1H), 7.10 (d, *J* = 2.5 Hz, 1H), 5.43 – 4.71 (m, 1H), 4.59 – 4.39 (m, 2H), 4.20 (d, *J* = 12.5 Hz, 1H), 4.01 (dt, *J* = 42.2, 10.6 Hz, 2H), 3.43 (s, 3H), 3.08 – 2.91 (m, 5H), 2.76 (td, *J* = 8.8, 5.7 Hz, 1H), 2.20 – 1.89 (m, 3H), 1.88 – 1.69 (m, 3H), 1.63 – 1.41 (m, 4H).

Example 13: 4-((4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)methoxy)-5-ethynyl-6-fluoronaphthalen-2-ol



Step 1: Tert-butyl (1R,5S)-3-(4-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(methoxycarbonyl)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

To a stirred solution of tert-butyl (1R,5S)-3-(4-[[[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy]-6-chloro-1,3,5-triazin-2-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (4.00 g, 8.28 mmol, 1.0 equiv) and TEA (2.51 g, 24.84 mmol, 3.0 equiv) in 2-methyloxolane/ MeOH (4:1, 50 mL) were added Dppf (914.9 mg, 1.65 mmol, 0.2 equiv) and Pd(OAc)₂ (185.9 mg, 0.82 mmol, 0.1 equiv) at 20 °C under nitrogen atmosphere. The resulting mixture was stirred for 16 h at 90 °C under a carbon monoxide atmosphere. The mixture was allowed to cool down to 20 °C. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (4:1~3:1). The pure fraction was concentrated under reduced pressure to afford

tert-butyl (1R,5S)-3-(4-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(methoxycarbonyl)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.80 g, 33% yield) as a red solid. ESI-MS m/z = 507.25 $[M+H]^+$; Calculated MW: 506.3

5 Step 2: Tert-butyl (1R,5S)-3-(4-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(hydroxymethyl)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

To a stirred solution of tert-butyl (1R,5S)-3-(4-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(methoxycarbonyl)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.80 g, 3.55 mmol, 1.0 equiv) and CaCl_2 (1.38 g, 12.4 mmol, 3.5 equiv) in THF/ MeOH (2:1, 30 mL) was added NaBH_4 (336.1 mg, 8.88 mmol, 2.5 equiv) in portions at 0 °C under nitrogen atmosphere.

10 The resulting mixture was stirred for 16 h at 20 °C under nitrogen atmosphere. The reaction was quenched with water at 20 °C. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with DCM/MeOH (1:10~1:7). The pure fraction was concentrated under reduced pressure to afford tert-butyl (1R,5S)-3-(4-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(hydroxymethyl)-1,3,5-triazin-2-yl)-3,8-

15 diazabicyclo[3.2.1]octane-8-carboxylate (1.00 g, 56% yield) as a white solid. ESI-MS m/z = 479.25 $[M+H]^+$; Calculated MW: 478.3

Step 3: Tert-butyl (1R,5S)-3-(4-(((7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)oxy)methyl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

20 To a stirred mixture of 7-fluoro-3-(methoxymethoxy)-8-[2-((triisopropylsilyl)ethynyl)naphthalen-1-ol] (403.8 mg, 1.01 mmol, 1.2 equiv) and PPh_3 (679.6 mg, 2.59 mmol, 3.1 equiv) in THF (10 mL) was added DIAD (507.1 mg, 2.51 mmol, 3.0 equiv) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 0.5 h at 0 °C under nitrogen atmosphere. To the above mixture was added tert-butyl (1R,5S)-3-(4-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-

25 (hydroxymethyl)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (400.0 mg, 0.84 mmol, 1.0 equiv) at 20 °C. The resulting mixture was stirred for additional 16 h at 20 °C. The resulting mixture was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18; mobile phase, MeCN in Water (0.1% FA), 60% to 70% gradient in 10 min; detector, UV 254 nm. The resulting mixture was concentrated

30 under reduced pressure to afford tert-butyl (1R,5S)-3-(4-(((7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)oxy)methyl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (250 mg, 35% yield) as a yellow solid. ESI-MS m/z = 863.3 $[M+H]^+$; Calculated MW: 862.5.

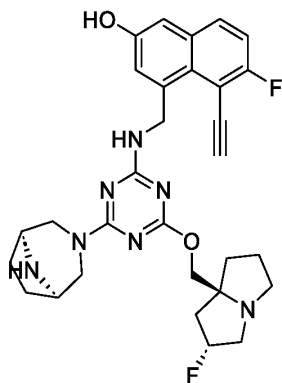
Steps 4-5: 4-((4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)methoxy)-5-ethynyl-6-fluoronaphthalen-2-ol

To a stirred solution of tert-butyl (1R,5S)-3-(4-(((7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)oxy)methyl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (200.0 mg, 0.23 mmol, 1.0 equiv) in DMF (2 mL) was added CsF (351.9 mg, 2.32 mmol, 10 equiv) at 20 °C under air atmosphere. The resulting mixture was stirred for 2 h at 20 °C under air atmosphere. The resulting mixture was filtered and the filter cake was washed with DCM (2 x 10 mL). The filtrate was concentrated under vacuum to afford tert-butyl (1R,5S)-3-(4-(((8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)oxy)methyl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (200.0 mg, crude) as a brown oil. To a stirred solution of tert-butyl (1R,5S)-3-(4-(((8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)oxy)methyl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (200.0 mg, crude) in DCM (0.5 mL) was added FA (2 mL) at 20 °C under air atmosphere. The resulting mixture was stirred for 2 h at 20 °C under air atmosphere. The resulting mixture was purified by prep-HPLC with the following conditions (Column: Xbridge Phenyl OBD Column, 19*150 mm, 5m; Mobile Phase A: water (10mmol/L NH₄HCO₃+0.05%NH₃.H₂O, Mobile Phase B: MeCN; Flow rate: 60 mL/min mL/min; Gradient: 27% B to 42% B in 10 min; wavelength: 254nm/220nm nm; RT1(min): 9.4). The pure fraction was lyophilized to afford 4-((4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)methoxy)-5-ethynyl-6-fluoronaphthalen-2-ol (23.4 mg, 14% yield) as a white solid.

ESI-MS *m/z* = 563.15 [M+H]⁺; Calculated MW: 562.3.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.73 (dd, *J* = 9.1, 5.7 Hz, 1H), 7.35 (t, *J* = 9.1 Hz, 1H), 6.79 (d, *J* = 2.1 Hz, 1H), 6.64 (d, *J* = 2.2 Hz, 1H), 5.29 – 5.10 (m, 1H), 5.06 (s, 2H), 4.35 (s, 1H), 4.19 (d, *J* = 12.6 Hz, 1H), 4.05 (d, *J* = 12.5 Hz, 1H), 4.00 – 3.84 (m, 2H), 3.48 – 3.44 (m, 1H), 3.32 – 3.25 (m, 1H), 3.06 – 2.89 (m, 4H), 2.86 – 2.70 (m, 2H), 2.04 – 1.92 (m, 2H), 1.91 – 1.74 (m, 2H), 1.74 – 1.64 (m, 2H), 1.64 – 1.49 (m, 2H), 1.43 (t, *J* = 10.5 Hz, 1H), 1.33 – 1.21 (m, 1H).

Example 14: 4-(((4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)amino)methyl)-5-ethynyl-6-fluoronaphthalen-2-ol



Step 1: tert-butyl (1R,5S)-3-(4-amino-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

A solution of added tert-butyl (1R,5S)-3-(4-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy)-6-chloro-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.00 g, 2.07 mmol, 1.0 equiv) in NH_3/MeOH (7M, 15 mL) was stirred for 4h at 50 °C under nitrogen atmosphere. The mixture was allowed to cool down to 20°C. The resulting mixture was concentrated under reduced pressure to afford tert-butyl (1R,5S)-3-(4-amino-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.20 g, crude) as a white solid. ESI-MS $m/z = 464.2$ $[\text{M}+\text{H}]^+$; Calculated MW: 463.3

Step 2: ((8-(bromomethyl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)ethynyl)triisopropylsilane

To a stirred solution of [7-fluoro-3-(methoxymethoxy)-8-[2-(triisopropylsilyl)ethynyl]naphthalen-1-yl]methanol (200.0 mg, 0.48 mmol, 1.0 equiv) and PPh_3 (151.1 mg, 0.58 mmol, 1.2 equiv) in DCM (2 mL) was added CBr_4 (191.0 mg, 0.58 mmol, 1.2 equiv) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 1.5h at 0 °C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE / EtOAc, the pure fraction was concentrated under reduced pressure to afford ((8-(bromomethyl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)ethynyl)triisopropylsilane (220.0 mg, 96% yield) as a white solid.

^1H NMR (400 MHz, Chloroform- d) δ 7.70 (dd, $J = 9.0, 5.8$ Hz, 1H), 7.36 (s, 2H), 7.29 – 7.23 (m, 1H), 5.67 (s, 2H), 5.27 (s, 2H), 3.51 (s, 3H), 1.30 – 1.17 (m, 21H).

Step 3: tert-butyl (1R,5S)-3-(4-(((7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)methyl)amino)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

To a stirred solution of tert-butyl (1R,5S)-3-(4-amino-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (200.0 mg, 0.43 mmol, 1.0 equiv) in DMF (10 mL) was added NaH (51.8 mg, 1.29 mmol, 3.0 equiv, 60%) in portions at 20 °C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 20 °C under nitrogen atmosphere. To the above mixture was added ((8-(bromomethyl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)ethynyl)triisopropylsilane (208.2 mg, 0.43 mmol, 1.0 equiv) at 20°C. The resulting mixture was stirred for additional 2 h at 50°C. The mixture was allowed to cool down to 20°C. The reaction was quenched with water at 0°C. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc and the pure fraction was concentrated under reduced pressure to afford tert-butyl (1R,5S)-3-(4-(((7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)methyl)amino)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (210.0 mg, 56% yield) as an off-white solid. ESI-MS m/z = 862.5 $[M+H]^+$; Calculated MW: 861.5

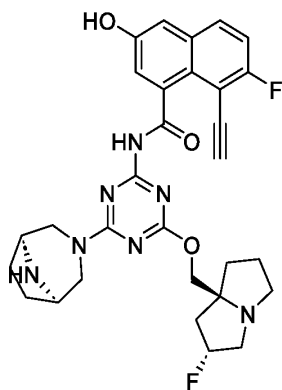
Step 4: 4-(((4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)amino)methyl)-5-ethynyl-6-fluoronaphthalen-2-ol

To a stirred solution of tert-butyl (1R,5S)-3-(4-(((7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)methyl)amino)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (200.0 mg, 0.23 mmol, 1.0 equiv) in DMF (5 mL) was added CsF (352.3 mg, 2.32 mmol, 10 equiv) at 20 °C under nitrogen atmosphere. The resulting mixture was stirred for 16 h at 20 °C under nitrogen atmosphere. The resulting mixture was filtered and the filter cake was washed with DMF (3x2 mL). The filtrate was concentrated under reduced pressure. To the above mixture was added HCOOH (3 mL) at 20°C. The resulting mixture was stirred for 16 h at 20 °C under nitrogen atmosphere. The resulting mixture was concentrated under vacuum. The crude product was purified by prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column 30*150 mm, 5m; Mobile Phase A: 10mmolNH₄HCO₃+0.05%NH₃H₂O, Mobile Phase B: MeCN; Flow rate: 60 mL/min; Gradient: 28% B to 48% B in 8 min; wavelength: 254/220 nm; RT1(min): 9.37). The pure fraction was concentrated and then lyophilized to afford 4-(((4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)amino)methyl)-5-ethynyl-6-fluoronaphthalen-2-ol (15.4 mg, 12% yield) as a white solid. ESI-MS m/z = 562.30 $[M+H]^+$; Calculated MW: 561.3.

¹H NMR (400 MHz, DMSO-*d*₆) δ 9.84 (s, 1H), 7.85 (ddd, *J* = 8.8, 6.2, 1.8 Hz, 1H), 7.54 (dt, *J* = 48.7, 6.2 Hz, 1H), 7.40 (td, *J* = 9.0, 1.9 Hz, 1H), 7.21 – 6.99 (m, 2H), 5.45 – 5.01 (m, 3H), 4.86 (d, *J* = 1.3

Hz, 1H), 4.33 – 3.68 (m, 4H), 3.43 (s, 1H), 3.25 – 3.18 (m, 1H), 3.12 – 2.52 (m, 7H), 2.14 – 1.33 (m, 10H).

Example 15: N-(4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-8-ethynyl-7-fluoro-3-hydroxy-1-naphthamide



5

Step 1: tert-Butyl 3-(4-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)-1-naphthamido)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

A mixture of 7-fluoro-3-(methoxymethoxy)-8-[2-((triisopropylsilyl)ethynyl)naphthalene-1-carboxamide (190.0 mg, 0.44 mmol, 1.0 equiv) and tert-butyl 3-(4-[[[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-chloro-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (426.5 mg, 0.88 mmol, 2.0 equiv), Cs₂CO₃ (288.1 mg, 0.88 mmol, 2.0 equiv), XPhos (126.4 mg, 0.26 mmol, 0.6 equiv) and XPhos Pd G3 (112.2 mg, 0.13 mmol, 0.3 equiv) in dioxane was stirred 16h at 80 °C under nitrogen atmosphere. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.1% FA), 0% to 100% gradient in 40 min; detector, UV 254 nm to afford tert-Butyl 3-(4-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)-1-naphthamido)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

(200 mg, 65%) as a reddish solid. ESI-MS m/z = 876.56 [M+H]⁺; Calculated MW: 875.46

Step 2: tert-butyl 3-(4-(8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthamido)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

The mixture of tert-Butyl 3-(4-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)-1-naphthamido)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

(200.0 mg, 0.22 mmol, 1.0 equiv) and CsF (173.3 mg, 1.1 mmol, 5.0 equiv) in DMF was stirred for 0.5 h at room temperature under nitrogen atmosphere. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with water and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to afford *tert*-butyl 3-(4-(8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthamido)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (160.0 mg, 65% yield) as a reddish solid. ESI-MS *m/z* = 720.31; [M+H]⁺; Calculated MW: 719.32

Step 3: N-(4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-8-ethynyl-7-fluoro-3-hydroxy-1-naphthamide

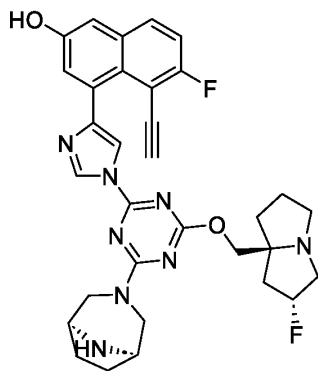
A mixture of *tert*-butyl 3-(4-(8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthamido)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

(160.0 mg, 0.15 mmol, 1.0 equiv) and HCl(gas) in dioxane (5 mL) was stirred for 3h at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under vacuum. The crude product was purified by prep-HPLC with the following conditions (NH₄HCO₃/MeCN/H₂O) to afford N-(4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-8-ethynyl-7-fluoro-3-hydroxy-1-naphthamide (36.3 mg, 40% yield) as a light yellow solid.

ESI-MS *m/z* = 576.24; [M+H]⁺; Calculated MW: 575.25

¹H NMR (400 MHz, DMSO-*d*₆) δ 10.88 – 10.83 (m, 1H), 10.01 (s, 1H), 7.91 – 7.85 (m, 1H), 7.51 – 7.42 (m, 1H), 7.23 (s, 1H), 6.90 (s, 1H), 5.21 (d, *J* = 54.2 Hz, 1H), 4.55 (s, 1H), 4.00 – 3.93 (m, 1H), 3.81 – 3.52 (m, 2H), 3.25 (s, 1H), 3.07 – 2.85 (m, 3H), 2.83 – 2.61 (m, 3H), 2.27 – 2.23 (m, 1H), 2.08 – 1.74 (m, 5H), 1.74 – 1.58 (m, 3H), 1.55 – 1.14 (m, 3H), 0.80 – 0.75 (m, 1H).

Example 16: 4-(1-(4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-1H-imidazol-4-yl)-5-ethynyl-6-fluoronaphthalen-2-ol



Step 1: Tert-butyl (1R,5S)-3-(4-((2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl)methoxy)-6-(4-iodoimidazol-1-yl)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

To a stirred mixture of tert-butyl (1R,5S)-3-(4-((2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl)methoxy)-6-chloro-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.00 g, 2.07 mmol, 1.0 equiv) and Cs₂CO₃ (2.02 g, 6.21 mmol, 3.0 equiv) in DMF (20 mL) was added 4-iodo-1H-imidazole (601.4 mg, 3.10 mmol, 1.5 equiv) in portions at 25 °C. The resulting mixture was stirred for 16 h at 100 °C under nitrogen atmosphere. The mixture was allowed to cool down to 20°C. The resulting mixture was diluted with water (50 mL). The resulting mixture was extracted with EtOAc (3x50 mL). The combined organic layers were washed with brine (3x50 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with DCM/MeOH (10:1) and the pure fraction was concentrated to afford tert-butyl (1R,5S)-3-(4-((2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl)methoxy)-6-(4-iodoimidazol-1-yl)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (860.0 mg, 65% yield) as a brown solid. ESI-MS m/z = 641.1 M+H]⁺; Calculated MW: 640.1

Step 2: Tert-butyl (1R,5S)-3-(4-((2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl)methoxy)-6-(4-[7-fluoro-3-(methoxymethoxy)-8-[2-(triisopropylsilyl)ethynyl]naphthalen-1-yl]imidazol-1-yl)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

To a stirred mixture of tert-butyl (1R,5S)-3-(4-((2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl)methoxy)-6-(4-iodoimidazol-1-yl)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (500.0 mg, 0.78 mmol, 1.0 equiv) and {2-[2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl]ethynyl}triisopropylsilane (600.1 mg, 1.17 mmol, 1.5 equiv) in water (2 mL) and dioxane (10 mL) were added K₂CO₃ (323.6 mg, 2.34 mmol, 3.0 equiv) and butyl[(3R,5S,7s)-adamantan-1-yl][(1s,3R,5S,7s)-adamantan-1-yl]phosphane {2'-amino-[1,1'-biphenyl]-2-yl}palladium(II) methanesulfonate (113.7 mg, 0.16 mmol, 0.2 equiv) in portions at 20°C. The resulting mixture was stirred for 2 h at 100 °C under nitrogen atmosphere. The mixture was

allowed to cool down to 20°C. The resulting mixture was diluted with water (100 mL). The resulting mixture was extracted with EtOAc (3x100 mL). The combined organic layers were washed with brine (3x100 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1:1) and the pure fraction was concentrated to afford tert-butyl (1R,5S)-3-(4-([(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy)-6-{4-[7-fluoro-3-(methoxymethoxy)-8-[2-(triisopropylsilyl)ethynyl]naphthalen-1-yl]imidazol-1-yl}-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (285.0 mg, 41% yield) as a yellow solid. ESI-MS m/z = 899.4 [M+H]⁺; Calculated MW: 898.4

- 10 Step 3: Tert-butyl (1R,5S)-3-(4-(4-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1H-imidazol-1-yl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

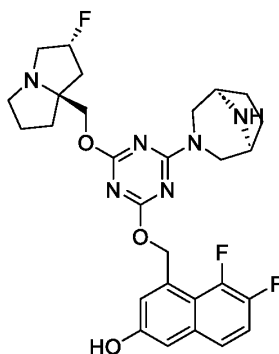
To a stirred mixture of tert-butyl (1R,5S)-3-(4-([(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy)-6-{4-[7-fluoro-3-(methoxymethoxy)-8-[2-(triisopropylsilyl)ethynyl]naphthalen-1-yl]imidazol-1-yl}-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (285.0 mg, 0.32 mmol, 1.0 equiv) in DMF (5 mL) was added CsF (481.4 mg, 3.17 mmol, 10 equiv) in portions at 20°C. The resulting mixture was stirred for 2 h at 20°C. The resulting mixture was concentrated under reduced pressure. The resulting mixture was used in the next step directly without further purification. ESI-MS m/z = 743.3 [M+H]⁺; Calculated MW: 742.3

- 20 Step 4: 4-[1-(4-([(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy)-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-1,3,5-triazin-2-yl)imidazol-4-yl]-5-ethynyl-6-fluoronaphthalen-2-ol; formic acid

A mixture of tert-butyl (1R,5S)-3-(4-([(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy)-6-{4-[8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl]imidazol-1-yl}-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (280.0 mg, 0.38 mmol, 1.0 equiv) in MeCN (4 mL) was added HCl(gas) in dioxane (4 mL, 4M) and the resulting mixture was stirred for 2 h at 20 °C under nitrogen atmosphere. The mixture was concentrated to give the product (280.0 mg, crude) which was purified by prep-HPLC with the following conditions (Column: YMC-Actus Triart C18 ExRS Column, 19*150 mm, 5µm; Mobile Phase A: Water (10mmol/L NH₄HCO₃), Mobile Phase B: MeCN; Flow rate: 60mL/min; Gradient: 36%B to 56%B in10min; wavelength: 254nm/220 nm; RT1(min): 6.4). The pure fraction was lyophilized to afford 4-[1-(4-([(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy)-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-1,3,5-triazin-2-yl)imidazol-4-yl]-5-ethynyl-6-fluoronaphthalen-2-ol (47.0 mg, 21% yield) as a yellow solid. ESI-MS m/z = 599.2 [M+H]⁺; Calculated MW:598.2. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.63 (s, 1H), 8.24 (s, 1H), 7.90 (t, *J* = 10.4,

0.0 Hz, 2H), 7.48 – 7.08 (m, 3H), 5.28 (d, $J = 54.1$ Hz, 1H), 4.56 (d, $J = 13.0$ Hz, 1H), 4.38 (d, $J = 12.3$ Hz, 1H), 4.24 (s, 1H), 4.10 (dt, $J = 43.5, 10.2$ Hz, 2H), 3.75 (s, 2H) 3.05 (d, $J = 30.1$ Hz, 3H), 2.83 (s, 1H), 2.20-1.83 (m, 3H), 1.81 (d, $J = 31.8$ Hz, 5H), 1.61 (s, 2H).

Example 17: 4-(((4-(((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-(((2R,7aS)-2-fluorotetrahydro-
5 1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)oxy)methyl)-5,6-difluoronaphthalen-2-ol



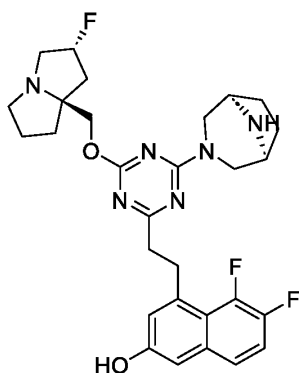
Step 1: Tert-butyl (1R,5S)-3-(4-{[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-{[7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl]methoxy}-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

10 To a stirred solution of [7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl]methanol (252.7 mg, 0.99 mmol, 1.2 equiv) in THF (5 mL) was added LiHMDS (0.76 mL, 0.99 mmol, 1.2 equiv, 1.3 M in THF) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 0 °C under nitrogen atmosphere. To the above mixture was added tert-butyl (1R,5S)-3-(4-{[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-chloro-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-
15 carboxylate (100.0 mg, 0.20 mmol, 1.0 equiv) at 0 °C. The resulting mixture was stirred for additional 2 h at 20 °C. The resulting mixture was diluted with water (10 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (3 x 10 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (10:1), and the pure
20 fraction was concentrated under reduced pressure to afford tert-butyl (1R,5S)-3-(4-{[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-{[7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl]methoxy}-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (280.0 mg, 48% yield) as a brown solid. ESI-MS $m/z = 701.3$ [M+H]⁺; Calculated MW: 700.3

Step 2: 4-{[(4-{[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-1,3,5-triazin-2-yl)oxy]methyl}-5,6-difluoronaphthalen-2-ol
25

Into a 8 mL vial were added tert-butyl (1R,5S)-3-(4-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-[[7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl]methoxy}-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (130.0 mg, 0.18 mmol, 1.0 equiv) and HCOOH (2 mL) at 20 °C. The resulting mixture was stirred for 2h at 20 °C under nitrogen atmosphere. The resulting mixture was concentrated under vacuum. The crude product (130.0 mg) was purified by prep-HPLC with the following conditions (Column: Kinetex EVO C18 Column, 30*150 mm, 5µm; Mobile Phase A: water (10mmol/L NH₄HCO₃), Mobile Phase B: MeCN; Flow rate: 60 mL/min mL/min; Gradient: 29% B to 38% B in 10 min; wavelength: 254nm/220nm nm; RT1(min): 9.8). The pure fraction was concentrated and lyophilized to afford 4-[[4-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-1,3,5-triazin-2-yl)oxy]methyl}-5,6-difluoronaphthalen-2-ol (26.9 mg, 26% yield) as a white solid. ESI-MS *m/z* = 557.4 [M+H]⁺; Calculated MW: 556.2. ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.12 (brs, 1H), 7.70-7.45 (m, 2H), 7.32 (d, *J* = 2.3 Hz, 1H), 7.20 (t, *J* = 2.2 Hz, 1H), 5.86-5.65 (m, 2H), 5.23 (d, *J* = 54.3 Hz, 1H), 4.21 (d, *J* = 12.5 Hz, 2H), 4.09 – 3.83 (m, 2H), 3.43 (s, 2H), 3.09 – 2.74 (m, 7H), 2.11-2.03 (m, 1H), 2.01-1.89 (m, 2H), 1.87 – 1.66 (m, 3H), 1.65-1.56 (m, 2H), 1.53-1.40 (m, 2H).

Example 18: 4-(2-(4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)ethyl)-5,6-difluoronaphthalen-2-ol



Step 1: Tert-butyl (1R,5S)-3-(4-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-(E)-2-[7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl]ethenyl]-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

To a stirred mixture of tert-butyl (1R,5S)-3-(4-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-ethenyl-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.00 g, 2.11 mmol, 1.0 equiv) and 8-bromo-1,2-difluoro-6-(methoxymethoxy)naphthalene (702.5 mg, 2.32 mmol, 1.1 equiv) in dioxane (2 mL) were added DIEA (817.0 mg, 6.32 mmol, 3.0 equiv), PPh₃ (55.3 mg, 0.21 mmol, 0.1 equiv) and Pd(OAc)₂ (47.3 mg, 0.21 mmol, 0.1 equiv) in portions at 100 °C under

nitrogen atmosphere. The resulting mixture was stirred for 16h at 100 °C under nitrogen atmosphere. The mixture was allowed to cool down to 20°C. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (1:4) to afford tert-butyl (1R,5S)-3-(4-[[[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-[(E)-2-
5 [7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl]ethenyl]-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (420.0 mg, 29% yield) as a yellow solid. ESI-MS m/z = 697.3 [M+H]⁺; Calculated MW: 696.3

Step 2: Tert-butyl (1R,5S)-3-(4-[[[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-{2-[7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl]ethyl]-1,3,5-triazin-2-yl)-3,8-
10 diazabicyclo[3.2.1]octane-8-carboxylate

To a stirred mixture of tert-butyl (1R,5S)-3-(4-[[[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-[(E)-2-[7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl]ethenyl]-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (400.0 mg, 0.57 mmol, 1.0 equiv) in EtOAc (10 mL) was added Pd(OH)₂/C (305.5 mg, 2.87 mmol, 5.0 equiv) in portions at 20 °C under
15 nitrogen atmosphere. The resulting mixture was stirred for 1h at 20 °C under H₂. The resulting mixture was filtered and the filter cake was washed with EtOAc (3x10 mL). The filtrate was concentrated under reduced pressure. This resulted in tert-butyl (1R,5S)-3-(4-[[[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-{2-[7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl]ethyl]-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (210.0 mg, 52% yield) as a
20 white solid. ESI-MS m/z = 699.3 [M+H]⁺; Calculated MW: 698.3.

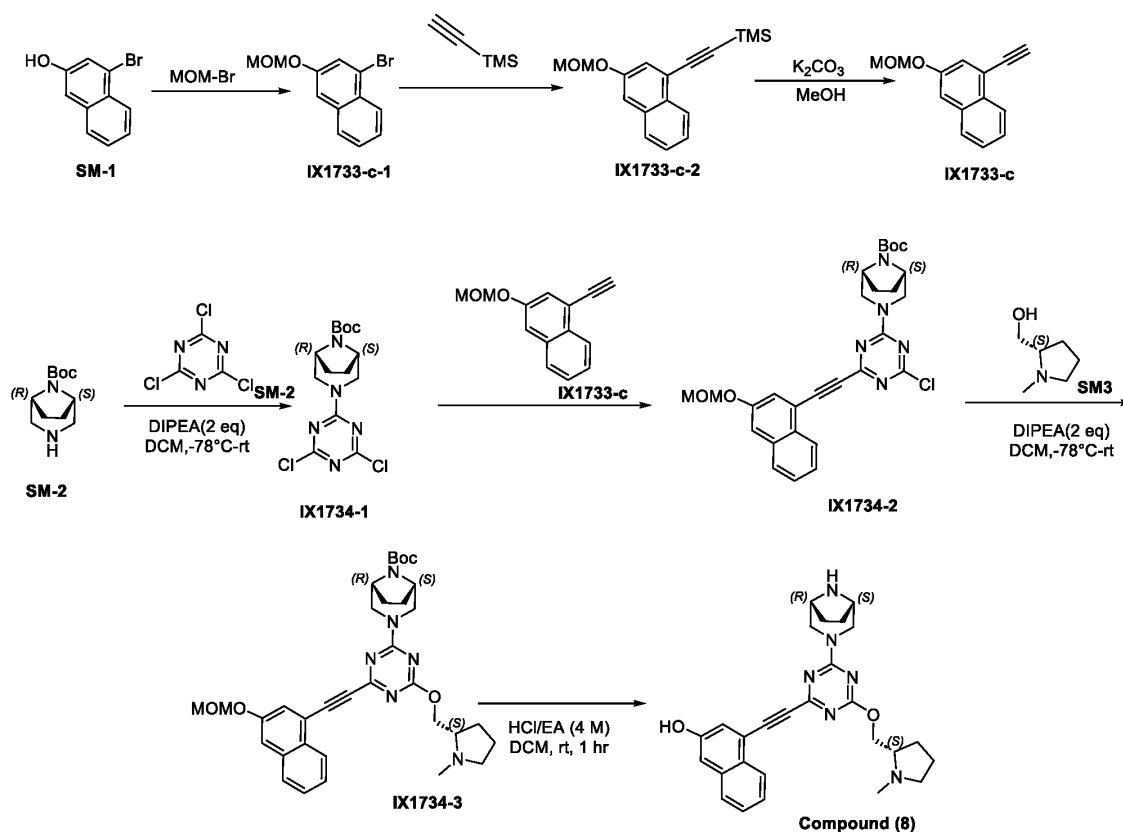
Step 3: 4-[2-(4-[[[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-1,3,5-triazin-2-yl)ethyl]-5,6-difluoronaphthalen-2-ol

Into a 8 mL vial were added tert-butyl (1R,5S)-3-(4-[[[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-{2-[7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl]ethyl]-1,3,5-triazin-2-yl)-3,8-
25 diazabicyclo[3.2.1]octane-8-carboxylate (180.0 mg, 0.26 mmol, 1.0 equiv) and HCOOH (2 mL) at 20°C. The resulting mixture was stirred for 16 h at 20 °C. The resulting mixture was concentrated under reduced pressure. The crude product (100.0 mg) was purified by prep-HPLC with the following conditions (Column: Kinetex EVO C18 Column, 30*150 mm, 5µm; Mobile Phase A: Water (10mmol/L NH₄HCO₃), Mobile Phase B: MeCN; Flow rate: 60 mL/min mL/min; Gradient: 32% B to
30 40% B in 10 min; wavelength: 254nm/220nm nm; RT1(min): 9.1). The pure fraction was lyophilized to afford 4-[2-(4-[[[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-1,3,5-triazin-2-yl)ethyl]-5,6-difluoronaphthalen-2-ol (17.4 mg, 12% yield) as a white solid. ESI-MS m/z = 555.3 [M+H]⁺; Calculated MW: 554.3.

^1H NMR (400 MHz, DMSO- d_6) δ 9.97 (s, 1H), 7.64 – 7.41 (m, 2H), 7.02 (d, J = 20.7 Hz, 2H), 5.24 (d, J = 54.3 Hz, 1H), 4.25 (dd, J = 33.1, 12.5 Hz, 2H), 3.93 (dt, J = 42.1, 10.5 Hz, 2H), 3.51 – 3.38 (m, 4H), 3.08 – 2.77 (m, 8H), 2.06 (s, 1H), 2.00 – 1.88 (m, 2H), 1.85 – 1.67 (m, 3H), 1.65 – 1.54 (m, 2H), 1.45 (q, J = 8.3, 6.0 Hz, 2H). ^{19}F NMR (377 MHz, DMSO) δ -144.21, -146.09, -172.13.

5 **Example 19:** Synthesis of compound (8)

Compound (8) was synthesized based on the chemistry shown in the reaction scheme below:

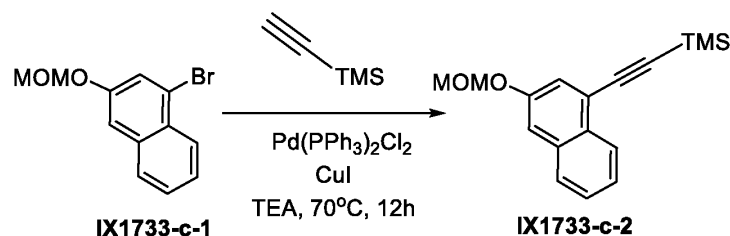


a. Synthesis of EXP-21-IX1733-c-1



To a solution of **SM-1** (25 g, 112 mmol) in 500 mL of DCM was added DIPEA(36.1 g, 2.5 eq) at 0°C, MOM-Br (23.8 g) was added and stirred at 0°C for 1 hr. The mixture was concentrated to give **IX1733-c-1**(21 g, 70%) as yellow oil.

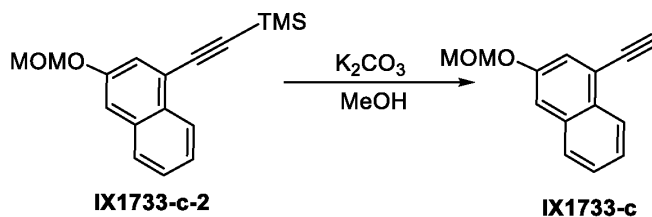
b. Synthesis of EXP-21-IX1733-c-2



5

To a solution of **IX1733-c-1** (5 g, 18.7 mmol) in 50 mL TEA was added PdCl₂(PPh₃)₂(657 mg, 0.05 eq) and CuI(356 mg, 0.1 eq) at 0°C, Trimethylsilylacetylene (3.68 g) was added and stirred at 70°C for 12 hrs. The mixture was concentrated and purified by gel column to give **IX1733-c-2**(5 g, 94%) as yellow solid.

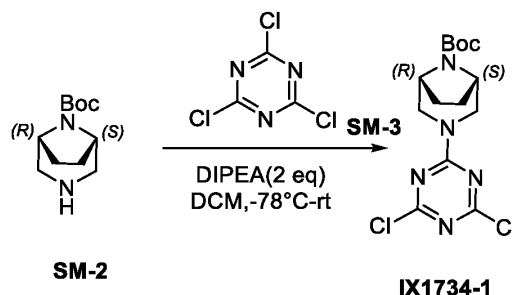
10 c. Synthesis of EXP-21-IX1733-c



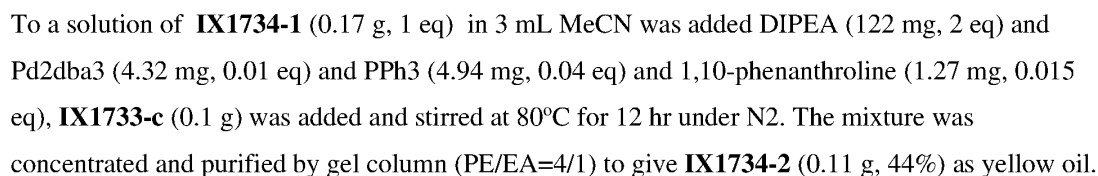
To a solution of **IX1733-c-2**(5 g, 17.6 mmol) in 50 mL MeOH was added K₂CO₃ (4.86 g, 2 eq) and stirred at rt for 2 hrs. The mixture was concentrated and purified by gel column to give **IX1733-**

15 **c**(3.1 g, 84%) as yellow solid.

d. Synthesis of EXP-21-IX1734-1

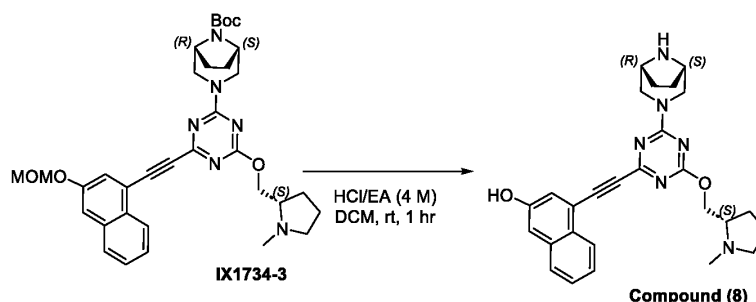


e. Synthesis of EXP-21-IX1734-2



253

g. Synthesis of Compound (8)



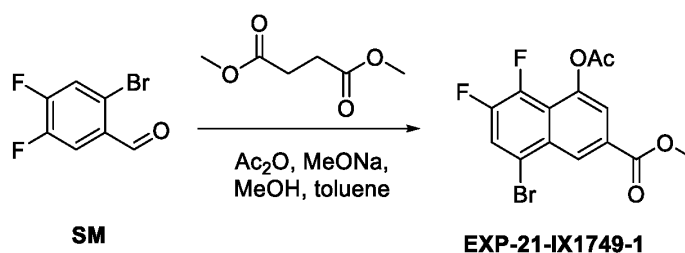
To a solution of **IX1734-3** (0.08 g, 1 eq) in 3 mL EtOAc was added HCl/EtOAc (1 mL, 4 M) at 0°C and stirred at rt for 1 hr. The mixture was diluted with EtOAc, washed by NaHCO₃(sat), separated, and the organic layer was concentrated and purified by reverse combi-flash(0 to 90% MeCN in water) to give **Compound (8)** (32 mg, 52%) as yellow solid. LCMS; M+H=471, Ref=1.937 mins.

¹H NMR (500 MHz, CDCl₃) δ 8.32 (d, J = 6.4 Hz, 1H), 7.66 (dd, J = 8.0, 3.9 Hz, 1H), 7.45 – 7.36 (m, 3H), 7.23 (d, J = 2.5 Hz, 1H), 4.46 – 4.17 (m, 4H), 3.56 (s, 2H), 3.17 – 2.89 (m, 3H), 2.78 (d, J = 14.2 Hz, 2H), 2.58 (d, J = 6.9 Hz, 3H), 2.34 (s, 2H), 2.05 (d, J = 11.9 Hz, 3H), 1.88 (s, 2H), 1.61 (d, J = 6.8 Hz, 1H).

Example 20: Synthesis of Compound (1)

Compound (1) was synthesized based on the chemistry shown in the reaction scheme of Fig. 1 and as now explained in further detail below.

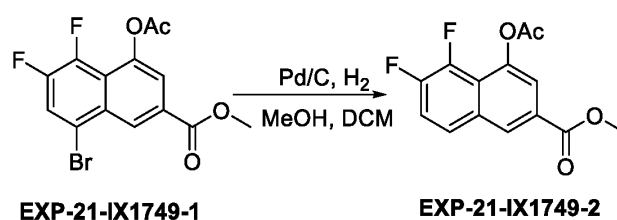
a. Synthesis of EXP-21-IX1749-1



To a solution of dimethyl butanedioate (49.6 g, 339 mmol) in toluene (400 mL) was added MeONa (20.8, 30% solution in MeOH) under N₂, the mixture was stirred at 70 °C under N₂ for 30 minutes, and then a solution of 2-bromo-4,5-difluorobenzaldehyde (25 g, 113 mmol) in toluene (100 mL) was added dropwise, after addition the mixture was heated at 85 °C for 5 hours. The mixture was cooled down to room temperature, poured into water (200 mL) and washed with Et₂O (100 mL x 2). The

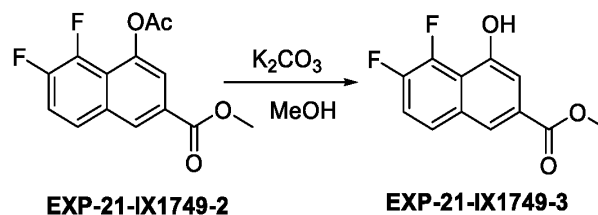
water layer was acidified to pH 2 and extracted with EtOAc (100 mL x 2), the combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated to leave a residue. To the residue was added Ac₂O (85 mL) and NaOAc (11.1 g), the resulting mixture was stirred at 140 °C overnight. The mixture was concentrated in vacuum, the residue was diluted with water (100 mL), acidified to pH 2 and extracted with EtOAc (100 mL x 2), the combined organic was washed with brine (100 mL), dried over anhydrous Na₂SO₄, concentrated and purified by column chromatography (0~50% DCM in petrol) to give the target product of methyl 4-acetoxy-8-bromo-5,6-difluoro-naphthalene-2-carboxylate (19 g, 35% yield).

b. Synthesis of EXP-21-IX1749-2



A mixture of methyl 4-acetoxy-8-bromo-5,6-difluoro-naphthalene-2-carboxylate (25.6 g, 49.9 mmol) and Pd-C (10%, 10.6 g) in DCM (200 mL) and MeOH (200 mL) was stirred at room temperature under H₂ (1 atm) for 2 h. LCMS showed the start material was consumed. The mixture was filtered and concentrated to leave the crude product, which was used in the next step without further purification.

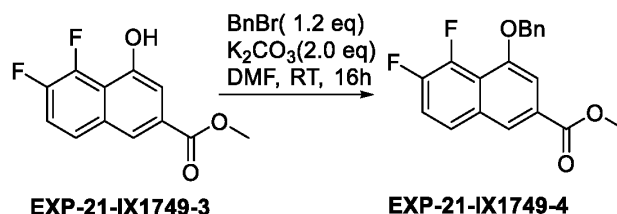
c. Synthesis of EXP-21-IX1749-3



A mixture of methyl 4-acetoxy-5,6-difluoro-naphthalene-2-carboxylate (17.2 g, 43 mmol) and K₂CO₃ (23.9 g, 129 mmo) in MeOH (400 mL) was stirred at room temperature for 3 h. The mixture was concentrated in vacuum, the residue was diluted with water (400 mL) and extracted with DCM (400 mL*2), the combined organic layer was dried over anhydrous Na₂SO₄, concentrated and purified by column chromatography (0~40% DCM in Petrol) to give the target product of methyl 5,6-difluoro-4-hydroxy-naphthalene-2-carboxylate (8.6 g, 75% yield).

LCMS: RT: 2.52 min; M+1=239.2

d. Synthesis of EXP-21-IX1749-4



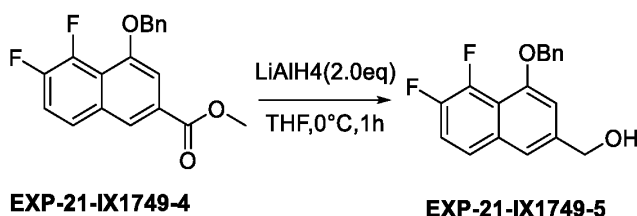
5

A mixture of methyl 5,6-difluoro-4-hydroxy-naphthalene-2-carboxylate (8.6 g, 36.1 mmol), BnBr (7.41 g, 43.3 mmol) and K₂CO₃ (9.98 g, 72.2 mmol) in DMF (150 mL) was stirred at room temperature overnight. The mixture was diluted with water (500 mL) and extracted by EtOAc (1000 mL), the organic was washed with saturated LiCl solution (200 mL x 3), dried over anhydrous Na₂SO₄, concentrated and purified by column chromatography (0~60% DCM in Petrol) to give the target product of methyl 4-benzyloxy-5,6-difluoro-naphthalene-2-carboxylate (10.2 g, 82% yield).

10

LCMS: RT: 2.19 min; M+23=341.1

e. Synthesis of EXP-21-IX1749-5



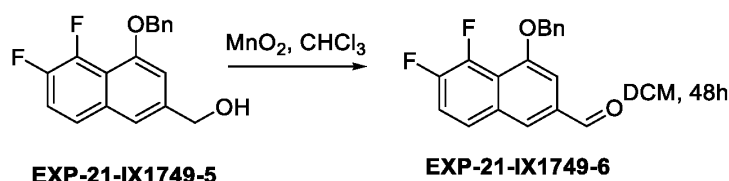
15

To a stirred solution of methyl 4-benzyloxy-5,6-difluoro-naphthalene-2-carboxylate (1.2 g, 3.66) in THF (20 mL) was added LiAlH₄ solution (3.66 mL, 2 M in THF, 2.0 eq) at 0 °C dropwise under N₂, the mixture was stirred at 0 °C for 1 h, quenched carefully with 10% NaOH solution (5 mL) at 0 °C and diluted with EtOAc (100 mL), the organic was washed with water (200 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to leave crude product of (4-benzyloxy-5,6-difluoro-2-(hydroxymethyl)naphthalene) as yellow solid (0.7 g, 63.8% yield).

20

LCMS: RT: 2.03 min; M+23=323.1

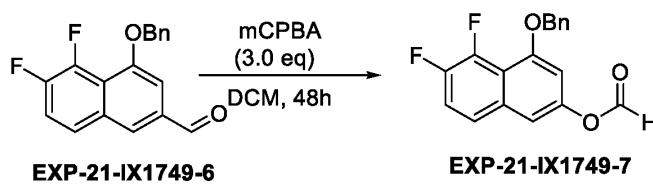
f. Synthesis of EXP-21-IX1749-6



- 5 To a stirred solution of (4-benzyloxy-5,6-difluoro-2-naphthyl) methanol (12 g, 1.0 eq) in CHCl_3 (150 mL) was added MnO_2 (17.4 g, 5.0 eq) at rt, then the mixture was stirred at reflux under N_2 for 2 hours, the mixture was filtered and the filtrate was concentrated to leave crude product of 4-benzyloxy-5,6-difluoro-naphthalene-2-carbaldehyde (5.6 g, 47% yield) as yellow solid.

LCMS: RT: 2.20 min; $\text{M}+1=299.1$

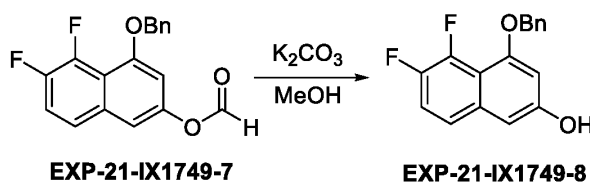
10 g. Synthesis of EXP-21-IX1749-7



- To a stirred solution of 4-benzyloxy-5,6-difluoro-naphthalene-2-carbaldehyde (5.6 g, 1.0 eq) in DCM (100 mL) was added m-CPBA (9.72 g, 3.0 eq) at rt, then the mixture was stirred at rt for 12 h, the mixture was partitioned between DCM (100 mL) and Na_2SO_3 solution (150 mL), the organic layer was separated, dried and concentrated to dryness to leave the crude product of [7,8-difluoro-3-(methoxymethoxy)-1-naphthyl] trifluoromethanesulfonate (5.3 g, 75.8% yield) as yellow solid.

LCMS: RT: 2.17 min; $\text{M}+1=315.0$

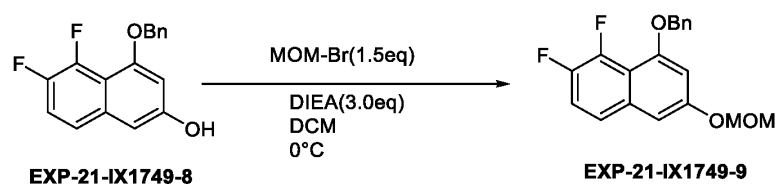
h. Synthesis of EXP-21-IX1749-8



To a stirred solution of (4-benzyloxy-5,6-difluoro-2-naphthyl) formate (5.3 g, 1.0 eq) in MeOH (50 mL) and DCM (50 mL) was added K₂CO₃ (11.7 g, 5.0 eq) at rt, then the mixture was stirred at rt for 12 h. The mixture was filtered and the filtrate was concentrated and purified by column chromatography on silica gel (DCM in PE=90%) to afford the product of 4-benzyloxy-5,6-difluoro-naphthalen-2-ol (1.2 g, 24.9% yield) as yellow solid.

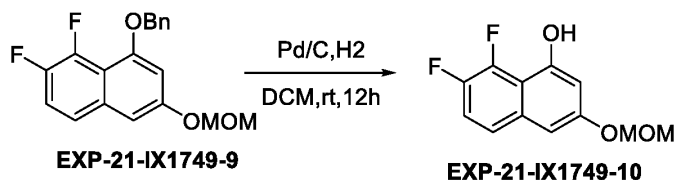
LCMS: RT: 2.08 min; MS was weak

i. Synthesis of EXP-21-IX1749-9



To a stirred solution of 4-benzyloxy-5,6-difluoro-naphthalen-2-ol (400 mg, 1.4 mmol) in DCM (5 mL) was added DIEA (483 mg), the mixture was cooled to 0°C, bromo(methoxy)methane (262 mg, 1.5 eq) was added by dropwise, then the mixture was stirred at 0 °C under N₂ for 1 h. The mixture was concentrated and purified by column chromatography on silica gel (DCM in PE=13%) to afford the product of 8-benzyloxy-1,2-difluoro-6-(methoxymethoxy)naphthalene (180 mg, 39% yield) as white solid.

