SUBSTITUTED STRAIGHT CHAIN SPIRO DERIVATIVES

FIELD OF THE INVENTION

The present invention relates to pharmaceutical agents useful for therapy and/or prophylaxis in a mammal, pharmaceutical composition comprising such compounds, and their use as menin/MLL protein/protein interaction inhibitors, useful for treating diseases such as cancer, including but not limited to leukemia, myelodysplastic syndrome (MDS), and myeloproliferative neoplasms (MPN); and diabetes.

BACKGROUND OF THE INVENTION

Chromosomal rearrangements affecting the mixed lineage leukemia gene (*MLL*; *MLL1*; *KMT2A*) result in aggressive acute leukemias across all age groups and still represent mostly incurable diseases emphasizing the urgent need for novel therapeutic approaches. Acute leukemias harboring these chromosomal translocations of *MLL* represent as lymphoid, myeloid or biphenotypic disease and constitute 5 to 10% of acute leukemias in adults and approximately 70% in infants (Marschalek, Br J Haematol 2011. 152(2), 141-54; Tomizawa et al., Pediatr Blood Cancer 2007. 49(2), 127-32).

MLL is a histone methyltransferase that methylates histone H3 on lysine 4 (H3K4) and functions in multiprotein complexes. Use of inducible loss-of-function alleles of *Mll1* demonstrated that Mll1 plays an essential role in sustaining hematopoietic stem cells (HSCs) and developing B cells although its histone methyltransferase activity is dispensable for hematopoiesis (Mishra et al., Cell Rep 2014. 7(4), 1239-47).

Fusion of MLL with more than 60 different partners has been reported to date and has been associated with leukemia formation/progression (Meyer et al., Leukemia 2013. 27, 2165–2176). Interestingly, the SET (Su(var)3–9, enhancer of zeste, and trithorax) domain of MLL is not retained in chimeric proteins but is replaced by the fusion partner (Thiel et al., Bioessays 2012. 34, 771-80). Recruitment of chromatin modifying enzymes like Dot1L and/or the pTEFb complex by the fusion partner leads to enhanced transcription and transcriptional elongation of MLL target genes including *HOXA* genes (e.g. *HOXA9*) and the *HOX* cofactor *MEIS1* as the most prominent ones. Aberrant expression of these genes in turn blocks hematopoietic differentiation and enhances proliferation.

Menin which is encoded by the Multiple Endocrine Neoplasia type 1 (*MEN1*) gene is expressed ubiquitously and is predominantly localized in the nucleus. It has been shown to interact with numerous proteins and is, therefore, involved in a variety of cellular processes. The best understood function of menin is its role as an oncogenic cofactor of MLL fusion proteins. Menin interacts with two motifs within the N-terminal fragment of MLL that is retained in all fusion proteins, MBM1 (menin-binding motif 1) and MBM2 (Thiel et al., Bioessays 2012. 34, 771-

80). Menin/MLL interaction leads to the formation of a new interaction surface for lens epithelium-derived growth factor (LEDGF). Although MLL directly binds to LEDGF, menin is obligatory for the stable interaction between MLL and LEDGF and the gene specific chromatin recruitment of the MLL complex via the PWWP domain of LEDGF (Cermakova et al., Cancer Res 2014. 15, 5139-51; Yokoyama & Cleary, Cancer Cell 2008. 8, 36-46). Furthermore, numerous genetic studies have shown that menin is strictly required for oncogenic transformation by MLL fusion proteins suggesting the menin/MLL interaction as an attractive therapeutic target. For example, conditional deletion of *Men1* prevents leukomogenesis in bone marrow progenitor cells ectopically expressing MLL fusions (Chen et al., Proc Natl Acad Sci 2006. 103, 1018-23). Similarly, genetic disruption of menin/MLL fusion interaction by loss-of-function mutations abrogates the oncogenic properties of the MLL fusion proteins, blocks the development of leukemia *in vivo* and releases the differentiation block of MLL-transformed leukemic blasts. These studies also showed that menin is required for the maintenance of *HOX* gene expression by MLL fusion proteins (Yokoyama et al., Cell 2005. 123, 207-18). In addition, small molecule inhibitors of menin/MLL interaction have been developed suggesting druggability of this protein/protein interaction and have also demonstrated efficacy in preclinical models of AML (Borkin et al., Cancer Cell 2015. 27, 589-602; Cierpicki and Grembecka, Future Med Chem 2014. 6, 447-462). Together with the observation that menin is not a requisite cofactor of MLL1 during normal hematopoiesis (Li et al., Blood 2013. 122, 2039-2046), these data validate the disruption of menin/MLL interaction as a promising new therapeutic approach for the treatment of MLL rearranged leukemia and other cancers with an active *HOX/MEIS1* gene signature. For example, an internal partial tandem duplication (PTD) within the 5'region of the *MLL* gene represents another major aberration that is found predominantly in de novo and secondary AML as well as myeloid dysplasia syndromes. Although the molecular mechanism and the biological function of MLL-PTD is not well understood, new therapeutic targeting strategies affecting the menin/MLL interaction might also prove effective in the treatment of MLL-PTD-related leukemias. Furthermore, castration-resistant prostate cancer has been shown to be dependent on the menin/MLL interaction (Malik et al., Nat Med 2015. 21, 344-52).