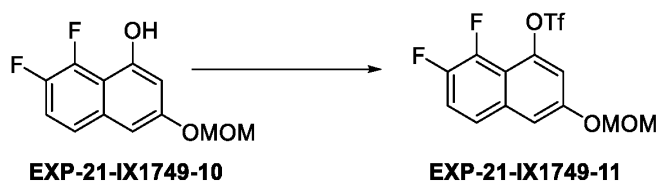
Synthesis of compound EXP-21-IX1749-10



To a stirred solution of 8-benzyloxy-1,2-difluoro-6-(methoxymethoxy)naphthalene (1 g, 1.0 eq) in DCM (20 mL) was added Pd/C (10%, 200 mg), the mixture was stirred at rt under H₂ (1 atm) for 2 h and filtered, the filtrate was concentrated to dryness to leave the crude product of 7,8-difluoro-3-(methoxymethoxy)naphthalen-1-ol (680 mg, 93.5%) as white solid.

LCMS: RT: 1.87 min; MS was weak

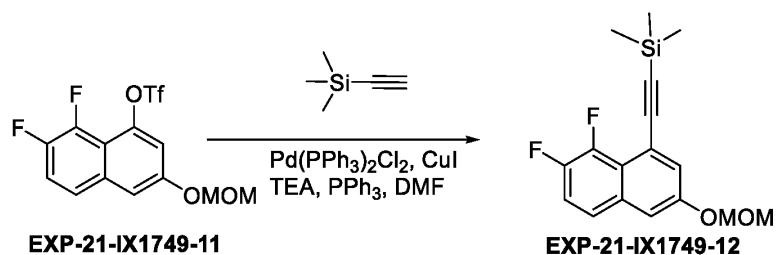
j. Synthesis of compound EXP-21-IX1749-11



5 To a stirred solution of 7,8-difluoro-3-(methoxymethoxy)naphthalen-1-ol (620 mg, 2.58 mmol) in DCM (15 mL) was added DIEA (1.33 g, 10.3 mmol) under N₂, the mixture was cooled to 0°C, Tf₂O (2.91 g, 10.3 mmol) was added and the resulting mixture was stirred at 0 °C for 1 h. The mixture was eluted with DCM (15 mL), washed by brine (10 mL), dried over anhydrous Na₂SO₄, concentrated and purified by column chromatography on silica gel (0~85% DCM in petrol) to give the target product (510 mg, 53% yield).

10 LCMS: RT: 2.20 min; MS was weak

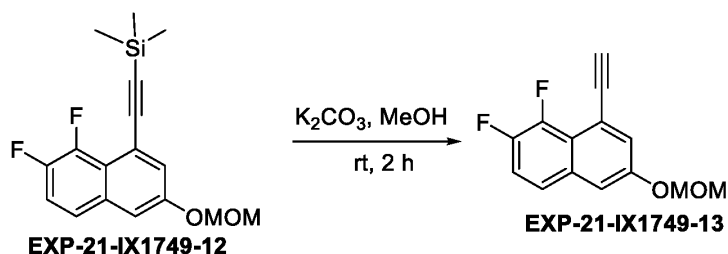
k. Synthesis of EXP-21-IX1749-12



15 A mixture of [7,8-difluoro-3-(methoxymethoxy)-1-naphthyl] trifluoromethanesulfonate (510 mg, 1.37 mmol), CuI (26.1 mg, 0.14 mmol), Pd(PPh₃)₂Cl₂ (96.2 mg, 0.14 mmol), PPh₃ (71.9 mg, 0.27 mmol) and ethynyl(trimethyl)silane (404 mg, 4.11 mmol) in TEA (2 mL) and DMF (6 mL) was heated in a sealed tube at 80 °C under N₂ for 4 h. The mixture was diluted with EtOAc (20 mL), washed with brine (20 mL), dried over anhydrous Na₂SO₄, concentrated and purified by column chromatography (0~100% DCM in Petrol) to give the target product (365 mg, 83% yield).

20 LCMS: RT: 2.43 min, MS was weak

l. Synthesis of EXP-21-IX1749-13

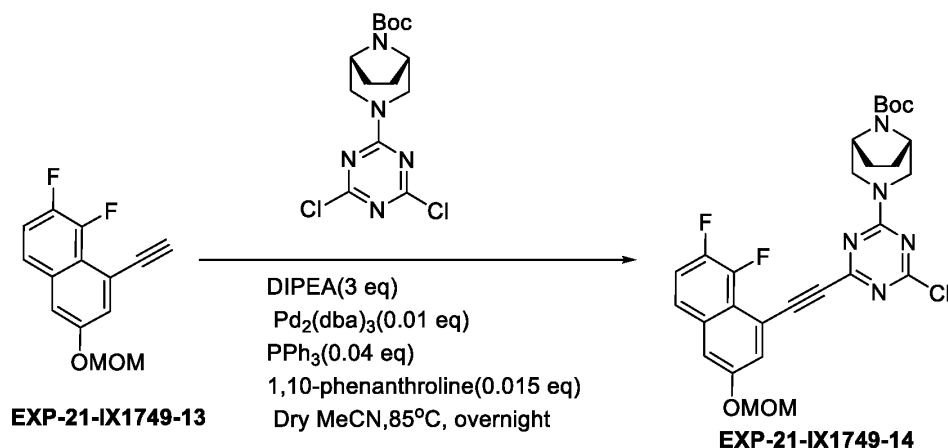


5

A solution of 2-[7,8-difluoro-3-(methoxymethoxy)-1-naphthyl]ethynyl-trimethyl-silane (365 mg, 1.14 mmol) and K_2CO_3 (476 mg, 3.42 mmol) in MeOH (6 mL) was stirred at rt for 2 h. The mixture was concentrated and purified by column chromatograph (0~100% DCM in Petrol) to give the target product (210 mg, 74% yield) as a gray solid.

10 LCMS: RT: 2.11 min; MS was weak

m. Synthesis of EXP-21-IX1749-14



To a solution of 8-ethynyl-1,2-difluoro-6-(methoxymethoxy)naphthalene (210 mg, 0.846 mmol) in MeCN (5 mL) was added DIEA (328 mg, 2.54 mmol), Pd_2dba_3 (77.5 mg, 0.085 mmol), PPh_3 (22.2 mg, 0.085 mmol), 1,10-phenanthroline (15.2 mg, 0.085 mmol) and tert-butyl (1S,5R)-3-(4,6-dichloro-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (457 mg, 1.27 mmol), and the mixture was stirred at 85°C under N_2 overnight. The mixture was concentrated and purified by column chromatography on silica gel (0~70% DCM in Petrol) to give EXP-21-IX1749-14 (180 mg, 37% yield)

yellow

solid.

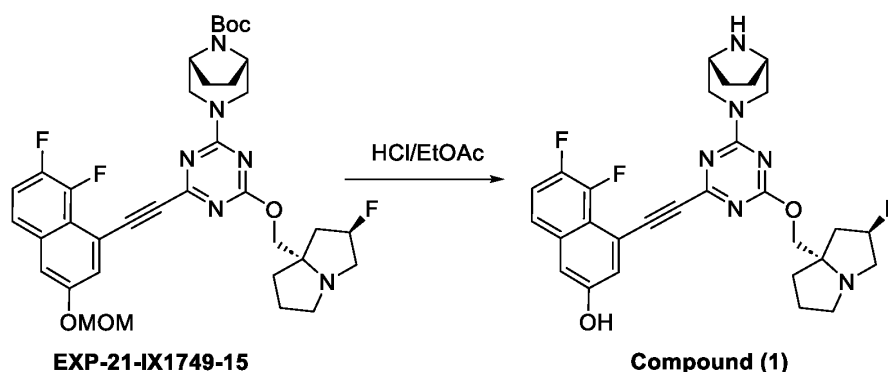
n.



10

15

o. Synthesis of Compound (1)



- 5 To a solution of EXP-21-IX1749-15 (100 mg, 0.13 mmol) in EtOAc (5 mL) was added HCl (4 mL, 3 M in dioxane) at room temperature. The mixture was stirred at rt for 6 hours and neutralized by saturated NaHCO₃ solution, the mixture was extracted with EtOAc (50 mL), the organic layer was dried over anhydrous Na₂SO₄, concentrated and purified by prep-HPLC (MeCN/H₂O/0.05% NH₃·H₂O) to give the target product (11.9 mg, 0.022 mmol, 17% yield) as a yellow solid.

- 10 LCMS: RT: 1.76 min; M+1=551.2

¹H NMR (400 MHz, CD₃OD) δ (ppm) 7.60 – 7.50 (m, 2H), 7.41 (td, *J* = 9.6, 7.4 Hz, 1H), 7.29 (t, *J* = 1.8 Hz, 1H), 5.44 – 5.20 (m, 1H), 4.53 (dd, *J* = 36.9, 13.0 Hz, 2H), 4.19 (dd, *J* = 26.7, 10.7 Hz, 2H), 3.68 (s, 2H), 3.23 (dt, *J* = 24.8, 7.3 Hz, 5H), 3.02 (td, *J* = 9.3, 5.7 Hz, 1H), 2.26 (ddd, *J* = 24.3, 17.1, 6.1 Hz, 2H), 2.08 (d, *J* = 9.1 Hz, 1H), 2.03 – 1.81 (m, 5H), 1.79 – 1.68 (m, 2H).

- 15 **Example 21:** Synthesis of compound (**55**): (*S*)-4-(3-(4-(((1*R*,5*S*)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-2-amino-4-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile

Compound (**55**) was synthesised according to the synthetic route shown in detail in Fig. 2 and as now further described in the following protocol.

- 20 Intermediate 1 was synthesized in line with the method described above. The following steps were then performed:

- (a) to a stirred mixture of intermediate 1 (2.00 g, 4.14 mmol, 1.0 equiv) and Zn(CN)₂ (970.1 mg, 8.28 mmol, 2.0 equiv) in DMF were added Xantphos Pd G4 (800.0 mg, 0.82 mmol, 0.2

equiv) at RT under argon atmosphere. The resulting mixture was stirred for 2h at 80 °C under argon atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:5) to afford *tert*-butyl (1*R*,5*S*)-3-(4-cyano-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.00 g, 51%) as a white solid. ESI-MS *m/z* = 474.2 [M+H]⁺; Calculated MW: 473.3.

(b) to a stirred solution of *tert*-butyl (1*R*,5*S*)-3-(4-cyano-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.50 g, 3.17 mmol, 1.0 equiv) in THF (10 mL) was added NH₂OH (50% in water) (1.05 g, 31.7 mmol, 10 equiv) dropwise at 0 °C under argon atmosphere. The resulting mixture was stirred for additional 1h at RT. The resulting mixture was concentrated under reduced pressure to afford *tert*-butyl (1*R*,5*S*)-3-(4-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-6-(*N*-hydroxycarbamimidoyl)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.50 g, 93% yield) as a yellow solid. ESI-MS *m/z* = 507.3 [M+H]⁺; Calculated MW: 506.3

(c) to a stirred solution of *tert*-butyl (1*R*,5*S*)-3-(4-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-6-(*N*-hydroxycarbamimidoyl)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (750.0 mg, 1.48 mmol, 1.0 equiv) and (*S*)-2-amino-3-cyano-4-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-4-carboxylic acid (524.7 mg, 2.22 mmol, 1.5 equiv) in DMF (10 mL) were added DIEA (1.91 g, 14.8 mmol, 10 equiv) and HATU (1.13 g, 2.96 mmol, 2.0 equiv) at 0 °C under argon atmosphere. The resulting mixture was stirred for additional 1h at 0 °C to RT. The resulting mixture was diluted with water (20 mL). The resulting mixture was extracted with EtOAc. The combined organic layers were washed with NaCl(aq), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1:1) to afford *tert*-butyl (1*R*,5*S*)-3-(4-(*N*-(((*S*)-2-amino-3-cyano-4-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-4-carbonyl)oxy)carbamimidoyl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (900.0 mg, 90% yield) as a brown solid. ESI-MS *m/z* = 725.3 [M+H]⁺; Calculated MW: 724.3. ¹H NMR (400

MHz, DMSO-d₆) δ 8.28 – 8.24 (m, 1H), 7.30 – 7.25 (m, 1H), 6.90 – 6.84 (m, 2H), 5.23 – 5.18 (m, 1H), 4.06 – 4.02 (m, 2H), 3.19 – 3.11 (m, 6H), 2.89 – 2.81 (m, 3H), 2.78 – 2.74 (m, 1H), 2.46 – 2.37 (m, 2H), 2.03 – 1.82 (m, 14H), 1.60 (s, 3H), 1.24 (s, 9H).

- (d) To a stirred solution of *tert*-butyl (1*R*,5*S*)-3-(4-(*N*-(((*S*)-2-amino-3-cyano-4-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-4-carbonyl)oxy)carbamimidoyl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (900.0 mg, 1.24 mmol, 1.0 equiv) in DMF (10 mL) was added DBU (10 mL) dropwise at 25°C under argon atmosphere. The resulting mixture was stirred for additional 1h at 60°C. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (20mL). The resulting mixture was extracted with EtOAc. The combined organic layers were washed with NaCl(aq) dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1:1) to afford *tert*-butyl (1*R*,5*S*)-3-(4-(5-(((*S*)-2-amino-3-cyano-4-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophen-4-yl)-1,2,4-oxadiazol-3-yl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (700.0 mg, 90% yield) as a brown solid. ESI-MS *m/z* = 707.3 [*M*+*H*]⁺; Calculated MW: 706.3. ¹H NMR (400 MHz, DMSO-d₆) δ 7.10 (s, 2H), 5.24 – 5.14 (m, 1H), 4.50 – 4.41 (m, 2H), 4.15 – 4.08 (m, 2H), 3.21 – 3.16 (m, 3H), 3.14 – 3.06 (m, 3H), 3.04 – 2.98 (m, 1H), 2.87 – 2.77 (m, 1H), 2.60 – 2.52 (m, 2H), 2.13 – 1.71 (m, 15H), 1.61 – 1.52 (m, 2H), 1.43 (s, 9H).
- (e) To a stirred solution of *tert*-butyl (1*R*,5*S*)-3-(4-(5-(((*S*)-2-amino-3-cyano-4-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophen-4-yl)-1,2,4-oxadiazol-3-yl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (250.0 mg, 0.35 mmol, 1.0 equiv) in 1,4-dioxane (1mL) was added HCl(gas) in 1,4-dioxane (4mL) dropwise at 0°C under argon atmosphere. The resulting mixture was stirred for additional 1h at 0°C to RT. The resulting mixture was concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep Phenyl OBD Column 19*250 mm, 5m; Mobile Phase A: Water (10mmol/L NH₄HCO₃), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 5% B to 5% B in 1 min, 5% B to 30% B in 2 min, 30% to 47% B in 10 min; wavelength: 254nm/220nm nm; RT1(min): 7.98) to afford (S)-4-(3-(4-((1*R*,5*S*)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-2-amino-4-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (48.6 mg, 22% yield, 95.1% @ 254nm, 97.7% @ 220nm) as a white solid. ESI-MS *m/z* = 607.3

[M+H]⁺ ; Calculated MW: 606.3. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.11 (s, 2H), 5.33-5.20 (m, 1H), 4.40-4.32 (m, 2H), 4.13-4.08 (m, 1H), 3.99-3.97 (m, 1H), 3.64 (s, 1H), 3.17-3.07 (m, 4H), 3.00 (s, 1H), 2.85-2.79 (m, 1H), 2.57-2.53 (m, 2H), 2.12-2.04 (m, 3H), 1.97-1.95 (m, 2H), 1.84-1.75 (m, 8H), 1.72-1.70 (m, 2H), 1.57-1.54 (m, 2H). Total proton count from structure: 35. Total proton count from spectrum: 34.

Example 22: Synthesis of compound (56)

Compound (56) was synthesised according to the synthetic route shown in detail in Fig. 3 and as now further described in the following protocol.

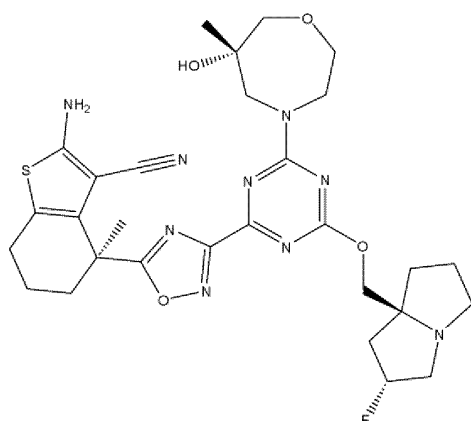
- 10 Synthesis was performed in line with the synthesis of compound (55) according to Example 21, up to and including step (b) of that Example, to generate *tert*-butyl (1*R*,5*S*)-3-(4-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-6-(*N*-hydroxycarbamimidoyl)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.60 g, 99% yield) as a yellow solid. The crude product was used in the next step directly without further purification. ESI-MS *m/z* = 507.3 [M+H]⁺ ; Calculated MW: 506.3.

Subsequently, the following steps were performed:

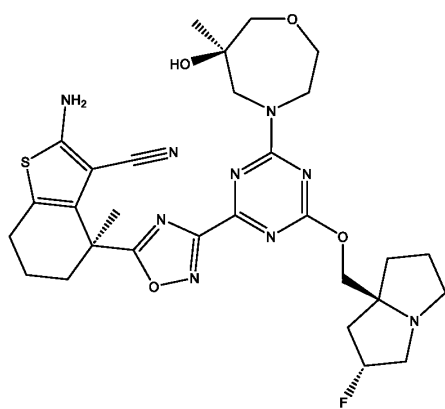
- a. To a stirred solution of *tert*-butyl (1*R*,5*S*)-3-(4-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-6-(*N*-hydroxycarbamimidoyl)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (800.0 mg, 1.58 mmol, 1.0 equiv) and (*R*)-2-amino-3-cyano-4-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-4-carboxylic acid (560.7 mg, 2.37 mmol, 1.5 equiv) in DMF (10 mL) were added DIEA (2.10 g, 15.8 mmol, 10 equiv) and HATU (1.20 g, 3.12 mmol, 2.0 equiv) at 0°C under argon atmosphere. The resulting mixture was stirred for additional 1h at 0°C to RT. The resulting mixture was diluted with water. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with NaCl(aq), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1:1) to afford *tert*-butyl (1*R*,5*S*)-3-(4-(*N*-(((*R*)-2-amino-3-cyano-4-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-4-carbonyl)oxy)carbamimidoyl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.08 g, 94% yield) as a brown solid. ESI-MS *m/z* = 725.3 [M+H]⁺ ; Calculated MW: 724.3
- b. To a stirred solution of *tert*-butyl (1*R*,5*S*)-3-(4-(*N*-(((*R*)-2-amino-3-cyano-4-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-4-carbonyl)oxy)carbamimidoyl)-6-(((2*R*,7*aS*)-2-

fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate(1.00g, 1.38 mmol, 1.0 equiv) in DMF(10 mL) was added DBU(10 mL, 66.9 mmol, 48 equiv) dropwise at 25°C under argon atmosphere. The resulting mixture was stirred for additional 1h at 60°C. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with NaCl(aq), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1:1) to afford *tert*-butyl (1*R*,5*S*)-3-(4-(5-((*R*)-2-amino-3-cyano-4-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophen-4-yl)-1,2,4-oxadiazol-3-yl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1H-pyrrolizin-7a(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate(860.0 mg, 88% yield) as a brown solid. ESI-MS *m/z* = 707.3 [M+H]⁺; Calculated MW: 706.3

- c. To a stirred solution of *tert*-butyl (1*R*,5*S*)-3-(4-(5-((*R*)-2-amino-3-cyano-4-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophen-4-yl)-1,2,4-oxadiazol-3-yl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1H-pyrrolizin-7a(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate(250.0 mg, 0.35 mmol, 1.0 equiv) in 1,4-dioxane(1mL) was added HCl(gas)in 1,4-dioxane (4mL) dropwise at 0°C under argon atmosphere. The resulting mixture was stirred for additional 1h at 0°C to RT. The resulting mixture was concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep Phenyl OBD Column 19*250 mm, 5m; Mobile Phase A: Water(10mmol/L NH₄HCO₃), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 5% B to 5% B in 1 min, 5% B to 30% B in 2 min, 30% to 47% B in 10 min; wavelength: 254nm/220nm nm; RT1(min): 7.98) to afford (*R*)-4-(3-(4-((1*R*,5*S*)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1H-pyrrolizin-7a(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-2-amino-4-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile(117.2 mg, 54% yield, 98.6% @254nm, 99.2% @220nm) as a white solid. ESI-MS *m/z* = 607.3 [M+H]⁺; Calculated MW: 606.3. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.11 (s, 2H), 5.33-5.20 (m, 1H), 4.40-4.22 (m, 2H), 4.15-3.95 (m, 2H), 3.54 (s, 2H), 3.14-2.96 (m, 5H), 2.85-2.79 (m, 1H), 2.57-2.53 (m, 2H), 2.12-2.04 (m, 3H), 1.97-1.95 (m, 2H), 1.84-1.75 (m, 8H), 1.72-1.70 (m, 2H), 1.57-1.54 (m, 2H). Total proton count from structure: 35. Total proton count from spectrum: 34.

Example 23: Synthesis of Compounds (89) and (90)

Compound (89)



Compound (90)

5 **Step 1:** Rac-6-[(tert-butyl)diphenylsilyl]oxy]-6-methyl-1,4-oxazepane

To a stirred mixture of rac-6-methyl-1,4-oxazepan-6-ol hydrochloride (5.00 g, 29.8 mmol, 1.0 equiv), Imidazole (6.09 g, 89.5 mmol, 3.0 equiv) and DIEA (11.57 g, 89.5 mmol, 3.0 equiv) in DCM (100 mL) was added tert-butyl(chloro)diphenylsilane (9.84 g, 35.7 mmol, 1.2 equiv) in portions at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 16 h at 20°C under nitrogen atmosphere. The resulting mixture was diluted with water (30 mL). The resulting mixture was extracted with CH₂Cl₂ (3 x 30 mL). The combined organic layers were washed with brine (2 x 30 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EtOAc (1:10~1:1) and the pure fraction was concentrated to afford Rac-6-[(tert-butyl)diphenylsilyl]oxy]-6-methyl-1,4-oxazepane (6.00 g, 63.5% yield) as a white oil.

ESI-MS m/z = 370.3 $[M+H]^+$; Calculated MW: 369.2

Step 2: Rac-6-[(tert-butyldiphenylsilyl)oxy]-4-(4,6-dichloro-1,3,5-triazin-2-yl)-6-methyl-1,4-oxazepane

- To a stirred mixture of cyanuric chloride (1.20 g, 6.49 mmol, 1.2 equiv) and DIEA (2.10 g, 16.24 mmol, 3.0 equiv) in DCM (30 mL) was added Rac-6-[(tert-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepane (2.00 g, 5.41 mmol, 1.0 equiv) in DCM (10mL) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 20°C under nitrogen atmosphere. The resulting mixture was diluted with water (30 mL). The resulting mixture was extracted with CH₂Cl₂ (3 x 30 mL). The combined organic layers were washed with brine (2 x 30 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EtOAc (1:10~3:2) and the pure fraction was concentrated to afford Rac-6-[(tert-butyldiphenylsilyl)oxy]-4-(4,6-dichloro-1,3,5-triazin-2-yl)-6-methyl-1,4-oxazepane (2.50 g, 89.3% yield) as a yellow oil.
- ESI-MS $m/z = 517.1$ $[M+H]^+$; Calculated MW: 516.2.

Step 3: (2R,7aS)-7a-[(4-[(6RS)-6-[(tert-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl]-6-chloro-1,3,5-triazin-2-yl)oxy)methyl]-2-fluoro-hexahydropyrrolizine

- To a stirred mixture of Rac-6-[(tert-butyldiphenylsilyl)oxy]-4-(4,6-dichloro-1,3,5-triazin-2-yl)-6-methyl-1,4-oxazepane (2.50 g, 4.83 mmol, 1.0 equiv) and Cs₂CO₃ (4.72 g, 14.5 mmol, 3.0 equiv) in ACN (30 mL) was added [(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methanol (692.2 mg, 4.35 mmol, 0.9 equiv) in portions at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 16 h at 20°C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:10~2:1) and the pure fraction was concentrated to afford (2R,7aS)-7a-[(4-[(6RS)-6-[(tert-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl]-6-chloro-1,3,5-triazin-2-yl)oxy)methyl]-2-fluoro-hexahydropyrrolizine (2.40 g, 77.6% yield) as a white solid.
- ESI-MS $m/z = 640.2$ $[M+H]^+$; Calculated MW: 639.3.

Step 4: 4-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-[(6RS)-6-[(tert-butyl)diphenylsilyl]oxy]-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazine-2-carbonitrile

- To a stirred mixture of (2R,7aS)-7a-[(4-[(6RS)-6-[(tert-butyl)diphenylsilyl]oxy]-6-methyl-1,4-oxazepan-4-yl]-6-chloro-1,3,5-triazin-2-yl)oxy)methyl]-2-fluoro-hexahydropyrrolizine (2.40 g, 3.74 mmol, 1.0 equiv) and Zn(CN)₂ (528.2 mg, 4.50 mmol, 1.2 equiv) in DMA (20 mL) was added Xantphos Pd G₄ (360.8 mg, 0.38 mmol, 0.1 equiv) in portions at 20°C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 80 °C under nitrogen atmosphere. The mixture was allowed to cool down to 20°C. The resulting mixture was filtered and the filter cake was washed with DCM (3 x 50 mL). The filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18; mobile phase, MeCN in Water (10 mmol/L NH₄HCO₃), 80% to 90% gradient in 10 min; detector, UV 254 nm. The pure fraction was concentrated under reduced pressure to afford 4-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-[(6RS)-6-[(tert-butyl)diphenylsilyl]oxy]-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazine-2-carbonitrile (1.60 g, 67.7% yield) as a yellow oil.
- ESI-MS m/z = 631.2 [M+H]⁺ ; Calculated MW: 630.3.

Step 5: 4-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-[(6RS)-6-[(tert-butyl)diphenylsilyl]oxy]-6-methyl-1,4-oxazepan-4-yl]-N-hydroxy-1,3,5-triazine-2-carboximidamide

- To a stirred mixture of 4-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-[(6RS)-6-[(tert-butyl)diphenylsilyl]oxy]-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazine-2-carbonitrile (1.60 g, 2.54 mmol, 1.0 equiv) and NH₂OH·HCl (352.6 mg, 5.08 mmol, 2.0 equiv) in EtOH (10 mL) was added Na₂CO₃ (806.4 mg, 7.60 mmol, 3.0 equiv) in portions at 20°C under nitrogen atmosphere. The resulting mixture was stirred for 1h at 80°C under nitrogen atmosphere. The mixture was allowed to cool down to 20°C. The resulting mixture was filtered and the filter cake was washed with EtOH (3 x 30 mL). The filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18; mobile phase, MeCN in Water (10mmol/L NH₄HCO₃), 60% to 70% gradient in 10 min; detector, UV 254 nm. The pure fraction was concentrated under reduced pressure to afford 4-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-[(6RS)-6-[(tert-butyl)diphenylsilyl]oxy]-6-methyl-1,4-oxazepan-4-yl]-N-hydroxy-1,3,5-triazine-2-carboximidamide (1.40 g, 83.2% yield) as a yellow solid.
- ESI-MS m/z = 664.3 [M+H]⁺ ; Calculated MW: 663.3.

Step 6: (4-{[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-[(6RS)-6-[(tert-butyl)diphenylsilyl]oxy]-6-methyl-1,4-oxazepan-4-yl)-1,3,5-triazin-2-yl)methanimidamido (4S)-2-amino-3-cyano-4-methyl-6,7-dihydro-5H-1-benzothiophene-4-carboxylate

To a stirred mixture of 4-{[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-[(6RS)-6-[(tert-butyl)diphenylsilyl]oxy]-6-methyl-1,4-oxazepan-4-yl]-N-hydroxy-1,3,5-triazine-2-carboximidamide (1.40 g, 2.10 mmol, 1.0 equiv) and (4S)-2-amino-3-cyano-4-methyl-6,7-dihydro-5H-1-benzothiophene-4-carboxylic acid (498.4 mg, 2.10 mmol, 1.0 equiv) in DMF (7 mL) was added DIEA (817.6 mg, 6.32 mmol, 3.0 equiv) and PyBOP (1.65 g, 3.16 mmol, 1.5 equiv) in portions at 20°C under nitrogen atmosphere. The resulting mixture was stirred for 1h at 20°C under nitrogen atmosphere. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18; mobile phase, MeCN in Water (10mmol/L NH_4HCO_3), 70% to 80% gradient in 10 min; detector, UV 254 nm. The pure fraction was concentrated under reduced pressure to afford (4-{[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-[(6RS)-6-[(tert-butyl)diphenylsilyl]oxy]-6-methyl-1,4-oxazepan-4-yl)-1,3,5-triazin-2-yl)methanimidamido (4S)-2-amino-3-cyano-4-methyl-6,7-dihydro-5H-1-benzothiophene-4-carboxylate (1.30 g, 69.9% yield) as a yellow solid.

ESI-MS m/z = 882.4 $[\text{M}+\text{H}]^+$; Calculated MW: 881.4

Step 7: (4S)-4-[3-(4-{[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-[(6RS)-6-[(tert-butyl)diphenylsilyl]oxy]-6-methyl-1,4-oxazepan-4-yl)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl]-2-amino-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile

To a stirred mixture of (4-{[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-[(6RS)-6-[(tert-butyl)diphenylsilyl]oxy]-6-methyl-1,4-oxazepan-4-yl)-1,3,5-triazin-2-yl)methanimidamido (4S)-2-amino-3-cyano-4-methyl-6,7-dihydro-5H-1-benzothiophene-4-carboxylate (1.30 g, 1.58 mmol, 1.0 equiv) in DMF (5 mL) was added DBU (483.2 mg, 3.16 mmol, 2.0 equiv) in portions at 20°C under nitrogen atmosphere. The resulting mixture was stirred for 2h at 80°C under nitrogen atmosphere. The mixture was allowed to cool down to 20°C. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18; mobile phase, MeOH in Water (0.1% $\text{NH}_3\cdot\text{H}_2\text{O}$), 100% to 100% gradient in 3 min; detector, UV 254 nm. The pure fraction was concentrated to afford (4S)-4-[3-(4-{[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-[(6RS)-6-[(tert-butyl)diphenylsilyl]oxy]-6-methyl-1,4-oxazepan-4-yl)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl]-2-amino-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (1.20 g, 87.5% yield) as a yellow solid.

ESI-MS m/z = 864.3 $[\text{M}+\text{H}]^+$; Calculated MW: 863.4

Step 8: (4S)-4-[3-(4-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy)-6-[(6RS)-6-hydroxy-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl]-2-amino-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile hydrochloride

- 5 Into a 40mL vial were added (4S)-4-[3-(4-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy)-6-[(6RS)-6-[(tert-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl]-2-amino-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (600.0 mg, 0.69 mmol, 1.0 equiv) and 1M TBAF in THF(10.42 mL, 10.4 mmol, 15 equiv) at 20°C. The resulting mixture was stirred for 16h at 20°C under nitrogen atmosphere. The residue was basified to pH 8 with
- 10 NH₃·H₂O. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The crude product (500 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column 30*150 mm, 5m; Mobile Phase A: Water(0.05% HCL), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 2% B to 2% B in 1.5 min, 2% B to 17% B in 2 min, 17% B to 36% B in 9 min; Wavelength: 254nm/220nm
- 15 nm; RT1(min): 7.97). The pure fraction was concentrated to afford (4S)-4-[3-(4-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy)-6-[(6RS)-6-hydroxy-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl]-2-amino-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (120.0 mg, 27.6% yield) as a yellow solid.
- 20 ESI-MS m/z = 626.35 [M+H]⁺ ; Calculated MW: 625.3

- Step 9: (4S)-4-[3-(4-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy)-6-[(6R*)-6-hydroxy-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl]-2-amino-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile and (4S)-4-[3-(4-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy)-6-[(6R)-6-hydroxy-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl]-2-amino-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile
- 25 (4S)-2-amino-4-(3-(4-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(6-hydroxy-6-methyl-1,4-oxazepan-4-yl)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (120.0 mg) was isolated by prep-chiral-HPLC with the
- 30 following conditions: (Column: Chiral NX(2) 5um, 250*30mm; Mobile Phase A: Hex(10mM NH₃-MeOH), Mobile Phase B: ETOH; Flow rate: 40 mL/min; Gradient: isocratic 30; Wave Length: 220/240 nm; RT1(min): 30.29; RT2(min): 38.89; Sample Solvent: EtOH; Injection Volume: 0.5 mL; Number Of Runs: 5 ; The 1st pure fraction was concentrated, then lyophilized to afford compound

- (89) (4S)-4-[3-(4-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy)-6-[(6R*)-6-hydroxy-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl]-2-amino-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (32.0 mg, 26.1% yield, 97.8% purity @254nm; 98.2% purity@220nm,100%ee) as a white solid. The 2nd pure fraction was concentrated, then lyophilized to afford compound (90), ((4S)-4-[3-(4-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy)-6-[(6R)-6-hydroxy-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl]-2-amino-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (35.5 mg, 29.2% yield, 98.8% purity @254nm; 98.6% purity@220nm,100%ee) as a white solid.

Compound (89):

- ESI-MS m/z = 626.20 $[M+H]^+$; Calculated MW: 625.3; CHIRAL_HPLC R_t =3.39 min. ee value: 100%.

^1H NMR (400 MHz, DMSO- d_6) δ 7.10 (s, 2H), 5.35 – 5.21 (m, 1H), 4.86 (s, 1H), 4.86 – 3.98 (m, 4H), 3.86 – 3.63 (m, 4H), 3.50 – 3.36 (m, 2H), 3.11 (d, 4H), 2.85 (d, 1H), 2.55 (t, J = 6.4 Hz, 2H), 2.18 – 1.74 (m, 12H), 1.10 (d, J = 8.9 Hz, 3H).

15

^{19}F NMR (376 MHz, DMSO) δ -172.26.

Total proton count from structure: 36.

Total proton count from spectrum: 36.

- Compound (90):

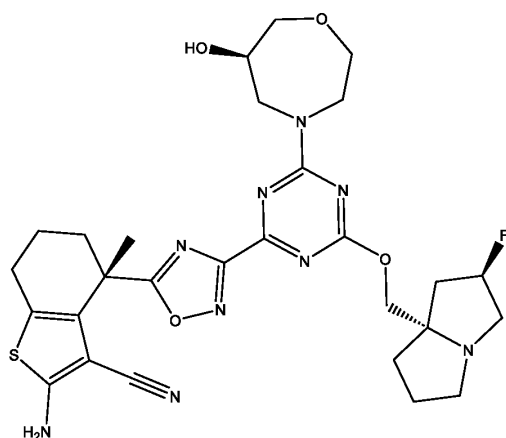
ESI-MS m/z = 626.20 $[M+H]^+$; Calculated MW: 625.3; CHIRAL_HPLC R_t =4.49 min. ee value: 100%.

- ^1H NMR (400 MHz, DMSO- d_6) δ 7.09 (s, 2H), 5.36 - 5.21 (m, 1H), 4.30 – 3.94 (m, 4H), 3.89 – 3.75 (m, 2H), 3.75 – 3.60 (m, 2H), 3.56 – 3.41 (m, 2H), 3.26 – 2.92 (m, 4H), 2.83 (dq, J = 11.4, 5.9, 5.0 Hz, 1H), 2.65 – 2.52 (m, 2H), 2.22 – 1.54 (m, 12H), 1.10 (d, J = 6.3 Hz, 3H).

- ^{19}F NMR (376 MHz, DMSO) δ -172.23.

Total proton count from structure: 36.

Total proton count from spectrum: 36.

Example 24: Synthesis of Compound (112)5 **Step 1:** (6R)-6-[(tert-butyldiphenylsilyl)oxy]-1,4-oxazepane

To a stirred mixture of (6R)-6-methyl-1,4-oxazepan-6-ol (4.00 g, 30.5 mmol, 1.0 equiv) and 1H-imidazole (4.65 g, 68.3 mmol, 2.0 equiv) in DCM (100 ml) were added TBDPS-Cl (14.08 g, 51.2 mmol, 1.5 equiv) and DIEA (13.24 g, 102.4 mmol, 3.0 equiv) dropwise at 25°C under air atmosphere. The resulting mixture was stirred at 25°C for 2 h under air atmosphere. The resulting mixture was diluted with water (100 mL). The resulting mixture was extracted with DCM (3x100 mL). The combined organic layers were washed with brine (3x100 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to give the residue. It was purified by silica gel column chromatography, eluted with PE/EA (100%~10%). The pure fraction was concentrated under vacuum to afford (6R)-6-[(tert-butyldiphenylsilyl)oxy]-1,4-oxazepane (10.5 g, 86.49% yield) as a yellow oil.

ESI-MS $m/z = 356.1$ $M+H]^+$; Calculated MW: 355

20 **Step 2:** (6R)-6-[(tert-butyldiphenylsilyl)oxy]-4-(4,6-dichloro-1,3,5-triazin-2-yl)-1,4-oxazepane

To a stirred mixture of cyanuric chloride (2.08 g, 11.3 mmol, 1.0 equiv) and DIEA (2.19 g, 16.9 mmol, 1.5 equiv) in DCM (40 ml) were added (6R)-6-[(tert-butyldiphenylsilyl)oxy]-1,4-oxazepane (4.01 g, 11.3 mmol, 1.0 equiv) in portions at 25°C under air atmosphere. The resulting mixture was stirred at 25°C for 2 h under air atmosphere. The resulting mixture was diluted with water (60 mL). The resulting mixture was extracted with DCM (3x60 mL). The combined organic layers were washed with brine (3x60 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to give the residue. It was purified by silica gel column chromatography, eluted with

PE/EA (100%~20%). The pure fraction was concentrated under vacuum to afford (6R)-6-[(tert-butylidiphenylsilyl)oxy]-4-(4,6-dichloro-1,3,5-triazin-2-yl)-1,4-oxazepane (5.20 g, 89.1% yield) as a white solid.

ESI-MS m/z = 503.0 $[M+H]^+$; Calculated MW: 502.0

5

Step 3: (2R,7aS)-7a-[(4-[(6R)-6-[(tert-butylidiphenylsilyl)oxy]-1,4-oxazepan-4-yl]-6-chloro-1,3,5-triazin-2-yl)oxy)methyl]-2-fluoro-hexahydropyrrolizine

To a stirred mixture of (6R)-6-[(tert-butylidiphenylsilyl)oxy]-4-(4,6-dichloro-1,3,5-triazin-2-yl)-1,4-oxazepane (5.00 g, 9.93 mmol, 1.0 equiv) and Cs_2CO_3 (4.85 g, 14.9 mmol, 1.5 equiv) in ACN (100 ml) were added [(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methanol (1.90 g, 11.9 mmol, 1.20 equiv) dropwise at 25°C under air atmosphere. The resulting mixture was stirred at 25°C for 1 h under air atmosphere. After filtration, the filtrate was diluted with water (100 mL). The resulting mixture was extracted with DCM (3x100 mL). The combined organic layers were washed with brine (3x100 mL) and dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure to give the residue. It was purified by silica gel column chromatography, eluted with PE/EA (100~20%). The pure fraction was concentrated under vacuum to afford (2R,7aS)-7a-[(4-[(6R)-6-[(tert-butylidiphenylsilyl)oxy]-1,4-oxazepan-4-yl]-6-chloro-1,3,5-triazin-2-yl)oxy)methyl]-2-fluoro-hexahydropyrrolizine (5.30 g, 85.22% yield) as a yellow solid.

ESI-MS m/z = 626.2 $[M+H]^+$; Calculated MW:

20 625.0

Step 4: 4-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy-6-[(6R)-6-[(tert-butylidiphenylsilyl)oxy]-1,4-oxazepan-4-yl]-1,3,5-triazine-2-carbonitrile

To a stirred mixture of (2R,7aS)-7a-[(4-[(6R)-6-[(tert-butylidiphenylsilyl)oxy]-1,4-oxazepan-4-yl]-6-chloro-1,3,5-triazin-2-yl)oxy)methyl]-2-fluoro-hexahydropyrrolizine (3.00 g, 4.79 mmol, 1.0 equiv) and $\text{Zn}(\text{CN})_2$ (560.0 mg, 4.79 mmol, 1.0 equiv) in DMA (30 ml) were added Xantphos PD G₄ (450.0 mg, 0.48 mmol, 0.1 equiv) in portions at 25°C under nitrogen atmosphere. The resulting mixture was stirred at 60°C for 2 h under nitrogen atmosphere. The mixture was allowed to cool down to 25°C. The resulting mixture was diluted with water (100 mL). The resulting mixture was extracted with EtOAc (3x100 mL). The combined organic layers were washed with brine (3x100 mL) and dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure to give the residue. It was purified by silica gel column chromatography, eluted with PE/EA (100%~25%). The pure fraction was concentrated under vacuum to afford 4-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-

7a-yl)methoxy}-6-[(6R)-6-[(tert-butyldiphenylsilyl)oxy]-1,4-oxazepan-4-yl]-1,3,5-triazine-2-carbonitrile (2.10 g, 71.07% yield) as a yellow solid.

ESI-MS m/z = 617.2 $[M+H]^+$; Calculated

MW:616.0

5

Step 5: 4-[[[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy]-6-[(6R)-6-[(tert-butyldiphenylsilyl)oxy]-1,4-oxazepan-4-yl]-N-hydroxy-1,3,5-triazine-2-carboximidamide

To a stirred mixture of 4-[[[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy]-6-[(6R)-6-[(tert-butyldiphenylsilyl)oxy]-1,4-oxazepan-4-yl]-1,3,5-triazine-2-carbonitrile (2.00 g, 3.24 mmol, 1.0 equiv) and Na_2CO_3 (690.0 mg, 6.48 mmol, 2.0 equiv) in EtOH (20 ml) were added $\text{NH}_2\text{OH}\cdot\text{HCl}$ (270.0 mg, 3.89 mmol, 1.2 equiv) in portions at 25°C under air atmosphere. The resulting mixture was stirred at 25°C for 2 h under air atmosphere. The resulting mixture was diluted with water (60 mL). The resulting mixture was extracted with EtOAc (3x60 mL). The combined organic layers were washed with brine (2x50 mL) and dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure to give the crude product. It was purified by silica gel column chromatography, eluted with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (100%~90%). The pure fraction was concentrated under vacuum to afford 4-[[[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy]-6-[(6R)-6-[(tert-butyldiphenylsilyl)oxy]-1,4-oxazepan-4-yl]-N-hydroxy-1,3,5-triazine-2-carboximidamide (1.70 g, 80.68% yield) as a yellow solid.

20 ESI-MS m/z = 650.2 $[M+H]^+$; Calculated MW:649.0

Step 6: (4-[[[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy]-6-[(6R)-6-[(tert-butyldiphenylsilyl)oxy]-1,4-oxazepan-4-yl]-1,3,5-triazine-2-yl)methanimidamido (4S)-2-amino-3-cyano-4-methyl-6,7-dihydro-5H-1-benzothiophene-4-carboxylate

25 To a stirred mixture of 4-[[[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy]-6-[(6R)-6-[(tert-butyldiphenylsilyl)oxy]-1,4-oxazepan-4-yl]-N-hydroxy-1,3,5-triazine-2-carboximidamide (900.0 mg, 1.39 mmol, 1.0 equiv) and DIEA (537.0 mg, 4.16 mmol, 3.0 equiv) in DMF (10 ml) were added (4S)-2-amino-3-cyano-4-methyl-6,7-dihydro-5H-1-benzothiophene-4-carboxylic acid (323.9 mg, 1.371 mmol, 0.99 equiv) and PyBOP (1.08 g, 2.08 mmol, 1.5 equiv) in portions at 25°C under air atmosphere.
30 The resulting mixture was stirred at 25°C for 2 h under air atmosphere. The mixture was purified by reversed-phase flash chromatography with the following conditions: column, C18; mobile phase, MeCN in Water (10 mmol/L NH_4HCO_3), 75% to 75% gradient in 15 min; detector, UV 254 nm. The

pure fraction was concentrated under vacuum to afford (4-[[[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy]-6-[(6R)-6-[(tert-butyl)diphenylsilyl]oxy]-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl)methanimidamido (4S)-2-amino-3-cyano-4-methyl-6,7-dihydro-5H-1-benzothiophene-4-carboxylate (965.0 mg, 80.26% yield) as a yellow solid.

- 5 ESI-MS m/z = 868.5 $[M+H]^+$; Calculated MW:867.0

Step 7: (4S)-4-[3-(4-[[[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy]-6-[(6R)-6-[(tert-butyl)diphenylsilyl]oxy]-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl]-2-amino-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile

- 10 To a stirred solution of (4-[[[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy]-6-[(6R)-6-[(tert-butyl)diphenylsilyl]oxy]-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl)methanimidamido (4S)-2-amino-3-cyano-4-methyl-6,7-dihydro-5H-1-benzothiophene-4-carboxylate (900.0 mg, 1.04 mmol, 1.0 equiv) in DMF (10 ml) was added DBU (315.6 mg, 2.07 mmol, 2.0 equiv) dropwise at 25°C under air atmosphere. The resulting mixture was stirred at 80°C for 1 h under nitrogen atmosphere. The mixture
15 was allowed to cool down to 25°C. The mixture was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10mmol/L NH_4HCO_3), 75% to 75% gradient in 10 min; detector, UV 254 nm. The pure fraction was concentrated under vacuum to afford (4S)-4-[3-(4-[[[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy]-6-[[[(6R)-6-[(tert-butyl)diphenylsilyl]oxy]-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl]-2-
20 amino-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (710.0 mg, 80.56% yield) as a yellow solid.

ESI-MS m/z = 850.3 $[M+H]^+$; Calculated MW:849.0

- Step 8: (4S)-4-[3-(4-[[[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy]-6-[(6R)-6-hydroxy-
25 1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl]-2-amino-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile

- A solution of (4S)-4-[3-(4-[[[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy]-6-[(6R)-6-[(tert-butyl)diphenylsilyl]oxy]-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl]-2-amino-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (400.0 mg, 0.47 mmol, 1.0 equiv) and CsF
30 (1.43 g, 9.40 mmol, 20.0 equiv) in DMF (4 ml) was stirred at 80°C for 2 h under air atmosphere. The mixture was allowed to cool down to 25°C. The crude product (400.0 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column 30*150 mm, 5m; Mobile

Phase A: Water (10mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 ml/min ml/min; Gradient: 30% B to 45% B in 10 min; Wavelength: 254nm/220nm; RT1(min): 8.4). The pure fraction was concentrated under vacuum and lyophilized to afford (4S)-4-[3-(4-[(2R,7aS)-2-fluoro-

5 1,2,4-oxadiazol-5-yl]-2-amino-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (112.4 mg, 37.61% yield) as a yellow solid.

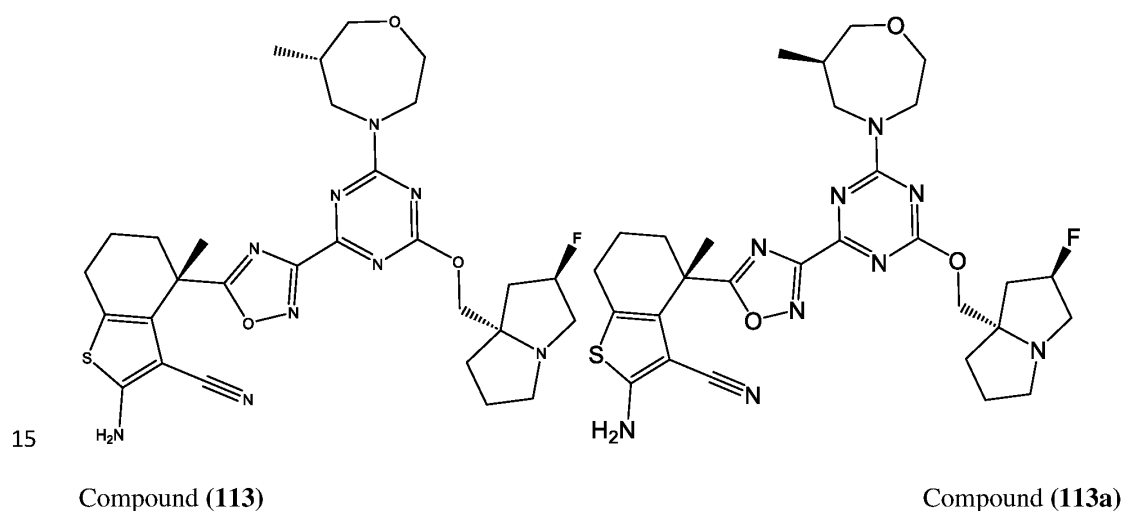
ESI-MS $m/z = 612.2$ $[\text{M}+\text{H}]^+$; Calculated MW: 611.0

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.09 (s, 2H), 5.36 – 5.17 (m, 1H), 5.12 (t, 1H), 4.41 – 4.07 (m, 3H), 4.01 (t, 1H), 3.95 – 3.80 (m, 2H), 3.73 – 3.51 (m, 4H), 3.43 (td, 1H), 3.04 (d, 3H), 2.82 (s, 1H),
 10 2.54 (d, 2H), 2.09 (dd, 3H), 1.95 (d, 2H), 1.90 – 1.66 (m, 8H).

Total proton count from structure: 34.

Total proton count from spectrum: 34.

Example 25: Synthesis of Compound (113) and (113a)



Step 1: 4-(4,6-Dichloro-1,3,5-triazin-2-yl)-6-methyl-1,4-oxazepane

To a stirred mixture of rac-6-methyl-1,4-oxazepane hydrochloride (5.00 g, 33.0 mmol, 1.0 equiv) and DIEA (12.79 g, 99.0 mmol, 3.0 equiv) in DCM (100 mL) was added cyanuric chloride (6.08 g, 33.0
 20 mmol, 1.0 equiv) in portions at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 1h at 20°C under nitrogen atmosphere. The resulting mixture was diluted with water (100 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 100mL). The combined organic layers were washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated

under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EtOAc (1:3~1:5). The pure fraction was concentrated under reduced pressure to afford 4-(4,6-dichloro-1,3,5-triazin-2-yl)-6-methyl-1,4-oxazepane (5.50 g, 63.4% yield) as a yellow solid.

ESI-MS $m/z = 263.0$ $[M+H]^+$; Calculated MW: 262.0

5

Step 2: 4-(4-Chloro-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-6-methyl-1,4-oxazepane

To a stirred mixture of 4-(4,6-dichloro-1,3,5-triazin-2-yl)-6-methyl-1,4-oxazepane (5.00 g, 19.0 mmol, 1.0 equiv) and Cs_2CO_3 (18.57 g, 57.0 mmol, 3.0 equiv) in ACN (250 mL) was added [(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methanol (3.03 g, 19.0 mmol, 1.0 equiv) in portions at 20°C under nitrogen atmosphere. The resulting mixture was stirred for 2h at 20°C under nitrogen atmosphere. The resulting mixture was filtered and the filter cake was washed with CH_2Cl_2 (3 x 100 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/ EtOAc(1:5~1:8). The pure fraction was concentrated under reduced pressure to afford 4-(4-chloro-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-6-methyl-1,4-oxazepane (5.50 g, 75.0% yield) as a yellow oil.

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ESI-MS $m/z = 386.1$ $[M+H]^+$; Calculated MW: 385.2.

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Step 3: 4-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(6-methyl-1,4-oxazepan-4-yl)-1,3,5-triazine-2-carbonitrile

25

30

To a stirred mixture of 4-(4-chloro-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-6-methyl-1,4-oxazepane (3.00 g, 7.78 mmol, 1.0 equiv) and $\text{Zn}(\text{CN})_2$ (1.10 g, 9.33 mmol, 1.2 equiv) in DMA (20 mL) was added Xantphos Pd G₄ (374.1 mg, 0.39 mmol, 0.05 equiv) in portions at 20°C under nitrogen atmosphere. The resulting mixture was stirred for 2h at 80°C under nitrogen atmosphere. The mixture was allowed to cool down to 20°C. The resulting mixture was filtered and the filter cake was washed with DCM (3 x 50 mL). The filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18; mobile phase, MeCN in Water (10mmol/L NH_4HCO_3), 90% to 100% gradient in 10 min; detector, UV 254 nm. The pure fraction was concentrated to afford 4-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(6-methyl-1,4-oxazepan-4-yl)-1,3,5-triazine-2-carbonitrile (2.20 g, 75.2% yield) as a yellow oil.

ESI-MS $m/z = 377.2$ $[M+H]^+$; Calculated MW: 376.2.

Step 4: 4-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-N-hydroxy-6-(6-methyl-1,4-oxazepan-4-yl)-1,3,5-triazine-2-carboximidamide

To a stirred mixture of 4-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(6-methyl-1,4-oxazepan-4-yl)-1,3,5-triazine-2-carbonitrile (2.00 g, 5.31 mmol, 1.0 equiv) and
 5 NH₂OH·HCl (553.8 mg, 7.97 mmol, 1.5 equiv) in EtOH (20 mL) was added Na₂CO₃ (1.13 g, 10.6 mmol, 2.0 equiv) in portions at 20°C under nitrogen atmosphere. The resulting mixture was stirred for 1h at 20°C under nitrogen atmosphere. The resulting mixture was extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were washed with brine (3 x 50 mL), dried over anhydrous Na₂SO₄.
 10 After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18; mobile phase, MeCN in Water (10mmol/L NH₄HCO₃), 80% to 90% gradient in 10 min; detector, UV 254 nm. The pure fraction was concentrated to afford 4-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-N-hydroxy-6-(6-methyl-1,4-oxazepan-4-yl)-1,3,5-triazine-2-carboximidamide (1.80 g,
 15 83.7% yield) as a yellow solid.

ESI-MS m/z = 410.2 [M+H]⁺; Calculated MW: 409.2.

Step 5: 4-{[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-N-hydroxy-6-[(6R*)-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazine-2-carboximidamide and 4-{[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-N-hydroxy-6-[(6R*)-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazine-2-carboximidamide
 20 hexahydropyrrolizin-7a-yl]methoxy}-N-hydroxy-6-[(6R*)-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazine-2-carboximidamide

4-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-N-hydroxy-6-(6-methyl-1,4-oxazepan-4-yl)-1,3,5-triazine-2-carboximidamide (1.00 g, 2.44 mmol, 1.0 equiv) was isolated by prep-SFC with the following conditions: ((Column: CHIRALPAK-IK, 3*25mm, 5μm; Mobile Phase A:
 25 CO₂, Mobile Phase B: IPA: DCM=1: 1(20mMNH₃); Flow rate: 80 mL/min; Gradient: isocratic 35% B; Column Temperature(°C): 25; Back Pressure(bar): 100; Wave Length: 255/280 nm; RT1(min): 14.48; RT2(min): 18.77; Sample Solvent: MEOH; Injection Volume: 0.2 mL; Number Of Runs: 45); The 1st eluting fraction was concentrated, and then lyophilized to afford a first stereoisomer ("isomer 1"), which was *i.e.* 4-{[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-N-hydroxy-6-[(6R*)-
 30 6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazine-2-carboximidamide (480.0 mg, 48.0% yield, ee100%) as a yellow solid. The 2nd eluting fraction was concentrated and then lyophilized to afford a second stereoisomer ("isomer 2"), which was 4-{[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-N-

hydroxy-6-[(6R*)-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazine-2-carboximidamide (500.0 mg, 50.0% yield, 98.2% ee) as a yellow solid.

Isomer 1: ESI-MS $m/z = 410.2$ $[M+H]^+$; Calculated MW: 409.2. SFC $R_t=4.04$ min. ee value: 98.2%.

Isomer 2: ESI-MS $m/z = 410.2$ $[M+H]^+$; Calculated MW: 409.2. SFC $R_t=4.43$ min. ee value: 100%.

5

Step 6: (4-{[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-[(6R*)-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl)methanimidamido (4S)-2-amino-3-cyano-4-methyl-6,7-dihydro-5H-1-benzothiophene-4-carboxylate

To a stirred mixture of 4-{[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-N-hydroxy-6-
10 [(6R*)-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazine-2-carboximidamide (200.0 mg, 0.49 mmol, 1.0 equiv) and (4S)-2-amino-3-cyano-4-methyl-6,7-dihydro-5H-1-benzothiophene-4-carboxylic acid (127.0 mg, 0.54 mmol, 1.1 equiv) in DMF (5 mL) were added DIEA (189.4 mg, 1.46 mmol, 3.0 equiv) and PyBOP (381.3 mg, 0.73 mmol, 1.5 equiv) in portions at 20°C under nitrogen atmosphere. The resulting mixture was stirred for 1h at 20°C under nitrogen atmosphere. The residue was purified by
15 reversed-phase flash chromatography with the following conditions: column, C18; mobile phase, MeCN in Water (10mmol/L NH_4HCO_3), 90% to 100% gradient in 3 min; detector, UV 254 nm. The pure fraction was concentrated to afford (4-{[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-[(6R*)-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl)methanimidamido (4S)-2-amino-3-cyano-4-methyl-6,7-dihydro-5H-1-benzothiophene-4-carboxylate (260.0 mg, 84.8% yield)
20 as a yellow solid.

ESI-MS $m/z = 524.3$ $[M+H]^+$; Calculated MW: 627.3.

Step 7: (4S)-4-[3-(4-{[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-[(6S)-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl]-2-amino-4-methyl-6,7-dihydro-5H-1-
25 benzothiophene-3-carbonitrile

To a stirred mixture of (4-{[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-[(6R*)-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl)methanimidamido (4S)-2-amino-3-cyano-4-methyl-6,7-dihydro-5H-1-benzothiophene-4-carboxylate (200.0 mg, 0.32 mmol, 1.0 equiv) in DMF (2 mL) was added DBU (72.8 mg, 0.48 mmol, 1.5 equiv) dropwise at 20°C under nitrogen atmosphere. The
30 resulting mixture was stirred for 2h at 80°C under nitrogen atmosphere. The mixture was allowed to cool down to 20°C. The resulting mixture was concentrated under reduced pressure. The crude product (200.0 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD

C18 Column 30*150 mm, 5m; Mobile Phase A: Water(10 mmol/L NH_4HCO_3 +0.05% $\text{HN}_3\text{H}_2\text{O}$), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 37% B to 57% B in 8 min; Wavelength: 254nm/220nm nm; RT1(min): 9.23). The pure fraction was lyophilized to afford (4S)-4-[3-(4-[[[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-[(6S)-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl]-2-amino-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (90.5 mg, 45.8% yield, 98.2% purity @254nm; 98.5% purity@220nm, ee100%) as a yellow solid.

ESI-MS m/z = 610.25 $[\text{M}+\text{H}]^+$; Calculated MW: 609.3; CHIRAL_HPLC R_t =10.44 min. ee value: 100%.

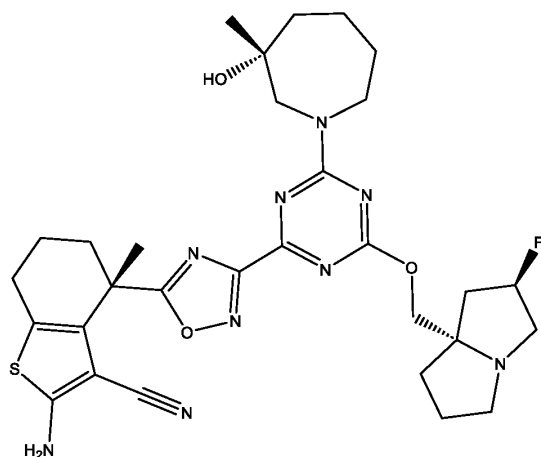
^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.09 (s, 2H), 5.27 (d, J = 54.2 Hz, 1H), 4.23 – 3.98 (m, 4H), 3.88 – 3.79 (m, 1H), 3.77 – 3.60 (m, 3H), 3.49 – 3.36 (m, 2H), 3.15 – 2.96 (m, 3H), 2.82 (q, J = 8.0 Hz, 1H), 2.62 – 2.52 (m, 2H), 2.17 – 1.90 (m, 6H), 1.89 – 1.70 (m, 8H), 0.88 (t, J = 7.6 Hz, 3H).

^{19}F NMR (376 MHz, DMSO) δ -172.53.

Total proton count from structure: 36.

Total proton count from spectrum: 36.

Example 26: Synthesis of Compound (107)



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Step 1: 3-((Tert-butyl)diphenylsilyl)oxy)-3-methylazepane

To a stirred mixture of 3-methylazepan-3-ol hydrogen chloride (3.00 g, 18.1 mmol, 1.0 equiv) and imidazole (4.93 g, 72.5 mmol, 4.0 equiv) in DCM (30 mL) were added a solution of TBDPS-Cl (6.47 g, 23.6 mmol, 1.3 equiv) in DCM (15 mL) dropwise at 0°C under N₂ atmosphere. The resulting mixture was stirred at 25°C for 16h. The resulting mixture was quenched with H₂O at 0°C. The resulting mixture was extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (1:1) to afford 3-((tert-butylidiphenylsilyl)oxy)-3-methylazepane (1.30 g, 19% yield) as a yellow oil. ESI-MS *m/z* = 368.1 [M+H]⁺; Calculated MW: 367.2

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.69-7.64 (m, 4H), 7.48-7.38 (m, 6H), 3.31 (s, 1H), 2.80-2.59 (m, 4H), 1.77-1.34 (m, 6H), 0.97-0.96 (m, 12H).

Step 2: 3-((Tert-butylidiphenylsilyl)oxy)-1-(4,6-dichloro-1,3,5-triazin-2-yl)-3-methylazepane

To a stirred mixture of 2,4,6-trichloro-1,3,5-triazine (652.1 mg, 3.54 mmol, 1.0 equiv) in DCM (10 mL) was added DIEA (914.1 mg, 7.07 mmol, 2.0 equiv) dropwise at 0°C under N₂ atmosphere. To the above mixture was added a solution of 3-((tert-butylidiphenylsilyl)oxy)-3-methylazepane (1.30 g, 3.54 mmol, 1.0 equiv) in DCM (10 mL) dropwise at 0°C. The resulting mixture was stirred at 0°C for additional 10min. The resulting mixture was diluted with H₂O. The resulting mixture was extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to afford 3-((tert-butylidiphenylsilyl)oxy)-1-(4,6-dichloro-1,3,5-triazin-2-yl)-3-methylazepane (1.80 g, crude) as a yellow solid. ESI-MS *m/z* = 515.1 [M+H]⁺; Calculated MW: 514.1

Step 3: (2*R*,7*aS*)-7*a*-(((4-(3-((Tert-butylidiphenylsilyl)oxy)-3-methylazepan-1-yl)-6-chloro-1,3,5-triazin-2-yl)oxy)methyl)-2-fluorohexahydro-1*H*-pyrrolizine

To a stirred mixture of 3-((tert-butylidiphenylsilyl)oxy)-1-(4,6-dichloro-1,3,5-triazin-2-yl)-3-methylazepane (1.80 g, 3.49 mmol, 1.0 equiv) and [(2*R*,7*aS*)-2-fluoro-hexahydropyrrolizin-7*a*-yl]methanol (1.11 g, 6.98 mmol, 2.0 equiv) in 1,4-dioxane (20 mL) were added Cs₂CO₃ (2.28 g, 6.98 mmol, 2.0 equiv) at 25°C under N₂ atmosphere. The resulting mixture was stirred at 80°C for additional 1h. The resulting mixture was cooled down to room temperature and then H₂O was added. The resulting mixture was extracted with EA. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (1:4) to afford

(2*R*,7*aS*)-7*a*-(((4-(3-((tert-butyl)diphenylsilyl)oxy)-3-methylazepan-1-yl)-6-chloro-1,3,5-triazin-2-yl)oxy)methyl)-2-fluorohexahydro-1*H*-pyrrolizine (1.50 g, 67% yield) as a white solid. ESI-MS m/z = 638.2 $[M+H]^+$; Calculated MW: 637.3

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.74-7.60 (m, 4H), 7.49-7.35 (m, 6H), 4.08-3.96 (m, 2H), 3.40-3.36 (m, 1H), 3.13-2.76 (m, 4H), 2.51-2.50 (m, 2H), 2.50-2.49 (m, 2H), 2.01-1.32 (m, 12H), 1.05-1.02 (m, 3H), 0.88-0.83 (m, 9H).

Step 4: 4-(3-((Tert-butyl)diphenylsilyl)oxy)-3-methylazepan-1-yl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazine-2-carbonitrile

To a stirred mixture of (2*R*,7*aS*)-7*a*-(((4-(3-((tert-butyl)diphenylsilyl)oxy)-3-methylazepan-1-yl)-6-chloro-1,3,5-triazin-2-yl)oxy)methyl)-2-fluorohexahydro-1*H*-pyrrolizine (1.47 g, 2.30 mmol, 1.0 equiv) and Zn(CN)₂ (540.8 mg, 4.60 mmol, 2.0 equiv) in DMA (15 mL) were added Xantphos Pd G₄ (221.6 mg, 0.23 mmol, 0.1 equiv) at 25°C under Ar atmosphere. The resulting mixture was stirred at 80°C for additional 1h. The resulting mixture was cooled down to room temperature and then filtered, the filter cake was washed with EA. The filtrate was concentrated under reduced pressure. The resulting mixture was diluted with H₂O at 0°C. The resulting mixture was extracted with EA. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (1:4) to afford 4-(3-((tert-butyl)diphenylsilyl)oxy)-3-methylazepan-1-yl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazine-2-carbonitrile (800.0 mg, 55% yield) as a yellow solid. ESI-MS m/z = 629.2 $[M+H]^+$; Calculated MW: 628.3

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.73-7.58 (m, 4H), 7.50-7.35 (m, 6H), 4.22-4.00 (m, 2H), 3.40-3.35 (m, 1H), 3.07-2.99 (m, 2H), 2.89-2.88 (m, 2H), 2.51-2.50 (m, 2H), 2.49-2.48 (m, 2H), 2.06-1.35 (m, 12H), 1.06-1.03 (m, 3H), 0.88-0.84 (m, 9H).

Step 5: (Z)-4-(3-((Tert-butyl)diphenylsilyl)oxy)-3-methylazepan-1-yl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-*N*-hydroxy-1,3,5-triazine-2-carboximidamide

To a stirred mixture of 4-(3-((tert-butyl)diphenylsilyl)oxy)-3-methylazepan-1-yl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazine-2-carbonitrile (750.0 mg, 1.19 mmol, 1.0 equiv) in THF (1 mL) was added NH₂OH(50% in water) (118.2 mg, 1.79 mmol, 1.5 equiv) dropwise at 0°C under N₂ atmosphere. The resulting mixture was stirred at 25°C for additional 30min.

The resulting mixture was concentrated under reduced pressure to afford (Z)-4-(3-((tert-butyl)diphenylsilyl)oxy)-3-methylazepan-1-yl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-N'-hydroxy-1,3,5-triazine-2-carboximidamide (870.0 mg, crude) as a white solid. ESI-MS m/z = 662.3 [M+H]⁺; Calculated MW: 661.3

- 5 Step 6: (Z)-N'-(((S)-2-amino-3-cyano-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-4-carbonyl)oxy)-4-(3-((tert-butyl)diphenylsilyl)oxy)-3-methylazepan-1-yl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazine-2-carboximidamide

To a stirred mixture of (Z)-4-(3-((tert-butyl)diphenylsilyl)oxy)-3-methylazepan-1-yl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-N'-hydroxy-1,3,5-triazine-2-carboximidamide
 10 (850.0 mg, 1.28 mmol, 1.0 equiv) and (S)-2-amino-3-cyano-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-4-carboxylic acid (364.1 mg, 1.54 mmol, 1.2 equiv) in DMF (10 mL) were added DIEA (829.9 mg, 6.42 mmol, 5.0 equiv) and HATU (732.4 mg, 1.93 mmol, 1.5 equiv) in portions at 0°C under N₂ atmosphere. The resulting mixture was stirred at 25°C for additional 1h. The resulting mixture was diluted with H₂O at 0°C. The resulting mixture was extracted with EA. The
 15 combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, H₂O in ACN, 0% to 100% gradient in 30 min; detector, UV 254 nm to afford (Z)-N'-(((S)-2-amino-3-cyano-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-4-carbonyl)oxy)-4-(3-((tert-butyl)diphenylsilyl)oxy)-3-
 20 methylazepan-1-yl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazine-2-carboximidamide (670.0 mg, 59% yield) as a white solid. ESI-MS m/z = 880.3 [M+H]⁺; Calculated MW: 879.4

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.71-7.62 (m, 4H), 7.49-7.33 (m, 6H), 7.06-6.97 (m, 2H), 5.76 (s, 2H), 4.19-3.95 (m, 2H), 3.86-3.57 (m, 4H), 3.30-3.28 (m, 1H), 3.15-2.65 (m, 6H), 2.22-1.54 (m, 19H), 1.09-1.05 (m, 3H), 0.91-0.76 (m, 9H).
 25

Step 7: (4S)-2-Amino-4-(3-(4-(3-((tert-butyl)diphenylsilyl)oxy)-3-methylazepan-1-yl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile

30 To a stirred mixture of (Z)-N'-(((S)-2-amino-3-cyano-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-4-carbonyl)oxy)-4-(3-((tert-butyl)diphenylsilyl)oxy)-3-methylazepan-1-yl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazine-2-carboximidamide (650.0 mg, 0.74 mmol, 1.0 equiv) in DMF (7 mL) was added DBU (1.12 g, 7.38

mmol, 10 equiv) at 25°C under N₂ atmosphere. The resulting mixture was stirred at 60°C for additional 1h. The resulting mixture was cooled down to room temperature and diluted with H₂O at 0°C. The resulting mixture was extracted with EA. The combined organic layers were washed with H₂O, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The

- 5 residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, H₂O in ACN, 0% to 100% gradient in 30 min; detector, UV 254 nm to afford (4*S*)-2-amino-4-(3-(4-(3-((tert-butyldiphenylsilyl)oxy)-3-methylazepan-1-yl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (500.0 mg, 78% yield) as a white solid.
- 10 ESI-MS *m/z* = 862.3 [M+H]⁺; Calculated MW: 861.4

Step 8: *Rel*-(*R*)-(4*S*)-2-amino-4-(3-(4-(3-((tert-butyldiphenylsilyl)oxy)-3-methylazepan-1-yl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile

- (4*S*)-2-amino-4-(3-(4-(3-((tert-butyldiphenylsilyl)oxy)-3-methylazepan-1-yl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (500.0 mg) was separated by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK-*IK*, 3*25mm, 5μm; Mobile Phase A: Hex(10mM NH₃-MeOH), Mobile Phase B: IPA--HPLC; Flow rate: 40 mL/min; Gradient: isocratic 40; Wave Length: 200/210 nm; RT1(min): 14.6; RT2(min): 25.4; Sample Solvent: EtOH--HPLC;
- 15 Injection Volume: 1 mL; Number Of Runs: 7) to afford first peak, “isomer 1” *rel*-(*S*)-(4*S*)-2-amino-4-(3-(4-(3-((tert-butyldiphenylsilyl)oxy)-3-methylazepan-1-yl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile, (230 mg, 46% yield, ee: 100%) as a white solid and second peak, “isomer 2” *rel*-(*R*)-(4*S*)-2-amino-4-(3-(4-(3-((tert-butyldiphenylsilyl)oxy)-3-methylazepan-1-yl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile
- 25 (200.0 mg, 40% yield, ee: 100%) as a white solid.

Isomer 1: ESI-MS *m/z* = 862.3 [M+H]⁺; Calculated MW: 861.3. CHIRAL_HPLC Rt=2.97 min. ee value: 100%.

- 30 ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.69-7.60 (m, 4H), 7.49-7.23 (m, 6H), 7.11 (s, 2H), 4.22-3.97 (m, 3H), 3.75-3.72 (m, 1H), 3.70-3.58 (m, 2H), 3.10-2.78 (m, 4H), 2.57-2.533 (m, 2H), 2.15-1.93 (m, 6H), 1.84-1.71 (m, 8H), 1.48-1.33 (m, 3H), 1.26-1.22 (m, 1H), 1.19-1.16 (m, 1H), 1.12-1.01 (m, 3H), 0.89-0.78 (m, 9H).

Isomer 2: ESI-MS $m/z = 862.3$ $[M+H]^+$; Calculated MW: 861.3. CHIRAL_HPLC $R_t=5.185$ min. ee value: 100%.

1H NMR (400 MHz, DMSO- d_6) δ 7.69-7.60 (m, 4H), 7.49-7.23 (m, 6H), 7.11 (s, 2H), 4.22-3.97 (m, 3H), 3.75-3.72 (m, 1H), 3.70-3.58 (m, 2H), 3.10-2.78 (m, 4H), 2.57-2.533 (m, 2H), 2.15-1.93 (m, 6H), 1.84-1.71 (m, 8H), 1.48-1.33 (m, 3H), 1.26-1.22 (m, 1H), 1.19-1.16 (m, 1H), 1.12-1.01 (m, 3H), 0.89-0.78 (m, 9H).

Step 9: (4S)-4-[3-(4-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy)-6-[(3S)-3-hydroxy-3-methylazepan-1-yl]-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl]-2-amino-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile

To a stirred mixture of rel-(R)-(4S)-2-amino-4-(3-(4-(3-((tert-butyldiphenylsilyl)oxy)-3-methylazepan-1-yl)-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (200.0 mg, 0.23 mmol, 1.0 equiv) in THF (1 mL) was added 70% HF Pyridine (2 mL) dropwise at 0°C under N₂ atmosphere. The resulting mixture was stirred at 40°C for additional 1h. The mixture was basified to pH 8 with sat.NaHCO₃. The resulting mixture was extracted with EA. The combined organic layers were washed with H₂O, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column 30*150 mm, 5m; Mobile Phase A: Water(10 mmol/L NH₄HCO₃+0.05%NH₃.H₂O), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 42% B to 56% B in 10 min; Wave Length: 254nm/220nm nm; RT1(min): 8.5); This resulted in (4S)-4-[3-(4-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy)-6-[(3S)-3-hydroxy-3-methylazepan-1-yl]-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl]-2-amino-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (9.2 mg, 6.3% yield, 99.6%purity @254nm; 99.4% purity@220nm) as a white solid.

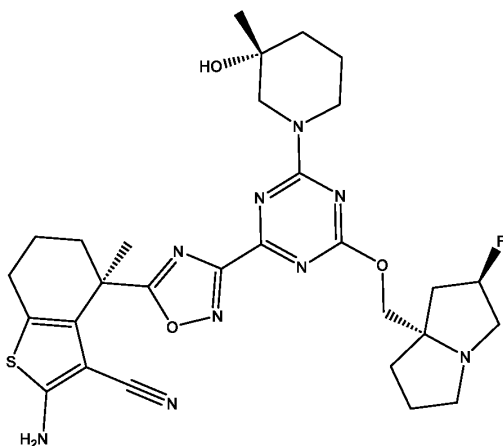
ESI-MS $m/z = 624.2$ $[M+H]^+$; Calculated MW: 623.2. CHIRAL_HPLC $R_t=1.854$ min. ee value: 100%.

1H NMR (400 MHz, DMSO- d_6) δ 7.07 (s, 2H), 5.26 (d, $J = 54.2$ Hz, 1H), 4.55 (d, $J = 6.9$ Hz, 1H), 4.13-3.78 (m, 4H), 3.65-3.55 (m, 2H), 3.29-3.28 (m, 1H), 3.08-3.00 (m, 3H), 2.83-2.80 (m, 1H), 2.56-2.53 (m, 1H), 2.14-2.04 (m, 3H), 2.01-1.91 (m, 2H), 1.88-1.68 (m, 11H), 1.62-1.48 (m, 2H), 1.45-1.35 (m, 1H), 1.16 (s, 3H).

Total proton count from structure: 38.

Total proton count from spectrum: 38.

Example 27: Synthesis of Compound (114)



5

Step 1: (3R)-1-(4,6-Dichloro-1,3,5-triazin-2-yl)-3-methylpiperidin-3-ol

A solution of cyanuric chloride (4.50 g, 24.4 mmol, 1.0 equiv) in DCM (50.0 mL) was treated with DIEA (9.46 g, 73.2 mmol, 3.0 equiv) for 10 min at 0°C under nitrogen atmosphere followed by the addition of (3R)-3-methylpiperidin-3-ol (2.24 g, 19.5 mmol, 0.8 equiv) in portions at 0°C. The resulting mixture was stirred for 30 min and then quenched by water. The resulting mixture was extracted with DCM. The combined organic layers were washed with water, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE:EA (1:1) to afford (3R)-1-(4,6-dichloro-1,3,5-triazin-2-yl)-3-methylpiperidin-3-ol (3.4 g, 52.9%) as a white solid. ESI-MS *m/z* = 263.1 [M+H]⁺; Calculated MW: 262.0

Step 2: (3R)-1-(4-[(2R,7aS)-2-Fluoro-hexahydropyrrolizin-7a-yl]methoxy)-6-chloro-1,3,5-triazin-2-yl)-3-methylpiperidin-3-ol

A mixture of (3R)-1-(4,6-dichloro-1,3,5-triazin-2-yl)-3-methylpiperidin-3-ol (2.00 g, 7.60 mmol, 1.0 equiv); Cs₂CO₃ (4.89 g, 15.2 mmol, 2.0 equiv) and [(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methanol (968.1 mg, 6.08 mmol, 0.8 equiv) in acetonitrile (30 mL) was stirred for 2h at 80°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. Water was added

and the resulting mixture was extracted with EA. The combined organic layers were washed with water, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water, 0% to 100% gradient in 30 min; detector, UV 254 nm. This resulted in (3R)-1-(4-([(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy)-6-chloro-1,3,5-triazin-2-yl)-3-methylpiperidin-3-ol (1.90 g, 64.7%) as a light yellow solid. ESI-MS m/z = 386.2 [M+H]⁺; Calculated MW: 385.2

Step 3: 4-([(2R,7aS)-2-Fluoro-hexahydropyrrolizin-7a-yl]methoxy)-6-[(3R)-3-hydroxy-3-methylpiperidin-1-yl]-1,3,5-triazine-2-carbonitrile

- 10 A mixture of (3R)-1-(4-([(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy)-6-chloro-1,3,5-triazin-2-yl)-3-methylpiperidin-3-ol (3.00 g, 7.77 mmol, 1.0 equiv) and zinc cyanide (1.83 g, 15.5 mmol, 2.0 equiv) in DMF (30 mL) was stirred for 1h at 80°C under argon atmosphere. The mixture was allowed to cool down to room temperature. Water was added and the resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water. 0% to 100% gradient in 30min; detector, UV 254 nm. This resulted in 4-([(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy)-6-[(3R)-3-hydroxy-3-methylpiperidin-1-yl]-1,3,5-triazine-2-carbonitrile (2.00 g, 68.3%) as a light yellow solid. ESI-MS m/z = 376.2 [M+H]⁺;
20 Calculated MW: 376.2.

Step 4: 4-([(2R,7aS)-2-Fluoro-hexahydropyrrolizin-7a-yl]methoxy)-N-hydroxy-6-[(3R)-3-hydroxy-3-methylpiperidin-1-yl]-1,3,5-triazine-2-carboximidamide

- A solution of 4-([(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy)-6-[(3R)-3-hydroxy-3-methylpiperidin-1-yl]-1,3,5-triazine-2-carbonitrile (1.00 g, 2.65 mmol, 1.0 equiv) and NH₂OH (1.75 g, 26.5 mmol, 10 equiv) in EOH(10 mL) was stirred for 2h at 25°C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The crude product was used in the next step directly without further purification. ESI-MS m/z = 410.3 [M+H]⁺; Calculated MW: 409.2

- Step 5: (4-([(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy)-6-[(3R)-3-hydroxy-3-methylpiperidin-1-yl]-1,3,5-triazin-2-yl)methanimidamido 2-amino-3-cyano-4-methyl-6,7-dihydro-5H-1-benzothiophene-4-carboxylate
30

A solution of 4-([(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy)-N-hydroxy-6-[(3R)-3-hydroxy-3-methylpiperidin-1-yl]-1,3,5-triazine-2-carboximidamide (1.00 g, 2.44 mmol, 1.0 equiv); 2-

amino-3-cyano-4-methyl-6,7-dihydro-5H-1-benzothiophene-4-carboxylic acid (0.63 g, 2.68 mmol, 1.1 equiv) in DMF was treated with DIEA (1.89 g, 14.6 mmol, 6.0 equiv) for 10min at 0°C under nitrogen atmosphere followed by the addition of HATU (1.86 g, 4.88 mmol, 2.0 equiv) in portions at 0°C. The resulting mixture was stirred for 1h at 25°C and water was added. The resulting mixture was
5 extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water, 0% to 100% gradient in 30 min; detector, UV 254 nm. This resulted in (4-
10 {[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-[(3R)-3-hydroxy-3-methylpiperidin-1-yl]-1,3,5-triazin-2-yl)methanimidamido(4S)-2-amino-3-cyano-4-methyl-6,7-dihydro-5H-1-benzothiophene-4-carboxylate (480.0 mg, 31.3%) as a Brown yellow solid. ESI-MS m/z = 628.4 [M+H]⁺; Calculated MW: 627.3.

Step 6: Rac-(4S)-4-[3-(4-{[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-[(3R)-3-hydroxy-3-methylpiperidin-1-yl]-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl]-2-amino-4-methyl-6,7-
15 dihydro-5H-1-benzothiophene-3-carbonitrile; formic acid

A solution of (4-{[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-[(3R)-3-hydroxy-3-methylpiperidin-1-yl]-1,3,5-triazin-2-yl)methanimidamido(4S)-2-amino-3-cyano-4-methyl-6,7-dihydro-5H-1-benzothiophene-4-carboxylate (400.0 mg, 0.63 mmol, 1.0 equiv) and DBU (510.7 mg, 3.36 mmol, 42 equiv) in DMF(10 mL) was stirred for 1h at 60°C under nitrogen atmosphere. The
20 mixture was allowed to cool down to room temperature. Water was added and the resulting mixture was extracted with EtOAc. The combined organic layers were washed with water, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5µm; Mobile Phase A: Water(0.1% FA), Mobile Phase B: ACN; Flow rate: 60
25 mL/min mL/min; Gradient: 20% B to 50% B in 10 min; Wave Length: 254nm/220nm nm; RT1(min): 23) to afford Rac-(4S)-4-[3-(4-{[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy}-6-[(3R)-3-hydroxy-3-methylpiperidin-1-yl]-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl]-2-amino-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (70.0 mg, 18.0%) as a white solid. ESI-MS m/z = 610.30 [M+H]⁺; Calculated MW: 609.26.

30 ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.18 (s, 0.6H), 7.08 (s, 2H), 5.39 – 5.17 (m, 1H), 4.15 – 3.75 (m, 4H), 3.81-3.74 (m, 1H), 3.67-3.59(m, 1H), 3.45 – 3.42 (m, 1H), 3.16 – 3.06 (m, 3H), 2.90 – 2.77 (m, 1H), 2.59 – 2.53 (m, 2H), 2.15 – 1.91(m, 5H), 1.90 – 1.68 (m, 9H), 1.68 – 1.45 (m, 3H), 1.13 (d, *J* = 2.9 Hz, 3H).

Total proton count from structure: 36

Total proton count from spectrum: 36

Step 7: (R*)-2-Amino-4-(3-(4-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-((R)-3-hydroxy-3-methylpiperidin-1-yl)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile

5

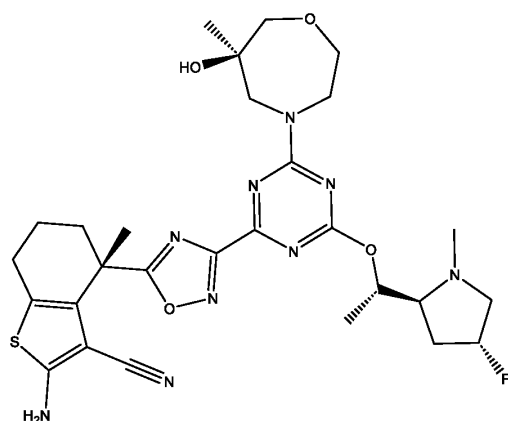
The 4-[3-(4-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy)-6-[(3R)-3-hydroxy-3-methylpiperidin-1-yl]-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl]-2-amino-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (70.0 mg) was separated by Prep-chiral with the following conditions (Column: CHIRALPAK IE, 3*25 cm, 5 µm; Mobile Phase A: Hex: MtBE=1: 1(0.5% 2M NH₃-MEOH), Mobile Phase B: MEOH; Flow rate: 40 mL/min; Gradient: isocratic 20; Wave Length: 220/240 nm; RT1(min): 19.67; RT2(min): 26.11; Sample Solvent: MEOH; Injection Volume: 0.5 mL; Number Of Runs: 4) to afford the second peak (R*)-4-[3-(4-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy)-6-[(3R)-3-hydroxy-3-methylpiperidin-1-yl]-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl]-2-amino-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (23.4 mg, 33.4%yield) as a white solid.

ESI-MS m/z = 610.30 [M+H]⁺; Calculated MW: 609.26. CHIRAL_HPLC Rt=3.01 min. ee value: 100%.

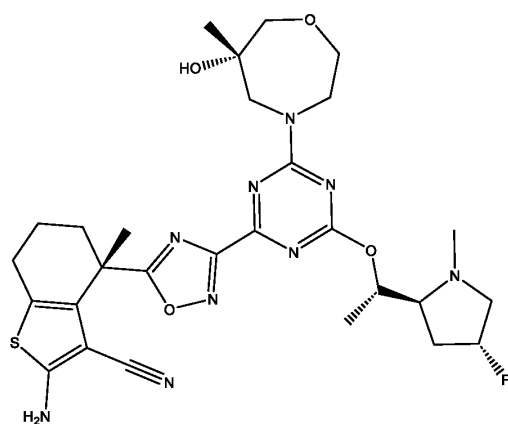
¹H NMR (400 MHz, DMSO-*d*₆) δ 7.10 (s, 2H), 5.27 (d, *J* = 54.4 Hz, 1H), 4.60 (d, *J* = 4.4 Hz, 1H), 4.14 – 3.91 (m, 3H), 3.81 – 3.39 (m, 3H), 3.16 – 2.98 (m, 3H), 2.88-2.76 (m, 1H), 2.61-2.52 (m, 2H), 2.17 – 1.88 (m, 5H), 1.89-1.70 (m, 9H), 1.67 – 1.47 (m, 3H), 1.12 (d, *J* = 4.1 Hz, 3H).

Total proton count from structure: 36

Total proton count from spectrum: 36

Example 28: Synthesis of Compound (115) and Compound (116)

Compound (115)



Compound (116)

- 5 Step 1: Rac-6-[(tert-butyldiphenylsilyl)oxy]-4-{4-chloro-6-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl}-6-methyl-1,4-oxazepane

To a stirred mixture of 6-[(tert-butyldiphenylsilyl)oxy]-4-(4,6-dichloro-1,3,5-triazin-2-yl)-6-methyl-1,4-oxazepane (3.00 g, 5.80 mmol, 1.0 equiv) and DIEA (2.25 g, 17.4 mmol, 3.0 equiv) in DCM (100 mL) were added (1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethanol (1.02 g, 6.96 mmol, 1.2 equiv) in portions at 20°C under air atmosphere. The resulting mixture was stirred at 20 °C for 16 h under air atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1:10~1:4). The pure fraction was concentrated under vacuum to afford Rac-6-[(tert-butyldiphenylsilyl)oxy]-4-{4-chloro-6-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl}-6-methyl-1,4-oxazepane (3.30 g, 90% yield) as a white oil.

ESI-MS m/z = 628.6 $M+H]^+$; Calculated MW: 627.0

Step 2: 4-[6-[(tert-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl]-6-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazine-2-carbonitrile

To a stirred mixture of Rac-6-[(tert-butyldiphenylsilyl)oxy]-4-{4-chloro-6-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl}-6-methyl-1,4-oxazepane (1.70 g, 2.71 mmol, 1.0 equiv) and Zn(CN)₂ (160.0 mg, 1.35 mmol, 0.5 equiv) in DMA (20 mL) were added Xantphos Pd 4G (520.0 mg, 0.54 mmol, 0.2 equiv) in portions at 25°C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 80 °C under nitrogen atmosphere. The mixture was allowed to cool down to 25°C. The resulting mixture was diluted with water (100 mL). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (3 x 100 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1:5~1:1). The pure fraction was concentrated under vacuum to afford 4-[6-[(tert-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl]-6-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazine-2-carbonitrile (1.40 g, 83% yield) as a yellow oil.

ESI-MS m/z = 619.2 [M+H]⁺; Calculated MW: 618.0

Step 3: (Z)-4-[6-[(tert-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl]-6-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-N'-hydroxy-1,3,5-triazine-2-carboximidamide

To a stirred mixture of 4-[6-[(tert-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl]-6-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazine-2-carbonitrile (1.30 g, 2.10 mmol, 1.0 equiv) and Na₂CO₃ (450.0 mg, 4.20 mmol, 2.0 equiv) in EtOH (20 mL) was added NH₂OH·HCl (160.0 mg, 2.31 mmol, 1.1 equiv) in portions at 25°C under air atmosphere. The resulting mixture was stirred for 2 h at 25°C under air atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH₂Cl₂/MeOH (10:1). The pure fraction was concentrated under vacuum to afford (Z)-4-[6-[(tert-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl]-6-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-N'-hydroxy-1,3,5-triazine-2-carboximidamide (1.10 g, 93% yield) as a yellow solid..

ESI-MS m/z = 652.3 [M+H]⁺; Calculated MW: 651.0

Step 4: {4-[6-[(tert-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl]-6-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl}methanimidamido (4S)-2-amino-3-cyano-4-methyl-6,7-dihydro-5H-1-benzothiophene-4-carboxylate

To a stirred mixture of (Z)-4-[6-[(tert-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl]-6-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-N'-hydroxy-1,3,5-triazine-2-carboximidamide (1.00 g, 1.53 mmol, 1.0 equiv) and DIEA (590.0 mg, 4.60 mmol, 3.0 equiv) in N,N-Dimethylformamide (10 mL) were added (4S)-2-amino-3-cyano-4-methyl-6,7-dihydro-5H-1-benzothiophene-4-carboxylic acid (400.0 mg, 1.69 mmol, 1.1 equiv) and Benzotriazole-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (1.20 g, 2.30 mmol, 1.5 equiv) in portions at 20°C under air atmosphere. The resulting mixture was stirred at 20°C for 2 h under air atmosphere. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18; mobile phase, MeCN in Water (0.1% NH₃.H₂O), 75% to 75% gradient in 10 min; detector, UV 254 nm. The pure fraction was concentrated under vacuum to afford {4-[6-[(tert-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl]-6-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl}methanimidamido (4S)-2-amino-3-cyano-4-methyl-6,7-dihydro-5H-1-benzothiophene-4-carboxylate (850 mg, 61% yield) as a yellow solid.

ESI-MS m/z = 870.2 [M+H]⁺; Calculated MW:869.4

Step 5: (4S)-2-amino-4-(3-{4-[6-[(tert-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl]-6-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile

A solution of {4-[6-[(tert-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl]-6-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl}methanimidamido (4S)-2-amino-3-cyano-4-methyl-6,7-dihydro-5H-1-benzothiophene-4-carboxylate (800.0 mg, 0.92 mmol, 1.0 equiv) and DBU (279.9 mg, 1.84 mmol, 2.0 equiv) in DMF (8 mL) was stirred at 80°C for 2 h under air atmosphere. The mixture was allowed to cool down to 20°C. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C₁₈ silica gel; mobile phase, MeCN in Water (10mmol/L NH₄HCO₃), 70% to 70% gradient in 10 min; detector, UV 254 nm. The pure fraction was concentrated under vacuum to afford (4S)-2-amino-4-(3-{4-[6-[(tert-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl]-6-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (630 mg, 80% yield) as a yellow solid.

ESI-MS m/z = 852.9 [M+H]⁺; Calculated MW:851.0

Step 6: Rac-(4S)-2-amino-4-(3-(4-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-6-(6-hydroxy-6-methyl-1,4-oxazepan-4-yl)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile

A solution of (4S)-2-amino-4-(3-{4-[6-[(tert-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl]-6-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (200.0 mg, 0.24 mmol, 1.0 equiv) and CsF (106.9 mg, 0.71 mmol, 3.0 equiv) in DMF (3 mL) was stirred at 80°C for 2 h under air atmosphere.

- 5 The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep Phenyl OBD Column 19*250 mm, 5m; Mobile Phase A: 10mmol/L NH₄HCO₃+0.05%NH₃H₂O), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 5% B to 5% B in 1 min, 5% B to 33% B in 2 min, 33% to 50% B in 10 min; Wavelength: 254nm/220nm nm; RT1(min): 9.47). The pure fraction was concentrated under vacuum and lyophilized to afford Rac-(4S)-2-amino-4-(3-(4-((S)-1-
10 ((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-6-(6-hydroxy-6-methyl-1,4-oxazepan-4-yl)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (27.8 mg, 19.30% yield) as a white solid.

ESI-MS m/z = 614.2 [M+H]⁺; Calculated MW: 613.0

- Step 7: (4S)-2-amino-4-(3-{4-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-6-[(6R*)-
15 6-hydroxy-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile and (4S)-2-amino-4-(3-{4-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-6-[(6R*)-6-hydroxy-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile

- Rac-(4S)-2-amino-4-(3-(4-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-6-(6-hydroxy-
20 6-methyl-1,4-oxazepan-4-yl)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (27.8 mg) was isolated by Chiral-HPLC with the following conditions (Column: Chiral NX(2) 5um, 250*30mm; Mobile Phase A: Hex(10mM NH₃-MeOH), Mobile Phase B: ETOH; Flow rate: 40 mL/min; Gradient: isocratic 30; Wave Length: 220/240 nm; RT1(min): 16.8; RT2(min): 19.7; Sample Solvent: ETOH; Number Of Runs: 7). The 1st
25 eluting fraction was concentrated under vacuum and lyophilized to afford a first isomer, compound (115) *rel*-(4S)-2-amino-4-(3-{4-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-6-[(6R)-6-hydroxy-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (10.4 mg, 98.0%purity@254nm, 37.4%yield, 100%ee) as a white solid, and the 2nd eluting fraction was concentrated under vacuum and lyophilized to afford
30 a second isomer, compound (116) *rel*-(4S)-4-[3-(6-[[[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methoxy]-2-[(6R)-6-hydroxy-6-methyl-1,4-oxazepan-4-yl]pyrimidin-4-yl]-1,2,4-oxadiazol-5-yl)-2-amino-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (10.2 mg, 97%purity@254nm, 37.4%yield, 100%ee) as a white solid.

Isomer 1 (compound (115)):

ESI-MS $m/z = 614.2$ $[M+H]^+$; Calculated MW: 613.0. CHIRAL_HPLC $R_t=2.041$ min. ee value: 100%.

1H NMR (400 MHz, DMSO- d_6) δ 7.08 (s, 2H), 5.35 – 5.06 (m, 2H), 4.82 (d, 1H), 4.21 – 3.95 (m, 2H), 3.78 (ddt, 4H), 3.50 – 3.34 (m, 3H), 2.96 (dd, 1H), 2.53 (d, 2H), 2.40 (d, 3H), 2.17–1.56 (m, 9H), 1.31–1.20 (m, 3H), 1.10 (d, 3H).

Isomer 2 (compound 116):

ESI-MS $m/z = 614.2$ $[M+H]^+$; Calculated MW: 613.0. CHIRAL_HPLC $R_t=2.471$ min. ee value: 96.52%.

1H NMR (400 MHz, DMSO- d_6) δ 7.08 (s, 2H), 5.35 – 5.06 (m, 2H), 4.82 (d, 1H), 4.21 – 3.95 (m, 2H), 3.78 (ddt, 4H), 3.50 – 3.34 (m, 3H), 2.96 (dd, 1H), 2.53 (d, 2H), 2.40 (d, 3H), 2.17–1.56 (m, 9H), 1.31–1.20 (m, 3H), 1.10 (d, 3H).

Total proton count from structure: 36.

Total proton count from spectrum: 35.

15 **Example 29:** Synthesis of Compound (132a)

Step 1: *Tert*-butyl 6-(difluoromethyl)-6-hydroxy-1,4-oxazepane-4-carboxylate

A mixture of *tert*-butyl 6-oxo-1,4-oxazepane-4-carboxylate (10.40 g, 48.3 mmol, 1.0 equiv) and (difluoromethyl)trimethylsilane (18.00 g, 144.9 mmol, 3.0 equiv) and CsF (36.70 g, 241.5 mmol, 5.0 equiv) in DMF (100 mL) was stirred at 80°C for 2h under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine, and dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water, 10% to 100% gradient in 30 min; detector, UV 200 nm. This resulted in *tert*-butyl 6-(difluoromethyl)-6-hydroxy-1,4-oxazepane-4-carboxylate (5.86 g, 45.3% yield) as a brown solid.

Step 2: 6-(Difluoromethyl)-1,4-oxazepan-6-ol

To a stirred solution of *tert*-butyl 6-(difluoromethyl)-6-hydroxy-1,4-oxazepane-4-carboxylate (4.80 g, 17.9 mmol, 1.0 equiv) in 1,4-dioxane (50 mL) was added HCl in 1,4-dioxane (4.0 M) (50 mL) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 30 min

under nitrogen atmosphere. The resulting mixture was concentrated under vacuum. This resulted in 6-(difluoromethyl)-1,4-oxazepan-6-ol (3.00 g, crude) as a brown solid.

Step 3: 4-(4,6-Dichloro-1,3,5-triazin-2-yl)-6-(difluoromethyl)-1,4-oxazepan-6-ol

To a stirred mixture of 6-(difluoromethyl)-1,4-oxazepan-6-ol (3.00 g, 17.9 mmol, 1.0 equiv) and 2,4,6-trichloro-1,3,5-triazine (3.97 g, 21.5 mmol, 1.2 equiv) in DCM (50 mL) was added DIEA (6.96 g, 53.8 mmol, 3 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 30 min under nitrogen atmosphere. The resulting mixture was diluted with water. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine, and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford 4-(4,6-dichloro-1,3,5-triazin-2-yl)-6-(difluoromethyl)-1,4-oxazepan-6-ol (5.57 g, 98.5% yield) as a yellow solid.