MLL protein is also known as Histone-lysine N-methyltransferase 2A (KMT2A) protein in the scientific field (UniProt Accession # Q03164).

Several references describe inhibitors targeting the menin-MLL interaction: WO2011029054, J Med Chem 2016, 59, 892-913 describe the preparation of thienopyrimidine and benzodiazepine derivatives; WO2014164543 describes thienopyrimidine and thienopyridine derivatives; *Nature Chemical Biology* March 2012, *8*, 277-284 and Ren, J.; *et al. Bioorg Med Chem Lett* (2016), *26(18)*, 4472-4476 describe thienopyrimidine derivatives; *J Med Chem* 2014,

57, 1543-1556 describes hydroxy- and aminomethylpiperidine derivatives; *Future Med Chem* 2014, *6*, 447-462 reviews small molecule and peptidomimetic compounds; WO2016195776 describes furo[2,3-d]pyrimidine, 9H-purine, [1,3]oxazolo[5,4-d]pyrimidine, [1,3]oxazolo[4,5-d]pyrimidine, [1,3]thiazolo[5,4-d]pyrimidine, thieno[2,3-b]pyridine and thieno[2,3-d]pyrimidine derivatives; WO2016197027 describes 5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine, 5,6,7,8-tetrahydropyrido]4,3-d]pyrimidine, pyrido[2,3-d]pyrimidine and quinoline derivatives; and WO2016040330 describes thienopyrimidine and thienopyridine compounds. WO2017192543 describes piperidines as Menin inhibitors. WO2017112768, WO2017207387, WO2017214367, WO2018053267 and WO2018024602 describe inhibitors of the menin-MLL interaction. WO2017161002 and WO2017161028 describe inhibitors of menin-MLL. WO2018050686, WO2018050684 and WO2018109088 describe inhibitors of the menin-MLL interaction. WO2018226976 describes methods and compositions for inhibiting the interaction of menin with MLL proteins. WO2018175746 provides methods of treatment for hematological malignancies and Ewing's sarcoma. WO2018106818 and WO2018106820 provide methods of promoting proliferation of a pancreatic cell. WO2018153312 discloses azaspiro compounds relating to the field of medicinal chemistry. WO2017132398 discloses methods comprising contacting a leukemia cell exhibiting an NPM1 mutation with a pharmacologic inhibitor of interaction between MLL and Menin. WO2019060365 describes substituted inhibitors of menin-MLL. WO2020069027 describes the treatment of hematological malignancies with inhibitors of menin. Krivtsov et al., Cancer Cell 2019. No.6 Vol.36, 660-673 describes a menin-MLL inhibitor.

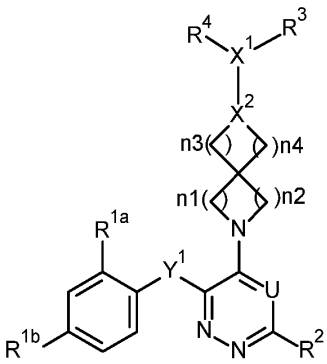
BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1: Efficacy study in Molm-14 subcutaneous (sc) model.

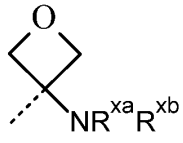
Fig. 2: Efficacy study in disseminated OCI-AML3 model.

DESCRIPTION OF THE INVENTION

The present invention concerns novel compounds of Formula (I),


(I)

and the tautomers and the stereoisomeric forms thereof, wherein

R^{1a} represents -C(=O)-$NR^{xa}R^{xb}$; Het; or  ;

Het represents a 5- or 6-membered monocyclic aromatic ring containing one, two or three nitrogen atoms and optionally a carbonyl moiety;
wherein said 5- or 6-membered monocyclic aromatic ring is optionally substituted with one or two substituents selected from the group consisting of C_{3-6}cycloalkyl and C_{1-4}alkyl;

R^{xa} and R^{xb} are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl and C_{3-6}cycloalkyl;

R^{1b} represents F or Cl;

Y^1 represents -$CR^{5a}R^{5b}$-, -O- or -NR^{5c}-;

R^2 is selected from the group consisting of hydrogen, halo, C_{1-4}alkyl, -O-C_{1-4}alkyl, and -$NR^{7a}R^{7b}$;

U represents N or CH;

n1, n2, n3 and n4 are each independently selected from 1 and 2;

X^1 represents CH, and X^2 represents N;

R^4 represents isopropyl;

R^{5a}, R^{5b}, R^{5c}, R^{7a}, and R^{7b}, are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl and C_{3-6}cycloalkyl;

R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$, -C_{1-6}alkyl-C(=O)-$NR^{9a}R^{9b}$, -C_{1-6}alkyl-OH, or -C_{1-6}alkyl-NR^{11}-C(=O)-O-C_{1-4}alkyl-O-C(=O)-C_{1-4}alkyl;
wherein each of the C_{1-4}alkyl or C_{1-6}alkyl moieties in the R^3 definitions independently of each

other may be substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo, -OH, and -O-C_{1-4}alkyl;

R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; -C(=O)-C_{1-4}alkyl; -C(=O)-O-C_{1-4}alkyl; -C(=O)-$NR^{12a}R^{12b}$; and C_{1-6}alkyl substituted with one, two or three substituents each independently selected from the group consisting of -OH, cyano, halo, -S(=O)$_2$-C_{1-4}alkyl, -O-C_{1-4}alkyl, -C(=O)-$NR^{10a}R^{10b}$, and -NR^{10c}-C(=O)-C_{1-4}alkyl;

R^{9a}, R^{9b}, R^{10a}, R^{10b}, R^{10c}, R^{11}, R^{12a}, and R^{12b} are each independently selected from the group consisting of hydrogen and C_{1-6}alkyl;

and the pharmaceutically acceptable salts and the solvates thereof.

The present invention also relates to a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I), a pharmaceutically acceptable salt, or a solvate thereof, and a pharmaceutically acceptable carrier or excipient.

Additionally, the invention relates to a compound of Formula (I), a pharmaceutically acceptable salt, or a solvate thereof, for use as a medicament, and to a compound of Formula (I), a pharmaceutically acceptable salt, or a solvate thereof, for use in the treatment or in the prevention of cancer, including but not limited to leukemia, myelodysplastic syndrome (MDS), and myeloproliferative neoplasms (MPN); and diabetes.

In a particular embodiment, the invention relates to a compound of Formula (I), a pharmaceutically acceptable salt, or a solvate thereof, for use in the treatment or in the prevention of cancer.

In a specific embodiment said cancer is selected from leukemias, lymphomas, myelomas or solid tumor cancers (e.g. prostate cancer, lung cancer, breast cancer, pancreatic cancer, colon cancer, liver cancer, melanoma and glioblastoma, etc.). In some embodiments, the leukemias include acute leukemias, chronic leukemias, myeloid leukemias, myelogeneous leukemias, lymphoblastic leukemias, lymphocytic leukemias, Acute myelogeneous leukemias (AML), Chronic myelogenous leukemias (CML), Acute lymphoblastic leukemias (ALL), Chronic lymphocytic leukemias (CLL), T cell prolymphocytic leukemias (T-PLL), Large granular lymphocytic leukemia, Hairy cell leukemia (HCL), MLL-rearranged leukemias, MLL-PTD leukemias, MLL amplified leukemias, MLL-positive leukemias, leukemias exhibiting *HOX/MEIS1* gene expression signatures etc.