Step 4: 4-(4-Chloro-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-6-(difluoromethyl)-1,4-oxazepan-6-ol

A mixture of 4-(4,6-dichloro-1,3,5-triazin-2-yl)-6-(difluoromethyl)-1,4-oxazepan-6-ol (3.40 g, 10.7 mmol, 1.0 equiv) and (S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethan-1-ol (1.58 g, 10.7 mmol, 1.0 equiv) and Cs₂CO₃ (7.04 g, 21.5 mmol, 2.0 equiv) in 1,4-dioxane (30 mL) was stirred at 80°C for 1 h under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water, 30% to 70% gradient in 30 min; detector, UV 254 nm. This resulted in 4-(4-chloro-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-6-(difluoromethyl)-1,4-oxazepan-6-ol (4.41 g, 96.0% yield) as a yellow oil.

Step 5: 4-(6-(Difluoromethyl)-6-hydroxy-1,4-oxazepan-4-yl)-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazine-2-carbonitrile

A mixture of 4-(4-chloro-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-6-(difluoromethyl)-1,4-oxazepan-6-ol (4.41 g, 10.5 mmol, 1.0 equiv) and trimethylsilanecarbonitrile (1.04 g, 10.5 mmol, 1 equiv) and CsF (3.21 g, 21.1 mmol, 2.0 equiv) in DMF (30 mL) was stirred at 80°C for 1 h under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified

by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water, 30% to 80% gradient in 30 min; detector, UV 254 nm. This resulted in 4-(6-(difluoromethyl)-6-hydroxy-1,4-oxazepan-4-yl)-6-((*S*)-1-((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazine-2-carbonitrile (845.0 mg, 19.2% yield) as a brown solid.

- 5 Step 6: 4-(6-(Difluoromethyl)-6-hydroxy-1,4-oxazepan-4-yl)-6-((*S*)-1-((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-*N*-hydroxy-1,3,5-triazine-2-carboximidamide

To a stirred solution of 4-(6-(difluoromethyl)-6-hydroxy-1,4-oxazepan-4-yl)-6-((*S*)-1-((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazine-2-carbonitrile (800.0 mg, 1.92 mmol, 1.0 equiv) in THF (8 mL) was added hydroxylamine, 50% (253.8 mg, 7.68 mmol, 4.0 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 30 min under nitrogen atmosphere. The resulting mixture was concentrated under vacuum. This resulted in 4-(6-(difluoromethyl)-6-hydroxy-1,4-oxazepan-4-yl)-6-((*S*)-1-((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-*N*-hydroxy-1,3,5-triazine-2-carboximidamide (785.0 mg, crude) as a yellow solid.

- 15 Step 7: 4-((*S*)-6-(difluoromethyl)-6-hydroxy-1,4-oxazepan-4-yl)-6-((*S*)-1-((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-*N*-hydroxy-1,3,5-triazine-2-carboximidamide

The product 4-(6-(difluoromethyl)-6-hydroxy-1,4-oxazepan-4-yl)-6-((*S*)-1-((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-*N*-hydroxy-1,3,5-triazine-2-carboximidamide (785.0 mg, 0.17 mmol, 1.0 equiv) was separated by Chiral-HPLC with the following conditions (Column: Enantiocel- A4-5, 3.0*25CM, 5um; Mobile Phase A: Hex(10mM NH₃-MeOH), Mobile Phase B: EtOH; Flow rate: 40 mL/min; Gradient: isocratic 50; Wavelength: 222/284 nm; RT1(min): 6; RT2(min): 7.8; Sample Solvent: ETOH; Number Of Runs: 14) to afford first peak, isomer 1 4-((*S*)-6-(difluoromethyl)-6-hydroxy-1,4-oxazepan-4-yl)-6-((*S*)-1-((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-*N*-hydroxy-1,3,5-triazine-2-carboximidamide (327.5 mg, ee:100%, 41.7% yield) as a yellow solid and second peak, isomer 2 4-((*R*)-6-(difluoromethyl)-6-hydroxy-1,4-oxazepan-4-yl)-6-((*S*)-1-((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-*N*-hydroxy-1,3,5-triazine-2-carboximidamide (308.7 mg, ee:99.7%, 39.3% yield) as a yellow solid.

- 25 Step 8: *N*-(((*S*)-2-amino-3-cyano-4-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-4-carbonyl)oxy)-4-((*S*)-6-(difluoromethyl)-6-hydroxy-1,4-oxazepan-4-yl)-6-((*S*)-1-((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazine-2-carboximidamide

30 To a stirred mixture of 4-((*S*)-6-(difluoromethyl)-6-hydroxy-1,4-oxazepan-4-yl)-6-((*S*)-1-((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-*N*-hydroxy-1,3,5-triazine-2-carboximidamide (300.0 mg, 0.66 mmol, 1.0 equiv) and (*S*)-2-amino-3-cyano-4-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-4-carboxylic acid (189.2 mg, 0.80 mmol, 1.2 equiv) and DIEA (431.3 mg, 3.34 mmol, 5.0 equiv) in DMF (5 mL) was added HATU (380.7 mg, 1.00 mmol, 1.5 equiv) in portions at 0°C under nitrogen

atmosphere. The resulting mixture was stirred at 30°C for 1 h under nitrogen atmosphere. The resulting mixture was diluted with water. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water, 20% to 70% gradient in 30 min; detector, UV 254 nm. This resulted in *N*-(((*S*)-2-amino-3-cyano-4-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-4-carbonyl)oxy)-4-((*S*)-6-(difluoromethyl)-6-hydroxy-1,4-oxazepan-4-yl)-6-((*S*)-1-((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazine-2-carboximidamide (255.5 mg, 57.3% yield) as a yellow solid.

- Step 9: (*S*)-2-amino-4-(3-(4-((*S*)-6-(difluoromethyl)-6-hydroxy-1,4-oxazepan-4-yl)-6-((*S*)-1-((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile

- To a stirred solution of *N*-(((*S*)-2-amino-3-cyano-4-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-4-carbonyl)oxy)-4-((*S*)-6-(difluoromethyl)-6-hydroxy-1,4-oxazepan-4-yl)-6-((*S*)-1-((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazine-2-carboximidamide (250.0 mg, 0.37 mmol, 1.0 equiv) in DMF (2 mL) was added DBU (570.0 mg, 3.74 mmol, 10 equiv) dropwise at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 80°C for 1 h under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase flash with the following conditions (Column: XBridge Shield RP18 OBD Column 19*250 mm, 10m; Mobile Phase A: 10mmol/L NH₄HCO₃+0.05%NH₃H₂O), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 5% B to 5% B in 1 min, 5% B to 38% B in 2 min, 38% to 53% B in 12 min; Wavelength: 254nm/220nm nm; RT1(min): 9.02) to afford (*S*)-2-amino-4-(3-(4-((*S*)-6-(difluoromethyl)-6-hydroxy-1,4-oxazepan-4-yl)-6-((*S*)-1-((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (64.1 mg, 97.3% @254 nm, 98.6% @220 nm, ee: 100%, 26.3% yield) as an off-white solid.

ESI-MS *m/z* = 650.2 [M+H]⁺; Calculated MW: 649.2.

- ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.08 (s, 2H), 6.01 (td, *J* = 54.6, 14.8 Hz, 1H), 5.68 (d, *J* = 3.6 Hz, 1H), 5.35 – 5.07 (m, 2H), 4.34 (dd, *J* = 35.6, 14.6 Hz, 1H), 4.19 (dd, *J* = 27.3, 13.5 Hz, 1H), 3.94 – 3.57 (m, 6H), 3.41 (ddd, *J* = 22.2, 11.8, 6.0 Hz, 1H), 2.99 – 2.86 (m, 1H), 2.54 (t, *J* = 5.8 Hz, 2H), 2.39 (s, 3H), 2.13 – 1.74 (m, 9H), 1.24 (dd, *J* = 6.4, 2.9 Hz, 3H).

Example 30: Synthesis of Compounds (106) and (120)

Step 1: (4S)-4-(3-{4-[(1R*)-1-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]ethoxy]-6-[(6R*)-6-hydroxy-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-2-amino-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile, ("isomer 3") & (4S)-4-(3-{4-[(1R*)-1-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]ethoxy]-6-[(6R*)-6-hydroxy-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-2-amino-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile, ("isomer 4"):

(4S)-4-(3-{4-[(1S)-1-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]ethoxy]-6-[(6R)-6-hydroxy-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-2-amino-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (60.0 mg) was purified by Prep-HPLC with the following conditions (Column: Chiral NX(2) 5um, 250*30mm; Mobile Phase A: Hex(10mM NH₃-MeOH), Mobile Phase B: ETOH; Flow rate: 40 mL/min; Gradient: isocratic 30; Wavelength: 220/240 nm; RT1(min): 16.5; RT2(min): 20.2; Sample Solvent: ETOH; Number Of Runs: 3. The 1st eluting fraction ("isomer 3") was lyophilized to afford (4S)-4-(3-{4-[(1R*)-1-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]ethoxy]-6-[(6R*)-6-hydroxy-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-2-amino-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (5.9 mg, 99.6% purity @254nm, 99.7% purity@220nm, 9.83% yield, ee: 100%) as a white solid. The 2nd eluting fraction ("isomer 4") was lyophilized to afford (4S)-4-(3-{4-[(1R*)-1-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]ethoxy]-6-[(6R*)-6-hydroxy-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-2-amino-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (9.6 mg, 99.8% purity@254nm, 99.5% purity@220nm, 16.00% yield, ee: 99.28%) as a white solid.

isomer 3: ESI-MS m/z = 639.3 [M+H]⁺; Calculated MW:640.35 CHIRAL_HPLC Rt=1.88 min. ee value: 100%.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.09 (s, 2H), 5.28 (d, J = 53.4 Hz, 1H), 5.10 – 4.98 (m, 1H), 4.86 (d, J = 9.1 Hz, 1H), 4.21 – 3.93 (m, 2H), 3.88 – 3.56 (m, 4H), 3.52 – 3.36 (m, 2H), 3.14 – 2.93 (m, 3H), 2.90 – 2.76 (m, 1H), 2.55 (t, J = 6.2 Hz, 2H), 2.26 – 1.91 (m, 5H), 1.88 – 1.66 (m, 8H), 1.24 (t, J = 6.9 Hz, 3H), 1.10 (d, J = 4.2 Hz, 3H).

¹⁹F NMR (376 MHz, DMSO) δ -171.185

isomer 4: ESI-MS m/z = 639.3 [M+H]⁺; Calculated MW:640.35 CHIRAL_HPLC Rt=2.36 min. ee value: 99.28%.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.09 (s, 2H), 5.08 (dq, J = 28.0, 6.2 Hz, 1H), 5.10 – 4.98 (m, 1H), 4.86 (d, J = 9.1 Hz, 1H), 4.21 – 3.93 (m, 2H), 3.88 – 3.55 (m, 4H), 3.52 – 3.36 (m, 2H), 3.14 – 2.93

(m, 3H), 2.90 – 2.76 (m, 1H), 2.55 (t, J = 6.2 Hz, 2H), 2.26 – 1.91 (m, 5H), 1.88 – 1.66 (m, 8H), 1.24 (t, J = 6.9 Hz, 3H), 1.10 (d, J = 4.2 Hz, 3H).

¹⁹F NMR (376 MHz, DMSO) δ -171.410

5 **Example 31:** Synthesis of compound (133)

Step 1: Tert-butyl 3-methyl-6-methylene-1,4-oxazepane-4-carboxylate

To a stirred mixture of 2-aminopropan-1-ol (10.00 g, 131.4 mmol, 1.0 equiv) in *t*-BuOH (150 mL) was added *t*-BuOK (1.8M in THF) (148 mL, 2.0 equiv) dropwise at 0°C under N₂ atmosphere. To the above mixture was added 3-chloro-2-(chloromethyl)prop-1-ene (19.70 g, 157.7 mmol, 1.2 equiv) dropwise at 0°C. The resulting mixture was stirred at 80°C for additional 2h. To the above mixture was added Boc₂O (57.34 g, 262.7 mmol, 2.0 equiv) in *t*-BuOH (20 mL) dropwise at 0°C. The resulting mixture was stirred at 25°C for additional 1h. The resulting mixture was concentrated under reduced pressure. The resulting mixture was diluted with H₂O. The resulting mixture was extracted with EA. The combined organic layers were washed with H₂O, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE:EA (10:1) to afford tert-butyl 3-methyl-6-methylene-1,4-oxazepane-4-carboxylate (21.00 g, 69.4% yield) as a yellow oil.

Step 2: Tert-butyl 3-methyl-6-oxo-1,4-oxazepane-4-carboxylate

To a stirred mixture of tert-butyl 3-methyl-6-methylene-1,4-oxazepane-4-carboxylate (15.00 g, 66.0 mmol, 1.0 equiv) and K₂OsO₄·2H₂O (486.3 mg, 1.32 mmol, 0.02 equiv) in THF (150 mL) and H₂O (150 mL) were added NaIO₄ (56.46 g, 263.9 mmol, 4.0 equiv) in portions at 0°C under N₂ atmosphere. The resulting mixture was stirred at 25°C for additional 3h. The resulting mixture was diluted with H₂O. The resulting mixture was extracted with EA. The combined organic layers were washed with H₂O, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to afford tert-butyl 3-methyl-6-oxo-1,4-oxazepane-4-carboxylate (13.90 g, crude) as a brown-yellow oil.

Step 3: Tert-butyl 6-hydroxy-3,6-dimethyl-1,4-oxazepane-4-carboxylate

To a stirred mixture of tert-butyl 3-methyl-6-oxo-1,4-oxazepane-4-carboxylate (13.90 g, 60.6 mmol, 1.0 equiv) in THF (140 mL) was added CH₃MgBr (1 M) (91 mL, 1.5 equiv) dropwise at 0°C under Ar atmosphere. The resulting mixture was stirred at 0°C for additional 30min. The reaction was quenched with sat. NH₄Cl(aq) at 0°C. The resulting mixture was diluted with H₂O. The resulting mixture was extracted with EA. The combined organic layers were washed with H₂O, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified

by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, H₂O in ACN, 0% to 100% gradient in 8 min; detector, UV 200 nm to afford tert-butyl 6-hydroxy-3,6-dimethyl-1,4-oxazepane-4-carboxylate (6.10 g, 40.6%yield) as a yellow oil.

Step 4: 3,6-Dimethyl-1,4-oxazepan-6-ol

- 5 To a stirred mixture of tert-butyl 6-hydroxy-3,6-dimethyl-1,4-oxazepane-4-carboxylate (6.10 g, 24.9 mmol, 1.0 equiv) in 1,4-dioxane (60 mL) was added HCl in 1,4-dioxane(4.0 M) (60 mL) dropwise at 0°C under N₂ atmosphere. The resulting mixture was stirred at 25°C for additional 2h. The resulting mixture was concentrated under reduced pressure to afford 3,6-dimethyl-1,4-oxazepan-6-ol (4.60 g, crude) as a yellow solid.

10 Step 5: 6-((Tert-butyldiphenylsilyl)oxy)-3,6-dimethyl-1,4-oxazepane

- To a stirred mixture of 3,6-dimethyl-1,4-oxazepan-6-ol (4.60 g, 31.7 mmol, 1.0 equiv) and Imidazole (10.78 g, 158.4 mmol, 5.0 equiv) in DCM (36 mL) were added TBDPSCl (17.42 g, 63.3 mmol, 2.0 equiv) in DCM (10 mL) dropwise at 0°C under N₂ atmosphere. The resulting mixture was stirred at 30°C for additional 16h. The resulting mixture was diluted with H₂O. The resulting mixture was
15 extracted with DCM. The combined organic layers were washed with H₂O, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, H₂O in ACN, 0% to 100% gradient in 5 min; detector, UV 254 nm to afford 6-((tert-butyldiphenylsilyl)oxy)-3,6-dimethyl-1,4-oxazepane (6.10 g, 50.2%yield) as a yellow oil.

20 Step 6: 6-((tert-butyldiphenylsilyl)oxy)-4-(4,6-dichloro-1,3,5-triazin-2-yl)-3,6-dimethyl-1,4-oxazepane

- To a stirred mixture of 2,4,6-trichloro-1,3,5-triazine (2.84 g, 15.4 mmol, 1.0 equiv) in DCM (50 mL) was added DIEA (3.98 g, 30.8 mmol, 2.0 equiv) dropwise at 0°C under N₂ atmosphere. To the above mixture was added 6-((tert-butyldiphenylsilyl)oxy)-3,6-dimethyl-1,4-oxazepane (5.90 g, 15.4 mmol,
25 1.0 equiv) in DCM (10 mL) dropwise at 0°C. The resulting mixture was stirred at 0°C for additional 30min. The resulting mixture was diluted with H₂O at 0°C. The resulting mixture was extracted with DCM. The combined organic layers were washed with H₂O, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to afford 6-((tert-butyldiphenylsilyl)oxy)-4-(4,6-dichloro-1,3,5-triazin-2-yl)-3,6-dimethyl-1,4-oxazepane (8.00 g,
30 crude) as a yellow solid.

Step 7: 6-((Tert-butyldiphenylsilyl)oxy)-4-(4-chloro-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-3,6-dimethyl-1,4-oxazepane

To a stirred mixture of (S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethan-1-ol (1.08 g, 7.34 mmol, 1.3 equiv) in THF (30 mL) was added KHMDS(1M) (7.4 mL, 1.3 equiv) dropwise at 0°C under

N₂ atmosphere. The resulting mixture was stirred at 0°C for additional 30min. To above mixture was added 6-((tert-butyldiphenylsilyl)oxy)-4-(4,6-dichloro-1,3,5-triazin-2-yl)-3,6-dimethyl-1,4-oxazepane (3.00 g, 5.64 mmol, 1.0 equiv) in THF (10 mL) dropwise at -78°C. The resulting mixture was stirred at -78°C for additional 10min. The reaction was quenched with H₂O at 0°C. The resulting mixture was diluted with H₂O. The resulting mixture was extracted with EA. The combined organic layers were washed with H₂O, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to afford 6-((tert-butyldiphenylsilyl)oxy)-4-(4-chloro-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-3,6-dimethyl-1,4-oxazepane (2.50 g, crude) as a white solid.

- 10 Step 8: (3R,6S)-6-((tert-butyldiphenylsilyl)oxy)-4-(4-chloro-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-3,6-dimethyl-1,4-oxazepane, "isomer 1" 6-((tert-butyldiphenylsilyl)oxy)-4-(4-chloro-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-3,6-dimethyl-1,4-oxazepane (2.50 g, 3.90 mmol, 1.0 equiv.) was separated by reversed-phase flash chromatography with the following conditions (Column: C18 silica gel; mobile phase, H₂O in ACN, 0% to 100% gradient in 8 min; detector, UV 254 nm) to afford first peak, "isomer 1" (3R,6S)-6-((tert-butyldiphenylsilyl)oxy)-4-(4-chloro-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-3,6-dimethyl-1,4-oxazepane (1.80 g, 72.0% yield, purity: 91.2% @ 254 nm, 89.6% @ 220 nm) as a white solid and second peak, "isomer 2" (3R,6R)-6-((tert-butyldiphenylsilyl)oxy)-4-(4-chloro-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-3,6-dimethyl-1,4-oxazepane (490.0 mg, 19.6% yield, purity: 89.6% @ 254 nm, 93.5% @ 220 nm) as a white solid.

- 20 Step 9: 4-((3R,6S)-6-((tert-butyldiphenylsilyl)oxy)-3,6-dimethyl-1,4-oxazepan-4-yl)-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazine-2-carbonitrile To a stirred mixture of (3R,6S)-6-((tert-butyldiphenylsilyl)oxy)-4-(4-chloro-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-3,6-dimethyl-1,4-oxazepane (1.00 g, 1.56 mmol, 1.0 equiv) and Zn(CN)₂ (365.6 mg, 3.11 mmol, 2.0 equiv) in DMA (10 mL) were added Xantphos Pd G4 (149.8 mg, 0.16 mmol, 0.1 equiv) in portions at 25°C under Ar atmosphere. The resulting mixture was stirred at 80°C for additional 1h. The mixture was allowed to cool down to 25°C. The resulting mixture was filtered, the filter cake was washed with EA. The filtrate was concentrated under reduced pressure. The resulting mixture was diluted with H₂O at 0°C. The resulting mixture was extracted with EA. The combined organic layers were washed with H₂O, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, H₂O in ACN, 0% to 100% gradient in 6 min; detector, UV 254 nm to afford 4-((3R,6S)-6-((tert-

butyldiphenylsilyl)oxy)-3,6-dimethyl-1,4-oxazepan-4-yl)-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazine-2-carbonitrile (830.0 mg, 84.2% yield) as a white solid.

Step 10: 4-((3R,6S)-6-((tert-butyldiphenylsilyl)oxy)-3,6-dimethyl-1,4-oxazepan-4-yl)-6-(1-((2R,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-N-hydroxy-1,3,5-triazine-2-carboximidamide

- 5 To a stirred mixture of 4-((3R,6S)-6-((tert-butyldiphenylsilyl)oxy)-3,6-dimethyl-1,4-oxazepan-4-yl)-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazine-2-carbonitrile (830.0 mg, 1.31 mmol, 1.0 equiv) in THF (6 mL) was added NH₂OH(50% in H₂O)(130.0 mg, 1.97 mmol, 1.5 equiv) in THF (2 mL) dropwise at 0°C under N₂ atmosphere. The resulting mixture was stirred at 25°C for additional 1h. The resulting mixture was concentrated under reduced pressure to afford 4-((3R,6S)-6-((tert-butyldiphenylsilyl)oxy)-3,6-dimethyl-1,4-oxazepan-4-yl)-6-(1-((2R,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-N-hydroxy-1,3,5-triazine-2-carboximidamide (890.0 mg, crude) as a white solid.

- Step 11: N-(((S)-2-amino-3-cyano-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-4-carbonyl)oxy)-4-((3R,6S)-6-((tert-butyldiphenylsilyl)oxy)-3,6-dimethyl-1,4-oxazepan-4-yl)-6-(1-((2R,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazine-2-carboximidamide

- 15 To a stirred mixture of 4-((3R,6S)-6-((tert-butyldiphenylsilyl)oxy)-3,6-dimethyl-1,4-oxazepan-4-yl)-6-(1-((2R,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-N-hydroxy-1,3,5-triazine-2-carboximidamide (300.0 mg, 0.45 mmol, 1.0 equiv), nd (S)-2-amino-3-cyano-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-4-carboxylic acid (127.8 mg, 0.54 mmol, 1.2 equiv) in DMF (3 mL) were added DIEA (291.0 mg, 2.26 mmol, 5.0 equiv) and PyBOP (351.9 mg, 0.68 mmol, 1.5 equiv) in portions at 0°C under N₂ atmosphere. The resulting mixture was stirred at 25°C for additional 1h. The resulting mixture was diluted with H₂O at 0°C. The resulting mixture was extracted with EA. The combined organic layers were washed with H₂O, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, H₂O in ACN, 0% to 100% gradient in 8 min; detector, UV 254 nm to afford N-(((S)-2-amino-3-cyano-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-4-carbonyl)oxy)-4-((3R,6S)-6-((tert-butyldiphenylsilyl)oxy)-3,6-dimethyl-1,4-oxazepan-4-yl)-6-(1-((2R,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazine-2-carboximidamide (280.0 mg, 70.3% yield) as a yellow solid.

- 30 Step 12: (4S)-2-amino-4-(3-(4-((3R,6S)-6-((tert-butyldiphenylsilyl)oxy)-3,6-dimethyl-1,4-oxazepan-4-yl)-6-(1-((2R,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile

To a stirred mixture of N-(((S)-2-amino-3-cyano-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-4-carbonyl)oxy)-4-((3R,6S)-6-((tert-butyldiphenylsilyl)oxy)-3,6-dimethyl-1,4-oxazepan-4-yl)-6-(1-

((2R,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazine-2-carboximidamide (280.0 mg, 0.32 mmol, 1.0 equiv) in DMF (3 mL) was added DBU (482.0 mg, 3.17 mmol, 10 equiv) dropwise at 25°C under N₂ atmosphere. The resulting mixture was stirred at 80°C for additional 1h. The mixture was allowed to cool down to 25°C. The resulting mixture was filtered, the filter cake was washed with
5 EA. The filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, H₂O in ACN, 0% to 100% gradient in 5 min; detector, UV 254 nm to afford (4S)-2-amino-4-(3-(4-((3R,6S)-6-((tert-butyldiphenylsilyl)oxy)-3,6-dimethyl-1,4-oxazepan-4-yl)-6-(1-((2R,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (210.0 mg, 76.6% yield) as a yellow solid.

Step 13: (S)-2-amino-4-(3-(4-((3R,6S)-6-((tert-butyldiphenylsilyl)oxy)-3,6-dimethyl-1,4-oxazepan-4-yl)-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile, "isomer 1"

(4S)-2-amino-4-(3-(4-((3R,6S)-6-((tert-butyldiphenylsilyl)oxy)-3,6-dimethyl-1,4-oxazepan-4-yl)-6-(1-((2R,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (210.0 mg, 0.24 mmol, 1.0 equiv) was separated by Prep-Chiral-HPLC with the following conditions (Column: (S, S)-WHELK-O1, 2*25cm, 5µm; Mobile Phase A: Hex(10mM NH₃-MeOH), Mobile Phase B: ETOH; Flow rate: 20 mL/min; Gradient: isocratic 20; Wavelength: 220/254 nm; RT1(min): 18.25; RT2(min): 21.63; Sample Solvent: ETOH; Injection Volume: 0.4 mL; Number Of Runs: 15) to afford first peak, isomer 1 (S)-2-amino-4-(3-(4-((3R,6S)-6-((tert-butyldiphenylsilyl)oxy)-3,6-dimethyl-1,4-oxazepan-4-yl)-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (90.0 mg, 42.9% yield, ee: 98.54%) as a white solid and second peak, isomer 2 (S)-2-amino-4-(3-(4-((3S,6R)-6-((tert-butyldiphenylsilyl)oxy)-3,6-dimethyl-1,4-oxazepan-4-yl)-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (70.0 mg, 33.3% yield, ee: 96.74%) as a white solid.

Step 14: (S)-2-amino-4-(3-(4-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-6-((3R,6S)-6-hydroxy-3,6-dimethyl-1,4-oxazepan-4-yl)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile

To a stirred solution of (S)-2-amino-4-(3-(4-((3R,6S)-6-((tert-butyldiphenylsilyl)oxy)-3,6-dimethyl-1,4-oxazepan-4-yl)-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (90.0 mg, 0.10 mmol, 1.0 equiv) was added pyridine hydrofluoride (0.72 mL) dropwise at 0°C under N₂ atmosphere.
35 The resulting mixture was stirred at 25°C for additional 1h. The mixture was basified to pH 8 with

NaHCO₃ at 0°C. The resulting mixture was diluted with H₂O. The resulting mixture was extracted with EA. The combined organic layers were washed with H₂O, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column 30*150 mm, 5m; Mobile Phase A: 10mmol/L NH₄HCO₃+0.05%NH₃H₂O), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 5% B to 5% B in 1 min, 5% B to 35% B in 2 min, 35% to 53% B in 11 min; Wavelength: 254nm/220nm nm; RT1(min): 9.32); This resulted in (S)-2-amino-4-(3-(4-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-6-((3R,6S)-6-hydroxy-3,6-dimethyl-1,4-oxazepan-4-yl)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (22.8 mg, 34.9%yield, 99.2%purity@254nm; 99.4%purity@220nm) as a white solid.

ESI-MS m/z = 628.3 [M+H]⁺; Calculated MW: 627.2

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.08 (s, 2H), 5.30-5.06 (m, 2H), 4.85-4.65 (m, 1H), 4.57-4.27 (m, 2H), 4.05-3.98 (m, 1H), 3.52-3.43 (m, 3H), 3.40-3.32 (m, 2H), 3.01-2.93 (m, 1H), 2.56-2.53 (m, 3H), 2.43-2.42 (m, 3H), 2.14-1.67 (m, 9H), 1.27-1.24 (m, 3H), 1.09-0.95 (m, 6H).

Example 32: Synthesis of Compounds (134) and (134a)

Step 1: 6-[(tert-butyldiphenylsilyl)oxy]-4-{4-chloro-6-[(1S)-1-[(2S)-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl}-6-methyl-1,4-oxazepane

To a stirred mixture of (1S)-1-[(2S)-1-methylpyrrolidin-2-yl]ethanol (870.0 mg, 6.76 mmol, 1.0 equiv) and 6-[(tert-butyldiphenylsilyl)oxy]-4-(4,6-dichloro-1,3,5-triazin-2-yl)-6-methyl-1,4-oxazepane (3.50 g, 6.76 mmol, 1.0 equiv) in MeCN (35 mL) was added Cs₂CO₃ (4.41 g, 13.5 mmol, 2.0 equiv) in portions at room temperature under argon atmosphere. The resulting mixture was stirred at 80°C for 2h under argon atmosphere. The mixture was allowed to cool down to room temperature. The precipitated solids were collected by filtration and washed with MeCN (35 mL) (3x10 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford 6-[(tert-butyldiphenylsilyl)oxy]-4-{4-chloro-6-[(1S)-1-[(2S)-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl}-6-methyl-1,4-oxazepane (3.00 g, 72.6%yield) as a white solid.

Step 2: 4-{6-[(tert-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl}-6-[(1S)-1-[(2S)-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazine-2-carbonitrile

To a stirred mixture of 6-[(tert-butyldiphenylsilyl)oxy]-4-{4-chloro-6-[(1S)-1-[(2S)-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl}-6-methyl-1,4-oxazepane (2.90 g, 4.75 mmol, 1.0

equiv) and trimethylsilanecarbonitrile (940.0 mg, 9.50 mmol, 2.0 equiv) in DMF (30 mL) was added CsF (2.17 g, 14.2 mmol, 3.0 equiv) in portions at room temperature under argon atmosphere. The resulting mixture was stirred at 80°C for 2h under argon atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (30 mL). The resulting mixture was extracted with EtOAc (3 x 20mL). The combined organic layers were washed with brine (3x10 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:10) to afford 4-{6-[(tert-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl}-6-[(1S)-1-[(2S)-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazine-2-carbonitrile (1.40 g, 49%yield) as a white solid.

Step 3: (Z)-4-{6-[(tert-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl}-N'-hydroxy-6-[(1S)-1-[(2S)-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazine-2-carboximidamide
To a stirred mixture of 4-{6-[(tert-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl}-6-[(1S)-1-[(2S)-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazine-2-carbonitrile (1.35 g, 2.24 mmol, 1.0 equiv) in THF (20 mL) was added Hydroxylamine, 50% (150.0 mg, 4.49 mmol, 2.0 equiv) dropwise at 0°C under argon atmosphere. The resulting mixture was stirred at 30°C for 1h under argon atmosphere. The resulting mixture was concentrated under vacuum to afford (Z)-4-{6-[(tert-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl}-N'-hydroxy-6-[(1S)-1-[(2S)-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazine-2-carboximidamide (1.30 g, 91.2%yield) as a white solid. Calculated MW: 633.3

Step 4: (Z)-[amino(4-{6-[(tert-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl}-6-[(1S)-1-[(2S)-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazine-2-yl)methylidene]amino (4S)-2-amino-3-cyano-4-methyl-6,7-dihydro-5H-1-benzothiophene-4-carboxylate
To a stirred mixture of (Z)-4-{6-[(tert-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl}-N'-hydroxy-6-[(1S)-1-[(2S)-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazine-2-carboximidamide (1.35 g, 2.13 mmol, 1.0 equiv) and (4S)-2-amino-3-cyano-4-methyl-6,7-dihydro-5H-1-benzothiophene-4-carboxylic acid (1.01 g, 4.26 mmol, 2.0 equiv) in DMF (20 mL) were added DIEA (2.75 g, 21.3 mmol, 10 equiv) and HATU (1.62 g, 4.26 mmol, 2.0 equiv) in portions at 0°C under argon atmosphere. The resulting mixture was stirred at room temperature for 2h under argon atmosphere. The resulting mixture was filtered, the filter cake was washed with MeOH (3x10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeOH in Water (0.1% FA), 10% to 50% gradient in 10 min; detector, UV 254 nm. This resulted in (Z)-[amino(4-{6-[(tert-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl}-6-[(1S)-1-[(2S)-1-methylpyrrolidin-2-

yl]ethoxy]-1,3,5-triazin-2-yl)methylidene]amino (4*S*)-2-amino-3-cyano-4-methyl-6,7-dihydro-5*H*-1-benzothiophene-4-carboxylate (900.0 mg, 49.5%yield) as a yellow solid. ESI-MS m/z = 852.2 $[M+H]^+$; Calculated MW: 851.4

Step 5: (4*S*)-2-amino-4-[3-(4-{6-[(*tert*-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl})-6-[(1*S*)-1-[(2*S*)-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl]-4-methyl-6,7-dihydro-5*H*-1-benzothiophene-3-carbonitrile

To a stirred solution of (*Z*)-[amino(4-{6-[(*tert*-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl})-6-[(1*S*)-1-[(2*S*)-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl)methylidene]amino (4*S*)-2-amino-3-cyano-4-methyl-6,7-dihydro-5*H*-1-benzothiophene-4-carboxylate (900. mg, 1.056 mmol, 1.0 equiv) in DMF (20 mL) was added DBU (1.61 g, 10.5 mmol, 10 equiv) dropwise at room temperature under argon atmosphere. The resulting mixture was stirred at 60°C for 2h under argon atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was filtered, the filter cake was washed with MeOH (3x10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeOH in Water (0.1% FA), 10% to 50% gradient in 10 min; detector, UV 254 nm to afford (4*S*)-2-amino-4-[3-(4-{6-[(*tert*-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl})-6-[(1*S*)-1-[(2*S*)-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl]-4-methyl-6,7-dihydro-5*H*-1-benzothiophene-3-carbonitrile (700.0 mg, 79.4%yield, 100%purity) as a yellow solid.. ESI-MS m/z = 834.5 $[M+H]^+$; Calculated MW: 833.4

Step 6: (4*S*)-2-amino-4-{3-[4-(6-hydroxy-6-methyl-1,4-oxazepan-4-yl)-6-[(1*S*)-1-[(2*S*)-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl]-4-methyl-6,7-dihydro-5*H*-1-benzothiophene-3-carbonitrile

To a stirred mixture of (4*S*)-2-amino-4-[3-(4-{6-[(*tert*-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl})-6-[(1*S*)-1-[(2*S*)-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl]-4-methyl-6,7-dihydro-5*H*-1-benzothiophene-3-carbonitrile (400.0 mg, 0.48 mmol, 1.0 equiv) and TBAF (626.9 mg, 2.40 mmol, 5.0 equiv) in THF (4 mL) at 0°C under argon atmosphere. The resulting mixture was stirred at room temperature for 2h under argon atmosphere. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.1% FA), 10% to 50% gradient in 10 min; detector, UV 254 nm to afford (4*S*)-2-amino-4-{3-[4-(6-hydroxy-6-methyl-1,4-oxazepan-4-yl)-6-[(1*S*)-1-[(2*S*)-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl]-4-methyl-6,7-dihydro-5*H*-1-benzothiophene-3-carbonitrile (260.0 mg, 91%yield, 100%purity) as a yellow solid. ESI-MS m/z = 596.2 $[M+H]^+$; Calculated MW: 595.3.

Step 7: (4*S*)-2-amino-4-(3-{4-[(6*R**)-6-hydroxy-6-methyl-1,4-oxazepan-4-yl]-6-[(1*S*)-1-[(2*S*)-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methyl-6,7-dihydro-5*H*-1-benzothiophene-3-carbonitrile

The (4*S*)-2-amino-4-{3-[4-(6-hydroxy-6-methyl-1,4-oxazepan-4-yl)-6-[(1*S*)-1-[(2*S*)-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl]-1,2,4-oxadiazol-5-yl}-4-methyl-6,7-dihydro-5*H*-1-benzothiophene-3-carbonitrile (200.0 mg) was separated by CHIRAL_HPLC with the following conditions (Column: Enantiocel- A4-5, 3.0*25CM, 5μm; Mobile Phase A: Hex(0.1% DEA)--HPLC, Mobile Phase B: EtOH; Flow rate: 40 mL/min; Gradient: isocratic 30; Wavelength: 220/240 nm; RT1(min): 12.3; RT2(min): 14.8; Sample Solvent: EtOH; Number Of Runs: 13) to afford first peak, isomer 1, which is compound (**134**), (4*S*)-2-amino-4-(3-{4-[(6*R**)-6-hydroxy-6-methyl-1,4-oxazepan-4-yl]-6-[(1*S*)-1-[(2*S*)-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methyl-6,7-dihydro-5*H*-1-benzothiophene-3-carbonitrile, (50.1 mg, 50% yield, 99.0%purity@254nm, 98.7%purity@220nm, ee: 100%) as a white solid and second peak, isomer 2, which is compound (**134a**), (4*S*)-2-amino-4-(3-{4-[(6*R**)-6-hydroxy-6-methyl-1,4-oxazepan-4-yl]-6-[(1*S*)-1-[(2*S*)-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methyl-6,7-dihydro-5*H*-1-benzothiophene-3-carbonitrile (33.3 mg, 37% yield, 95.0%purity@254nm, 95.4%purity@220nm, ee: 97.8%) as a white solid.

Isomer 1: ESI-MS m/z = 596.3 $[M+H]^+$; Calculated MW: 595.3. CHIRAL_HPLC R_t =2.843 min. ee value: 98.7%.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.09 (s, 2H), 5.29-5.20 (m, 1H), 4.85-4.80 (m, 1H), 4.22-3.91 (m, 2H), 3.87-3.67 (m, 4H), 3.52-3.37 (m, 2H), 3.01(s, 1H), 2.72-2.53 (m, 3H), 2.37 (s, 3H), 2.24-2.12 (m, 1H), 2.10-2.00 (m, 1H), 1.97-1.88 (m, 1H), 1.86-1.71 (m, 6H), 1.69-1.57 (m, 2H), 1.30-1.22 (m, 4H), 1.15-1.04 (m, 3H),

Isomer 2: ESI-MS m/z = 596.3 $[M+H]^+$; Calculated MW: 595.3. CHIRAL_HPLC R_t =3.566 min. ee value: 97.8%.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.09 (s, 2H), 5.30-5.15 (m, 1H), 4.85-4.80 (m, 1H), 4.21-4.10 (m, 1H), 4.04-3.95 (m, 1H), 3.89-3.75 (m, 2H), 3.71-3.56 (m, 2H), 3.52-3.39 (m, 2H), 2.94(s, 1H), 2.68-2.53 (m, 3H), 2.42-2.31 (m, 3H), 2.24-2.14 (m, 1H), 2.10-2.02 (m, 1H), 1.99-1.90 (m, 1H), 1.86-1.72 (m, 6H), 1.69-1.57 (m, 2H), 1.29-1.19 (m, 4H), 1.13-1.08 (m, 3H).

30

Example 33: synthesis of compound (135a)

Step 1: (R)-2-Amino-4-(3-(4-((S)-6-((tert-butyldiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methoxy-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile

- 5 The product 2-amino-4-(3-(4-((S)-6-((tert-butyldiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methoxy-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (430 mg, 0.495 mmol, 1.0 equiv) was separated by Chiral-HPLC with the following conditions (Column: NB-CHIRALPAK-IE, 3*25 cm, 5 µm; Mobile Phase A: Hex(10mM NH₃-MeOH), Mobile Phase B: EtOH; Flow rate: 40 mL/min; 10 Gradient: isocratic 30; Wavelength: 220/240 nm; RT1(min): 30.57; RT2(min): 37.235; Sample Solvent: IPA: DCM=1: 1; Injection Volume: 0.9 mL; Number Of Runs: 9) to afford first peak, isomer 1, (R)-2-amino-4-(3-(4-((S)-6-((tert-butyldiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methoxy-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (180 mg, ee:100%) as a yellow solid and 15 second peak, isomer 2, (R)-2-amino-4-(3-(4-((S)-6-((tert-butyldiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methoxy-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (177 mg, ee:98.96%) as a yellow solid.

- Step 2: (R)-2-Amino-4-(3-(4-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-6-((S)-6-hydroxy-6-methyl-1,4-oxazepan-4-yl)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methoxy-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile
- 20 To a stirred mixture of (R)-2-amino-4-(3-(4-((S)-6-((tert-butyldiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methoxy-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (177.0 mg, 0.20 mmol, 1.0 equiv) in THF (2 mL) was added TBAF (0.40 mL, 0.40 mmol, 2.0 equiv) dropwise at 0°C 25 under N₂ atmosphere. The resulting mixture was stirred at 25°C for additional 6h. The resulting mixture was diluted with H₂O at 25°C. The resulting mixture was extracted with EA. The combined organic layers were washed with H₂O, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH=10:1) to 30 afford crude product. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column 30*150 mm, 5µm; Mobile Phase A: Water(10mmol/L NH₄HCO₃+0.05%NH₃H₂O), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 5% B to 5% B in 1 min, 5% B to 28% B in 2 min, 28% to 48% B in 12 min; Wavelength: 254nm/220 nm; RT1(min): 9.12); This resulted in (R)-2-amino-4-(3-(4-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-6-((S)-6-hydroxy-6-methyl-1,4-oxazepan-4-yl)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)- 35

4-methoxy-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (27.6 mg, 21.5% yield, 98.0%purity@254nm; 98.3%purity@220nm) as a white solid.

ESI-MS m/z = 630.25 $[M+H]^+$; Calculated MW: 629.3.

1H NMR (400 MHz, DMSO- d_6) δ 7.11 (s, 2H), 5.36 – 5.07 (m, 2H), 4.87-4.80 (m, 1H), 4.22 – 3.97 (m, 2H), 3.92 – 3.66 (m, 4H), 3.50 – 3.36 (m, 3H), 3.10 (s, 3H), 3.00-2.91 (m, 1H), 2.68-2.52 (m, 3H), 2.43-2.37 (m, 3H), 2.29 – 2.16 (m, 2H), 2.06 – 1.76 (m, 4H), 1.30-1.20 (m, 3H), 1.16-1.06 (m, 3H).

Example 34: Synthesis of Compound (136)

Step 1: Tert-butyl (2S,4R)-4-fluoro-2-((S)-1-hydroxyethyl)pyrrolidine-1-carboxylate

10 A mixture of (3aR)-1-methyl-3,3-diphenyl-hexahydropyrrolo[1,2-c][1,3,2]oxazaborole (4.32 mL, 4.32 mmol, 0.2 equiv) and 10M Borane-dimethyl sulfide complex(94%) (2.81 mL, 28.1 mmol, 1.3 equiv) in THF (50 mL) was stirred at -15°C for 1h under nitrogen atmosphere. To the above mixture was added tert-butyl (2S,4R)-2-acetyl-4-fluoropyrrolidine-1-carboxylate (5.00 g, 21.6 mmol, 1.0 equiv) dropwise at 0°C. The resulting mixture was stirred at 20°C for additional 2h. The reaction was
15 quenched with sat. NH_4Cl (aq.) at 20°C. The resulting mixture was extracted with EtOAc (2 x 200mL). The combined organic layers were washed with HCl (aq.) (2 x 100 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column 30*150 mm, 5 μ m; Mobile Phase A: 10mmol/L NH_4HCO_3 +0.05% NH_3H_2O), Mobile Phase B: ACN;
20 Flow rate: 60 mL/min mL/min; Gradient: 5% B to 5% B in 1 min, 5% B to 38% B in 2 min, 38% to 58% B in 11 min; Wavelength: 254nm/220nm nm; RT1(min): 8.28). The pure fraction was concentrated under reduced pressure to afford tert-butyl (2S,4R)-4-fluoro-2-((S)-1-hydroxyethyl)pyrrolidine-1-carboxylate (2.5 g, 49.57%yield, 95%purity) as a colorless oil.

Step 2: Tert-butyl (2S,4R)-2-((S)-1-((4-((S)-6-((tert-butyldiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-
25 4-yl)-6-chloro-1,3,5-triazin-2-yl)oxy)ethyl)-4-fluoropyrrolidine-1-carboxylate

To a stirred mixture of tert-butyl (2S,4R)-4-fluoro-2-((S)-1-hydroxyethyl)pyrrolidine-1-carboxylate (300 mg, 1.29 mmol, 1 equiv) and LiHMDS(1.0 M in THF) (1.67 mL, 1.67 mmol, 1.3 equiv) in THF (3 mL) was added (6S)-6-[(tert-butyldiphenylsilyl)oxy]-4-(4,6-dichloro-1,3,5-triazin-2-yl)-6-methyl-1,4-oxazepane (665 mg, 1.29 mmol, 1.0 equiv) at 0°C under nitrogen atmosphere. The resulting
30 mixture was stirred at 20°C for 1h under nitrogen atmosphere. The reaction was quenched with sat. NH_4Cl (aq.) at 0°C. The aqueous layer was extracted with EtOAc (2x20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column

chromatography, eluted with PE / EtOAc (3:1). The pure fraction was concentrated under reduced pressure to afford tert-butyl (2S,4R)-2-((S)-1-((4-((S)-6-((tert-butyldiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-chloro-1,3,5-triazin-2-yl)oxy)ethyl)-4-fluoropyrrolidine-1-carboxylate (600 mg, 65.31%yield, 90%purity) as a yellow solid.

- 5 Step 3: Tert-butyl (2S,4R)-2-((S)-1-((4-((S)-6-((tert-butyldiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-cyano-1,3,5-triazin-2-yl)oxy)ethyl)-4-fluoropyrrolidine-1-carboxylate

To a stirred mixture of tert-butyl (2S,4R)-2-((S)-1-((4-((S)-6-((tert-butyldiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-chloro-1,3,5-triazin-2-yl)oxy)ethyl)-4-fluoropyrrolidine-1-carboxylate (600 mg, 0.84 mmol, 1.0 equiv) and Zn(CN)₂ (118 mg, 1.01 mmol, 1.2 equiv) in N,N-Dimethylacetamide
10 (6 mL) was added XantPhos Pd G4 (80mg, 0.08 mmol, 0.1 equiv) at 20°C under nitrogen atmosphere. The resulting mixture was stirred at 80°C for 1h under nitrogen atmosphere. The mixture was allowed to cool down to 20°C. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EtOAc (1:1). The pure fraction was concentrated under reduced pressure to afford tert-butyl (2S,4R)-2-((S)-1-((4-((S)-6-((tert-butyldiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-cyano-1,3,5-triazin-2-yl)oxy)ethyl)-4-
15 fluoropyrrolidine-1-carboxylate (500 mg, 84.45%yield, 90%purity) as a yellow solid.

Steps 4-5: 4-((S)-6-((tert-butyldiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-((S)-1-((2S,4R)-1-(ethyl-d5)-4-fluoropyrrolidin-2-yl)ethoxy)-1,3,5-triazine-2-carbonitrile

A mixture of tert-butyl (2S,4R)-2-((S)-1-((4-((S)-6-((tert-butyldiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-cyano-1,3,5-triazin-2-yl)oxy)ethyl)-4-fluoropyrrolidine-1-carboxylate (500 mg, 0.71 mmol, 1.0 equiv) and trifluoroacetic acid (1 mL) in DCM (4 mL) was stirred at 20°C for 1h under
20 nitrogen atmosphere. The resulting mixture was concentrated under vacuum to afford 4-((S)-6-((tert-butyldiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-((S)-1-((2S,4R)-4-fluoropyrrolidin-2-yl)ethoxy)-1,3,5-triazine-2-carbonitrile (400 mg, crude) as a yellow oil.

25 To a stirred mixture of 4-((S)-6-((tert-butyldiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-((S)-1-((2S,4R)-4-fluoropyrrolidin-2-yl)ethoxy)-1,3,5-triazine-2-carbonitrile (350 mg, 0.58 mmol, 1.0 equiv) and (2,2,2-²H₃)acetaldehyde (81 mg, 1.74 mmol, 3.0 equiv) in O-methylhydrogenol (5 mL) was added sodium cyanoborodeuteride (57 mg, 0.89 mmol, 1.5 equiv) at 20°C under nitrogen atmosphere. The resulting mixture was stirred at 50°C for 1h under nitrogen atmosphere. The mixture was allowed to
30 cool down to 20°C. The reaction was quenched with Water at 20°C. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 ; mobile phase, MeCN in Water (10mmol/L NH₄HCO₃), 90% to 100% gradient in 10 min; detector, UV 254 nm. The pure fraction was concentrated under reduced pressure to afford 4-((S)-6-((tert-

butyldiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-((S)-1-((2S,4R)-1-(ethyl-d5)-4-fluoropyrrolidin-2-yl)ethoxy)-1,3,5-triazine-2-carbonitrile (300 mg, 81.27%yield, 95%purity) as a yellow solid.

Step 6: (Z)-4-((S)-6-((tert-butyldiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-((S)-1-((2S,4R)-1-(ethyl-d5)-4-fluoropyrrolidin-2-yl)ethoxy)-N'-hydroxy-1,3,5-triazine-2-carboximidamide

To a stirred mixture of 4-((S)-6-((tert-butyldiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-((S)-1-((2S,4R)-1-(ethyl-d5)-4-fluoropyrrolidin-2-yl)ethoxy)-1,3,5-triazine-2-carbonitrile (300 mg, 0.47 mmol, 1.0 equiv) and Na₂CO₃ (149 mg, 1.41 mmol, 3.0 equiv) in EtOH (5 mL) was added Hydroxylamine hydrochloride (49 mg, 0.71 mmol, 1.5 equiv) at 20°C under nitrogen atmosphere. The resulting mixture was stirred at 20°C for 1h under nitrogen atmosphere. The resulting mixture was diluted with water (50mL). The aqueous layer was extracted with EtOAc (2x50 mL). The resulting mixture was concentrated under vacuum to afford (Z)-4-((S)-6-((tert-butyldiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-((S)-1-((2S,4R)-1-(ethyl-d5)-4-fluoropyrrolidin-2-yl)ethoxy)-N'-hydroxy-1,3,5-triazine-2-carboximidamide (300 mg, 95.08%yield, 95%purity) as a white solid.