In particular, compounds according to the present invention and the pharmaceutical compositions thereof may be useful in the treatment or prevention of leukemias, in particular nucleophosmin (NPM1)-mutated leukemias, e.g. NPM1c.

In an embodiment, compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, may have improved metabolic stability properties.
In an embodiment, compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, may have extended in vivo half-life (T1/2).
In an embodiment, compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, may have improved oral bioavailability.
In an embodiment, compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, may reduce tumor growth e.g., tumours harbouring MLL (KMT2A) gene rearrangements/alterations and/or NPM1 mutations.
In an embodiment, compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, may have improved PD properties *in vivo* during a prolonged period of time, e.g. inhibition of target gene expression such as MEIS1 and upregulation of differentiation marker over a period of at least 16 hours.
In an embodiment, compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, may have an improved safety profile (e.g. reduced hERG inhibition; improved cardiovascular safety).
In an embodiment, compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, may be suitable for Q.D. dosing (once daily).

The invention also relates to the use of a compound of Formula (I), a pharmaceutically acceptable salt, or a solvate thereof, in combination with an additional pharmaceutical agent for use in the treatment or prevention of cancer, including but not limited to leukemia, myelodysplastic syndrome (MDS), and myeloproliferative neoplasms (MPN); and diabetes.

Furthermore, the invention relates to a process for preparing a pharmaceutical composition according to the invention, characterized in that a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound of Formula (I), a pharmaceutically acceptable salt, or a solvate thereof.

The invention also relates to a product comprising a compound of Formula (I), a pharmaceutically acceptable salt, or a solvate thereof, and an additional pharmaceutical agent, as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of cancer, including but not limited to leukemia, myelodysplastic syndrome (MDS), and myeloproliferative neoplasms (MPN); and diabetes .

Additionally, the invention relates to a method of treating or preventing a cell proliferative disease in a warm-blooded animal which comprises administering to the said animal an effective amount of a compound of Formula (I), a pharmaceutically acceptable salt, or a solvate thereof, as defined herein, or a pharmaceutical composition or combination as defined herein.

DETAILED DESCRIPTION OF THE INVENTION

The term 'halo' or 'halogen' as used herein represents fluoro, chloro, bromo and iodo.

The prefix 'C_{x-y}' (where x and y are integers) as used herein refers to the number of carbon atoms in a given group. Thus, a C_{1-6}alkyl group contains from 1 to 6 carbon atoms, and so on.

The term 'C_{1-4}alkyl' as used herein as a group or part of a group represents a straight or branched chain saturated hydrocarbon radical having from 1 to 4 carbon atoms, such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *s*-butyl, *t*-butyl and the like.

Similar, the term 'C_{1-6}alkyl' as used herein as a group or part of a group represents a straight or branched chain saturated hydrocarbon radical having from 1 to 6 carbon atoms, such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *s*-butyl, *t*-butyl, *n*-pentyl, *n*-hexyl and the like.

The term 'C_{3-6}cycloalkyl' as used herein as a group or part of a group defines a saturated, cyclic hydrocarbon radical having from 3 to 6 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

It will be clear for the skilled person that $S(=O)_2$ or SO_2 represents a sulfonyl moiety.

It will be clear for the skilled person that CO or C(=O) represents a carbonyl moiety.

It will be clear for the skilled person that a group such as -CRR- represents

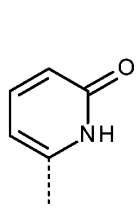
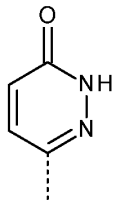
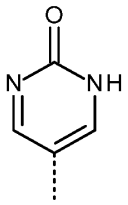


. An example of such a group is $-CR^{5a}R^{5b}-$.

It will be clear for the skilled person that a group such as -NR- represents  . An example of such a group is $-NR^{5c}-$.

Non-limiting examples of 'monocyclic 5- or 6-membered aromatic rings containing one, two or three nitrogen atoms and optionally a carbonyl moiety', include, but are not limited to pyrazolyl, imidazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl or 1,2-dihydro-2-oxo-4-pyridinyl.

The skilled person will understand that a 5- or 6-membered monocyclic aromatic ring containing one, two or three nitrogen atoms and a carbonyl moiety includes, but is not limited to

, , and .