Step 7: (Z)-N'-(((S)-2-amino-3-cyano-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-4-carbonyl)oxy)-4-((S)-6-((tert-butyldiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-((S)-1-((2S,4R)-1-(ethyl-d5)-4-fluoropyrrolidin-2-yl)ethoxy)-1,3,5-triazine-2-carboximidamide

To a stirred mixture of (4S)-2-amino-3-cyano-4-methyl-6,7-dihydro-5H-1-benzothiophene-4-carboxylic acid (126 mg, 0.54 mmol, 1.2 equiv) and (Z)-4-((S)-6-((tert-butyldiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-((S)-1-((2S,4R)-1-(ethyl-d5)-4-fluoropyrrolidin-2-yl)ethoxy)-N'-hydroxy-1,3,5-triazine-2-carboximidamide (300 mg, 0.45 mmol, 1.0 equiv) in DMF (5 mL) were added Benzotriazole-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (349mg, 0.67 mmol, 1.5 equiv) and DIEA (173 mg, 1.34 mmol, 3.0 equiv) at 20°C under nitrogen atmosphere. The resulting mixture was stirred at 20°C for 1h under nitrogen atmosphere. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18; mobile phase, MeCN in Water (0.1% NH₃.H₂O), 90% to 100% gradient in 10 min; detector, UV 254 nm. The pure fraction was concentrated under vacuum to afford (Z)-N'-(((S)-2-amino-3-cyano-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-4-carbonyl)oxy)-4-((S)-6-((tert-butyldiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-((S)-1-((2S,4R)-1-(ethyl-d5)-4-fluoropyrrolidin-2-yl)ethoxy)-1,3,5-triazine-2-carboximidamide (250 mg, 62.88%yield, 90%purity) as a white solid.

Step 8: (S)-2-amino-4-(3-(4-((S)-6-((tert-butyldiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-((S)-1-((2S,4R)-1-(ethyl-d5)-4-fluoropyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile

A mixture of (Z)-N'-(((S)-2-amino-3-cyano-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-4-carbonyl)oxy)-4-((S)-6-((tert-butyldiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-((S)-1-((2S,4R)-1-(ethyl-d5)-4-fluoropyrrolidin-2-yl)ethoxy)-1,3,5-triazine-2-carboximidamide (250 mg, 0.28 mmol, 1.0 equiv) and DBU (85 mg, 0.56 mmol, 2.0 equiv) in DMF (3 mL) was stirred at 80°C for 1h under nitrogen atmosphere. The mixture was allowed to cool down to 20°C. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18; mobile phase, MeCN in Water (10mmol/L NH₄HCO₃), 95% to 100% gradient in 10 min; detector, UV 254 nm. The pure fraction was concentrated under vacuum to afford (S)-2-amino-4-(3-(4-((S)-6-((tert-butyldiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-((S)-1-((2S,4R)-1-(ethyl-d5)-4-fluoropyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (150 mg, 61.24%yield, 95%purity) as a yellow solid.

Step 9: (S)-2-amino-4-(3-(4-((S)-1-((2S,4R)-1-(ethyl-d5)-4-fluoropyrrolidin-2-yl)ethoxy)-6-((S)-6-hydroxy-6-methyl-1,4-oxazepan-4-yl)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile

A mixture of (S)-2-amino-4-(3-(4-((S)-6-((tert-butyldiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-((S)-1-((2S,4R)-1-(ethyl-d5)-4-fluoropyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (140 mg) in pyridine hydrofluoride (2 mL) was stirred at 0°C for 1h under nitrogen atmosphere. The mixture was basified to pH=9 with saturated Na₂CO₃ (aq.). The aqueous layer was extracted with EtOAc (2x50 mL). The resulting mixture was concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column 30*150 mm, 5µm; Mobile Phase A: 10mmol/L NH₄HCO₃+0.05%NH₃H₂O), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 5% B to 5% B in 1 min, 5% B to 38% B in 2 min, 38% to 58% B in 11 min; Wavelength: 254nm/220nm nm; RT1(min): 8.28). The pure fraction was concentrated and lyophilized to afford (S)-2-amino-4-(3-(4-((S)-1-((2S,4R)-1-(ethyl-d5)-4-fluoropyrrolidin-2-yl)ethoxy)-6-((S)-6-hydroxy-6-methyl-1,4-oxazepan-4-yl)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (32.1 mg, 31.57%yield, 98.9%purity@254nm, 99.2%purity@220nm) as a white solid.

ESI-MS m/z = 633.3 [M+H]⁺; Calculated MW: 632.3.

¹H NMR (400 MHz, DMSO-d₆) δ 7.09 (s, 2H), 5.34 – 5.27 (m, 1H), 5.27 – 5.07 (m, 1H), 4.83 (d, J = 17.9 Hz, 1H), 4.24 – 4.03 (m, 1H), 4.02 – 3.92 (m, 1H), 3.87 – 3.67 (m, 4H), 3.51 – 3.39 (m, 2H), 3.32 – 3.25 (m, 1H), 3.17 (dddd, J = 9.3, 7.1, 5.2, 2.1 Hz, 1H), 2.70 – 2.59 (m, 1H), 2.59 – 2.53 (m, 2H), 2.14 – 1.99 (m, 2H), 1.99 – 1.81 (m, 4H), 1.79 (d, J = 2.6 Hz, 3H), 1.25 (t, J = 6.7 Hz, 3H), 1.10 (d, J = 2.4 Hz, 3H).

¹⁹F NMR (376 MHz, DMSO) δ -170.78.

Example 35: Synthesis of Compound (98)

Step 1: Methyl (2S)-1-[(2-bromophenyl)methyl]pyrrolidine-2-carboxylate

5 To a stirred solution of 1-bromo-2-(bromomethyl)benzene (30.00 g, 120.0 mmol, 1.0 equiv) and methyl (2S)-pyrrolidine-2-carboxylate hydrochloride (23.86 g, 144.0 mmol, 1.2 equiv) in ACN (200 mL) was added K₂CO₃ (41.47 g, 300.1 mmol, 2.5 equiv) at 20°C under nitrogen atmosphere. The resulting mixture was stirred for 16h at 80°C under nitrogen atmosphere. The mixture was allowed to cool down to 20°C. The resulting
10 mixture was filtered and the filter cake was washed with acetonitrile (2x100 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1). The pure fraction was concentrated under reduced pressure to afford methyl (2S)-1-[(2-bromophenyl)methyl]pyrrolidine-2-carboxylate (30.00 g, 66.2% yield) as a colorless liquid.

15

Step 2: Tert-butyl 2,3-dihydro-1H-pyrrolo[2,1-a]isoindole-9b(5H)-carboxylate

A solution of t-BuOLi (31.29 g, 390.9 mmol, 3.5 equiv) in 1,4-dioxane (500 mL) was treated with DavePhos (4.40 g, 11.2 mmol, 0.1 equiv), Pd₂(dba)₃ (5.11 g, 5.58 mmol, 0.05 equiv) for 5min at 25°C under nitrogen atmosphere followed by the addition of tert-butyl (2S)-1-[(2-
20 bromophenyl)methyl]pyrrolidine-2-carboxylate (38.00 g, 111.6 mmol, 1.0 equiv), dodecane (5.71 g, 33.5 mmol, 0.3 equiv) in portions at 25°C under nitrogen atmosphere. The resulting mixture was stirred for 12h at 85°C under nitrogen atmosphere. The mixture was allowed to cool down to 20°C. The resulting mixture was extracted with CH₂Cl₂ (2x300 mL). The combined organic layers were washed with brine (2x200 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated
25 under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (4:1). The pure fraction was concentrated under reduced pressure to afford tert-butyl 2,3-dihydro-1H-pyrrolo[2,1-a]isoindole-9b(5H)-carboxylate (20.00 g, 55.2% yield) as a brown oil.

Step 3: (2,3-Dihydro-1H-pyrrolo[2,1-a]isoindol-9b(5H)-yl)methanol

To a stirred solution of tert-butyl 2,3-dihydro-1H-pyrrolo[2,1-a]isoindole-9b(5H)-carboxylate (19.00
30 g, 73.2 mmol, 1.0 equiv) in THF (200 mL) was added 2M AlH₄Li (54.95 mL, 109.9 mmol, 1.5 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 1h at 0°C under nitrogen atmosphere. The reaction was quenched with sodium sulfate decahydrate at 0°C. The resulting mixture was filtered and the filter cake was washed with tetrahydrofuran (2x500 mL).

The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH₂Cl₂ / MeOH (10:1). The pure fraction was concentrated under reduced pressure to afford (2,3-dihydro-1H-pyrrolo[2,1-a]isoindol-9b(5H)-yl)methanol (6.80 g, 41.4% yield) as a brown solid.

- 5 Step 4: 6-((Tert-butyldiphenylsilyl)oxy)-4-(4-chloro-6-((2,3-dihydro-1H-pyrrolo[2,1-a]isoindol-9b(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-6-methyl-1,4-oxazepane

To a stirred solution of 6-((tert-butyldiphenylsilyl)oxy)-4-(4,6-dichloro-1,3,5-triazin-2-yl)-6-methyl-1,4-oxazepane (11.70 g, 22.6 mmol, 1.0 equiv) and (2,3-dihydro-1H-pyrrolo[2,1-a]isoindol-9b(5H)-yl)methanol (4.71 g, 24.9 mmol, 1.1 equiv) in ACN (200 mL) was added Cs₂CO₃ (14.73 g, 45.2 mmol, 2.0 equiv) at 20 °C under nitrogen atmosphere. The resulting mixture was stirred for 1h at 60 °C under nitrogen atmosphere. The mixture was allowed to cool down to 20°C. The resulting mixture was filtered, the filter cake was washed with ACN (2x200 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1). The pure fraction was concentrated under reduced pressure to afford 6-((tert-butyldiphenylsilyl)oxy)-4-(4-chloro-6-((2,3-dihydro-1H-pyrrolo[2,1-a]isoindol-9b(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-6-methyl-1,4-oxazepane (9.80 g, 62.8% yield) as a yellow solid.

- 15 Step 5: 4-(6-((Tert-butyldiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-((2,3-dihydro-1H-pyrrolo[2,1-a]isoindol-9b(5H)-yl)methoxy)-1,3,5-triazine-2-carbonitrile

To a stirred solution of 6-((tert-butyldiphenylsilyl)oxy)-4-(4-chloro-6-((2,3-dihydro-1H-pyrrolo[2,1-a]isoindol-9b(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-6-methyl-1,4-oxazepane (9.80 g, 14.6 mmol, 1.0 equiv) and Xantphos Pd G₄ (1.41 g, 1.46 mmol, 0.1 equiv) in DMA (100 mL) were added Zn(CN)₂ (2.57 g, 21.9 mmol, 1.5 equiv) at 20°C under nitrogen atmosphere. The resulting mixture was stirred for 1h at 80°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was filtered, the filter cake was washed with CH₂Cl₂ (2x100 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1). The pure fraction was concentrated under reduced pressure to afford 4-(6-((tert-butyldiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-((2,3-dihydro-1H-pyrrolo[2,1-a]isoindol-9b(5H)-yl)methoxy)-1,3,5-triazine-2-carbonitrile (8.00 g, 71.7% yield) as a yellow oil.

- 25 Step 6: 4-(6-((Tert-butyldiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-((2,3-dihydro-1H-pyrrolo[2,1-a]isoindol-9b(5H)-yl)methoxy)-N-hydroxy-1,3,5-triazine-2-carboximidamide

To a stirred solution of 4-(6-((tert-butyldiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-((2,3-dihydro-1H-pyrrolo[2,1-a]isoindol-9b(5H)-yl)methoxy)-1,3,5-triazine-2-carbonitrile (8.00 g, 12.1

mmol, 1.0 equiv) and Na₂CO₃ (3.21 g, 30.3 mmol, 2.5 equiv) in EtOH (100 mL) was added hydroxylamine hydrochloride (1.68 g, 24.2 mmol, 2.0 equiv) at 20°C under nitrogen atmosphere. The resulting mixture was stirred for 1h at 20°C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C₁₈; mobile phase, MeCN in Water (10mmol/L NH₄HCO₃), 95% to 100% gradient in 10 min; detector, UV 254 nm. The pure fraction was concentrated under reduced pressure to afford 4-(6-((tert-butyl)diphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-((2,3-dihydro-1H-pyrrolo[2,1-a]isoindol-9b(5H)-yl)methoxy)-N-hydroxy-1,3,5-triazine-2-carboximidamide (5.50 g, 62.0% yield) as a yellow oil.

Step 7: N-(((S)-2-amino-3-cyano-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-4-carbonyl)oxy)-4-(6-((tert-butyl)diphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-((2,3-dihydro-1H-pyrrolo[2,1-a]isoindol-9b(5H)-yl)methoxy)-1,3,5-triazine-2-carboximidamide

To a stirred solution of 4-(6-((tert-butyl)diphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-((2,3-dihydro-1H-pyrrolo[2,1-a]isoindol-9b(5H)-yl)methoxy)-N-hydroxy-1,3,5-triazine-2-carboximidamide (5.50 g, 7.93 mmol, 1.0 equiv) and (4S)-2-amino-3-cyano-4-methyl-6,7-dihydro-5H-1-benzothiophene-4-carboxylic acid (1.87 g, 7.93 mmol, 1.0 equiv) in DMF (80 mL) were added DIEA (3.07 g, 23.8 mmol, 3.0 equiv) and PyBOP (6.19 g, 11.9 mmol, 1.5 equiv) at 20°C under nitrogen atmosphere. The resulting mixture was stirred for 1h at 20°C under nitrogen atmosphere. The resulting mixture was diluted with water (100 mL). The resulting mixture was extracted with EtOAc (3x100 mL). The combined organic layers were washed with brine (2x100 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to afford N-(((S)-2-amino-3-cyano-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-4-carbonyl)oxy)-4-(6-((tert-butyl)diphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-((2,3-dihydro-1H-pyrrolo[2,1-a]isoindol-9b(5H)-yl)methoxy)-1,3,5-triazine-2-carboximidamide (6.00 g, crude) as a yellow oil. The crude product was used in the next step directly without further purification.

Step 8: (4S)-2-amino-4-(3-(4-(6-((tert-butyl)diphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-((2,3-dihydro-1H-pyrrolo[2,1-a]isoindol-9b(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile

To a stirred solution of N-(((S)-2-amino-3-cyano-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-4-carbonyl)oxy)-4-(6-((tert-butyl)diphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-((2,3-dihydro-1H-pyrrolo[2,1-a]isoindol-9b(5H)-yl)methoxy)-1,3,5-triazine-2-carboximidamide (6.00 g, 6.58 mmol, 1.0 equiv) in DMF (60 mL) was added DBU (2.00 g, 13.2 mmol, 2.0 equiv) dropwise at 20°C

under nitrogen atmosphere. The resulting mixture was stirred for 1h at 80°C under nitrogen atmosphere. The mixture was allowed to cool down to 20°C. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C₁₈ silica gel; mobile phase, MeCN in Water (10mmol/L NH₄HCO₃), 95% to 100% gradient in 10 min; detector, UV 254 nm to afford (4S)-2-amino-4-(3-(4-(6-((tert-butyl)diphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-((2,3-dihydro-1H-pyrrolo[2,1-a]isoindol-9b(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (4.90 g, 77.4% yield) as a yellow solid.

- Step 9: (4S)-2-amino-4-(3-{4-[(9bR*)-1H,2H,3H,5H-benzo[a]pyrrolizin-9b-ylmethoxy]-6-[(6R**)-6-[(tert-butyl)diphenylsilyl]oxy]-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile, isomer 1; (4S)-2-amino-4-(3-{4-[(9bR*)-1H,2H,3H,5H-benzo[a]pyrrolizin-9b-ylmethoxy]-6-[(6R**)-6-[(tert-butyl)diphenylsilyl]oxy]-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile, isomer 2
- (4S)-2-amino-4-(3-(4-(6-((tert-butyl)diphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-((2,3-dihydro-1H-pyrrolo[2,1-a]isoindol-9b(5H)-yl)methoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (3.00 g) was separated by Prep-Chiral-HPLC with the following conditions (Column: NB_ASA CHIRALPAK IE, 5*25 cm, 10 µm; Mobile Phase A: Hex(0.1% DEA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 140 mL/min; Gradient: isocratic 50; Wavelength: 210/220 nm; RT1(min): 21; RT2(min): 30; Sample Solvent: EtOH--HPLC; Injection Volume: 3 mL; Number Of Runs: 11) to afford first peak, isomer1 (4S)-2-amino-4-(3-{4-[(9bR*)-1H,2H,3H,5H-benzo[a]pyrrolizin-9b-ylmethoxy]-6-[(6R**)-6-[(tert-butyl)diphenylsilyl]oxy]-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (1.10 g, 36.7% yield, ee: 100%.) as a yellow solid and second peak, isomer2 (4S)-2-amino-4-(3-{4-[(9bR*)-1H,2H,3H,5H-benzo[a]pyrrolizin-9b-ylmethoxy]-6-[(6R**)-6-[(tert-butyl)diphenylsilyl]oxy]-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (900.0 mg, 30.0% yield, ee: 100%.) as a yellow solid.

- Step 10: (4S)-2-amino-4-(3-{4-[(9bR*)-1H,2H,3H,5H-benzo[a]pyrrolizin-9b-ylmethoxy]-6-[(6R**)-6-[(tert-butyl)diphenylsilyl]oxy]-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile, isomer 1; (4S)-2-amino-4-(3-{4-[(9bR*)-1H,2H,3H,5H-benzo[a]pyrrolizin-9b-ylmethoxy]-6-[(6R**)-6-[(tert-butyl)diphenylsilyl]oxy]-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile, isomer 2

- (4S)-2-amino-4-(3-{4-[(9bR*)-1H,2H,3H,5H-benzo[a]pyrrolizin-9b-ylmethoxy]-6-[(6R**)6-[(tert-butyl)diphenylsilyl]oxy]-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (1.10 g, 1.23 mmol, 1.0 equiv) was separated by Prep-Chiral-HPLC with the following conditions (Column: Chiral NX(2) 5 μ m, 250*30mm; Mobile Phase A: Hex(10mM NH₃-MeOH), Mobile Phase B: EtOH; Flow rate: 40 mL/min; Gradient: isocratic 20; Wavelength: 218/240 nm; RT1(min): 15.4; RT2(min): 17.6; Sample Solvent: EtOH: MeOH=1: 2 -HPLC; Number Of Runs: 74) to afford first peak, isomer 1 (4S)-2-amino-4-(3-{4-[(9bR*)-1H,2H,3H,5H-benzo[a]pyrrolizin-9b-ylmethoxy]-6-[(6R**)6-[(tert-butyl)diphenylsilyl]oxy]-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (420.0 mg, 38.2% yield, ee: 97.78%.) as a yellow solid and second peak, isomer2 (4S)-2-amino-4-(3-{4-[(9bR*)-1H,2H,3H,5H-benzo[a]pyrrolizin-9b-ylmethoxy]-6-[(6R**)6-[(tert-butyl)diphenylsilyl]oxy]-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (500.0 mg, 45.5% yield, 99.4% ee.) as a yellow solid.
- Step 11: (4S)-2-amino-4-(3-{4-[(9bR*)-1H,2H,3H,5H-benzo[a]pyrrolizin-9b-ylmethoxy]-6-[(6R**)6-hydroxy-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile, isomer1

- To a stirred solution of (4S)-2-amino-4-(3-{4-[(9bR*)-1H,2H,3H,5H-benzo[a]pyrrolizin-9b-ylmethoxy]-6-[(6R**)6-[(tert-butyl)diphenylsilyl]oxy]-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile, isomer1 (200.0 mg, 0.22 mmol, 1.0 equiv) in THF (5 mL) was added TBAF (1.29 g, 4.928 mmol, 22.0 equiv) at 20°C under nitrogen atmosphere. The resulting mixture was stirred at 20°C for 8h under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The resulting mixture was diluted with water (50 mL). The resulting mixture was extracted with EtOAc (3x50 mL). The combined organic layers were washed with brine (2x50 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The crude product (70 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep Shield RP₁₈ 5 μ m 19*10mm; Mobile Phase A: 10mmol/L NH₄HCO₃+0.05%NH₃H₂O), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 5% B to 5% B in 1 min, 5% B to 32% B in 2 min, 32% to 50% B in 11 min; Wavelength: 254nm/220nm nm; RT1(min): 10.02) to afford isomer 1 (4S)-2-amino-4-(3-{4-[(9bR*)-1H,2H,3H,5H-benzo[a]pyrrolizin-9b-ylmethoxy]-6-[(6R**)6-hydroxy-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (28.1 mg, 18.7% yield, purity: 97.7% @254 nm, 97.7% @220 nm, ee: 100%) as an off-white solid.

Isomer1: ESI-MS m/z = 656.22 $[M+H]^+$; Calculated MW: 655.3. CHIRAL_HPLC R_t =3.40 min. ee value: 100%

1H NMR (400 MHz, DMSO- d_6) δ 7.32 – 7.24 (m, 1H), 7.20 – 7.14 (m, 3H), 7.03 (s, 2H), 4.79 (t, J = 1.5 Hz, 1H), 4.31 – 4.18 (m, 3H), 4.07 (dd, J = 32.0, 13.8 Hz, 2H), 3.80 – 3.54 (m, 5H), 3.43 – 3.32 (m, 2H), 3.07 (dd, J = 8.6, 4.6 Hz, 1H), 2.48 (s, 3H), 2.16 (s, 1H), 2.01 (d, J = 1.2 Hz, 1H), 1.93 – 1.83 (m, 1H), 1.83 – 1.68 (m, 7H), 1.64 (s, 1H), 1.02 (d, J = 13.8 Hz, 3H).

Example 36: Synthesis of Compound (137a)

Step 1: (4S)-2-amino-4-(3-{4-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-6-[(2R*, 6R**) -6-hydroxy-2,6-dimethyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile, "ISOMER 3" & (4S)-2-amino-4-(3-{4-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-6-[(2R*,6R**) -6-hydroxy-2,6-dimethyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile, "ISOMER 4"

(4S)-2-amino-4-(3-{4-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-6-[(6R*)-6-hydroxy-2,6-dimethyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (Mix) (90 mg) was separated by Prep-SFC-HPLC with the following conditions (Column: CHIRALPAK IH 3*25 cm, 5 μ m; Mobile Phase A: CO₂, Mobile Phase B: IPA(20mMNH₃); Flow rate: 120 mL/min; Gradient: isocratic 20% B; Column Temperature(°C): 25; Back Pressure(bar): 100; Wavelength: 215 nm; RT1(min): 11.3; RT2(min): 14.5; Sample Solvent: EtOH; Injection Volume: 0.4 mL; Number of Runs: 14). The 1st eluting fraction was concentrated under vacuum to afford (ISOMER 3) (4S)-2-amino-4-(3-{4-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-6-[(2R*,6R**) -6-hydroxy-2,6-dimethyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (23.2 mg, 97.6% purity @254nm; 97.6% purity@220nm, ee value: 100%.) as a white solid and the 2nd eluting fraction was concentrated under vacuum to afford (ISOMER 4) (4S)-2-amino-4-(3-{4-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-6-[(2R*,6R**) -6-hydroxy-2,6-dimethyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (18.1 mg, 95.6% purity @254nm; 96.7% purity@220nm, ee value: 95.08%.) as a white solid.

Isomer 4:

ESI-MS m/z = 628.4 $[M+H]^+$; Calculated MW: 627.3. SFC_HPLC R_t =5.880 min. ee value: 95.08%.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.03 (s, 2H), 5.44 – 5.06 (m, 2H), 4.71 (d, *J* = 58.9 Hz, 1H), 4.17 – 3.75 (m, 4H), 3.62 (d, *J* = 14.1 Hz, 1H), 3.47 (t, *J* = 12.6 Hz, 2H), 3.25 (d, *J* = 12.3 Hz, 1H), 2.47 (t, *J* = 6.2 Hz, 5H), 2.43 – 2.08 (m, 2H), 2.06 – 1.73 (m, 6H), 1.72 (s, 3H), 1.26 – 1.05 (m, 9H).

¹⁹F NMR (376 MHz, DMSO) δ -172.10.

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Example 37: Synthesis of Compound (138a)

Step 1: Tert-butyl 6-cyclopropyl-6-hydroxy-1,4-oxazepane-4-carboxylate

To a stirred solution of tert-butyl 6-oxo-1,4-oxazepane-4-carboxylate (10.00 g, 46.4 mmol, 1.0 equiv) in THF (200 mL) was added bromo(cyclopropyl)magnesium(1.0 M in THF) (92.9 mL, 92.9 mmol, 2.0 equiv) dropwise at -20°C under nitrogen atmosphere. The resulting mixture was stirred at 20°C for 2h under nitrogen atmosphere. The reaction was poured into sat. NH₄Cl (aq.) at 0°C. The resulting mixture was extracted with CH₂Cl₂ (3 x 200 mL). The combined organic layers were washed with brine (3 x 200 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (2:1 - 1:2) and the pure fraction was concentrated under reduced pressure to afford tert-butyl 6-cyclopropyl-6-hydroxy-1,4-oxazepane-4-carboxylate (11.00 g, 92.0% yield) as a yellow oil.

Steps 2-3: Rac-(R)-6-((tert-butylidiphenylsilyl)oxy)-6-cyclopropyl-1,4-oxazepane

To a stirred mixture of tert-butyl 6-cyclopropyl-6-hydroxy-1,4-oxazepane-4-carboxylate (11.00 g, 42.8 mmol, 1.0 equiv) in DCM (60 mL) was added hydrogen chloride (4.0 M in 1,4-dioxane) (60 mL) at 20°C under nitrogen atmosphere. The resulting mixture was stirred at 20°C for 1h under nitrogen atmosphere. The resulting mixture was concentrated under vacuum to afford 6-cyclopropyl-1,4-oxazepan-6-ol (10.00 g, crude) as a brown solid.

To a stirred mixture of 6-cyclopropyl-1,4-oxazepan-6-ol (10.00 g, 63.6 mmol, 1.0 equiv) and Imidazole (12.99 g, 190.8 mmol, 3.0 equiv) in DCM (200 mL) were added Et₃N (12.87 g, 127.2 mmol, 2.0 equiv) and tert-butyl(chloro)diphenylsilane (26.22 g, 95.4 mmol, 1.5 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 20°C for 2 h under nitrogen atmosphere. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (100:1 - 2:1) and the pure fraction was concentrated under reduced pressure to afford rac-(R)-6-((tert-butylidiphenylsilyl)oxy)-6-cyclopropyl-1,4-oxazepane (1.7 g, 10.0% yield over two steps) as a brown oil.

Step 4: Rac-(R)-6-((tert-butyldiphenylsilyl)oxy)-6-cyclopropyl-4-(4,6-dichloro-1,3,5-triazin-2-yl)-1,4-oxazepane

To a stirred solution of cyanuric chloride (792.3 mg, 4.29 mmol, 1.0 equiv) and DIEA (1.67 g, 12.8 mmol, 3.0 equiv) in DCM (30 mL) was added rac-(R)-6-((tert-butyldiphenylsilyl)oxy)-6-cyclopropyl-1,4-oxazepane (1.70 g, 4.29 mmol, 1.0 equiv) at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 20°C for 1 h under nitrogen atmosphere. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (100:1 - 1:1) and the pure fraction was concentrated under reduced pressure to afford rac-(R)-6-((tert-butyldiphenylsilyl)oxy)-6-cyclopropyl-4-(4,6-dichloro-1,3,5-triazin-2-yl)-1,4-oxazepane (1.90 g, 81.3% yield) as a yellow oil.

Step 5: 6-((Tert-butyldiphenylsilyl)oxy)-4-(4-chloro-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-6-cyclopropyl-1,4-oxazepane

To a stirred solution of rac-(R)-6-((tert-butyldiphenylsilyl)oxy)-6-cyclopropyl-4-(4,6-dichloro-1,3,5-triazin-2-yl)-1,4-oxazepane (1.90 g, 3.49 mmol, 1.0 equiv) and DIEA (1.36 g, 10.4 mmol, 3.0 equiv) in DCM (30 mL) was added (1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethanol (565.9 mg, 3.84 mmol, 1.1 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 20°C for 2 h under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (100:1 - 5:1) and the pure fraction was concentrated under reduced pressure to afford 6-((tert-butyldiphenylsilyl)oxy)-4-(4-chloro-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-6-cyclopropyl-1,4-oxazepane (1.50 g, 65.5% yield) as a white solid.

Step 6: 4-[(6RS)-6-[(tert-butyldiphenylsilyl)oxy]-6-cyclopropyl-1,4-oxazepan-4-yl]-6-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazine-2-carbonitrile

To a stirred solution of 6-((tert-butyldiphenylsilyl)oxy)-4-(4-chloro-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-6-cyclopropyl-1,4-oxazepane (1.50 g, 2.29 mmol, 1.0 equiv) and zinc dicyanide (403.7 mg, 3.44 mmol, 1.5 equiv) in N,N-Dimethylacetamide (10 mL) was added XantPhos Pd G₄ (441.2 mg, 0.45 mmol, 0.2 equiv) at 20°C under nitrogen atmosphere. The resulting mixture was stirred at 60°C for 1h under nitrogen atmosphere. The residue was purified by reversed combi-flash chromatography with the following conditions: column, C18; mobile phase, A: NH₄HCO₃ (0.1%) in water, B: ACN, 80% to 100% gradient in 20 min; detector, UV 254 nm. The pure fraction was concentrated under vacuum to afford 4-[(6RS)-6-[(tert-butyldiphenylsilyl)oxy]-6-cyclopropyl-1,4-oxazepan-4-yl]-6-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazine-2-carbonitrile (1.30 g, 87.9% yield) as a brown solid.

Step 7: 4-[(6RS)-6-[(tert-butyldiphenylsilyl)oxy]-6-cyclopropyl-1,4-oxazepan-4-yl]-6-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-N-hydroxy-1,3,5-triazine-2-carboximidamide

To a stirred solution of 4-[(6RS)-6-[(tert-butyldiphenylsilyl)oxy]-6-cyclopropyl-1,4-oxazepan-4-yl]-6-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazine-2-carbonitrile (1.30 g, 2.01 mmol, 1.0 equiv) and Hydroxylamine hydrochloride (168.1 mg, 2.41 mmol, 1.2 equiv) in EtOH (10 mL) was added Na₂CO₃ (427.3 mg, 4.03 mmol, 2.0 equiv) at 20°C under nitrogen atmosphere. The resulting mixture was stirred at 20°C for 2 h under nitrogen atmosphere. The resulting mixture was diluted with water (20 mL). The resulting mixture was extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were washed with brine (3x20 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM / MeOH (100:1 - 15:1) and the pure fraction was concentrated under reduced pressure to afford 4-[(6RS)-6-[(tert-butyldiphenylsilyl)oxy]-6-cyclopropyl-1,4-oxazepan-4-yl]-6-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-N-hydroxy-1,3,5-triazine-2-carboximidamide (1.20 g, 87.8% yield) as a white solid.

Step 8: {4-[(6RS)-6-[(tert-butyldiphenylsilyl)oxy]-6-cyclopropyl-1,4-oxazepan-4-yl]-6-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl}methanimidamido (4S)-2-amino-3-cyano-4-methyl-6,7-dihydro-5H-1-benzothiophene-4-carboxylate

To a stirred solution of 4-[(6RS)-6-[(tert-butyldiphenylsilyl)oxy]-6-cyclopropyl-1,4-oxazepan-4-yl]-6-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-N-hydroxy-1,3,5-triazine-2-carboximidamide (1.20 g, 1.77 mmol, 1.0 equiv) and (4S)-2-amino-3-cyano-4-methyl-6,7-dihydro-5H-1-benzothiophene-4-carboxylic acid (418.28 mg, 1.770 mmol, 1 equiv) in DMF (20 mL) was added DIEA (686.3 mg, 5.31 mmol, 3.0 equiv) and Benzotriazole-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (1.38 g, 2.65 mmol, 1.5 equiv) at 20°C under nitrogen atmosphere. The resulting mixture was stirred at 20°C for 1h under nitrogen atmosphere. The residue was purified by reversed combi-flash chromatography with the following conditions: column, C18; mobile phase, A: NH₄HCO₃(0.1%) in water, B: ACN, 60% to 100% gradient in 20 min; detector, UV 254 nm. The pure fraction was concentrated under vacuum to afford {4-[(6RS)-6-[(tert-butyldiphenylsilyl)oxy]-6-cyclopropyl-1,4-oxazepan-4-yl]-6-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl}methanimidamido (4S)-2-amino-3-cyano-4-methyl-6,7-dihydro-5H-1-benzothiophene-4-carboxylate (1.29 g, 81.3% yield) as a brown solid.

Step 9: (4S)-2-amino-4-(3-(4-(6-((tert-butyldiphenylsilyl)oxy)-6-cyclopropyl-1,4-oxazepan-4-yl)-6-((S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile

To a stirred mixture of {4-[(6RS)-6-[(tert-butyldiphenylsilyl)oxy]-6-cyclopropyl-1,4-oxazepan-4-yl]-6-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl}methanimidamido

(4S)-2-amino-3-cyano-4-methyl-6,7-dihydro-5H-1-benzothiophene-4-carboxylate (1.20 g, 1.33 mmol, 1.0 equiv) in DMF (24 mL) was added DBU (407.7 mg, 2.67 mmol, 2.0 equiv) at 20°C under nitrogen atmosphere. The resulting mixture was stirred at 80 °C for 1 h under nitrogen atmosphere. The residue was purified by reversed combi-flash chromatography with the following conditions: column, C18; mobile phase, A: NH₄HCO₃(0.1%) in water, B: ACN, 60% to 100% gradient in 20 min; detector, UV 254 nm. The pure fraction was concentrated under vacuum to afford (4S)-2-amino-4-(3-(4-(6-((tert-butyl)diphenylsilyl)oxy)-6-cyclopropyl-1,4-oxazepan-4-yl)-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (910.0 mg, 77.3% yield) as a brown solid.

Step 10: (4S)-2-amino-4-(3-{4-[(6RS)-6-cyclopropyl-6-hydroxy-1,4-oxazepan-4-yl]-6-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile

To a stirred solution of (4S)-2-amino-4-(3-(4-(6-((tert-butyl)diphenylsilyl)oxy)-6-cyclopropyl-1,4-oxazepan-4-yl)-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (500.0 mg, 0.57 mmol, 1.0 equiv) in DMF (1 mL) was added Tetra-n-butylammonium fluoride(1.0 M in THF) (1 mL) at 20°C under nitrogen atmosphere. The resulting mixture was stirred at 20 °C for 1 h under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The crude product (400.0 mg) was purified by Prep-HPLC with the following conditions (Column: Chiral NQ(2)5u, 250*30mm; Mobile Phase A: Hex(10mM NH₃-MeOH), Mobile Phase B: IPA; Flow rate: 40 mL/min; Gradient: isocratic 50; Wavelength: 220/240 nm; RT1(min): 8.621; RT2(min): 12.319; Sample Solvent: EtOH; Injection Volume: 0.6 mL; Number Of Runs: 5) to afford (4S)-2-amino-4-(3-{4-[(6RS)-6-cyclopropyl-6-hydroxy-1,4-oxazepan-4-yl]-6-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (150.0 mg, 41.1% yield) as a yellow solid.

Step 11: (4S)-2-amino-4-(3-{4-[(6R*)-6-cyclopropyl-6-hydroxy-1,4-oxazepan-4-yl]-6-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile

(4S)-2-amino-4-(3-{4-[(6RS)-6-cyclopropyl-6-hydroxy-1,4-oxazepan-4-yl]-6-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (150.0 mg, 0.23 mmol, 1.0 equiv) was isolated by prep-chiral-HPLC with the following conditions: Column: Chiral NQ(2)5u, 250*30mm; Mobile Phase A: Hex(10mM NH₃-MeOH), Mobile Phase B: IPA; Flow rate: 40 mL/min; Gradient: isocratic 50; Wavelength: 220/240 nm; RT1(min): 8.621; RT2(min): 12.319; Sample Solvent: EtOH; Injection

Volume: 0.6 mL; Number Of Runs: 5; The 1st eluting fraction was lyophilized to afford isomer 1 (4S)-2-amino-4-(3-{4-[(6R*)-6-cyclopropyl-6-hydroxy-1,4-oxazepan-4-yl]-6-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (48.3 mg, 32.2%yield, 99.4%@254nm, 99.5%@220nm, ee=100%);

- 5 The 2nd eluting fraction was lyophilized to afford isomer 2 (4S)-2-amino-4-(3-{4-[(6S*)-6-cyclopropyl-6-hydroxy-1,4-oxazepan-4-yl]-6-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (51.1 mg, 34.0%yield, 96.9%@254nm, 97.1%@220nm, ee=99.1%) as a white solid.

- Isomer 1: ESI-MS m/z = 640.3 $[M+H]^+$; Calculated MW: 639.3. CHIRAL_HPLC R_t =2.05 min. ee value: 100%.

1H NMR (400 MHz, DMSO- d_6) δ 7.09 (d, J = 2.4 Hz, 2H), 5.38 – 5.05 (m, 2H), 4.42 (d, J = 3.8 Hz, 1H), 4.29 – 3.74 (m, 6H), 3.62 – 3.38 (m, 3H), 2.96 (s, 1H), 2.54 (t, J = 5.5 Hz, 3H), 2.40 (s, 3H), 2.14 – 1.81 (m, 6H), 1.79 (d, J = 1.6 Hz, 3H), 1.25 (dd, J = 4.3, 6.4 Hz, 3H), 0.93 (tdd, J = 5.3, 8.4, 13.6 Hz, 1H), 0.52 – 0.31 (m, 2H), 0.31 – 0.11 (m, 2H).

- 15 Isomer 2: ESI-MS m/z = 640.3 $[M+H]^+$; Calculated MW: 639.3. CHIRAL_HPLC R_t =3.01 min. ee value: 99.1%.

- 1H NMR (400 MHz, DMSO- d_6) δ 6.90 (d, J = 3.1 Hz, 2H), 5.20 – 5.06 (m, 1H), 4.98 (d, J = 55.8 Hz, 1H), 4.24 (d, J = 11.0 Hz, 1H), 4.00 (dd, J = 11.0, 14.0 Hz, 1H), 3.92 – 3.52 (m, 5H), 3.32 (qd, J = 7.3, 12.4 Hz, 3H), 2.74 (d, J = 10.9 Hz, 1H), 2.35 (t, J = 6.1 Hz, 2H), 2.21 (s, 3H), 1.97 – 1.62 (m, 6H),
20 1.59 (s, 3H), 1.04 (t, J = 6.5 Hz, 3H), 0.75 (ddq, J = 3.4, 4.2, 6.8, 9.5 Hz, 1H), 0.31 – 0.10 (m, 2H), 0.07 (dd, J = 5.1, 9.0 Hz, 2H).

Example 38: Synthesis of Compound (139a)

Step 1: Tert-butyl (2R,3R)-3-fluoro-2-(hydroxymethyl)pyrrolidine-1-carboxylate

- 25 To a stirred solution of (2R,3R)-1-(tert-butoxycarbonyl)-3-fluoropyrrolidine-2-carboxylic acid (1.00 g, 4.29 mmol, 1.0 equiv) in THF (10 mL) was added Borane-tetrahydrofuran complex (1.0M in THF) (6.43 mL, 6.43 mmol, 1.5 equiv) dropwise at 0 °C under air atmosphere. The resulting mixture was stirred at 20 °C for 16 h under air atmosphere. The reaction was quenched with MeOH at 0 °C. The resulting mixture was concentrated under reduced pressure to afford tert-butyl (2R,3R)-3-fluoro-2-(hydroxymethyl)pyrrolidine-1-carboxylate (900 mg, 95.74%yield) as a colorless oil.

Step 2: Tert-butyl (2R,3R)-3-fluoro-2-formylpyrrolidine-1-carboxylate

A mixture of tert-butyl (2R,3R)-3-fluoro-2-(hydroxymethyl)pyrrolidine-1-carboxylate (900 mg, 4.11 mmol, 1.0 equiv) and 1,1-bis(acetyloxy)-3-oxo-3H-1H-[5],2-benziodaoxol-1-yl acetate (2.26 g, 5.34

mmol, 1.3 equiv) in CH₂Cl₂ (20 mL) was stirred at 20 °C for 2 h under air atmosphere. The resulting mixture was filtered and the filter cake was washed with CH₂Cl₂ (2x20 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1-4:1). The pure fraction was concentrated under reduced pressure to afford
5 tert-butyl (2R,3R)-3-fluoro-2-formylpyrrolidine-1-carboxylate (800 mg, 80.74%yield) as a colorless oil.

Step 3: Tert-butyl (2R,3R)-3-fluoro-2-[(1R)-1-hydroxyethyl]pyrrolidine-1-carboxylate

To a stirred solution of tert-butyl (2R,3R)-3-fluoro-2-formylpyrrolidine-1-carboxylate (800 mg, 3.68 mmol, 1.0 equiv) in THF (15 mL) was added Methylmagnesium bromide, 3 M solution in diethyl ether
10 (2.46 mL, 7.37 mmol, 2.0 equiv) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred at 20 °C for 1h under nitrogen atmosphere. The reaction was quenched with sat. NH₄Cl (aq.) at 0 °C. The aqueous layer was extracted with EtOAc (2x50 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (3:1-1:1). The pure fraction was concentrated under reduced pressure to afford tert-butyl
15 (2R,3R)-3-fluoro-2-[(1R)-1-hydroxyethyl]pyrrolidine-1-carboxylate (600 mg, 69.84%yield) as a colorless oil.

Step 4: Tert-butyl (2R,3R)-2-[(1R)-1-({4-[(6S)-6-[(tert-butyl)diphenylsilyl]oxy]-6-methyl-1,4-oxazepan-4-yl]-6-chloro-1,3,5-triazin-2-yl}oxy)ethyl]-3-fluoropyrrolidine-1-carboxylate

To a stirred mixture of tert-butyl (2R,3R)-3-fluoro-2-[(1R)-1-hydroxyethyl]pyrrolidine-1-
20 carboxylate (495 mg, 2.13 mmol, 1.1 equiv) and (6S)-6-[(tert-butyl)diphenylsilyl]oxy]-4-(4,6-dichloro-1,3,5-triazin-2-yl)-6-methyl-1,4-oxazepane (1.00 g, 1.93 mmol, 1.0 equiv) in THF (10 mL) was added LiHMDS (1.0 M in THF) (2.51 mL, 2.51 mmol, 1.3 equiv) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred at 20 °C for 1 h under nitrogen atmosphere. The reaction was quenched with Water at 0 °C. The resulting mixture was concentrated under reduced pressure. The residue was
25 purified by silica gel column chromatography, eluted with PE / EA (3:1-1:1). The pure fraction was concentrated under reduced pressure to afford tert-butyl (2R,3R)-2-[(1R)-1-({4-[(6S)-6-[(tert-butyl)diphenylsilyl]oxy]-6-methyl-1,4-oxazepan-4-yl]-6-chloro-1,3,5-triazin-2-yl}oxy)ethyl]-3-fluoropyrrolidine-1-carboxylate (900 mg, 65.20%yield) as a white solid.

Step 5: Tert-butyl (2R,3R)-2-[(1R)-1-({4-[(6S)-6-[(tert-butyl)diphenylsilyl]oxy]-6-methyl-1,4-oxazepan-4-yl]-6-cyano-1,3,5-triazin-2-yl}oxy)ethyl]-3-fluoropyrrolidine-1-carboxylate

To a stirred mixture of tert-butyl (2R,3R)-2-[(1R)-1-({4-[(6S)-6-[(tert-butyl)diphenylsilyl]oxy]-6-methyl-1,4-oxazepan-4-yl]-6-chloro-1,3,5-triazin-2-yl}oxy)ethyl]-3-fluoropyrrolidine-1-carboxylate
30 (900 mg, 1.26 mmol, 1.0 equiv) and zinc dicyanide (177 mg, 1.51 mmol, 1.2 equiv) in N,N-Dimethylacetamide (10 mL) was added XantPhos Pd G4 (121 mg, 0.126 mmol, 0.1 equiv) at 20 °C

under nitrogen atmosphere. The resulting mixture was stirred at 80 °C for 1 h under nitrogen atmosphere. The mixture was allowed to cool down to 20 °C. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18; mobile phase, MeCN in Water (0.1% FA), 70% to 80% gradient in 10 min; detector, UV 254 nm. The pure fraction was concentrated under reduced pressure to afford tert-butyl (2R,3R)-2-[(1RS)-1-({4-[(6S)-6-[(tert-butyl)diphenylsilyl]oxy]-6-methyl-1,4-oxazepan-4-yl]-6-cyano-1,3,5-triazin-2-yl}oxy)ethyl]-3-fluoropyrrolidine-1-carboxylate (700 mg, 78.82%yield) as a yellow solid.

Steps 6-7: 4-[(6S)-6-[(tert-butyl)diphenylsilyl]oxy]-6-methyl-1,4-oxazepan-4-yl]-6-[(1RS)-1-[(2R,3R)-3-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazine-2-carbonitrile

- 10 A mixture of tert-butyl (2R,3R)-2-[(1RS)-1-({4-[(6S)-6-[(tert-butyl)diphenylsilyl]oxy]-6-methyl-1,4-oxazepan-4-yl]-6-cyano-1,3,5-triazin-2-yl}oxy)ethyl]-3-fluoropyrrolidine-1-carboxylate (700 mg, 0.99 mmol, 1.0 equiv) and trifluoroacetic acid (2 mL) in DCM (8 mL) was stirred at 20 °C for 0.5 h under air atmosphere. The resulting mixture was concentrated under vacuum to afford 4-[(6S)-6-[(tert-butyl)diphenylsilyl]oxy]-6-methyl-1,4-oxazepan-4-yl]-6-[(1RS)-1-[(2R,3R)-3-fluoropyrrolidin-2-yl]ethoxy]-1,3,5-triazine-2-carbonitrile (650 mg, crude) as a yellow oil.

- To a stirred mixture of 4-[(6S)-6-[(tert-butyl)diphenylsilyl]oxy]-6-methyl-1,4-oxazepan-4-yl]-6-[(1RS)-1-[(2R,3R)-3-fluoropyrrolidin-2-yl]ethoxy]-1,3,5-triazine-2-carbonitrile (650 mg, 1.08 mmol, 1.0 equiv) and paraformaldehyde (142 mg, 3.23 mmol, 3.0 equiv) in DCM (0.5 mL) was added NaBH(OAc)₃ (455 mg, 2.15 mmol, 2.0 equiv) at 20 °C under air atmosphere. The resulting mixture was stirred at 50 °C for 2 h under air atmosphere. The reaction was quenched with Water at 20°C. The resulting mixture was concentrated under vacuum. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18; mobile phase, MeCN in Water (10mmol/L NH₄HCO₃), 80% to 100% gradient in 10 min; detector, UV 254 nm. The pure fraction was concentrated under reduced pressure to afford 4-[(6S)-6-[(tert-butyl)diphenylsilyl]oxy]-6-methyl-1,4-oxazepan-4-yl]-6-[(1RS)-1-[(2R,3R)-3-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazine-2-carbonitrile (480 mg, 72.17%yield) as a white solid.

Step 8: 4-[(6S)-6-[(tert-butyl)diphenylsilyl]oxy]-6-methyl-1,4-oxazepan-4-yl]-6-[(1RS)-1-[(2R,3R)-3-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-N-hydroxy-1,3,5-triazine-2-carboximidamide

- 30 To a stirred mixture of 4-[(6S)-6-[(tert-butyl)diphenylsilyl]oxy]-6-methyl-1,4-oxazepan-4-yl]-6-[(1RS)-1-[(2R,3R)-3-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazine-2-carbonitrile (450 mg, 0.73 mmol, 1.0 equiv) and Na₂CO₃ (231 mg, 2.18 mmol, 3.0 equiv) in EtOH (10 mL) was added Hydroxylamine hydrochloride (75 mg, 1.09 mmol, 1.5 equiv) at 20 °C under nitrogen atmosphere. The resulting mixture was stirred at 20 °C for 1 h under nitrogen atmosphere. The resulting mixture was diluted with water (100 mL). The aqueous layer was extracted with EtOAc (2x100 mL). The resulting

mixture was concentrated under reduced pressure to afford 4-[(6S)-6-[(tert-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl]-6-[(1RS)-1-[(2R,3R)-3-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-N-hydroxy-1,3,5-triazine-2-carboximidamide (450 mg, 94.93% yield) as a white solid.

Step 9: {4-[(6S)-6-[(tert-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl]-6-[(1RS)-1-[(2R,3R)-3-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl}methanimidamido (4S)-2-amino-3-cyano-4-methyl-6,7-dihydro-5H-1-benzothiophene-4-carboxylate

To a stirred mixture of 4-[(6S)-6-[(tert-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl]-6-[(1RS)-1-[(2R,3R)-3-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-N-hydroxy-1,3,5-triazine-2-carboximidamide (450 mg, 0.69 mmol, 1.0 equiv) and (4S)-2-amino-3-cyano-4-methyl-6,7-dihydro-5H-1-benzothiophene-4-carboxylic acid (163 mg, 0.69 mmol, 1.0 equiv) in DMF (5 mL) were added Benzotriazole-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (467 mg, 0.90 mmol, 1.3 equiv) and DIEA (267 mg, 2.1 mmol, 3.0 equiv) at 20 °C under nitrogen atmosphere. The resulting mixture was stirred at 20 °C for 1 h under nitrogen atmosphere. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18; mobile phase, MeCN in Water (0.1% NH₃·H₂O), 80% to 100% gradient in 10 min; detector, UV 254 nm. The pure fraction was concentrated under vacuum to afford {4-[(6S)-6-[(tert-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl]-6-[(1RS)-1-[(2R,3R)-3-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl}methanimidamido (4S)-2-amino-3-cyano-4-methyl-6,7-dihydro-5H-1-benzothiophene-4-carboxylate (450 mg, 74.92% yield) as a white solid.

Step 10: (4S)-2-amino-4-(3-{4-[(6S)-6-[(tert-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl]-6-[(1RS)-1-[(2R,3R)-3-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile

To a stirred mixture of {4-[(6S)-6-[(tert-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl]-6-[(1RS)-1-[(2R,3R)-3-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl}methanimidamido (4S)-2-amino-3-cyano-4-methyl-6,7-dihydro-5H-1-benzothiophene-4-carboxylate (400 mg, 0.46 mmol, 1.0 equiv) in DMF (4 mL) was added DBU (140 mg, 0.92 mmol, 2.0 equiv) at 20 °C under nitrogen atmosphere. The resulting mixture was stirred at 80 °C for 1 h under nitrogen atmosphere. The mixture was allowed to cool down to 20 °C. The residue was purified by reversed combi-flash chromatography with the following conditions: column, C18; mobile phase, A: NH₄HCO₃ (0.1%) in water, B: ACN, 60% to 100% gradient in 20 min; detector, UV 254 nm. The pure fraction was concentrated under vacuum to afford (4S)-2-amino-4-(3-{4-[(6S)-6-[(tert-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl]-6-[(1RS)-1-[(2R,3R)-3-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (300 mg, 76.59% yield) as a brown solid.

Step 11: (4S)-2-amino-4-(3-{4-[(1RS)-1-[(2R,3R)-3-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-6-[(6S)-6-hydroxy-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile

A mixture of (4S)-2-amino-4-(3-{4-[(6S)-6-[(tert-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl]-6-[(1RS)-1-[(2R,3R)-3-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (250 mg) in pyridine hydrofluoride (5 mL) was stirred at 20 °C for 1 h under nitrogen atmosphere. The mixture was basified to pH=9 with saturated Na₂CO₃ (aq.). The aqueous layer was extracted with EtOAc (2x100 mL). The resulting mixture was concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column 30*150 mm, 5µm; Mobile Phase A: 10mmol/L NH₄HCO₃+0.05%NH₃H₂O), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 5% B to 5% B in 1 min, 5% B to 30% B in 2 min, 30% to 45% B in 11 min; Wavelength: 254nm/220nm nm; RT1(min): 9.65). The pure fraction was concentrated and lyophilized to afford (4S)-2-amino-4-(3-{4-[(1RS)-1-[(2R,3R)-3-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-6-[(6S)-6-hydroxy-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (104.1 mg, 57.82%yield, 99.8%purity@254nm, 99.8%purity@220nm) as a white solid. ESI-MS m/z = 614.3 [M+H]⁺; Calculated MW: 613.3.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.09 (s, 2H), 5.41 – 5.15 (m, 2H), 4.85 (d, *J* = 3.3 Hz, 1H), 4.22 – 3.93 (m, 2H), 3.92 – 3.61 (m, 4H), 3.55 – 3.37 (m, 2H), 3.18 – 3.09 (m, 1H), 2.59 – 2.51 (m, 3H), 2.30 (s, 3H), 2.23 – 2.00 (m, 3H), 1.98 – 1.80 (m, 4H), 1.79 (d, *J* = 2.9 Hz, 3H), 1.40 (ddd, *J* = 9.3, 6.3, 1.3 Hz, 3H), 1.10 (d, *J* = 2.2 Hz, 3H).

¹⁹F NMR (376 MHz, DMSO) δ -183.62.

Example 39: Synthesis of Compound (140a)

Step 1: {4-[(3R*)-3-[(tert-butyldiphenylsilyl)oxy]-3-methylazepan-1-yl]-6-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl}methanimidamido (4R)-2-amino-3-cyano-4-methoxy-6,7-dihydro-5H-1-benzothiophene-4-carboxylate

To a stirred mixture of 4-[(3R*)-3-[(tert-butyldiphenylsilyl)oxy]-3-methylazepan-1-yl]-6-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-N-hydroxy-1,3,5-triazine-2-carboximidamide (300 mg, 0.462 mmol, 1.0 equiv) and (4R)-2-amino-3-cyano-4-methoxy-6,7-dihydro-5H-1-benzothiophene-4-carboxylic acid (116 mg, 0.462 mmol, 1.0 equiv) in DMF (10 mL) were added DIEA (178 mg, 1.38 mmol, 3.0 equiv) and Benzotriazole-1-yl-oxytripyrrolidinophosphonium

hexafluorophosphate (360 mg, 0.693 mmol, 1.5 equiv) dropwise at 25°C under air atmosphere. The resulting mixture was stirred at 25°C for 2 h under air atmosphere. The reaction was monitored by LCMS. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C₁₈; mobile phase, MeCN in Water (10mmol/L NH₄HCO₃), 75% to 75% gradient in 10 min; detector, UV 254 nm. The pure fraction was concentrated under reduced pressure to afford {4-[(3R*)-3-[(tert-butyldiphenylsilyl)oxy]-3-methylazepan-1-yl]-6-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl}methanimidamido (4R)-2-amino-3-cyano-4-methoxy-6,7-dihydro-5H-1-benzothiophene-4-carboxylate (320 mg, 78.40%yield) as a yellow solid.

Step 2: (4R)-2-amino-4-(3-{4-[(3R*)-3-[(tert-butyldiphenylsilyl)oxy]-3-methylazepan-1-yl]-6-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methoxy-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile

A solution of {4-[(3R*)-3-[(tert-butyldiphenylsilyl)oxy]-3-methylazepan-1-yl]-6-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl}methanimidamido (4R)-2-amino-3-cyano-4-methoxy-6,7-dihydro-5H-1-benzothiophene-4-carboxylate (300 mg, 0.339 mmol, 1.0 equiv) and DBU (154 mg, 1.01 mmol, 3.0 equiv) in DMF (5 mL) was stirred at 80°C for 1-2 h under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to 25°C. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C₁₈; mobile phase, MeCN in Water (10mmol/L NH₄HCO₃), 80% to 80% gradient in 10 min; detector, UV 254 nm. The pure fraction was concentrated under reduced pressure to afford (4R)-2-amino-4-(3-{4-[(3R*)-3-[(tert-butyldiphenylsilyl)oxy]-3-methylazepan-1-yl]-6-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methoxy-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (190 mg, 63.25%yield) as a yellow solid.

Step 3: (4R)-2-amino-4-(3-{4-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-6-[(3R*)-3-hydroxy-3-methylazepan-1-yl]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methoxy-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile

A solution of (4R)-2-amino-4-(3-{4-[(3R*)-3-[(tert-butyldiphenylsilyl)oxy]-3-methylazepan-1-yl]-6-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methoxy-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (150 mg, 0.173 mmol, 1.0 equiv) in pyridine hydrofluoride (1 mL) and DCM (1 mL) was stirred at -40°C for 1 h under air atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water (50 mL). The mixture was basified to pH 9~10 with saturated Na₂CO₃ (aq.). The resulting mixture was extracted with EtOAc (3x50 mL). The combined organic layers were washed with brine (2x50 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The crude product (100 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Shield

RP18 OBD Column 30*150 mm, 5 μ m; Mobile Phase A: Water(10mmol/L NH₄HCO₃), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 35% B to 49% B in 12 min; Wavelength: 254nm/220nm nm; RT1(min): 10.28). The pure fraction was concentrated under reduced pressure and lyophilized to afford (4R)-2-amino-4-(3-{4-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-6-[(3R*)-3-hydroxy-3-methylazepan-1-yl]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methoxy-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (7.7 mg, 10.36%yield, 97.5%purity) as a white solid.

ESI-MS m/z = 628.4 [M+H]⁺; Calculated MW: 627.1 ¹⁹F NMR (376 MHz, DMSO) δ -170.5.
¹H NMR (400 MHz, DMSO-*d*₆) δ 7.10 (d, 2H), 5.33 – 5.07 (m, 2H), 4.53 (d, 1H), 3.95 (dd, 2H), 3.66 (dd, 2H), 3.46 – 3.35 (m, 1H), 3.33 (s, 3H), 2.95 (tt, 1H), 2.60 (td, 2H), 2.40 (d, 3H), 2.22 (d, 2H), 2.08 – 1.91 (m, 3H), 1.89 – 1.65 (m, 5H), 1.62 – 1.48 (m, 2H), 1.41 (d, 1H), 1.24 (dd, 3H), 1.17 (d, 3H).

Example 40: Synthesis of Compound (141a)

Step 1: Tert-butyl 3,3-dimethyl-6-methylidene-1,4-oxazepane-4-carboxylate

A solution of 2-amino-2-methyl-1-propanol (10.00 g, 112.2 mmol, 1.0 equiv) and 3-chloro-2-(chloromethyl)prop-1-ene (16.83 g, 134.6 mmol, 1.2 equiv) in 2-methylpropan-2-ol (100 mL) was stirred for 2 h at 80 °C under nitrogen atmosphere. To the above mixture was added Boc₂O (26.93 g, 123.4 mmol, 1.1 equiv) in 2-methylpropan-2-ol (100 mL) at 20 °C. The resulting mixture was stirred at 20 °C for additional 3 h under nitrogen atmosphere. The reaction was quenched by the addition of water (200 mL) at 20 °C. The resulting mixture was extracted with ethyl acetate (3 x 150 mL). The combined organic layers were washed with brine (2x100 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The crude product was used in the next step directly without further purification.

Step 2: Tert-butyl 3,3-dimethyl-6-oxo-1,4-oxazepane-4-carboxylate

To a mixture of tert-butyl 3,3-dimethyl-6-methylidene-1,4-oxazepane-4-carboxylate (3.75 g, 15.5 mmol, 1.0 equiv) in THF (20 mL) and H₂O (20 mL) was added NaIO₄ (7.64 g, 35.7 mmol, 2.3 equiv) followed by potassium osmate(VI) dihydrate (286 mg, 0.78 mmol, 0.05 equiv). The mixtures were stirred at 20 °C for 1 h. TLC (PE/EA=5:1, R_f=0.2) shown the reaction was completed. The resulting mixture was diluted with water (100 mL). The reaction solution was extracted with ethyl acetate (3x100 mL), washed with brine (3x60 mL) and dried over Na₂SO₄. The organic phase was concentrated to afford tert-butyl 3,3-dimethyl-6-oxo-1,4-oxazepane-4-carboxylate (2.30 g, 60%yield) as yellowed oil.

Step 3: Tert-butyl 6-hydroxy-3,3,6-trimethyl-1,4-oxazepane-4-carboxylate

To a mixture of tert-butyl 3,3-dimethyl-6-methylidene-1,4-oxazepane-4-carboxylate (2.20 g, 15.5 mmol, 1.0 equiv) in THF (25 mL) was added MeMgBr (5.94 mL, 17.8 mmol, 1.97 equiv) at 0 °C. The mixture was stirred at 20 °C for 3 h. TLC shown the reaction was completed. The reaction was quenched by the addition of water (200 mL) at 20 °C. The reaction solution was diluted with ethyl acetate, washed with brine (3x60 mL) and dried over Na₂SO₄. The organic phase was concentrated to afford tert-butyl 6-hydroxy-3,3,6-trimethyl-1,4-oxazepane-4-carboxylate (2.30 g, 88%yield) as yellow oil.

Step 4: 3,3,6-Trimethyl-1,4-oxazepan-6-ol

Into a 25 mL round-bottom flask were added tert-butyl 6-hydroxy-3,3,6-trimethyl-1,4-oxazepane-4-carboxylate (500 mg, 1.93 mmol, 1.0 equiv) and DCM (4 mL) at 20 °C. To the above mixture was added TFA (1 mL) at 20 °C. The resulting mixture was stirred for 1 h at 20 °C. The mixture was concentrated under reduced pressure. The crude product 3,3,6-Trimethyl-1,4-oxazepan-6-ol (380 mg, crude) was used in the next step directly without further purification.

Step 5: 6-((Tert-butyldiphenylsilyl)oxy)-3,3,6-trimethyl-1,4-oxazepane

Into a 50 mL round-bottom flask were added 3,3,6-Trimethyl-1,4-oxazepan-6-ol (380 mg, 2.39 mmol, 1.0 equiv) and DCM (12 mL) at 20 °C. To the above mixture was added Et₃N (483 mg, 4.77 mmol, 2.0 equiv), Imidazole (487 mg, 7.16 mmol, 3.0 equiv), TBDMSCl (540 mg, 3.58 mmol, 1.5 equiv) at 20 °C. The resulting mixture was stirred for 16 h at 20 °C. The reaction was then quenched by the addition of water (20 mL). The resulting solution was extracted with ethyl acetate (3 x 40 mL). The resulting mixture was washed with brine (2 x 50 mL). The resulting mixture was dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:4). The pure fraction was concentrated under reduced pressure to afford 6-((tert-butyldiphenylsilyl)oxy)-3,3,6-trimethyl-1,4-oxazepane (614 mg, 58%yield) as colorless oil.

Step 6: 6-((Tert-butyldiphenylsilyl)oxy)-4-(4,6-dichloro-1,3,5-triazin-2-yl)-3,3,6-trimethyl-1,4-oxazepane

Into a 100 mL round-bottom flask were added 6-((tert-butyldiphenylsilyl)oxy)-3,3,6-trimethyl-1,4-oxazepane (600 mg, 1.51 mmol, 1.0 equiv) and DCM (18 mL) at 20 °C. To the above mixture was added cyanuric chloride (306 mg, 1.66 mmol, 1.1 equiv), DIEA (585 mg, 4.53 mmol, 3.0 equiv) at 20 °C. The resulting mixture was stirred for 2 h at 20 °C. The reaction was then quenched by the addition of water (20 mL). The resulting solution was extracted with ethyl acetate (3 x 30 mL). The resulting

mixture was washed with brine (2 x 30 mL). The resulting mixture was dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (3:1). The pure fraction was concentrated under reduced pressure to afford 6-((tert-butyldiphenylsilyl)oxy)-4-(4,6-dichloro-1,3,5-triazin-2-yl)-3,3,6-trimethyl-1,4-oxazepane (840 mg, 70% yield) as a white solid.

Step 7: 6-((Tert-butyldiphenylsilyl)oxy)-4-(4-chloro-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-3,3,6-trimethyl-1,4-oxazepane

Into a 100 mL round-bottom flask were added 6-((tert-butyldiphenylsilyl)oxy)-4-(4,6-dichloro-1,3,5-triazin-2-yl)-3,3,6-trimethyl-1,4-oxazepane (1.50 g, 2.75 mmol, 1.0 equiv), (1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethanol (445.0 mg, 3.02 mmol, 1.1 equiv) and DCM (15 mL) at 20 °C. To the above mixture was added DIEA (1.06 g, 8.25 mmol, 3.0 equiv) at 20 °C. The resulting mixture was stirred for 2 h at 20 °C. The reaction was then quenched by the addition of water (100 mL). The resulting solution was extracted with ethyl acetate (3 x 100 mL). The resulting mixture was washed with brine (2 x 100 mL). The resulting mixture was dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (3:1). The pure fraction was concentrated under reduced pressure to afford 6-((tert-butyldiphenylsilyl)oxy)-4-(4-chloro-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-3,3,6-trimethyl-1,4-oxazepane (1.33 g, 66%yield) as a white solid.

Step 8: 4-(6-((Tert-butyldiphenylsilyl)oxy)-3,3,6-trimethyl-1,4-oxazepan-4-yl)-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazine-2-carbonitrile

Into a 100 mL round-bottom flask were added 6-((tert-butyldiphenylsilyl)oxy)-4-(4-chloro-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-3,3,6-trimethyl-1,4-oxazepane (1.70 g, 2.59 mmol, 1.0 equiv), N,N-Dimethylacetamide (30 mL), XantPhos Pd G₄ (498 mg, 0.52 mmol, 0.2 equiv), zinc dicyanide (365 mg, 3.11 mmol, 1.2 equiv) at 20 °C. The resulting mixture was stirred for 2 h at 80 °C. The mixture was allowed to cool down to 20 °C. The reaction was then quenched by the addition of water (100 mL). The resulting solution was extracted with ethyl acetate (3 x 100 mL). The resulting mixture was washed with brine (2 x 100 mL). The resulting mixture was dried over anhydrous sodium sulphate anhydrous. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18; mobile phase, acetonitrile in water, 10% to 80% gradient in 10 min; detector, UV 254 nm. This resulted in 4-(6-((tert-butyldiphenylsilyl)oxy)-3,3,6-trimethyl-1,4-oxazepan-4-yl)-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazine-2-carbonitrile (1.30 g, 70%yield) as a white solid.

Step 9: 4-(6-((Tert-butylidiphenylsilyl)oxy)-3,3,6-trimethyl-1,4-oxazepan-4-yl)-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-N-hydroxy-1,3,5-triazine-2-carboximidamide

Into a 50 mL round-bottom flask were added 4-(6-((tert-butylidiphenylsilyl)oxy)-3,3,6-trimethyl-1,4-oxazepan-4-yl)-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazine-2-carbonitrile (500 mg, 0.77 mmol, 1.0 equiv), EtOH (10 mL), Na₂CO₃ (205 mg, 1.93 mmol, 2.5 equiv), Hydroxylamine hydrochloride (107 mg, 1.55 mmol, 2.0 equiv) at 20 °C. The resulting mixture was stirred for 4h at 20°C. The reaction was then quenched by the addition of water (100 mL). The resulting solution was extracted with ethyl acetate (3 x 100 mL). The resulting mixture was washed with brine (1 x 100 mL). The resulting mixture was dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed flash chromatography with the following conditions: column, C18; mobile phase, acetonitrile in water, 10% to 80% gradient in 10 min; detector, UV 254 nm. This resulted in 4-(6-((tert-butylidiphenylsilyl)oxy)-3,3,6-trimethyl-1,4-oxazepan-4-yl)-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-N-hydroxy-1,3,5-triazine-2-carboximidamide (500 mg, 95% purity) as a white solid.

Step 10: N-(((S)-2-amino-3-cyano-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-4-carbonyl)oxy)-4-(6-((tert-butylidiphenylsilyl)oxy)-3,3,6-trimethyl-1,4-oxazepan-4-yl)-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazine-2-carboximidamide

Into a 100 mL round-bottom flask were added 4-(6-((tert-butylidiphenylsilyl)oxy)-3,3,6-trimethyl-1,4-oxazepan-4-yl)-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-N-hydroxy-1,3,5-triazine-2-carboximidamide (700 mg, 1.03 mmol, 1.0 equiv), (4S)-2-amino-3-cyano-4-methyl-6,7-dihydro-5H-1-benzothiophene-4-carboxylic acid (243 mg, 1.03 mmol, 1.0 equiv), PyBOP (803 mg, 1.55 mmol, 1.5 equiv), DMF (5 mL), DIEA (399 mg, 3.09 mmol, 3.0 equiv) at 20 °C. The resulting mixture was stirred for 4 h at 20 °C. Desired product could be detected by LCMS. The reaction was then quenched by the addition of water (50 mL). The resulting solution was extracted with ethyl acetate (3 x 40 mL). The resulting mixture was washed with brine (1 x 100 mL). The resulting mixture was dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18; mobile phase, acetonitrile in water, 10% to 80% gradient in 10 min; detector, UV 254 nm. This resulted in N-(((S)-2-amino-3-cyano-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-4-carbonyl)oxy)-4-(6-((tert-butylidiphenylsilyl)oxy)-3,3,6-trimethyl-1,4-oxazepan-4-yl)-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazine-2-carboximidamide (680 mg, 66% yield) as a yellow solid.

Step 11: (4S)-2-amino-4-(3-(4-(6-((tert-butyldiphenylsilyl)oxy)-3,3,6-trimethyl-1,4-oxazepan-4-yl)-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile

Into a 100 mL round-bottom flask were added N-(((S)-2-amino-3-cyano-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-4-carbonyl)oxy)-4-(6-((tert-butyldiphenylsilyl)oxy)-3,3,6-trimethyl-1,4-oxazepan-4-yl)-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazine-2-carboximidamide (680 mg, 0.76 mmol, 1.0 equiv), DMF (10 mL), DBU (230 mg, 1.51 mmol, 2.0 equiv) at 20 °C. The resulting mixture was stirred for 2h at 80 °C. The mixture was allowed to cool down to 20 °C. The reaction was then quenched by the addition of water (50 mL). The resulting solution was extracted with ethyl acetate (3 x 40 mL). The resulting mixture was washed with brine (2 x 40 mL). The resulting mixture was dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed flash chromatography with the following conditions: column, C18; mobile phase, acetonitrile in water, 10% to 100% gradient in 10 min; detector, UV 254 nm. This resulted in (4S)-2-amino-4-(3-(4-(6-((tert-butyldiphenylsilyl)oxy)-3,3,6-trimethyl-1,4-oxazepan-4-yl)-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (490 mg, 69%yield) as a white solid.

Step 12: (4S)-2-amino-4-(3-{4-[(6R*)-6-[(tert-butyldiphenylsilyl)oxy]-3,3,6-trimethyl-1,4-oxazepan-4-yl]-6-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile, isomer 1 & (4S)-2-amino-4-(3-{4-[(6R*)-6-[(tert-butyldiphenylsilyl)oxy]-3,3,6-trimethyl-1,4-oxazepan-4-yl]-6-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile, isomer 2

(4S)-2-amino-4-(3-(4-(6-((tert-butyldiphenylsilyl)oxy)-3,3,6-trimethyl-1,4-oxazepan-4-yl)-6-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (480 mg) was isolated by prep-chiral-HPLC with the following conditions: Column: CHIRALPAK IG, 3*25 cm, 5 µm; Mobile Phase A: Hex(10mM NH₃-MeOH), Mobile Phase B: ETOH; Flow rate: 40 mL/min; Gradient: isocratic 20; Wavelength: 220/240 nm; RT1(min): 8.4; RT2(min): 10.9; Sample Solvent: EtOH; Number Of Runs: 20. The 1st eluting fraction was lyophilized to afford isomer 1 (4S)-2-amino-4-(3-{4-[(6R*)-6-[(tert-butyldiphenylsilyl)oxy]-3,3,6-trimethyl-1,4-oxazepan-4-yl]-6-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (210 mg, ee=100%). The 2nd eluting fraction was lyophilized to afford isomer 2 (4S)-2-amino-4-(3-{4-[(6R*)-6-[(tert-butyldiphenylsilyl)oxy]-3,3,6-trimethyl-1,4-

oxazepan-4-yl]-6-[(1S)-1-[(2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl]ethoxy]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (200 mg, ee=100%) as a white solid.

ESI-MS m/z = 880.50 $[M+H]^+$; Calculated MW: 879.4.

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Example 41: Synthesis of Compound (143b)

Step 1: Tert-butyl (2S,4R)-4-fluoro-2-[methoxy(methyl)carbamoyl]pyrrolidine-1-carboxylate

To a stirred mixture of (2S,4R)-1-(tert-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (50.00 g, 214.3 mmol, 1.0 equiv) and Et₃N (54.23 g, 535.9 mmol, 2.5 equiv) in DCM (500 mL) was added 1-
10 [(1H-imidazol-1-yl)carbonyl]-1H-imidazole (52.14 g, 321.5 mmol, 1.5 equiv) in portions at 20°C under nitrogen atmosphere. The resulting mixture was stirred at 20°C for 1 h under nitrogen atmosphere. To the above mixtures was added methoxy(methyl)aminehydrochloride (23.00 g, 235.809 mmol, 1.1 equiv) in portions at 20°C. The resulting mixture was stirred at 20°C for additional 2 h. The reaction was quenched by the addition of water (500 mL) at 20°C. The resulting mixture was extracted
15 with CH₂Cl₂ (3 x 500 mL). The combined organic layers were washed with brine (3x100 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to afford tert-butyl (2S,4R)-4-fluoro-2-[methoxy(methyl)carbamoyl]pyrrolidine-1-carboxylate (45.00 g, 75.9% yield) as a colorless oil.

Step 2: Tert-butyl (2S,4R)-2-acetyl-4-fluoropyrrolidine-1-carboxylate

To a stirred solution of tert-butyl (2S,4R)-4-fluoro-2-(methoxy(methyl)carbamoyl)pyrrolidine-1-carboxylate (3.00 g, 10.86 mmol, 1.0 equiv) in THF (50 mL) was added MeMgBr (7.24 mL, 21.72 mmol, 2 equiv, 3M in THF) dropwise at 0°C under N₂ atmosphere. The resulting mixture was stirred at 0°C for 2 h under N₂ atmosphere. The reaction was quenched by the addition of NH₄Cl (20 mL) at 0°C. The resulting mixture was extracted with DCM (3 x 30 mL). The combined organic layers were
25 washed with brine (2x30 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (100%~30%). The pure fraction was concentrated to afford tert-butyl (2S,4R)-2-acetyl-4-fluoropyrrolidine-1-carboxylate (2.10 g, 83.63% yield) as a colourless oil.

Step 3: Tert-butyl (2S,4R)-4-fluoro-2-(1-hydroxyethyl)pyrrolidine-1-carboxylate

To a stirred solution of tert-butyl (2S,4R)-2-acetyl-4-fluoropyrrolidine-1-carboxylate (2.00 g, 8.66 mmol, 1.0 equiv) in MeOH (30 mL) was added NaBH₄ (329.0 mg, 8.66 mmol, 1.0 equiv) at 0°C under N₂ atmosphere. The resulting mixture was stirred at 0°C for 1 h under N₂ atmosphere. The reaction

was quenched by the addition of H₂O (20 mL) at 0°C. The resulting mixture was extracted with DCM (3 x 30 mL). The combined organic layers were washed with brine (2x30 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (100%~40%). The pure fraction was concentrated to afford tert-butyl (2S,4R)-4-fluoro-2-(1-hydroxyethyl)pyrrolidine-1-carboxylate (1.70 g, 84.28%yield) as a colourless oil.

Step 4: 1-((2S,4R)-4-fluoro-1-(methyl-d₃)pyrrolidin-2-yl)ethan-1-ol

To a stirred mixture of tert-butyl (2S,4R)-4-fluoro-2-(1-hydroxyethyl)pyrrolidine-1-carboxylate (1.50 g, 6.5 mmol, 1.0 equiv) in THF (30 mL) was added Lithium aluminum deuterium hydride (1.0M in THF) (16 mL, 16 mmol, 2.5 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 70°C for 2h under nitrogen atmosphere. The mixture was allowed to cool down to 20°C. The reaction was quenched by the addition of Na₂SO₄·10H₂O (5.00 g) at 20°C. The resulting mixture was filtered and the filter cake was washed with DCM (3x50 mL). The filtrate was concentrated under reduced pressure. This resulted in 1-((2S,4R)-4-fluoro-1-(methyl-d₃)pyrrolidin-2-yl)ethan-1-ol (500.0 mg, 51.77%yield) as a yellow oil.

Step 5: (S)-6-((tert-butyldiphenylsilyl)oxy)-4-(4-chloro-6-(1-((2S,4R)-4-fluoro-1-(methyl-d₃)pyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-6-methyl-1,4-oxazepane

To a stirred mixture of (6S)-6-[(tert-butyl diphenylsilyl)oxy]-4-(4,6-dichloro-1,3,5-triazin-2-yl)-6-methyl-1,4-oxazepane (600.0 mg, 1.16 mmol, 1.0 equiv) and DIEA (299.7 mg, 2.32 mmol, 2.0 equiv) in DCM (5mL) was added 1-((2S,4R)-4-fluoro-1-(methyl-d₃)pyrrolidin-2-yl)ethan-1-ol (261.2 mg, 1.74mmol, 1.5 equiv) in portions at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 20°C for 16h under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:6) and the pure fraction was concentrated under reduced pressure to afford (S)-6-((tert-butyldiphenylsilyl)oxy)-4-(4-chloro-6-(1-((2S,4R)-4-fluoro-1-(methyl-d₃)pyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-6-methyl-1,4-oxazepane (400.0 mg, 54.65%yield) as a yellow solid.

Step 6: 4-((S)-6-((tert-butyldiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-(1-((2S,4R)-4-fluoro-1-(methyl-d₃)pyrrolidin-2-yl)ethoxy)-1,3,5-triazine-2-carbonitrile

To a stirred mixture of (S)-6-((tert-butyldiphenylsilyl)oxy)-4-(4-chloro-6-(1-((2S,4R)-4-fluoro-1-(methyl-d₃)pyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-6-methyl-1,4-oxazepane (400.0 mg, 0.63 mmol, 1.0 equiv) and zinc dicyanide (89.3 mg, 0.76 mmol, 1.2 equiv) in N,N-Dimethylacetamide (3 mL) was added XantPhos Pd G₄ (60.98 mg, 0.063 mmol, 0.1 equiv) in portions at 20°C under nitrogen atmosphere. The resulting mixture was stirred at 60°C for 2h under nitrogen atmosphere. The

mixture was allowed to cool down to 20 °C. The resulting mixture was filtered and the filter cake was washed with MeOH (3x5 mL). The filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18; mobile phase, MeCN in Water (10mmol/L NH₄HCO₃), 90% to 100% gradient in 5 min; detector, UV 254 nm.

- 5 The resulting mixture was concentrated under reduced pressure. This resulted in 4-((S)-6-((tert-butyl-diphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-(1-((2S,4R)-4-fluoro-1-(methyl-d3)pyrrolidin-2-yl)ethoxy)-1,3,5-triazine-2-carbonitrile (350.0 mg, 88.83%yield) as a yellow solid.

Step 7: 4-((S)-6-((tert-butyl-diphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-(1-((2S,4R)-4-fluoro-1-(methyl-d3)pyrrolidin-2-yl)ethoxy)-N-hydroxy-1,3,5-triazine-2-carboximidamide

- 10 To a stirred mixture of 4-((S)-6-((tert-butyl-diphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-(1-((2S,4R)-4-fluoro-1-(methyl-d3)pyrrolidin-2-yl)ethoxy)-1,3,5-triazine-2-carbonitrile (350.0 mg, 0.56 mmol, 1.0 equiv) and Hydroxylamine hydrochloride (78.2 mg, 1.13 mmol, 2.0 equiv) in EtOH (3 mL) was added Na₂CO₃ (179.0 mg, 1.69 mmol, 3.0 equiv) in portions at 20°C under nitrogen atmosphere. The resulting mixture was stirred at 20°C for 1h under nitrogen atmosphere. The resulting mixture was
- 15 diluted with water (200 mL). The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2x10 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 4-((S)-6-((tert-butyl-diphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-(1-((2S,4R)-4-fluoro-1-(methyl-d3)pyrrolidin-2-yl)ethoxy)-N-hydroxy-1,3,5-triazine-2-carboximidamide (320.0 mg, 86.82%yield) as
- 20 a white solid.

Step 8: N-(((S)-2-amino-3-cyano-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-4-carbonyl)oxy)-4-((S)-6-((tert-butyl-diphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-(1-((2S,4R)-4-fluoro-1-(methyl-d3)pyrrolidin-2-yl)ethoxy)-1,3,5-triazine-2-carboximidamide

- To a stirred mixture of 4-((S)-6-((tert-butyl-diphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-(1-((2S,4R)-4-fluoro-1-(methyl-d3)pyrrolidin-2-yl)ethoxy)-N-hydroxy-1,3,5-triazine-2-
- 25 carboximidamide (350.0 mg, 0.53 mmol, 1.0 equiv) and (4S)-2-amino-3-cyano-4-methyl-6,7-dihydro-5H-1-benzothiophene-4-carboxylic acid (126.3 mg, 0.53 mmol, 1.0 equiv) in DMF (3 mL) were added DIEA (207.2 mg, 1.60 mmol, 3.0 equiv) and Benzotriazole-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (417.2 mg, 0.80 mmol, 1.5 equiv) in portions at 20°C under nitrogen atmosphere.
- 30 The resulting mixture was stirred at 20°C for 1h under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18; mobile phase, MeCN in Water (10mmol/L NH₄HCO₃), 90% to 100% gradient in 5 min; detector, UV 254 nm. The pure fraction was concentrated under reduced pressure to afford N-(((S)-2-amino-3-cyano-4-methyl-4,5,6,7-

tetrahydrobenzo[b]thiophene-4-carbonyl)oxy)-4-((S)-6-((tert-butyldiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-(1-((2S,4R)-4-fluoro-1-(methyl-d3)pyrrolidin-2-yl)ethoxy)-1,3,5-triazine-2-carboximidamide (350.0 mg, 75.00%yield) as a white solid.

Step 9: (S)-2-amino-4-(3-(4-((S)-6-((tert-butyldiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-(1-((2S,4R)-4-fluoro-1-(methyl-d3)pyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile

To a stirred mixture of N-(((S)-2-amino-3-cyano-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-4-carbonyl)oxy)-4-((S)-6-((tert-butyldiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-(1-((2S,4R)-4-fluoro-1-(methyl-d3)pyrrolidin-2-yl)ethoxy)-1,3,5-triazine-2-carboximidamide (350.0 mg, 0.40 mmol, 1.0 equiv) in DMF (2 mL) were added DBU (122.1 mg, 0.80 mmol, 2.0 equiv) in portions at 20°C under nitrogen atmosphere. The resulting mixture was stirred at 80°C for 2h under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18; mobile phase, MeCN in Water (10mmol/L NH₄HCO₃), 10% to 50% gradient in 10 min; detector, UV 254 nm. The resulting mixture was concentrated under reduced pressure. This resulted in (S)-2-amino-4-(3-(4-((S)-6-((tert-butyldiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-(1-((2S,4R)-4-fluoro-1-(methyl-d3)pyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (300.0 mg, 87.52%yield) as a yellow solid.

Step 10: (S)-2-amino-4-(3-(4-(1-((2S,4R)-4-fluoro-1-(methyl-d3)pyrrolidin-2-yl)ethoxy)-6-((S)-6-hydroxy-6-methyl-1,4-oxazepan-4-yl)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile

To a stirred mixture of (S)-2-amino-4-(3-(4-((S)-6-((tert-butyldiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-(1-((2S,4R)-4-fluoro-1-(methyl-d3)pyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (300.0 mg, 0.35 mmol, 1.0 equiv) in DCM (10 mL) were added boron trifluoride diethyl etherate (10 mL) in portions at 20°C under nitrogen atmosphere. The resulting mixture was stirred at 50°C for 16 h under nitrogen atmosphere. The mixture was basified to pH 9 with NH₃·H₂O. The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (2x30 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The crude product (200.0 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column 30*150 mm, 5m; Mobile Phase A: 10mmol/L NH₄HCO₃+0.05%NH₃H₂O), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 5% B to 5% B in 1 min, 5% B to 30% B in 2 min, 30% to 47% B in 11 min; Wavelength: 254nm/220nm nm; RT1(min): 10.47). The pure fraction was lyophilized to afford (S)-2-amino-4-(3-(4-(1-((2S,4R)-4-

fluoro-1-(methyl-*d*₃)pyrrolidin-2-yl)ethoxy)-6-((*S*)-6-hydroxy-6-methyl-1,4-oxazepan-4-yl)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (65.7 mg, 30.37% yield, 98.0% purity @ 254 nm, 98.6% purity @ 220 nm) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.09 (s, 2H), 5.33 – 5.25 (m, 1H), 5.10 – 5.06 (m, 1H), 4.83 (d, *J* = 14.9 Hz, 1H), 4.23 – 3.95 (m, 2H), 3.92 – 3.61 (m, 4H), 3.52 – 3.35 (m, 3H), 3.01 – 2.91 (m, 1H), 2.63 – 2.51 (m, 3H), 2.15 – 1.80 (m, 6H), 1.78 (d, *J* = 2.5 Hz, 3H), 1.25 (dd, *J* = 8.2, 6.4 Hz, 3H), 1.10 (d, *J* = 3.7 Hz, 3H).

Example 42: Synthesis of Compound (142b)

Step 1: *Tert*-butyl 6-hydroxy-6-(methyl-*d*₃)-1,4-oxazepan-4-carboxylate

To a stirred solution of *tert*-butyl 6-oxo-1,4-oxazepan-4-carboxylate (10.00 g, 46.4 mmol, 1.0 equiv) in THF (100 mL) was added methyl-*d*₃-magnesium iodide (1M in THF) (55.7 mL, 55.7 mmol, 1.2 equiv) dropwise at 0°C under argon atmosphere. The resulting mixture was stirred at room temperature for 30 min under argon atmosphere. The resulting mixture was quenched with water at 0°C. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water, 30% to 80% gradient in 30 min; detector, UV 200 nm. This resulted in *tert*-butyl 6-hydroxy-6-(methyl-*d*₃)-1,4-oxazepan-4-carboxylate (4.85 g, 44.5% yield) as a colorless oil.

Step 2: 6-(Methyl-*d*₃)-1,4-oxazepan-6-ol

To a stirred solution of *tert*-butyl 6-hydroxy-6-(methyl-*d*₃)-1,4-oxazepan-4-carboxylate (4.85 g, 20.6 mmol, 1.0 equiv) in 1,4-dioxane (50 mL) was added HCl(g) (4M in 1,4-dioxane) (50 mL) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 1 h under nitrogen atmosphere. The precipitated solids were collected by filtration and washed with 1,4-dioxane. This resulted in 6-(methyl-*d*₃)-1,4-oxazepan-6-ol (2.33 g, crude) as a white solid.

Step 3: 6-((*Tert*-butyldiphenylsilyl)oxy)-6-(methyl-*d*₃)-1,4-oxazepan

To a stirred mixture of 6-(methyl-*d*₃)-1,4-oxazepan-6-ol (2.33 g, 17.3 mmol, 1.0 equiv) and Imidazole (5.91 g, 86.8 mmol, 5.0 equiv) in DCM (50 mL) was added *tert*-butyl(chloro)diphenylsilane (9.54 g, 34.7 mmol, 2.0 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 12 h under nitrogen atmosphere. The resulting mixture was diluted with water at 0°C. The resulting mixture was extracted with DCM. The combined organic layers were washed

with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water, 10% to 100% gradient in 30 min; detector, UV 220 nm. This resulted in 6-((*tert*-butyldiphenylsilyl)oxy)-6-(methyl-*d*₃)-1,4-oxazepane (2.40 g, 37.5% yield) as a yellow oil.

Step 4: 6-((*Tert*-butyldiphenylsilyl)oxy)-4-(4,6-dichloro-1,3,5-triazin-2-yl)-6-(methyl-*d*₃)-1,4-oxazepane

To a stirred solution of cyanuric chloride (1.43 g, 7.72 mmol, 1.2 equiv) in DCM (25 mL) was added DIEA (2.50 g, 19.3 mmol, 3.0 equiv) dropwise at 0°C under nitrogen atmosphere. To the above mixture was added 6-((*tert*-butyldiphenylsilyl)oxy)-6-(methyl-*d*₃)-1,4-oxazepane (2.40 g, 6.44 mmol, 1.0 equiv) in portions at 0°C. The resulting mixture was stirred at room temperature for additional 30 min. The resulting mixture was diluted with DCM at 0°C. The resulting mixture was washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (4:1) to afford 6-((*tert*-butyldiphenylsilyl)oxy)-4-(4,6-dichloro-1,3,5-triazin-2-yl)-6-(methyl-*d*₃)-1,4-oxazepane (2.77 g, 82.6% yield) as a yellow solid.

Step 5: 6-((*Tert*-butyldiphenylsilyl)oxy)-4-(4-chloro-6-((*S*)-1-((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-6-(methyl-*d*₃)-1,4-oxazepane

A mixture of 6-((*tert*-butyldiphenylsilyl)oxy)-4-(4,6-dichloro-1,3,5-triazin-2-yl)-6-(methyl-*d*₃)-1,4-oxazepane (2.77 g, 5.18 mmol, 1.0 equiv), (*S*)-1-((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)ethan-1-ol (763.4 mg, 5.18 mmol, 1.0 equiv) and Cs₂CO₃ (3.38 g, 10.36 mmol, 2.0 equiv) in 1,4-dioxane (30 mL) was stirred at 80°C for 2 h under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford 6-((*tert*-butyldiphenylsilyl)oxy)-4-(4-chloro-6-((*S*)-1-((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-6-(methyl-*d*₃)-1,4-oxazepane (1.93 g, 59.1% yield) as a white solid.

Step 6: 4-(6-((*Tert*-butyldiphenylsilyl)oxy)-6-(methyl-*d*₃)-1,4-oxazepan-4-yl)-6-((*S*)-1-((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazine-2-carbonitrile

A mixture of 6-((*tert*-butyldiphenylsilyl)oxy)-4-(4-chloro-6-((*S*)-1-((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-6-(methyl-*d*₃)-1,4-oxazepane (1.93 g, 3.01 mmol, 1.0 equiv), trimethylsilanecarbonitrile (298.6 mg, 3.01 mmol, 1.0 equiv) and CsF (914.3 mg, 6.02

mmol, 2.0 equiv) in DMF (10 mL) was stirred at 80°C for 1 h under argon atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was quenched with water at 0°C. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water, 10% to 100% gradient in 30 min; detector, UV 254 nm. This resulted in 4-(6-((*tert*-butyldiphenylsilyl)oxy)-6-(methyl-*d*₃)-1,4-oxazepan-4-yl)-6-((*S*)-1-((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazine-2-carbonitrile (787.0 mg, 42.1% yield) as an orange solid.

10 Step 7: 4-(6-((*tert*-butyldiphenylsilyl)oxy)-6-(methyl-*d*₃)-1,4-oxazepan-4-yl)-6-((*S*)-1-((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-*N*-hydroxy-1,3,5-triazine-2-carboximidamide

To a stirred solution of 4-(6-((*tert*-butyldiphenylsilyl)oxy)-6-(methyl-*d*₃)-1,4-oxazepan-4-yl)-6-((*S*)-1-((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazine-2-carbonitrile (732.0 mg, 1.17 mmol, 1.0 equiv) in THF (8 mL) was added Hydroxylamine (50% in water)(310.2 mg, 4.70 mmol, 4.0 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 30 min under nitrogen atmosphere. The resulting mixture was concentrated under vacuum. This resulted in 4-(6-((*tert*-butyldiphenylsilyl)oxy)-6-(methyl-*d*₃)-1,4-oxazepan-4-yl)-6-((*S*)-1-((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-*N*-hydroxy-1,3,5-triazine-2-carboximidamide (780.0 mg, crude) as a yellow solid.

20 Step 8: *N*-(((*S*)-2-amino-3-cyano-4-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-4-carbonyl)oxy)-4-(6-((*tert*-butyldiphenylsilyl)oxy)-6-(methyl-*d*₃)-1,4-oxazepan-4-yl)-6-((*S*)-1-((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazine-2-carboximidamide

To a stirred mixture of 4-(6-((*tert*-butyldiphenylsilyl)oxy)-6-(methyl-*d*₃)-1,4-oxazepan-4-yl)-6-((*S*)-1-((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-*N*-hydroxy-1,3,5-triazine-2-carboximidamide (632.0 mg, 0.96 mmol, 1.0 equiv), (4*S*)-2-amino-3-cyano-4-methyl-6,7-dihydro-5*H*-1-benzothiophene-4-carboxylic acid (342.0 mg, 1.44 mmol, 1.5 equiv), DIEA (623.6 mg, 4.82 mmol, 5.0 equiv) in DMF (8 mL) was added Benzotriazole-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (1.00 g, 1.93 mmol, 2.0 equiv) in portions at 0°C under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 1 h under nitrogen atmosphere. The resulting mixture was quenched with water at 0°C. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water, 10% to 100% gradient in 30 min; detector, UV 254 nm. This resulted in *N*-(((*S*)-2-amino-3-cyano-4-

methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-4-carbonyl)oxy)-4-(6-((*tert*-butyldiphenylsilyl)oxy)-6-(methyl-*d*₃)-1,4-oxazepan-4-yl)-6-((*S*)-1-((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazine-2-carboximidamide (700.0 mg, crude) as a brown solid.

5 Step 9: (4*S*)-2-Amino-4-(3-(4-(6-((*tert*-butyldiphenylsilyl)oxy)-6-(methyl-*d*₃)-1,4-oxazepan-4-yl)-6-((*S*)-1-((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile

A mixture of *N*-(((*S*)-2-amino-3-cyano-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-4-carbonyl)oxy)-4-(6-((*tert*-butyldiphenylsilyl)oxy)-6-(methyl-*d*₃)-1,4-oxazepan-4-yl)-6-((*S*)-1-((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazine-2-carboximidamide (700.0 mg, 0.80 mmol, 1.0 equiv) and DBU (1.22 g, 8.02 mmol, 10 equiv) in DMF (7 mL) was stirred at 60-80°C for 1 h under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water, 10% to 100% gradient in 20 min; detector, UV 254 nm. This resulted in (4*S*)-2-amino-4-(3-(4-(6-((*tert*-butyldiphenylsilyl)oxy)-6-(methyl-*d*₃)-1,4-oxazepan-4-yl)-6-((*S*)-1-((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (525.0 mg, 76.5% yield) as a yellow solid. ESI-MS *m/z* = 855.5 [*M*+H]⁺; Calculated MW: 854.4.

20 Step 10: (4*S*)-2-amino-4-(3-(4-((*S*)-1-((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-6-(6-hydroxy-6-(methyl-*d*₃)-1,4-oxazepan-4-yl)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile

A solution of (4*S*)-2-amino-4-(3-(4-(6-((*tert*-butyldiphenylsilyl)oxy)-6-(methyl-*d*₃)-1,4-oxazepan-4-yl)-6-((*S*)-1-((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (300.0 mg, 0.35 mmol, 1.0 equiv) in hydrofluoride(70% in pyridine) (1.5 mL) was stirred at room temperature for 30 min under nitrogen atmosphere. The mixture was basified to pH 8 with saturated NaHCO₃ (aq.). The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase flash with the following conditions (Column: XBridge Prep OBD C18 Column 30*150 mm, 5m; Mobile Phase A: 10mmol/L NH₄HCO₃+0.05% NH₃H₂O), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 5% B to 5% B in 1 min, 5% B to 32% B in 2 min, 32% to 50% B in 11 min; Wavelength: 254nm/220nm; RT1(min): 9.43) to afford (4*S*)-2-amino-4-(3-(4-((*S*)-1-((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-6-(6-hydroxy-6-(methyl-*d*₃)-1,4-oxazepan-4-yl)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (80.4 mg, 37.1 %yield) as a white solid.

Step 11: (*S*)-2-amino-4-(3-(4-((*S*)-1-((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-6-((*S*)-6-hydroxy-6-(methyl-*d*₃)-1,4-oxazepan-4-yl)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile

The mixture (*S*)-2-amino-4-(3-(4-((*S*)-1-((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-6-((*S*)-6-hydroxy-6-(methyl-*d*₃)-1,4-oxazepan-4-yl)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (80.4 mg, 0.13 mmol, 1.0 equiv) was separated by Chiral-HPLC with the following conditions (Column: Enantiocel- A4-5, 3.0*25CM, 5μm; Mobile Phase A: Hex(10mM NH₃-MeOH), Mobile Phase B: EtOH; Flow rate: 40 mL/min; Gradient: isocratic 30; Wavelength: 220/254 nm; RT1(min): 15.6; RT2(min): 18; Sample Solvent: EtOH; Number Of
 10 Runs: 7) to afford first peak, isomer 1 (*S*)-2-amino-4-(3-(4-((*S*)-1-((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-6-((*S*)-6-hydroxy-6-(methyl-*d*₃)-1,4-oxazepan-4-yl)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (21.9 mg, 99.2% @254 nm, 99.6% @220 nm, ee:100%) as a white solid and second peak, isomer 2 (*S*)-2-amino-4-(3-(4-((*S*)-1-((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-6-((*R*)-6-hydroxy-6-(methyl-*d*₃)-1,4-oxazepan-4-yl)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-
 15 tetrahydrobenzo[*b*]thiophene-3-carbonitrile (22.6 mg, 99.2% @254 nm, 99.5% @220 nm, ee:97.7%) as a white solid.

isomer 1 CHIRAL_HPLC Rt=2.028 min. ee value: 100%.

ESI-MS *m/z* = 617.4 [M+H]⁺; Calculated MW: 616.3.

20 isomer 2 CHIRAL_HPLC Rt=2.452 min. ee value: 97.7%.

ESI-MS *m/z* = 617.4 [M+H]⁺; Calculated MW: 616.3.

Example 43: Synthesis of Compound (126)

Step 1: Tert-butyl (2*S*,4*R*)-2-(acetyl-*d*₃)-4-fluoropyrrolidine-1-carboxylate

25 To a stirred solution of tert-butyl (2*S*,4*R*)-4-fluoro-2-[methoxy(methyl)carbamoyl]pyrrolidine-1-carboxylate (5.0 g, 18.1 mmol, 1.0 equiv) in THF (100 mL) was added iodo((2*H*₃)methyl)magnesium (23.52 mL, 23.5 mmol, 1.3 equiv) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred at 20 °C for 2h under nitrogen atmosphere. The reaction was quenched by the addition of sat. NH₄Cl (aq.) (200 mL) at 0 °C. The aqueous layer was extracted with EtOAc (2x150 mL). The
 30 resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (2:1). The pure fraction was concentrated under reduced

pressure to afford tert-butyl (2S,4R)-2-(acetyl-d3)-4-fluoropyrrolidine-1-carboxylate (3.00 g, 70.76%yield) as a colorless oil.

Step 2: Tert-butyl (2S,4R)-4-fluoro-2-(1-hydroxyethyl-2,2,2-d3)pyrrolidine-1-carboxylate

To a stirred solution of tert-butyl (2S,4R)-2-(acetyl-d3)-4-fluoropyrrolidine-1-carboxylate (2.70 g, 11.5 mmol, 1.0 equiv) in methanol (20 mL) was added NaBH₄ (218.0 mg, 5.76 mmol, 0.5 equiv) at 0 °C under air atmosphere. The resulting mixture was stirred at 0 °C for 15 min under air atmosphere. The resulting mixture was diluted with water (50 mL). The aqueous layer was extracted with EtOAc (2x30 mL). The resulting mixture was concentrated under reduced pressure to afford tert-butyl (2S,4R)-4-fluoro-2-(1-hydroxyethyl-2,2,2-d3)pyrrolidine-1-carboxylate (2.50 g, 91.80%yield) as a colorless oil.

Step 3: 1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethan-2,2,2-d3-1-ol

To a stirred solution of tert-butyl (2S,4R)-4-fluoro-2-(1-hydroxyethyl-2,2,2-d3)pyrrolidine-1-carboxylate (2.5 g, 10.6 mmol, 1.0 equiv) in THF (30 mL) was added Lithium aluminum hydride (2.0 M in THF) (10.58 mL, 21.2 mmol, 2.0 equiv) dropwise at 0 °C under air atmosphere. The resulting mixture was stirred at 70 °C for 1 h under air atmosphere. The mixture was allowed to cool down to 20 °C. The reaction was quenched with Na₂SO₄·10H₂O at 0 °C. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH₂Cl₂ / MeOH (5:1). The pure fraction was concentrated under reduced pressure to afford 1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethan-2,2,2-d3-1-ol (1.0 g, 62.92%yield) as a colorless oil.

Step 4: (S)-6-((tert-butyldiphenylsilyl)oxy)-4-(4-chloro-6-(1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy-2,2,2-d3)-1,3,5-triazin-2-yl)-6-methyl-1,4-oxazepane

To a stirred mixture of 1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethan-2,2,2-d3-1-ol (290.3 mg, 1.93 mmol, 2.0 equiv) and DIEA (374.6 mg, 2.89 mmol, 3.0 equiv) in DCM (4 mL) was added (6S)-6-[(tert-butyldiphenylsilyl)oxy]-4-(4,6-dichloro-1,3,5-triazin-2-yl)-6-methyl-1,4-oxazepane (500.0 mg, 0.97 mmol, 1.0 equiv) at 20 °C under air atmosphere. The resulting mixture was stirred at 50 °C for 2h under air atmosphere. The mixture was allowed to cool down to 20 °C. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1). The pure fraction was concentrated under reduced pressure to afford (S)-6-((tert-butyldiphenylsilyl)oxy)-4-(4-chloro-6-(1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy-2,2,2-d3)-1,3,5-triazin-2-yl)-6-methyl-1,4-oxazepane (550.0 mg, 90.18%yield) as a yellow solid.

Step 5: 4-((S)-6-((tert-butylidiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-(1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy-2,2,2-d₃)-1,3,5-triazine-2-carbonitrile

To a stirred mixture of (S)-6-((tert-butylidiphenylsilyl)oxy)-4-(4-chloro-6-(1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy-2,2,2-d₃)-1,3,5-triazin-2-yl)-6-methyl-1,4-oxazepane (500.0 mg, 0.79 mmol, 1.0 equiv) and zinc dicyanide (111.6 mg, 0.95 mmol, 1.2 equiv) in N,N-Dimethylacetamide (5 mL) was added XantPhos Pd G4 (76.2 mg, 0.08 mmol, 0.1 equiv) at 20 °C under nitrogen atmosphere. The resulting mixture was stirred at 80 °C for 1 h under nitrogen atmosphere. The mixture was allowed to cool down to 20 °C. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:3). The pure fraction was concentrated under reduced pressure to afford 4-((S)-6-((tert-butylidiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-(1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy-2,2,2-d₃)-1,3,5-triazine-2-carbonitrile (450.0 mg, 91.37% yield) as a yellow solid.

Step 6: 4-((S)-6-((tert-butylidiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-(1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy-2,2,2-d₃)-N-hydroxy-1,3,5-triazine-2-carboximidamide

To a stirred mixture of 4-((S)-6-((tert-butylidiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-(1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy-2,2,2-d₃)-1,3,5-triazine-2-carbonitrile (450.0 mg, 0.72 mmol, 1.0 equiv) and Na₂CO₃ (75.4 mg, 1.09 mmol, 3.0 equiv) in EtOH (5 mL) was added Hydroxylamine hydrochloride (230.1 mg, 2.14 mmol, 1.5 equiv) at 20 °C under air atmosphere. The resulting mixture was stirred at 20 °C for 1 h under air atmosphere. The resulting mixture was diluted with water (20 mL). The aqueous layer was extracted with EtOAc (2 x 20 mL). The resulting mixture was concentrated under reduced pressure to afford 4-((S)-6-((tert-butylidiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-(1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy-2,2,2-d₃)-N-hydroxy-1,3,5-triazine-2-carboximidamide (450.0 mg, 90.21% yield) as a yellow solid.

Step 7: N-(((S)-2-amino-3-cyano-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-4-carbonyl)oxy)-4-((S)-6-((tert-butylidiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-(1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy-2,2,2-d₃)-1,3,5-triazine-2-carboximidamide

To a stirred mixture of 4-((S)-6-((tert-butylidiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-(1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy-2,2,2-d₃)-N-hydroxy-1,3,5-triazine-2-carboximidamide (450.0 mg, 0.69 mmol, 1.0 equiv) and (4S)-2-amino-3-cyano-4-methyl-6,7-dihydro-5H-1-benzothiophene-4-carboxylic acid (162.4 mg, 0.69 mmol, 1.0 equiv) in DMF (5 mL) were added Benzotriazole-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (536.4 mg, 1.03 mmol, 1.5 equiv) and DIEA (266.4 mg, 2.06 mmol, 3.0 equiv) at 20 °C under air atmosphere. The resulting mixture was stirred at 20 °C for 1 h under air atmosphere. The residue was purified by reversed-phase

flash chromatography with the following conditions: column, C18 ; mobile phase, MeCN in Water (0.1% FA), 40% to 50% gradient in 10 min; detector, UV 254 nm. The pure fraction was concentrated under reduced pressure to afford N-(((S)-2-amino-3-cyano-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-4-carbonyl)oxy)-4-((S)-6-((tert-butylidiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-(1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy-2,2,2-d3)-1,3,5-triazine-2-carboximidamide (500.0 mg, 83.34%yield) as a yellow solid.

Step 8: (S)-2-amino-4-(3-(4-((S)-6-((tert-butylidiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-(1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy-2,2,2-d3)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile

- 10 A mixture of N-(((S)-2-amino-3-cyano-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-4-carbonyl)oxy)-4-((S)-6-((tert-butylidiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-(1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy-2,2,2-d3)-1,3,5-triazine-2-carboximidamide (500 mg, 0.57 mmol, 1.0 equiv) and DBU (174.4 mg, 1.15 mmol, 2.0 equiv) in DMF (5 mL) was stirred at 80 °C for 1 h under air atmosphere. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 ; mobile phase, MeCN in Water (10mmol/L NH_4HCO_3), 80% to 100% gradient in 10 min; detector, UV 254 nm. The pure fraction was concentrated under reduced pressure to afford (S)-2-amino-4-(3-(4-((S)-6-((tert-butylidiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-(1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy-2,2,2-d3)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (400.0 mg, 81.68%yield) as a yellow solid.

Step 9: (S)-2-amino-4-(3-(4-(1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy-2,2,2-d3)-6-((S)-6-hydroxy-6-methyl-1,4-oxazepan-4-yl)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile

- A mixture of (S)-2-amino-4-(3-(4-((S)-6-((tert-butylidiphenylsilyl)oxy)-6-methyl-1,4-oxazepan-4-yl)-6-(1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy-2,2,2-d3)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (350.0 mg, 0.41 mmol, 1.0 equiv) and boron trifluoride diethyl etherate (7 mL) in DCM (7 mL) was stirred at 50 °C for 16 h under air atmosphere. The mixture was allowed to cool down to 20 °C. The resulting mixture was diluted with water (50mL). The mixture was basified to pH 9 with $\text{NH}_3 \cdot \text{H}_2\text{O}$. The aqueous layer was extracted with EtOAc (2 x 30 mL). The resulting mixture was concentrated under reduced pressure. The crude product (350 mg) was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18 ExRS 30*150 mm, 5m; Mobile Phase A: Water(10 mmol/L NH_4HCO_3 +0.05% $\text{HN}_3\text{H}_2\text{O}$), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 37% B to 57 % B in 8 min; Wavelength: 254nm/220nm nm; RT1(min): 8.22). The pure fraction was concentrated under reduced pressure and

lyophilized to afford (S)-2-amino-4-(3-(4-(1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy-2,2,2-d3)-6-((S)-6-hydroxy-6-methyl-1,4-oxazepan-4-yl)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl)-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (75.5 mg, 29.82%yield) as a white solid.

ESI-MS $m/z = 617.3 [M+H]^+$; Calculated MW: 616.3.

- 5 ^1H NMR (400 MHz, DMSO- d_6) δ 7.09 (s, 2H), 5.31 – 5.26 (m, 1H), 5.25 – 5.08 (m, 1H), 4.83 (d, $J = 15.3$ Hz, 1H), 4.19 – 4.05 (m, 1H), 4.04 – 3.95 (m, 1H), 3.89 – 3.68 (m, 4H), 3.51 – 3.36 (m, 3H), 3.01 – 2.89 (m, 1H), 2.54 (t, $J = 5.6$ Hz, 2H), 2.49 – 2.43 (m, 1H), 2.40 (d, $J = 5.9$ Hz, 3H), 2.12 – 1.81 (m, 6H), 1.79 (d, $J = 2.5$ Hz, 3H), 1.11 (d, $J = 3.5$ Hz, 3H).

10 **Example 44:** Synthesis of Compound (119)

Step 1: (2R,7aS)-2-fluoro-hexahydropyrrolizine-7a-carbaldehyde

- To a stirred solution of $(\text{COCl})_2$ (23.92 g, 188.4 mmol, 3.0 equiv) in DCM (200 mL) was added DMSO (24.54 g, 314.0 mmol, 5.0 equiv) in DCM (50 mL) dropwise at -78°C under nitrogen atmosphere. The resulting mixture was stirred for 1h at -78°C under nitrogen atmosphere. To the above mixture was
- 15 added [(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methanol (10.00 g, 62.8 mmol, 1.0 equiv) in DCM (50 mL) dropwise at -78°C . The resulting mixture was stirred for additional 1h at -78°C . To the above mixture was added TEA (63.56 g, 628.1 mmol, 10 equiv) at -78°C . The resulting mixture was stirred for additional 12h at 20°C . The reaction was quenched by the addition of Water (100 mL) at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3 x 100 mL). The combined
- 20 organic layers were washed with brine (3 x 100 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure to afford (2R,7aS)-2-fluoro-hexahydropyrrolizine-7a-carbaldehyde (9.70 g, 98.2% yield) as a brown oil.

Steps 2-3: (2R,7aS)-7a-{1-[(4-{6-[(tert-butyl)phenylsilyl]oxy}-6-methyl-1,4-oxazepan-4-yl)-6-chloro-1,3,5-triazin-2-yl]oxy}ethyl}-2-fluoro-hexahydropyrrolizine

- 25 To a stirred mixture of (2R,7aS)-2-fluoro-hexahydropyrrolizine-7a-carbaldehyde (4.00 g, 25.4 mmol, 1.0 equiv) in THF (160 mL) was added 1M bromo(methyl)magnesium in THF (76.3 mL, 76.3 mmol, 3.0 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 2h at 20°C under nitrogen atmosphere. The reaction was quenched by the addition of MeOH (50 mL) at 0°C . The resulting mixture was filtered, the filter cake was washed with MeOH (3 x 30 mL). The
- 30 filtrate was concentrated under reduced pressure to afford (1S)-1-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]ethanol (12.00 g crude) as a brown oil.

To a stirred solution of 6-[(tert-butyldiphenylsilyl)oxy]-4-(4,6-dichloro-1,3,5-triazin-2-yl)-6-methyl-1,4-oxazepane (3.01 g, 17.3 mmol, 3.0 equiv) and (6R)-6-[(tert-butyldiphenylsilyl)oxy]-4-(4,6-dichloro-1,3,5-triazin-2-yl)-6-methyl-1,4-oxazepane (3.00 g, 5.79 mmol, 1.0 equiv) in DMA (10 mL) was added DIEA (1.50 g, 11.5 mmol, 2.0 equiv) at 20°C under nitrogen atmosphere. The resulting mixture was stirred for 3h at 20°C under nitrogen atmosphere. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (2:1 - 1:2), the pure fraction was concentrated under reduced pressure to afford (2R,7aS)-7a-{1-[(4-{6-[(tert-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl}-6-chloro-1,3,5-triazin-2-yl)oxy]ethyl}-2-fluoro-hexahydropyrrolizine (2.00 g, 52.7% yield two steps) as a brown oil.

Step 4: 4-{1-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]ethoxy}-6-{6-[(tert-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl}-1,3,5-triazine-2-carbonitrile

To a stirred solution of (2R,7aS)-7a-{1-[(4-{6-[(tert-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl}-6-chloro-1,3,5-triazin-2-yl)oxy]ethyl}-2-fluoro-hexahydropyrrolizine (2.00 g, 3.05 mmol, 1.0 equiv) and Zn(CN)₂ (538.38 mg, 4.58 mmol, 1.5 equiv) in DMA (20 mL) was added Xantphos Pd 4G (294.1 mg, 0.30 mmol, 0.1 equiv) at 20°C under nitrogen atmosphere. The resulting mixture was stirred for 1h at 60°C under nitrogen atmosphere. The mixture was allowed to cool down to 20°C. The resulting mixture was filtered, the filter cake was washed with DCM (3 x 10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1 - 1:1) and the pure fraction was concentrated under reduced pressure to afford 4-{1-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]ethoxy}-6-{6-[(tert-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl}-1,3,5-triazine-2-carbonitrile (1.10 g, 55.8% yield) as a brown solid.

Step 5: 4-{1-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]ethoxy}-6-{6-[(tert-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl}-N-hydroxy-1,3,5-triazine-2-carboximidamide

To a stirred mixture of 4-{1-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]ethoxy}-6-{6-[(tert-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl}-1,3,5-triazine-2-carbonitrile (1.10 g, 1.70 mmol, 1.0 equiv) and hydroxylamine hydrochloride (142.2 mg, 2.04 mmol, 1.2 equiv) in EtOH (15 mL) was added Na₂CO₃ (361.5 mg, 3.41 mmol, 2.0 equiv) at 20°C under nitrogen atmosphere. The resulting mixture was stirred for 1h at 20°C under nitrogen atmosphere. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1 - 1:2) and the pure fraction was concentrated under reduced pressure to afford 4-{1-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]ethoxy}-6-{6-[(tert-butyldiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl}-N-hydroxy-1,3,5-triazine-2-carboximidamide (1.00 g, 86.4% yield) as a brown solid.

Step 6: (4-{1-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]ethoxy}-6-{6-[(tert-butyl)diphenylsilyl]oxy}-6-methyl-1,4-oxazepan-4-yl)-1,3,5-triazin-2-yl)methanimidamido (4S)-2-amino-3-cyano-4-methyl-6,7-dihydro-5H-1-benzothiophene-4-carboxylate

To a stirred mixture of 4-{1-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]ethoxy}-6-{6-[(tert-butyl)diphenylsilyl]oxy}-6-methyl-1,4-oxazepan-4-yl)-N-hydroxy-1,3,5-triazine-2-carboximidamide (918.0 mg, 1.35 mmol, 1.0 equiv) and (4S)-2-amino-3-cyano-4-methyl-6,7-dihydro-5H-1-benzothiophene-4-carboxylic acid (320.0 mg, 1.35 mmol, 1.0 equiv) in DMF (10 mL) was added PyBOP (1057.1 mg, 2.03 mmol, 1.5 equiv) and DIEA (525.1 mg, 4.06 mmol, 3.0 equiv) at 20°C under nitrogen atmosphere. The resulting mixture was stirred for 1h at 20°C under nitrogen atmosphere. The resulting mixture was concentrated under vacuum. The residue was purified by reversed combi-flash chromatography with the following conditions: column, C18; mobile phase, A: FA(0.1%) in water, B: ACN, 60% to 100% gradient in 20 min; detector, UV 254 nm. The pure fraction was concentrated under vacuum to afford (4-{1-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]ethoxy}-6-{6-[(tert-butyl)diphenylsilyl]oxy}-6-methyl-1,4-oxazepan-4-yl)-1,3,5-triazin-2-yl)methanimidamido (4S)-2-amino-3-cyano-4-methyl-6,7-dihydro-5H-1-benzothiophene-4-carboxylate (1.10 g, 90.6% yield) as a brown solid.

Step 7: (4S)-4-[3-(4-{1-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]ethoxy}-6-{6-[(tert-butyl)diphenylsilyl]oxy}-6-methyl-1,4-oxazepan-4-yl)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl]-2-amino-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile

To a stirred solution of (4-{1-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]ethoxy}-6-{6-[(tert-butyl)diphenylsilyl]oxy}-6-methyl-1,4-oxazepan-4-yl)-1,3,5-triazin-2-yl)methanimidamido (4S)-2-amino-3-cyano-4-methyl-6,7-dihydro-5H-1-benzothiophene-4-carboxylate (1.10 g, 1.22 mmol, 1.0 equiv) in DMF (10 mL) was added DBU (373.7 mg, 2.45 mmol, 2.0 equiv) at 20°C under nitrogen atmosphere. The resulting mixture was stirred for 2h at 80°C under nitrogen atmosphere. The mixture was allowed to cool down to 20°C. The resulting mixture was concentrated under vacuum. The residue was purified by reversed combi-flash chromatography with the following conditions: column, C18; mobile phase, A: NH₄HCO₃ (0.1%) in water, B: ACN, 60% to 100% gradient in 20 min; detector, UV 254 nm. The pure fraction was concentrated under vacuum to afford (4S)-4-[3-(4-{1-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]ethoxy}-6-{6-[(tert-butyl)diphenylsilyl]oxy}-6-methyl-1,4-oxazepan-4-yl)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl]-2-amino-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (1.00 g, 92.7% yield) as a brown solid.

Step 8: (4S)-4-[3-(4-{1-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]ethoxy}-6-(6-hydroxy-6-methyl-1,4-oxazepan-4-yl)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl]-2-amino-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile

To a stirred solution of (4S)-4-[3-(4-{1-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]ethoxy}-6-[(tert-butylidiphenylsilyl)oxy]-6-methyl-1,4-oxazepan-4-yl)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl]-2-amino-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (500.0 mg, 0.57 mmol, 1.0 equiv) in DMF (10 mL) was added TBAB (550.6 mg, 1.70 mmol, 3.0 equiv) at 20°C under nitrogen atmosphere. The resulting mixture was stirred for 2h at 50°C under nitrogen atmosphere. The resulting mixture was concentrated under vacuum. The crude product (500.0 mg) was purified by Prep-HPLC with the following conditions (Column: XSelect CSH Fluoro Phenyl 30*150 mm, 5m; Mobile Phase A: Water(0.1% FA), Mobile Phase B: MeOH; Flow rate: 60 mL/min mL/min; Gradient: 19% B to 35% B in 10 min; Wave Length: 254nm/220nm nm; RT1(min): 9.8) to afford (4S)-4-[3-(4-{1-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]ethoxy}-6-(6-hydroxy-6-methyl-1,4-oxazepan-4-yl)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl]-2-amino-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (100.0 mg, 27.4% yield) as a white solid.

Steps 9-10: isomer 1 (4S)-4-(3-{4-[(1R**)1-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]ethoxy]-6-[(6R*)-6-hydroxy-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-2-amino-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile & isomer 2 (4S)-4-(3-{4-[(1R**)1-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]ethoxy]-6-[(6R*)-6-hydroxy-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-2-amino-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile

(4S)-4-[3-(4-{1-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]ethoxy}-6-(6-hydroxy-6-methyl-1,4-oxazepan-4-yl)-1,3,5-triazin-2-yl)-1,2,4-oxadiazol-5-yl]-2-amino-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (100.0 mg) was purified by Prep-HPLC with the following conditions (Column: (S, S)-WHELK-O1, 2*25cm, 5um; Mobile Phase A: Hex(10mM NH₃-MeOH), Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 20; Wave Length: 210/220 nm; RT1(min): 32.1; RT2(min): 38.1; Sample Solvent: MeOH--HPLC; Injection Volume: 0.3 mL; Number Of Runs: 7). The 1st eluting fraction was concentrated under vacuum to afford, (4S)-4-(3-{4-[(1RS)-1-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]ethoxy]-6-[(6R*)-6-hydroxy-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-2-amino-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (50.0 mg) as a white solid. The 2nd eluting fraction was concentrated under vacuum to afford (4S)-4-(3-{4-[(1RS)-1-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]ethoxy]-6-[(6R*)-6-hydroxy-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-2-amino-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (30.0 mg) as a white solid.

(4S)-4-(3-{4-[(1RS)-1-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]ethoxy]-6-[(6R*)-6-hydroxy-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-2-amino-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (50.0 mg) was purified by Prep-HPLC with the following

conditions (Column: Chiral NX(2) 5um, 250*30mm; Mobile Phase A: Hex(10mM NH₃-MeOH), Mobile Phase B: ETOH; Flow rate: 40 mL/min; Gradient: isocratic 30; Wave Length: 220/240 nm; RT1(min): 14.5; RT2(min): 19.2; Sample Solvent: EtOH; Number Of Runs: 3). The 1st eluting fraction was lyophilized to afford isomer 1 (4S)-4-(3-{4-[(1R*)-1-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]ethoxy]-6-[(6R*)-6-hydroxy-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-2-amino-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (22.7 mg, 98.3% purity @254nm, 98.5% purity@220nm, 22.3% yield two steps, ee: 100%) as a white solid. The 2nd eluting fraction was lyophilized to afford isomer 2 (4S)-4-(3-{4-[(1R*)-1-[(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]ethoxy]-6-[(6R*)-6-hydroxy-6-methyl-1,4-oxazepan-4-yl]-1,3,5-triazin-2-yl}-1,2,4-oxadiazol-5-yl)-2-amino-4-methyl-6,7-dihydro-5H-1-benzothiophene-3-carbonitrile (16.1 mg, 98.9% purity@254nm, 98.9% purity@220nm, 15.9% yield two steps, ee: 100%) as a white solid.

Isomer 1: ESI-MS m/z = 640.4 $[M+H]^+$; Calculated MW: 639.4. CHIRAL_HPLC R_t =1.40 min. ee value: 100%.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.09 (s, 2H), 5.26 (d, J = 54.6 Hz, 1H), 5.17 – 5.03 (m, 1H), 4.84 (d, J = 1.5 Hz, 1H), 4.24 – 3.91 (m, 2H), 3.90 – 3.74 (m, 2H), 3.73 – 3.62 (m, 1H), 3.58 (d, J = 13.9 Hz, 1H), 3.51 – 3.35 (m, 2H), 3.09 – 2.84 (m, 3H), 2.80 (d, J = 8.7 Hz, 1H), 2.55 (t, J = 6.2 Hz, 2H), 2.29 – 1.90 (m, 5H), 1.90 – 1.61 (m, 8H), 1.31 – 1.24 (m, 3H), 1.11 (d, J = 7.2 Hz, 3H).

Isomer 2: ESI-MS m/z = 640.4 $[M+H]^+$; Calculated MW: 639.4. CHIRAL_HPLC R_t =1.90 min. ee value: 100%.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.09 (s, 2H), 5.26 (d, J = 54.6 Hz, 1H), 5.17 – 5.03 (m, 1H), 4.84 (d, J = 4.1 Hz, 1H), 4.23 – 3.91 (m, 2H), 3.90 – 3.56 (m, 4H), 3.53 – 3.35 (m, 2H), 3.08 – 2.73 (m, 4H), 2.55 (t, J = 6.2 Hz, 2H), 2.29 – 1.89 (m, 5H), 1.89 – 1.61 (m, 8H), 1.34 – 1.22 (m, 3H), 1.10 (d, J = 3.0 Hz, 3H).

Example 45: Synthesis of Compound (19)

Step 1: *Tert*-butyl 3-(4,6-dichloro-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

To a stirred solution of 2,4,6-trichloro-1,3,5-triazine (5.00 g, 27.1 mmol, 1.0 equiv) in DCM (50 mL) was added the solution of DCM (30 mL) contained DIEA (3.50 g, 27.1 mmol, 1.0 equiv) and *tert*-butyl 3,8-diazabicyclo[3.2.1]octane-8-carboxylate (5.76 g, 27.1 mmol, 1.0 equiv) dropwise at brine ice bath. The resulting mixture was warmed to RT and stirred for 1h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc (100mL) and washed with H₂O (50mL). The resulting mixture was concentrated under vacuum to afford *tert*-butyl 3-(4,6-

dichloro-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (8.00 g, 81.9% yield) as an off-white solid.

Step 2: *Tert*-butyl 3-(4-chloro-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

- 5 Into a 250mL round-bottom flask were added *tert*-butyl 3-(4,6-dichloro-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (8.00 g, 22.2 mmol, 1.0 equiv), ((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methanol (3.54 g, 22.2 mmol, 1.0 equiv), DCM (60 mL) and DIEA (2.87 g, 22.2 mmol, 1.0 equiv). The resulting mixture was stirred overnight at RT. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column
- 10 chromatography, eluted with DCM:MeOH (10:1) to afford *tert*-butyl 3-(4-chloro-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (10.00 g, 93.2% yield) as a white solid.

Step 3: *Tert*-butyl 3-(4-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-6-vinyl-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

- 15 Into a 250 mL round-bottom flask were added *tert*-butyl 3-(4-chloro-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (5.00 g, 10.3 mmol, 1.0 equiv), Pd(dppf)Cl₂ (1.51 g, 2.07 mmol, 0.20 equiv), K₃PO₄ (6.59 g, 31.0 mmol, 3.0 equiv), dioxane (30 mL), H₂O (3 mL) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (3.19 g, 20.7 mmol, 2.0 equiv). The resulting mixture was stirred for 2h at 100°C under N₂ atmosphere.
- 20 Added 100mL EtOAc to it, the solution was washed with H₂O(3x30 mL). The organic layer was dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE:EA (10:1) to afford *tert*-butyl 3-(4-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-6-vinyl-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (4.00 g, 81.4% yield) as a yellow solid.

- 25 Step 4: *Tert*-butyl 3-(4-((*E*)-2-(8-(benzyloxy)-7-fluoro-3-methoxynaphthalen-1-yl)vinyl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

- Into a 40mL vial were added *tert*-butyl 3-(4-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-6-vinyl-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.20 g, 2.53 mmol, 1.0 equiv), 1-(benzyloxy)-8-bromo-2-fluoro-6-methoxynaphthalene (0.91 g, 2.53 mmol, 1.0 equiv), Pd₂(dba)₃.CHCl₃ (0.26 g, 0.25 mmol, 0.10 equiv), P(*p*-Tol)₃ (0.15 g, 0.51 mmol, 0.20 equiv), DIEA (0.98 g, 7.59 mmol, 3.0 equiv) and DMF (15 mL). The resulting mixture was stirred for 4h at 130°C under N₂ atmosphere. The reaction of 2.53 mmol scale was repeated for 2 times. Added 50mL
- 30

H₂O to the combined solution, the resulting mixture was extracted with EtOAc (3 x 50mL). The combined organic layers were dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM:MeOH (20:1) to afford *tert*-butyl 3-(4-((*E*)-2-(8-(benzyloxy)-7-fluoro-3-methoxynaphthalen-1-yl)vinyl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.70 g, 45% yield) as a yellow solid.

Step 5: *Tert*-butyl 3-(4-(2-(7-fluoro-8-hydroxy-3-methoxynaphthalen-1-yl)ethyl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

Into a 250mL vial were added *tert*-butyl 3-(4-((*E*)-2-(8-(benzyloxy)-7-fluoro-3-methoxynaphthalen-1-yl)vinyl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.70 g, 2.25 mmol, 1.0 equiv), Pd/C (1.70 g, 10 wt. %) and MeOH (20 mL). The resulting mixture was stirred for 2 days at RT under H₂ atmosphere. The resulting mixture was filtered, the filter cake was washed with MeOH:DCM (1:1, 3x30mL). The filtrate was concentrated under reduced pressure to afford *tert*-butyl 3-(4-(2-(7-fluoro-8-hydroxy-3-methoxynaphthalen-1-yl)ethyl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.30 g, 86.5%) as a gray solid.

Step 6: *Tert*-butyl 3-(4-(2-(7-fluoro-3-methoxy-8-(((trifluoromethyl)sulfonyl)oxy)naphthalen-1-yl)ethyl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

Into a 250mL round-bottom flask were added *tert*-butyl 3-(4-(2-(7-fluoro-8-hydroxy-3-methoxynaphthalen-1-yl)ethyl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.10 g, 1.65 mmol, 1.0 equiv), 1,1,1-trifluoro-*N*-phenyl-*N*-(((trifluoromethyl)sulfonyl)methanesulfonamide (1.10 g, 3.08 mmol, 1.8 equiv), K₂CO₃ (549.5 mg, 3.97 mmol, 2.4 equiv) and THF (50 mL). The resulting mixture was stirred overnight at 60°C. The resulting mixture was filtered, the filter cake was washed with EtOAc (50mL). The filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH=10:1) to afford *tert*-butyl 3-(4-(2-(7-fluoro-3-methoxy-8-(((trifluoromethyl)sulfonyl)oxy)naphthalen-1-yl)ethyl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (520.0 mg, 39.5% yield) as a yellow solid.

Step 7: *Tert*-butyl 3-(4-(2-(7-fluoro-3-methoxy-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)ethyl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

Into a 40mL vial were added *tert*-butyl 3-(4-(2-(7-fluoro-3-methoxy-8-(((trifluoromethyl)sulfonyl)oxy)naphthalen-1-yl)ethyl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (520.0 mg, 0.65 mmol, 1.0 equiv), CuI (247.9 mg, 1.30 mmol, 2.0 equiv), Pd(PPh₃)₂Cl₂ (159.9 mg, 0.23 mmol, 0.35 equiv), Cs₂CO₃ (636.3 mg, 1.95 mmol, 3.0 equiv), MeCN (20 mL) and ethynyltriisopropylsilane (1.19 g, 6.51 mmol, 10 equiv). The resulting mixture was stirred overnight at 80°C under N₂ atmosphere. After diluted with 100mL EtOAc, the resulting mixture was washed with H₂O (3x30mL). The organic layer was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH=10:1) to afford *tert*-butyl 3-(4-(2-(7-fluoro-3-methoxy-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)ethyl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (250.0 mg, 46.2% yield) as a yellow solid.

Step 8: 4-(2-(4-(3,8-Diazabicyclo[3.2.1]octan-3-yl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)ethyl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol

To a stirred solution of *tert*-butyl 3-(4-(2-(7-fluoro-3-methoxy-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)ethyl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (50.0 mg, 0.06 mmol, 1.0 equiv) in DCM (5 mL) was added BBr₃ (0.3 mL, 3.00 mmol, 5.0 equiv, 1M in DCM) dropwise at 0°C. The resulting mixture was stirred for 40 mins at 0°C and then stirred for 30 mins at RT. Then, the reaction was quenched by the addition of MeOH (10 mL) at 0°C. The resulting mixture was concentrated under reduced pressure. The residue was used directly in next step without other purification.

Step 9: 4-(2-(4-((1*R*,5*S*)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)ethyl)-5-ethynyl-6-fluoronaphthalen-2-ol

Into a 8 mL vial were added 4-(2-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)ethyl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol (60.0 mg, 0.08 mmol, 1.0 equiv, crude), CsF (127.1 mg, 0.84 mmol, 10 equiv) and DMF (1 mL). The resulting mixture was stirred for 1.5h at RT. The reaction was monitored by LCMS. The resulting mixture was filtered, the filter cake was washed with MeOH (20mL). The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18 ExRS, 30*150 mm, 5µm; Mobile

Phase A: Water(10 mmol/L NH₄HCO₃), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 55% B in 7 min, 55% B; Wave Length: 254/220 nm; RT1(min): 6.42) to afford 4-(2-(4-((1*R*,5*S*)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-1,3,5-triazin-2-yl)ethyl)-5-ethynyl-6-fluoronaphthalen-2-ol (2.8 mg, 5.8% yield, 96.8% purity @ 220nm, 97.1% purity @ 254nm) as an off-white solid.

ESI-MS *m/z* = 561.30 [M+H]⁺ ; Calculated MW: 560.27.

¹H NMR (400 MHz, DMSO-*d*₆) δ 9.78 (s, 1H), 7.82 (dd, *J* = 9.1, 6.2 Hz, 1H), 7.38 (t, *J* = 8.9 Hz, 1H), 7.07 (d, *J* = 2.5 Hz, 1H), 6.99 (d, *J* = 2.6 Hz, 1H), 5.24 (d, *J* = 54.0 Hz, 1H), 4.64 (d, *J* = 1.2 Hz, 1H), 4.23 (dd, *J* = 35.0, 12.5 Hz, 2H), 3.98 (t, *J* = 10.8 Hz, 1H), 3.87 (dd, *J* = 13.2, 7.5 Hz, 3H), 3.46 – 3.40 (m, 2H), 3.32 – 3.25 (1H), 3.05 (s, 2H), 2.93 (dd, *J* = 14.7, 7.9 Hz, 4H), 2.80 (q, *J* = 8.6 Hz, 1H), 2.45 – 2.36 (m, 1H), 2.05 (s, 1H), 1.98 (d, *J* = 4.5 Hz, 1H), 1.92 (d, *J* = 5.7 Hz, 1H), 1.82 (s, 1H), 1.73 (dd, *J* = 12.3, 8.4 Hz, 2H), 1.59 (d, *J* = 5.6 Hz, 2H), 1.45 (q, *J* = 8.0, 5.6 Hz, 2H).

¹⁹F NMR (377 MHz, DMSO-*d*₆) δ -110.33, -172.13 (d, *J* = 4.3 Hz).

15 **Example 46:** KRAS inhibitory activity of compounds

Cell-free assays were performed according to the methods described below in order to determine the ability of compounds to bind KRAS G12D and WT KRAS. Results are shown in Table 3 below.

KRAS WT/G12D Binding Assays (Surface Plasmon Resonance (SPR)) (cell free)

Biacore T200 and S200 (Cytiva) instruments were used to screen the compounds for binding to KRAS WT and G12D proteins. KRAS (WT or G12D) was captured via the Avi tag on a Xantec BD chip after mixing with Switchavidin. To minimise mass transport of the compound/protein interaction capture level was kept between 2000-5000 RU. Compounds were screened initially at 50 μM using a flow rate 60 μL/min. Association was measured for 60 s and dissociation for 60-300 s depending on the off-rate of each compound. Each compound was screened at 6-8 concentrations in a 3-fold dilution concentration series at 10 °C. The top concentration was adjusted according to binding affinity in the initial experiment to 1-10 μM for repeat experiments. Running buffer contained 50 mM HEPES (pH 7.5), 150 mM NaCl, 5 mM MgCl₂, 5 μM GDP, 1 mM TCEP, 0.05% Tween 20, 3% DMSO. Data were analysed using Scrubber 2 (BioLogic software, Australia). All sensorgrams were corrected using DMSO calibration and double referenced for blank injection of buffer and reference surface. Data were fitted to a 1:1 binding model including mass transport coefficient.

Table 3: Results of KRAS WT/G12D SPR binding assay

Compound No.	KRAS G12Dhu SPR K _D (nM)	KRAS WT SPR K _D (nM)	Ratio WT K _D /G12D SPR K _D
(16)	53000	>1000000	>18868
(17)	320000	>1000000	>3125
(13)*	4358	>1000000	>229
(30)*	286	41830	146
(29)	7050	723400	103
(38)*	520	40391	77.7
(27)	563	40000	71.0
(57)	3.2	88	27.2
(19)*	9.6	244	25.5
(55)*	1.8	43.7	24.4
(41)	2.4	47.7	20.0
(28)	304	5853	19.2
(44)	49.3	836.3	17.0
(12)*	380	5761	15.1
(43)	6.7	101	15.1
(11)*	119	1750	14.7
(56)	394	4420	11.2
(8)*	1735	18390	10.6
(35)*	51.4	494	9.6
(3)*	545	4994	9.2
(39)	277	2457	8.9
(51)	77.9	673	8.6
(20)	3245	26804	8.3
(18)	883	7097	8.0
(5)*	11510	79983	6.9
(40)*	154	990	6.4
(14)*	444	2823	6.4
(21)	4170	26400	6.3

Compound No.	KRAS G12Dhu SPR K _D (nM)	KRAS WT SPR K _D (nM)	Ratio WT K _D /G12D SPR K _D
(31)	482	2676	5.6
(54)	3448	15982	4.6
(46)	165	681	4.1
(15)	4789	19600	4.1
(22)	3128	12781	4.1
(48)	149	519	3.5
(24)	19070	56200	2.9
(47)	180	499	2.8
(2)*	912	2499	2.7
(49)	308	787	2.6
(9)*	55000	118333	2.2
(7)*	21100	39700	1.9
(10)*	1248	1673	1.3
(119a)**	610	710	1.2
(50)	238	261	1.1
(133)*	590	590	1.0
(52)	517	526	1.0
(42)	4549	4540	1.0
(6)*	16268	16128	1.0
(134)*	600	520	0.9
(45)	574	482	0.8
(73)†	8570	6977	0.8
(87)‡	7041	5138	0.7
(53)	217	138	0.6
(89)*	1823	1095	0.6
(137)**	1270	690	0.5
(138)**	1220	610	0.5
(93a)**	11773	3800	0.3
(111)§	12134	3632	0.3
(135)**	3000	640	0.2
(142)**	850	180	0.2

Compound No.	KRAS G12Dhu SPR K _D (nM)	KRAS WT SPR K _D (nM)	Ratio WT K _D /G12D SPR K _D
(132)**	640	110	0.2
(93a)**	36380	5174	0.1
(126)*	930	100	0.1
(142)**	1700	240	0.1
(88)**	276402	26240	<0.1
(90)*	155400	11869	<0.1

* denotes that compounds in Table 3 were prepared in accordance with the synthetic routes exemplified for such compounds herein. Other compounds in Table 3 were prepared analogously.

** denotes isolated diastereomer of unknown absolute configuration

5 † denotes mixture of stereoisomers (73a) and (73b)

‡ denotes mixture of stereoisomers (87a) and (87b)

§ denotes mixture of stereoisomers (111a) and (111b)

10 The data in Table 3 demonstrate that compounds of the present disclosure are active in the micromolar to nanomolar concentration range in cell-free systems, and that compounds according to the present disclosure may also bind KRAS G12D preferentially to wild-type KRAS.

Example 47: Binding assay for GDP-bound KRAS G12D (cell-free)

15 Cell-free assays were performed in order to determine the ability of compounds to bind GDP-bound KRAS G12D and WT KRAS.

Assay buffer was prepared having the following composition:

Component	Concentration	Volume (μL)
HEPES, pH 7.5	40 mM	560
MgCl ₂	10 mM	140
DTT	1 mM	14
CHAPS	0.05%	233
BSA	0.1%	187
Distilled water		12866
		Total: 14000

Probe solution was prepared using 8 nM of biotinylated probe in 3000 μL of assay buffer.

Enzyme solution was prepared using 16 nM of KRAS G12D TG275-2 in assay buffer to give a total solution volume of 2500 μL. TG275-2 is a KRAS truncated DNA construct corresponding to amino acid residues 1-169. The DNA template used for construct cloning carried the G12D mutation. KRAS proteins were expressed in *E.coli* with polyhistidine tag and purified by nickel affinity chromatography and size exclusion. Proteins were delivered in GDP bound state as present naturally in *E.coli*.

10 Detection solution was prepared by adding 1 nM streptavidin-XL665 (Cisbio catalogue no. 610SAXLB) and 0.06 ng/μL Anti-His-Tb antibody (Cisbio catalogue no. 61HISTLA) to assay buffer to give a total solution volume of 5000 μL.

15 Samples of each compound dissolved in assay buffer (with addition of DMSO for improved solubilisation) were loaded onto a Corning® Echo-qualified microplate (product number 4514) at a volume of 200 nL per well at concentrations of up to about 10 μM. 5 μL of enzyme solution and 5 μL of probe solution were added per well and incubated for 10 minutes at 25 °C. 10 μL of detection solution were then added per well and incubated for 60 minutes at 25 °C. TR-FRET signals were then read on PheraStar, reading the fluorescence emission at two different wavelengths (665 nm and 615 nm).

20 The background TR-FRET signal was established by performing the procedure above but omitting the enzyme solution.

Data was analysed using XLfit model 205. Inhibition was calculated by subtracting the background TR-FRET signal from the TR-FRET signal obtained when the enzyme solution was also present.

Results are shown in Table 4 below.

Table 4: GDP-bound KRAS G12D binding assay

Compound	KRAS G12D-GDP (IC ₅₀ ; nM)
(115a)*	0.47
(132)*	0.73
(133)	0.66
(119a)*	0.3
(134)	0.37
(135)*	1.38
(89)	0.39
(119a)*	0.32
(136)	0.74
(93a)*	0.64
(137)*	0.41
(138)*	0.73
(139)**	1.17
(140)*	1.44

* denotes isolated diastereomer of unknown absolute configuration

** denotes mixture of stereoisomers (139a) and (139b)

5

Example 48: Inhibition of KRas-mutant mediated Phosphorylation of ERK

This Example illustrates that exemplary compounds disclosed herein inhibit the phosphorylation of ERK downstream of KRAS mutant cell lines.

10 The amount of phospho-ERK was determined using the advanced phospho-ERK1/2 (T202/Y204) (Cisbio catalogue # 64AERPEH, 10000 tests) kit. Advanced phospho-ERK1/2 (Thr202/Tyr204) is detected in a sandwich assay format using 2 different specific antibodies, one labelled with Eu³⁺-Cryptate (donor, 620nm) and the second with d₂ (acceptor, 665nm).

The cell information is shown in the following table, Table 5.

Table 5: cell information for phospho-ERK assays

Cell Line Name	Mutation	Medium	Cell density (cells/well)	Assay plate	Vendor	Cat No.
SW-1417	KRAS WT	RPMI-1640 + 15% FBS	25000	96w	ATCC	CCL-238
NCI-H2009	KRAS G12A	HITES medium + 5% FBS	8000	384w	ATCC	CRL-5911
Calu-1	KRAS G12C	McCoy's 5A medium + 10% FBS	8000	384w	ATCC	HTB-54
Panc10.05	KRAS G12D	RPMI-1640 + 15% FBS + 10 Units/mL human recombinant insulin.	25000	96w	ATCC	CRL-2547
NCI-H441	KRAS G12V	RPMI-1640 + 10%FBS	8000	384w	ATCC	HTB-174
Hs766T	KRAS Q61H	DMEM + 10%FBS	8000	384w	ATCC	HTB-134
LoVo	KRAS G13D	Ham's F12K (Kaighn's) medium + 10%FBS	8000	384w	ATCC	CCL-229

Cells were plated in tissue culture treated plates at specific density and allowed to attach for 20-24h.

- 5 Diluted compounds were then added in a final concentration of 0.5% DMSO. After 3 hours, the medium was removed, 50 µl of 1x supplemented lysis buffer were added and incubated for 30 minutes at room temperature under shaking.

After the lysis step, 16µl of cell lysate was transferred from the 96 well cell culture plate to a HTRF low volume white plate. 4µl of a premixed antibody solution was added (Vol/Vol, e.g. 12.5µl

- 10 Advanced Phospho-ERK ½ d₂ antibody + 12.5µl Advanced Phospho-ERK1/2 Eu³⁺ Cryptate antibody + 475µl detection buffer). The plate was covered with a plate sealer and incubated overnight at room temperature. The plates were read on PheraStar, reading the fluorescence emission at two different wavelengths (665nm and 620nm).

The phospho-ERK signals were calculated by the ratio of 665 and 620 nm emissions (665nm_{Em}X10000/620nm_{Em}). IC50 values were generated using a 4-parameter fit of the dose response curve.

Results are shown in Table 6.

Table 6: mutant KRAS profiling

Compound	pERK (IC50; nM)						
	Wildtype	G12A	G12C	G12D	G12V	Q61H	G13D
		NCI-			NCI-		
	SW-1417	H2009	Calu-1	Panc10.05	H441	Hs766T	LoVo
(115a)*	>10000	2.97	2.74	4.17	8.55	18.93	22.58
(132)*	>10000	0.62	0.22	1.81	2.09	3.43	0.73
(133)	>10000	1.32	0.82	6.62	8.01	14.89	2.33
(119a)*	>10000	40.96	17.58	26.88	301.68	171.87	18.41
(134)	>10000	2.89	1.93	10.58	5.27	11.59	1.63
(135)*	>10000	39.8	14.13	112.42	82.48	181.8	40.24
(89)	>10000	31.05	15.8	39.29	138.77	191.4	23.03
(119a)*	>10000	1.17	0.98	4.12	8.62	8.75	1.51
(136)	>10000	3.69	2.38	20.53	38.51	24.35	5.18
(93a)*	>10000	17.26	5.75	26.88	48.06	89.26	22.21
(137)*	>10000	4.35	2.75	35.39	83.84	10.87	1.94
(138)*	>10000	14.79	4.31	35.29	72.58	39.08	9.29
(139)**	>10000	7.79	2.5	44.61	34.69	33.61	3.58
(140)*	>10000	14.08	9.89	84.95	129.49	71.82	16.17

* denotes isolated diastereomer of unknown absolute configuration

** denotes mixture of stereoisomers (139a) and (139b)

* * * * *

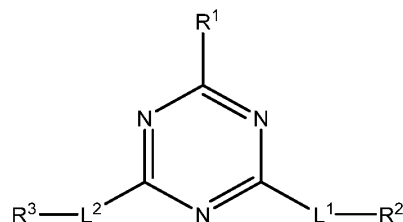
It is to be understood that while the disclosure has been described in conjunction with the above
embodiments, that the foregoing description and examples are intended to illustrate and not limit the
scope of the disclosure. Other aspects, advantages, and modifications within the scope of the disclosure
will be apparent to those skilled in the art to which the disclosure pertains.

In addition, where features or aspects are described in terms of Markush groups, those skilled in the art will recognize that such features or aspects are also thereby described in terms of any individual member or subgroup of members of the Markush group.

- 5 All publications, patent applications, patents, and other references mentioned herein are expressly incorporated by reference in their entirety, to the same extent as if each were incorporated by reference individually. In case of conflict, the present specification, including definitions, will control.

CLAIMS:

1. A compound of Formula (0):

**(Formula (0))**

- 5 or a pharmaceutically acceptable salt thereof, wherein:

- R^1 is a 6- to 10-membered, monocyclic or bicyclic heterocycloalkyl or heterocycloalkenyl group comprising at least one ring atom which is N, and wherein R^1 is optionally substituted by one or more groups independently selected from =O, CN, Cl, F, R^* , OH, OR^* , NH_2 , NHR^* , NR^{*2} , CHO, C(O)OH, C(O)NH₂, C(O)ONH₂, C(O) R^* , C(O) OR^* , OC(O) R^* , C(O) NHR^* , CH₂C(O) NHR^* , C(O) NR^{*2} , CH₂C(O) NR^{*2} , C(O)ON HR^* , CH₂C(O)ON HR^* , C(O)ON R^{*2} and CH₂C(O)ON R^{*2} ; or wherein R^1 is -L³- $R^{1'}$, wherein $R^{1'}$ is a 5-membered, monocyclic heterocycloalkyl or heterocycloalkenyl group comprising at least one ring atom which is N, and wherein $R^{1'}$ is optionally substituted by one or more groups independently selected from =O, CN, Cl, F, R^* , OH, OR^* , NH_2 , NHR^* , NR^{*2} , CHO, C(O)OH, C(O)NH₂, C(O)ONH₂, C(O) R^* , C(O) OR^* , C(O) NHR^* , C(O) NR^{*2} , C(O)ON HR^* , and C(O)ON R^{*2} ;
- 10 R^2 is a 5- to 9-membered, monocyclic or bicyclic heterocycloalkyl or heterocycloalkenyl group comprising at least one ring atom which is N or O; a 5- or 6-membered monocyclic heteroaryl group comprising at least one ring atom which is N; a fused, 8- to 10-membered bicyclic group wherein one or both rings are aromatic, and wherein at least one ring comprises at least one ring atom which is N; or a fused, 11- to 14-membered tricyclic group wherein at least one ring is aromatic, and wherein at least one ring comprises at least one ring atom which is N;
- 20 and wherein R^2 may be substituted by one or more groups independently selected from CN, Cl, F, R^* , OH, OR^* , NH_2 , NHR^* , NR^{*2} , CHO, C(O) R^* , C(O)OH, C(O) OR^* , C(O)NH₂, C(O) NHR^* , C(O) NR^{*2} , C(O)ONH₂, C(O)ON HR^* , C(O)ON R^{*2} , =O, (C₂-C₃)alkenyl, and (C₂-C₃)alkynyl;

- R^3 is a phenyl or naphthalenyl group which is substituted by OH and optionally by one or more additional groups independently selected from CN, Cl, F, R^* , OH, OR^* , NH_2 , NHR^* , NR^{*2} , CHO, C(O) R^* , C(O)OH, C(O) OR^* , C(O)NH₂, C(O) NHR^* , C(O) NR^{*2} , C(O)ONH₂, C(O)ON HR^* , C(O)ON R^{*2} , (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl; or R^3 is a fused, 8-to-10-membered bicyclic group comprising a saturated carbocyclic ring fused to a heterocyclic ring, wherein the carbocyclic ring, the
- 25

heterocyclic ring, or both, may optionally be substituted by one or more groups independently selected from CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)R*, C(O)OH, C(O)OR*, C(O)NH₂, C(O)NHR*, C(O)NR*₂, C(O)ONH₂, C(O)ONHR*, C(O)ONR*₂, NHC(O)R*, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl; or R³ is a fused, 8- to 10-membered bicyclic group comprising a saturated carbocyclic ring fused to an aryl ring, wherein the carbocyclic ring, the aryl ring, or both, may be optionally substituted by one or more groups independently selected from CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)R*, C(O)OH, C(O)OR*, C(O)NH₂, C(O)NHR*, C(O)NR*₂, C(O)ONH₂, C(O)ONHR*, C(O)ONR*₂, NHC(O)R*, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl; or R³ is a fused, 8- to 10-membered bicyclic group comprising a saturated heterocyclic ring fused to an aryl or heteroaryl ring, wherein the carbocyclic ring, the aryl or heteroaryl ring, or both, may be optionally substituted by one or more groups independently selected from CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)R*, C(O)OH, C(O)OR*, C(O)NH₂, C(O)NHR*, C(O)NR*₂, C(O)ONH₂, C(O)ONHR*, C(O)ONR*₂, NHC(O)R*, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl;

L¹ is a bond or is -O-, -(C₁-C₃)alkyl-, *-O-(C₁-C₃)alkyl-**, *-(C₁-C₃)alkyl-O-**, *-C(O)NR'-**, or *-NR'C(O)-**, wherein R' is H, OH, CN, Cl, F, or (C₁-C₃)alkyl, and * denotes a point of attachment to the triazole moiety of the compound of Formula (0) and ** denotes a point of attachment to R²;

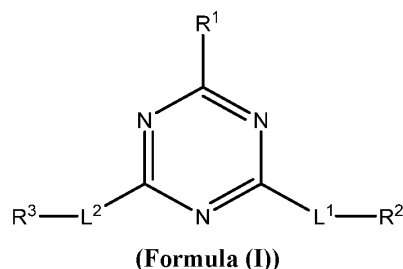
L² is -(C₁-C₃)alkyl-, C₅-heteroaryl optionally substituted with one or more R'', *-O-(C₁-C₃)alkyl-**, *-(C₁-C₃)alkyl-O-**, -(C₂-C₃)alkenyl-, -(C₂-C₃)alkynyl-, *-(C₁-C₃)alkyl-NR''-**, *-NR''(C₁-C₃)alkyl-**, *-C(O)NR''-**, *-NR''C(O)-**, *-NR''-(C₁-C₃)alkyl-**, or *-(C₁-C₃)alkyl-NR''-**, wherein R'' is H, OH, CN, Cl, F, or (C₁-C₃)alkyl, and wherein * denotes a point of attachment to R³ and ** denotes a point of attachment to the triazole moiety of the compound of Formula (0);

L³ is a bond or is -(C₁-C₃)alkyl-, -O-, -NH- or -N(C₁-C₃) alkyl;

and

wherein in R¹, R², and R³, each R* is independently selected from (C₁-C₄)alkyl, (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkenyl, and 5- or 6-membered monocyclic heteroaryl, wherein said (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkenyl or 5- or 6-membered monocyclic heteroaryl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, NH₂, NH((C₁-C₃)alkyl), (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or O(C₁-C₃) alkyl.

2. The compound or pharmaceutically acceptable salt of claim 1, wherein the compound is a compound of Formula (I):



wherein in Formula (I):

5 R^1 is a 6- to 10-membered bridged bicyclic heterocycloalkyl or heterocycloalkenyl group comprising at least one ring atom which is N, and wherein R^1 is optionally substituted by one or more groups independently selected from =O, CN, Cl, F, R^* , OH, OR^* , NH_2 , NHR^* , NR^{*2} , CHO, C(O)OH, C(O)NH₂, C(O)ONH₂, C(O)R^{*}, C(O)OR^{*}, C(O)NHR^{*}, C(O)NR^{*2}, C(O)ONHR^{*}, and C(O)ONR^{*2};

10 R^2 is a 5- to 8-membered, monocyclic or bicyclic heterocycloalkyl or heterocycloalkenyl group comprising at least one ring atom which is N or O; a 5- or 6-membered monocyclic heteroaryl group comprising at least one ring atom which is N; or a fused, 8- to 10-membered bicyclic group wherein one or both rings are aromatic, and wherein at least one ring comprises at least one ring atom which is N;

15 and wherein R^2 may be substituted by one or more groups independently selected from CN, Cl, F, R^* , OH, OR^* , NH_2 , NHR^* , NR^{*2} , CHO, C(O)R^{*}, C(O)OH, C(O)OR^{*}, C(O)NH₂, C(O)NHR^{*}, C(O)NR^{*2}, C(O)ONH₂, C(O)ONHR^{*}, C(O)ONR^{*2}, =O, (C₂-C₃)alkenyl, and (C₂-C₃)alkynyl;

20 R^3 is a phenyl or naphthalenyl group which is substituted by OH and optionally by one or more additional groups independently selected from CN, Cl, F, R^* , OH, OR^* , NH_2 , NHR^* , NR^{*2} , CHO, C(O)R^{*}, C(O)OH, C(O)OR^{*}, C(O)NH₂, C(O)NHR^{*}, C(O)NR^{*2}, C(O)ONH₂, C(O)ONHR^{*}, C(O)ONR^{*2}, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl; or R^3 is a fused, 8-to-10-membered bicyclic group comprising a saturated carbocyclic ring fused to a heterocyclic ring, wherein the carbocyclic ring, the heterocyclic ring, or both, may optionally be substituted by one or more groups independently selected from CN, Cl, F, R^* , OH, OR^* , NH_2 , NHR^* , NR^{*2} , CHO, C(O)R^{*}, C(O)OH, C(O)OR^{*}, C(O)NH₂, C(O)NHR^{*}, C(O)NR^{*2}, C(O)ONH₂, C(O)ONHR^{*}, C(O)ONR^{*2}, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl;

25 L^1 is -O-, -(C₁-C₃)alkyl-, *-O-(C₁-C₃)alkyl-**, *-(C₁-C₃)alkyl-O-**, *-C(O)NR[']**, or *-NR[']C(O)-**, wherein $R^{'}$ is H, OH, CN, Cl, F, or (C₁-C₃)alkyl, and * denotes a point of attachment to the triazole moiety of the compound of Formula (I) and ** denotes a point of attachment to R^2 ;

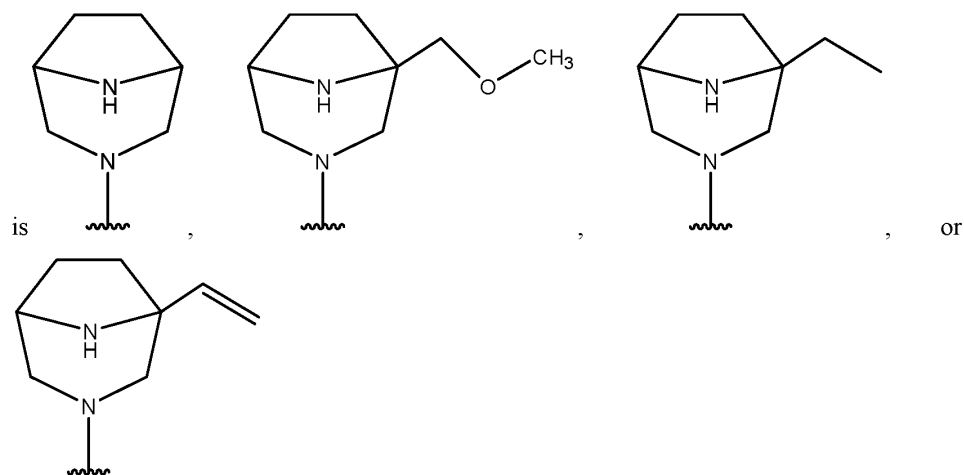
L^2 is -(C₁-C₃)alkyl-, C₅-heteroaryl optionally substituted with one or more $R^{''}$, *-O-(C₁-C₃)alkyl-**, *-(C₁-C₃)alkyl-O-**, -(C₂-C₃)alkenyl-, -(C₂-C₃)alkynyl-, *-(C₁-C₃)alkyl-NR^{''}**, *-NR^{''}(C₁-

C_3 alkyl-**, $^*-C(O)NR^{''}-**$, $^*-NR^{''}C(O)-**$, $^*-NR^{''}-(C_1-C_3)alkyl-**$, or $^*-(C_1-C_3)alkyl-NR^{''}-**$, wherein $R^{''}$ is H, OH, CN, Cl, F, or $(C_1-C_3)alkyl$, and wherein $*$ denotes a point of attachment to R^3 and $**$ denotes a point of attachment to the triazole moiety of the compound of Formula (I);

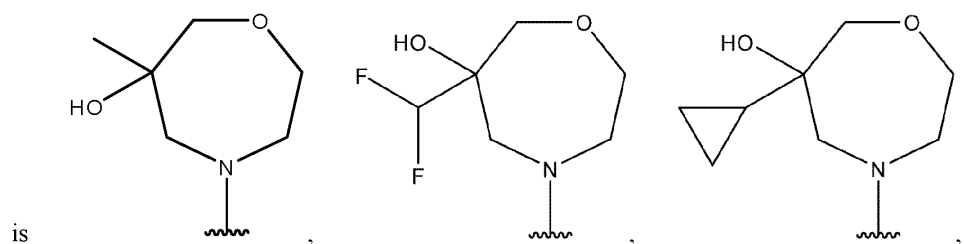
and

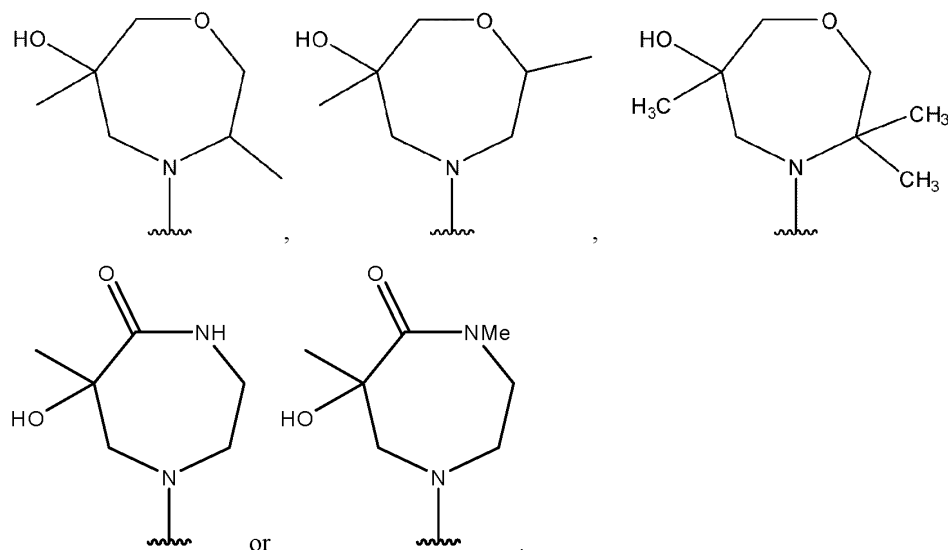
- 5 wherein in R^1 , R^2 , and R^3 , each R^* is independently selected from $(C_1-C_3)alkyl$, $(C_2-C_3)alkenyl$, $(C_3-C_6)cycloalkyl$, and $(C_3-C_6)cycloalkenyl$, wherein said $(C_1-C_3)alkyl$, $(C_2-C_3)alkenyl$, $(C_3-C_6)cycloalkyl$, or $(C_3-C_6)cycloalkenyl$ may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, NH_2 , $NH((C_1-C_3)alkyl)$, $(C_1-C_3)alkyl$, $(C_2-C_3)alkenyl$, $(C_2-C_3)alkynyl$, or $O(C_1-C_3)alkyl$.

- 10 3. The compound or pharmaceutically acceptable salt thereof of claim 1 or claim 2, wherein R^1

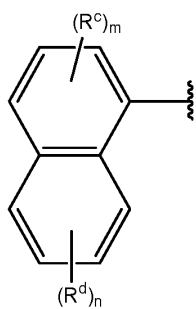


4. The compound or pharmaceutically acceptable salt thereof of claim 1 or claim 2, wherein R^1

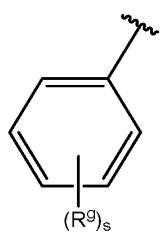




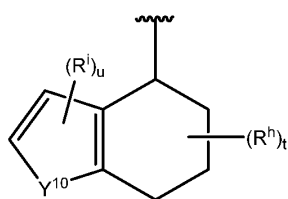
5. The compound or pharmaceutically acceptable salt thereof of any one of claims 1 to 4, wherein R^3 is selected from



- 5 wherein m is 1 or 2 and n is 0, 1, or 2; and each R^c and R^d is independently selected from F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, and (C₂-C₃)alkynyl, provided that at least one R^c is OH;

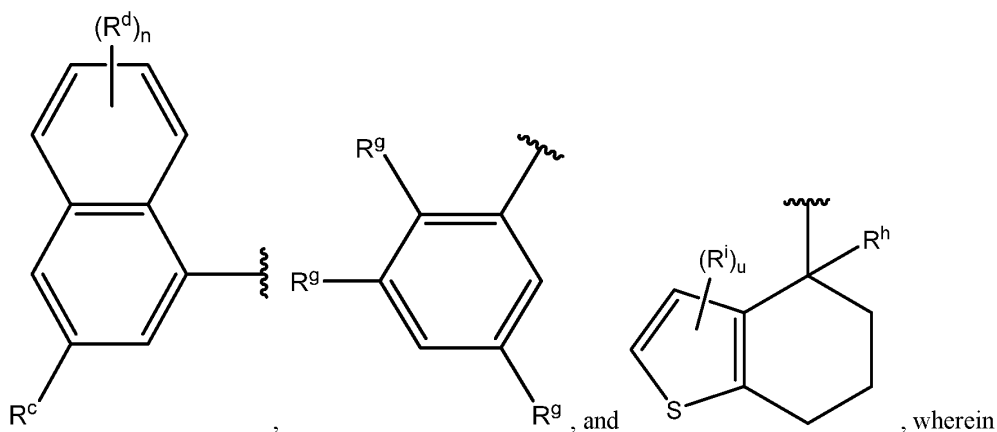


- 10 , wherein s is 1, 2, or 3, and wherein when s is 1 R^g is OH, and when s is 2 or 3, at least one R^g is OH and each remaining R^g is independently F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or (C₃-C₆)cycloalkyl, wherein said (C₃-C₆)cycloalkyl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl; and



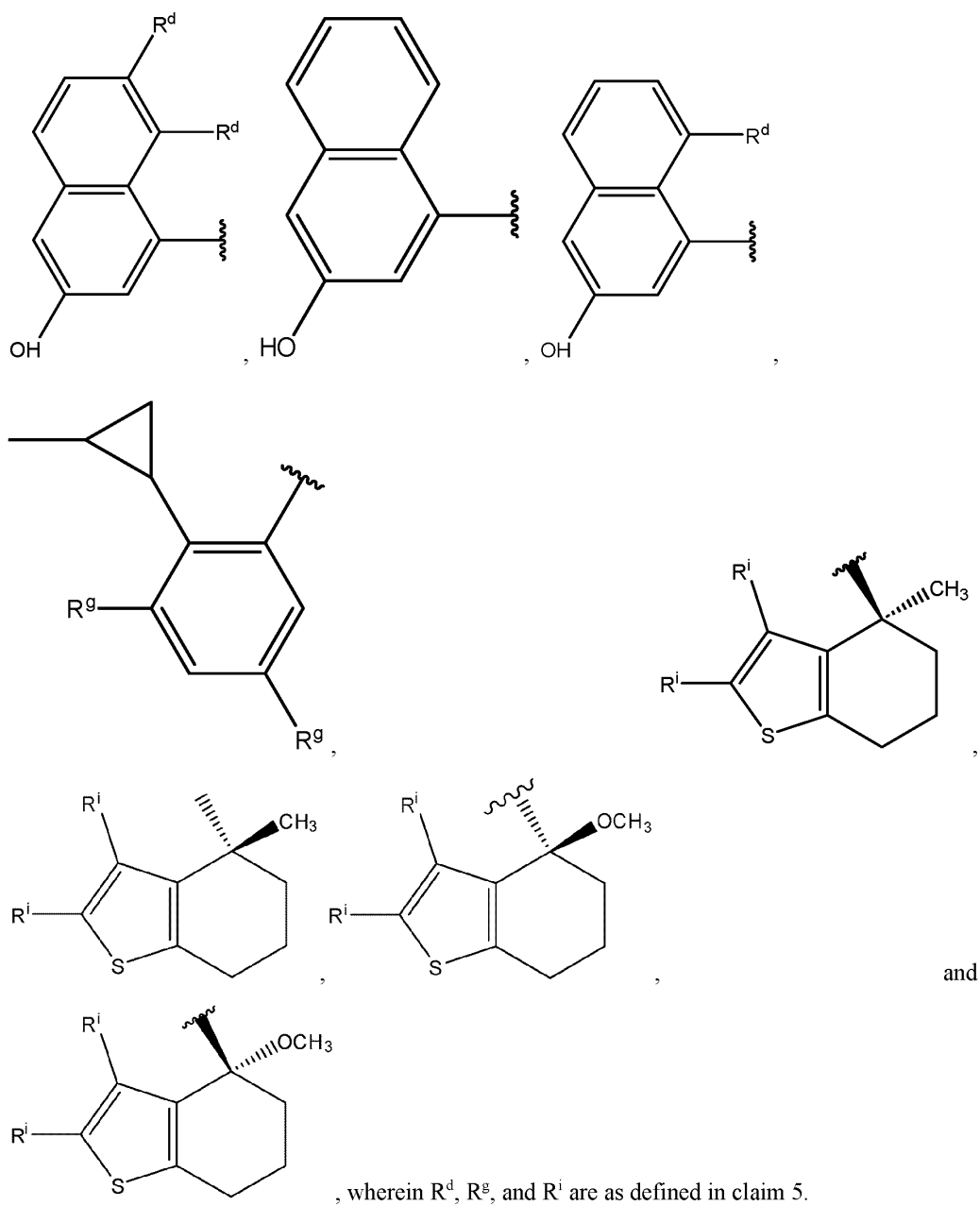
- , wherein Y^{10} is S, O, or $NR^{'''}$ wherein $R^{'''}$ is H, OH, CN, Cl, F, or (C_1-C_3) alkyl; t is 0, 1, 2, or 3 and u is 0, 1, or 2, with the proviso that when t is zero, u is nonzero, and that when u is zero, t is nonzero; and each R^h and R^i is independently selected from CN, Cl, F, R^* , OH, OR^* , NH_2 , NHR^* , NR^{*2} , CHO, $C(O)R^*$, $C(O)OH$, $C(O)OR^*$, $C(O)NH_2$, $C(O)NHR^*$, $C(O)NR^{*2}$, $C(O)ONH_2$, $C(O)ONHR^*$, $C(O)ONR^{*2}$, (C_2-C_3) alkenyl, and (C_2-C_3) alkynyl, wherein R^* is as defined in claim 1 or claim 2.

6. The compound or pharmaceutically acceptable salt thereof of any of claims 1 to 5, wherein R^3 is selected from:



- 10 R^c , R^d , R^g , R^h , R^i , n , and u are as defined in claim 5.

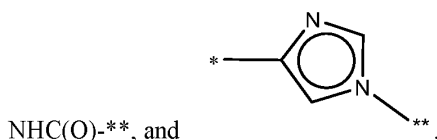
7. The compound or pharmaceutically acceptable salt thereof of any of claims 1 to 6, wherein R^3 is selected from:



5

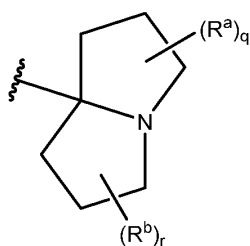
8. The compound or pharmaceutically acceptable salt thereof of any of claims 1 to 7, wherein L^2 is selected from:

-CH₂CH₂-, -C≡C-, *-CH₂O-**, *-OCH₂-**, *-C(O)-NH-**, *-CH₂NH-**, *-N(CH₃)C(O)-**, *-

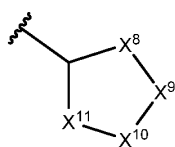


and wherein * and ** are as defined in claim 1 or claim 2.

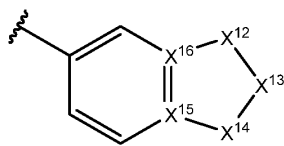
9. The compound or pharmaceutically acceptable salt thereof of any of claims 1 to 8, wherein R² is selected from:



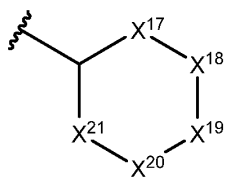
- , wherein q and r are each independently 0, 1, or 2, and each instance of R^a and R^b is independently selected from CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)R*, C(O)OH, C(O)OR*, C(O)NH₂, C(O)NHR*, C(O)NR*₂, C(O)ONH₂, C(O)ONHR*, C(O)ONR*₂, =O, (C₂-C₃)alkenyl, and (C₂-C₃)alkynyl, wherein R* is as defined in claim 1 or claim 2;



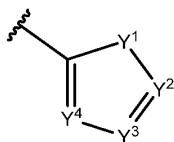
- , wherein X⁸, X⁹, X¹⁰, and X¹¹ are each independently selected from C(R^k)₂, C=O, N(R^k), O, or S, provided that at least one of X⁸, X⁹, X¹⁰, and X¹¹ is N(R^k);



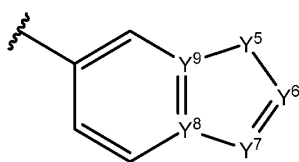
- , wherein X¹², X¹³, and X¹⁴ are each independently selected from C(R^k)₂, C=O, N(R^k), O, or S and X¹⁵ and X¹⁶ are each independently selected from C and N, provided that at least one of X¹², X¹³, and X¹⁴ is N(R^k) and/or at least one of X¹⁵ and X¹⁶ is N;



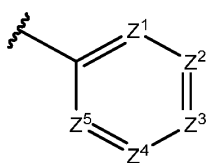
, wherein X^{17} , X^{18} , X^{19} , X^{20} , and X^{21} are each independently selected from $C(R^k)_2$, $C=O$, $N(R^k)$, O , or S , provided that at least one of X^{17} , X^{18} , X^{19} , X^{20} , and X^{21} is $N(R^k)$, O , or S ;



5 that at least one of Y^1 , Y^2 , Y^3 , and Y^4 is N or NR^k ;



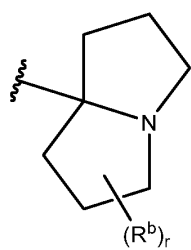
, wherein Y^5 , Y^6 , and Y^7 are each independently N , O , S , NR^k , or CR^k , and Y^8 and Y^9 are each independently N or C , provided that at least one of Y^5 , Y^6 , and Y^7 is N or NR^k and/or at least one of Y^8 and Y^9 is N ;



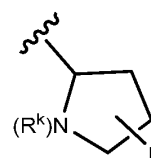
10 and provided that at least one of Z^1 , Z^2 , Z^3 , Z^4 , and Z^5 is N ;

wherein each R^k is independently selected from H , CN , Cl , F , R^* , OH , OR^* , NH_2 , NHR^* , NR^{*2} , CHO , $C(O)R^*$, $C(O)OH$, $C(O)OR^*$, $C(O)NH_2$, $C(O)NHR^*$, $C(O)NR^{*2}$, $C(O)ONH_2$, $C(O)ONHR^*$, $C(O)ONR^{*2}$, $(C_2-C_3)alkenyl$, and $(C_2-C_3)alkynyl$, and wherein R^* is as defined in claim 1 or claim 2.

15 10. The compound or pharmaceutically acceptable salt thereof of any of claims 1 to 9, wherein R^2 is selected from:

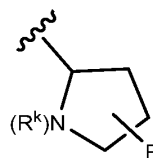


wherein R^b and r are as defined in claim 9,

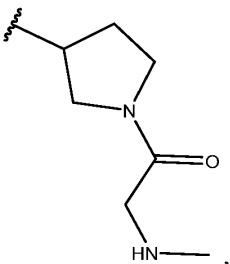
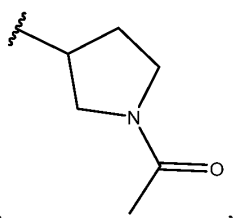
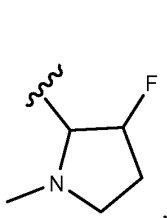
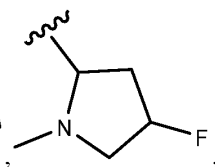
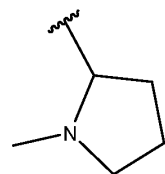


wherein R^k is as

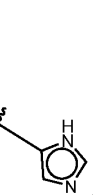
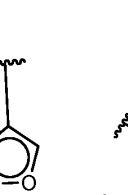
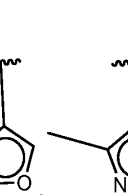
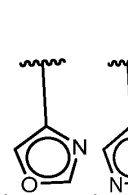
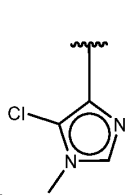
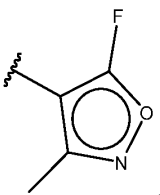
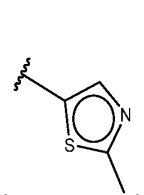
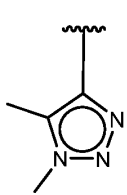
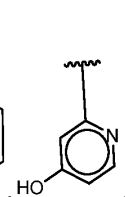
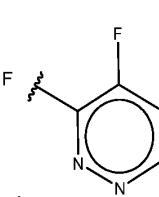
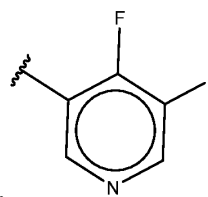
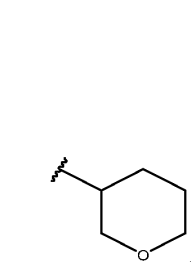
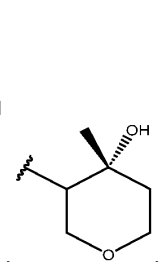
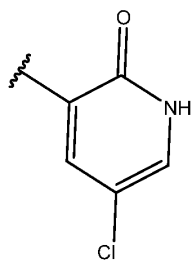
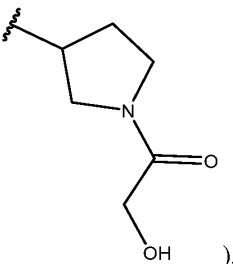
defined in claim 9 (e.g. wherein

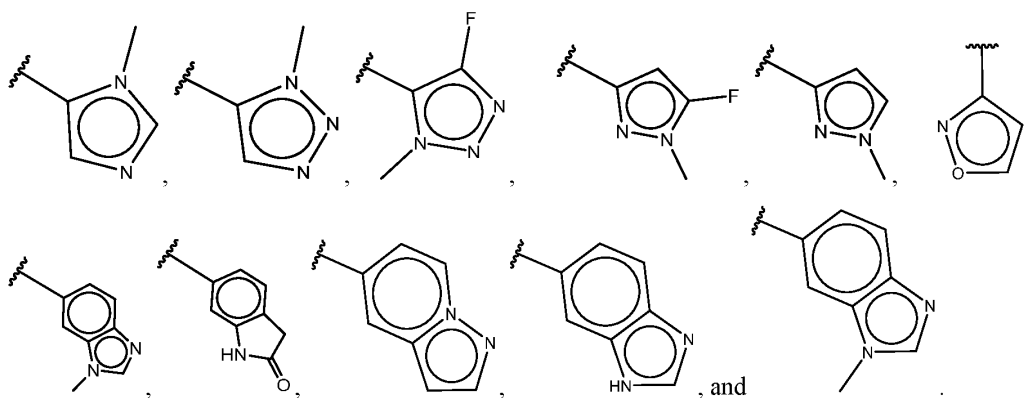


is

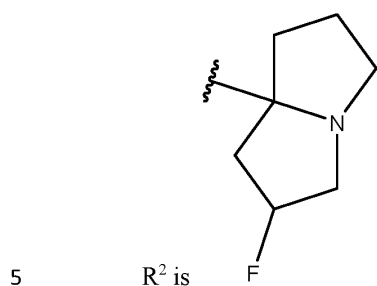


or

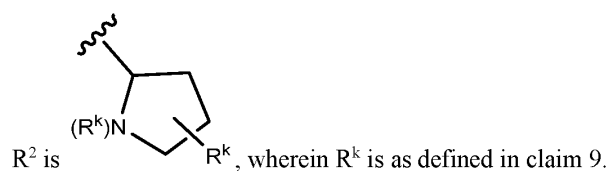




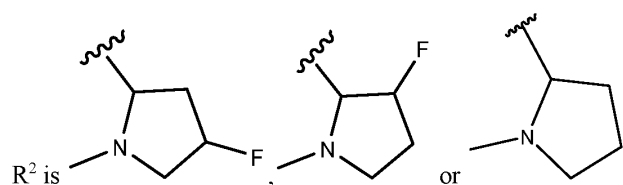
11. The compound or pharmaceutically acceptable salt thereof of any of claims 1 to 10, wherein



12. The compound or pharmaceutically acceptable salt thereof of any of claims 1 to 10, wherein

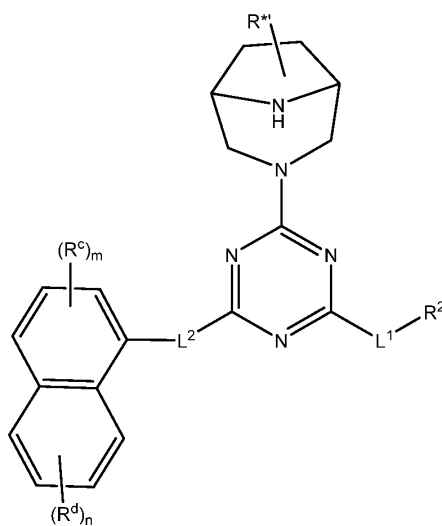


10 13. The compound or pharmaceutically acceptable salt thereof of any of claims 1 to 10, wherein

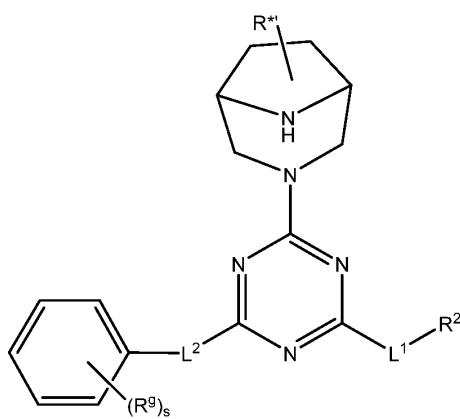


14. The compound or pharmaceutically acceptable salt of any of claims 1 to 13, wherein L^1 is -O-
 , *-OCH(CH₃)-*, or *-O-CH₂-*.

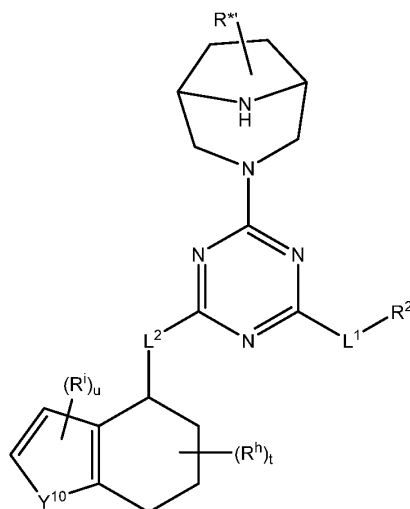
15. The compound or pharmaceutically acceptable salt thereof of claim 1 or claim 2, wherein the compound is a compound of Formula (III), Formula (IV), Formula (XXII) or Formula (XXII.I):



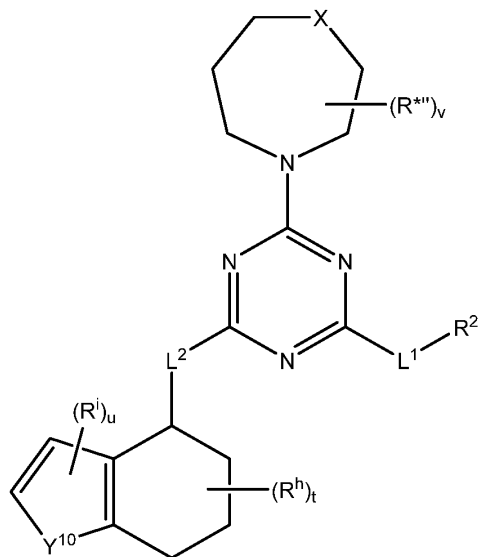
(Formula (III))



(Formula (IV))



(Formula (XXII));



(Formula (XXII.I))

5 wherein

in each of Formula (III), Formula (IV), Formula (XXII), L^1 is as defined in claim 1, claim 2, or claim 14; L^2 is as defined in claim 1, claim 2, or claim 8; R^{*1} is selected from H, CN, Cl, F, R^* , OR^* , NR^{*2} , CHO, $C(O)R^*$, $C(O)OR^*$, $C(O)NR^{*2}$, and $C(O)ONR^{*2}$, wherein R^* is as defined in claim 1 or claim 2; and R^2 is as defined in any of claims 9-13;

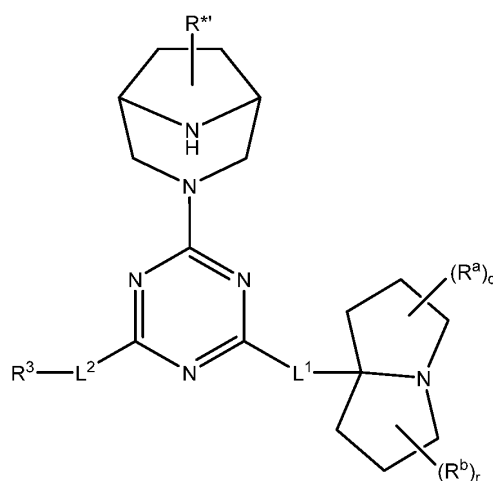
10 in Formula (III), R^c , R^d , n and m are as defined in claim 5;

in Formula (IV), R^g and s are as defined in claim 5; and

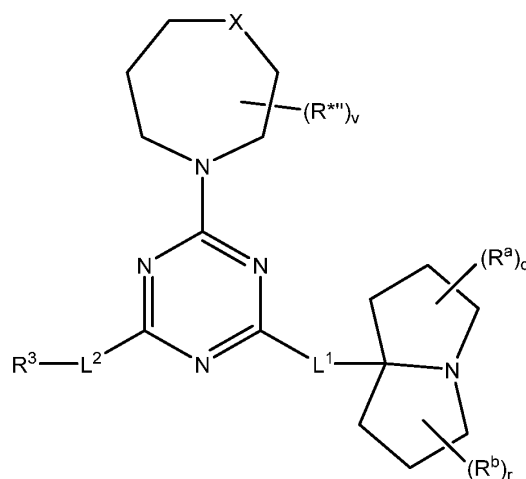
in Formula (XXII), R^h , R^i , t , u , and Y^{10} are as defined in claim 5; and

in Formula (XXII.I), L^1 is as defined in claim 1, claim 2, or claim 14; L^2 is as defined in claim 1, claim 2, or claim 8; R^2 is as defined in any of claims 9-13; R^h , R^i , t , u , and Y^{10} are as defined in claim 5; X is selected from NH , $N(C_{1-3}alkyl)$, O , or CH_2 ; v is an integer from 0 to 4; and each R^{*v} is independently selected from H , CN , Cl , F , R^* , OH , OR^* , NR^{*2} , CHO , $C(O)R^*$, $C(O)OR^*$, $C(O)NR^{*2}$, and $C(O)ONR^{*2}$, wherein R^* is as defined in claim 1 or claim 2.

16. The compound or pharmaceutically acceptable salt thereof of claim 1 or claim 2, wherein the compound is a compound of Formula (VI) or Formula (VI.I):



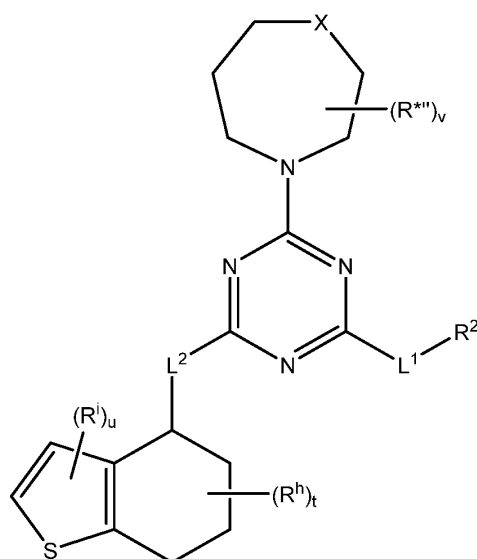
(Formula (VI))



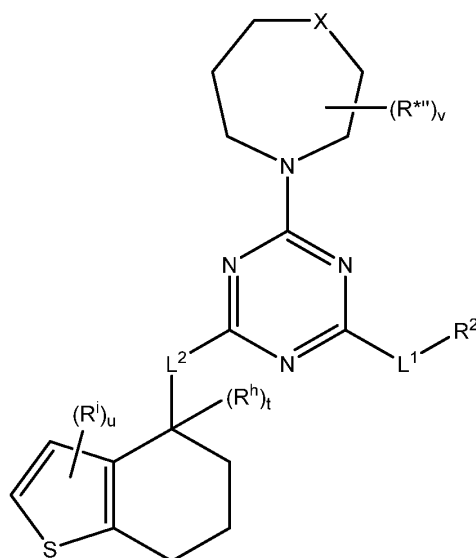
(Formula (VI.I))

wherein, in Formula (VI), L^1 is as defined in claim 1, claim 2, or claim 14; L^2 is as defined in claim 1, claim 2, or claim 8; $R^{*'} is selected from H, CN, Cl, F, R^*, OR^*, NR^{*}_2, CHO, C(O)R^*, C(O)OR^*, C(O)NR^{*}_2, and C(O)ONR^{*}_2, wherein R^* is as defined in claim 1 or claim 2; and R^3 is as defined in any of claims 5-7; and in Formula (VI.I), L^1 is as defined in claim 1, claim 2, or claim 10; L^2 is as defined in claim 1, claim 2, or claim 8; X is selected from NH, $N(C_{1-3})alkyl$, O, or CH_2 ; v is an integer from 0 to 4; each $R^{*''}$ is independently selected from H, CN, Cl, F, R^* , OH, OR^* , NR^{*}_2 , CHO, $C(O)R^*$, $C(O)OR^*$, $C(O)NR^{*}_2$, and $C(O)ONR^{*}_2$, wherein R^* is as defined in claim 1 or claim 2; and R^3 is as defined in any of claims 5-7.$

- 10 17. The compound or pharmaceutically acceptable salt of claim 1 or claim 2, wherein the compound is a compound of Formula (XXIII.I) or Formula (XXIV.I)



(Formula (XXIII.I))



(Formula XXIV.I)

wherein, in each of Formula (XXIII.I) and Formula (XXIV.I):

- 5 L^1 is as defined in claim 1, claim 2, or claim 14; L^2 is as defined in claim 1, claim 2, or claim 8; R^h , R^i , t , and u are as defined in claim 5; X is selected from NH, N(C₁₋₃)alkyl, O, or CH₂; v is an integer from 0 to 4; each R^{**} is independently selected from H, CN, Cl, F, R*, OH, OR*, NR*₂, CHO, C(O)R*, C(O)OR*, C(O)NR*₂, and C(O)ONR*₂, wherein R* is as defined in claim 1 or claim 2; and R^2 is as defined in any of claims 9-13.

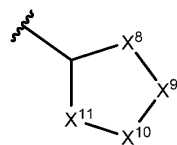
10

18. A compound of Formula (XXII) or Formula (XXII.I) as defined in claim 15 or a compound of Formula (XXIII.I) or Formula (XXIV.I) as defined in claim 17, or a pharmaceutically acceptable salt thereof, wherein R^2 is a 5- to 9-membered, monocyclic or bicyclic heterocycloalkyl or heterocycloalkenyl group comprising at least one ring atom which is N or O; a 5- or 6-membered monocyclic heteroaryl group comprising at least one ring atom which is N; a fused, 8- to 10-membered bicyclic group wherein one or both rings are aromatic, and wherein at least one ring comprises at least one ring atom which is N; and wherein R^2 may be substituted by one or more groups independently selected from CN, Cl, F, R*, OH, OR*, NH₂, NHR*, NR*₂, CHO, C(O)R*, C(O)OH, C(O)OR*, C(O)NH₂, C(O)NHR*, C(O)NR*₂, C(O)ONH₂, C(O)ONHR*, C(O)ONR*₂, =O, (C₂-C₃)alkenyl, and (C₂-C₃)alkynyl; and wherein each R* is independently selected from (C₁-C₄)alkyl (e.g. C₁-C₃)alkyl), (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkenyl, and 5- or 6-membered monocyclic heteroaryl,

20

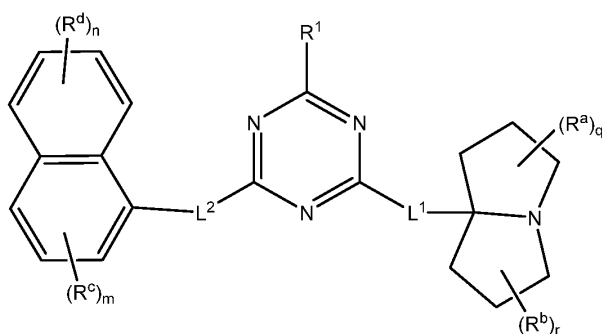
wherein said (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkenyl or 5- or 6-membered monocyclic heteroaryl may itself be substituted by one or more groups independently selected from F, Cl, CN, OH, NH₂, NH((C₁-C₃)alkyl), (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, or O(C₁-C₃) alkyl.

- 5 19. A compound or pharmaceutically acceptable salt thereof of claim 18, wherein R² is

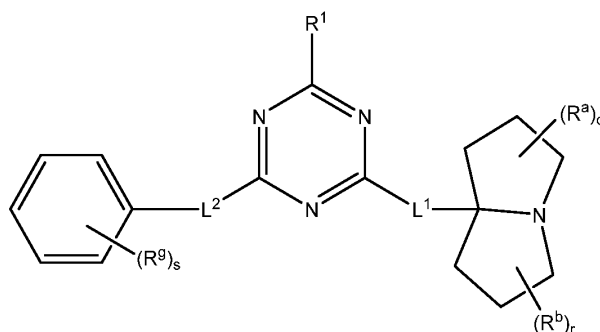


, wherein X⁸, X⁹, X¹⁰, and X¹¹ are as defined in claim 9.

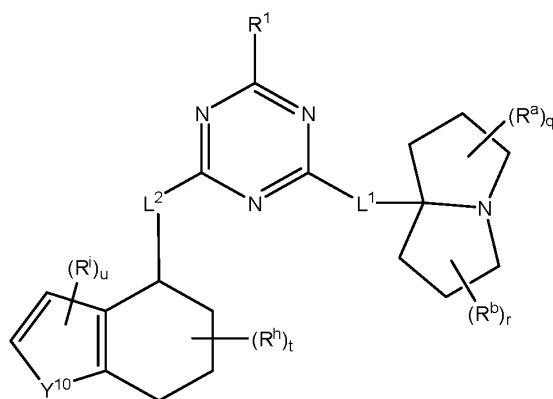
20. A compound or pharmaceutically acceptable salt thereof of claim 18 or claim 19, wherein R² is as defined in claim 12 or claim 13.
21. The compound or pharmaceutically acceptable salt of claim 1 or claim 2, wherein the
10 compound is a compound of Formula (VIII), Formula (X), or Formula (XXV):



Formula (VIII)



Formula (X)



(Formula (XXV),

wherein

- in each of Formula (VIII), Formula (X), and Formula (XXV), L^1 is as defined in claim 1, claim 2, or claim 14; L^2 is as defined in claim 1, claim 2, or claim 8; R^1 is as defined in claim 1, claim 2, or claim 3; and R^a , R^b , q , and r are as defined in claim 9;

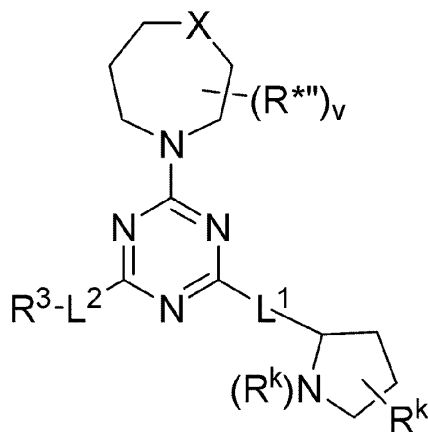
in Formula (VIII), R^c , R^d , n , and m are as defined in claim 5;

in Formula (X), R^g and s are as defined in claim 5; and

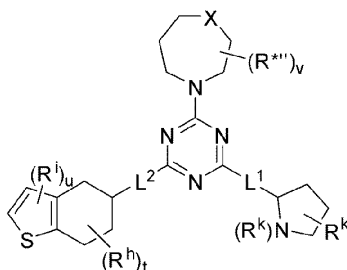
in Formula (XXV), R^h , R^i , t , u , and Y^{10} are as defined in claim 5.

10

22. The compound or pharmaceutically acceptable salt of claim 1 or claim 2, wherein the compound is a compound of Formula (XXVII) or Formula (XXVIII):



(Formula (XXVII))



(Formula (XXVIII))

5 wherein

in Formula (XXVII), L¹ is as defined in claim 1, claim 2, or claim 14; L² is as defined in claim 1, claim 2, or claim 8; R^k is as defined in claim 9; X is selected from NH, N(C₁₋₃)alkyl, O, or CH₂; v is an integer from 0 to 4; each R^{***} is independently selected from H, CN, Cl, F, R*, OH, OR*, NR*₂, CHO, C(O)R*, C(O)OR*, C(O)NR*₂, and C(O)ONR*₂, wherein R* is as defined in claim 1 or claim 2; and R³ is as defined in any of claims 5-7; and

in Formula (XXVIII), L¹ is as defined in claim 1, claim 2, or claim 14; L² is as defined in claim 1, claim 2, or claim 8; R^k is as defined in claim 9; X is selected from NH, N(C₁₋₃)alkyl, O, or CH₂; v is an integer from 0 to 4; each R^{***} is independently selected from H, CN, Cl, F, R*, OH, OR*, NR*₂, CHO, C(O)R*, C(O)OR*, C(O)NR*₂, and C(O)ONR*₂, wherein R* is as defined in claim 1 or claim 2; and wherein R^h, Rⁱ, t and u are as defined in claim 5.

23. A pharmaceutical composition comprising the compound of any one of claims 1-22 or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient or carrier.

24. A compound or pharmaceutically acceptable salt according to any one of claims 1-22, or a pharmaceutical composition according to claim 23, for use in therapy.

25 25. A compound or pharmaceutically acceptable salt according to any one of claims 1-22, or a pharmaceutical composition according to claim 23, for use in the treatment or prevention of cancer.

26. The compound or pharmaceutically acceptable salt thereof or pharmaceutical composition for
30 use according to claim 25, wherein the cancer is a KRAS G12D-associated cancer.

27. The compound or pharmaceutically acceptable salt thereof or pharmaceutical composition for use according to claim 25 or claim 26, wherein the cancer is selected from colorectal cancer, lung cancer, and pancreatic cancer.
- 5 28. A method of treatment comprising administering to a subject in need thereof a therapeutically effective amount of a compound or pharmaceutically acceptable salt according to any one of claims 1-22, or a pharmaceutical composition according to claim 23.
29. A method of treating or preventing a disease or disorder mediated by KRAS G12D, or a disease or disorder in which KRAS G12D is implicated, in a subject in need thereof, the method
10 comprising administering to the subject an effective amount of a compound or pharmaceutically acceptable salt according to any one of claims 1-22, or a pharmaceutical composition according to claim 23.
30. A method of treating or preventing a disease or disorder associated with KRAS G12D in a subject in need thereof, the method comprising administering to the subject an effective
15 amount of a compound or pharmaceutically acceptable salt according to any one of claims 1-22, or a pharmaceutical composition according to claim 23.
31. A method of treating or preventing a disease or disorder according to claim 30, wherein the disease or disorder is cancer.
32. A method of treating or preventing cancer in a subject in need thereof, the method comprising
20 administering to the subject an effective amount of a compound or pharmaceutically acceptable salt according to any one of claims 1-22, or a pharmaceutical composition according to claim 23.
33. A method of inhibiting KRAS G12D activity, the method comprising contacting KRAS G12D with a compound or pharmaceutically acceptable salt according to any one of claims 1-22, or
25 a pharmaceutical composition according to claim 23.
34. A method according to claim 31 or 32, wherein the cancer is a KRAS G12D-associated cancer.
35. A method according to claim 31, 32 or 34, wherein the cancer is selected from colorectal cancer, lung cancer, and pancreatic cancer.

30