When any variable occurs more than one time in any constituent, each definition is independent.

When any variable occurs more than one time in any formula (e.g. Formula (I)), each definition is independent.

In general, whenever the term 'substituted' is used in the present invention, it is meant, unless otherwise indicated or clear from the context, to indicate that one or more hydrogens, in particular from 1 to 4 hydrogens, more in particular from 1 to 3 hydrogens, preferably 1 or 2 hydrogens, more preferably 1 hydrogen, on the atom or radical indicated in the expression using 'substituted' are replaced with a selection from the indicated group, provided that the normal valency is not exceeded, and that the substitution results in a chemically stable compound, i.e. a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture (isolation after a reaction e.g. purification by silica gel chromatography). In a particular embodiment, when the number of substituents is not explicitly specified, the number of substituents is one.

Combinations of substituents and/or variables are permissible only if such combinations result in chemically stable compounds. 'Stable compound' is in this context meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture (isolation after a reaction e.g. purification by silica gel chromatography).

The skilled person will understand that the term 'optionally substituted' means that the atom or radical indicated in the expression using 'optionally substituted' may or may not be substituted (this means substituted or unsubstituted respectively).

When two or more substituents are present on a moiety they may, where possible and unless otherwise indicated or clear from the context, replace hydrogens on the same atom or they may replace hydrogen atoms on different atoms in the moiety.

Within the context of this invention 'saturated' means 'fully saturated', if not otherwise specified.

Unless otherwise specified or clear from the context, aromatic rings goups, can be attached to the remainder of the molecule of Formula (I) through any available ring carbon atom (C-linked) or nitrogen atom (N-linked).

Unless otherwise specified or clear from the context, aromatic rings goups, may optionally be substituted, where possible, on carbon and/or nitrogen atoms according to the embodiments.

The term "subject" as used herein, refers to an animal, preferably a mammal (e.g. cat, dog, primate or human), more preferably a human, who is or has been the object of treatment, observation or experiment.

The term "therapeutically effective amount" as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medicinal doctor or other clinician, which includes alleviation or reversal of the symptoms of the disease or disorder being treated.

The term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts.

The term "treatment", as used herein, is intended to refer to all processes wherein there may be a slowing, interrupting, arresting or stopping of the progression of a disease, but does not necessarily indicate a total elimination of all symptoms.

The term "compound(s) of the (present) invention" or "compound(s) according to the (present) invention" as used herein, is meant to include the compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof.

As used herein, any chemical formula with bonds shown only as solid lines and not as solid wedged or hashed wedged bonds, or otherwise indicated as having a particular configuration (e.g. *R*, *S*) around one or more atoms, contemplates each possible stereoisomer, or mixture of two or more stereoisomers.

Hereinbefore and hereinafter, the term "compound(s) of Formula (I)" is meant to include the tautomers thereof and the stereoisomeric forms thereof.

The terms "stereoisomers", "stereoisomeric forms" or "stereochemically isomeric forms" hereinbefore or hereinafter are used interchangeably.

The invention includes all stereoisomers of the compounds of the invention either as a pure stereoisomer or as a mixture of two or more stereoisomers.

Enantiomers are stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a racemate or racemic mixture.

Atropisomers (or atropoisomers) are stereoisomers which have a particular spatial configuration, resulting from a restricted rotation about a single bond, due to large steric hindrance. All atropisomeric forms of the compounds of Formula (I) are intended to be included within the scope of the present invention.

Diastereomers (or diastereoisomers) are stereoisomers that are not enantiomers, i.e. they are not related as mirror images. If a compound contains a double bond, the substituents may be in the *E* or the *Z* configuration.

Substituents on bivalent cyclic saturated or partially saturated radicals may have either the cis- or trans-configuration; for example if a compound contains a disubstituted cycloalkyl group, the substituents may be in the cis or trans configuration.

Therefore, the invention includes enantiomers, atropisomers, diastereomers, racemates, *E* isomers, *Z* isomers, cis isomers, trans isomers and mixtures thereof, whenever chemically possible.

The meaning of all those terms, i.e. enantiomers, atropisomers, diastereomers, racemates, *E* isomers, *Z* isomers, cis isomers, trans isomers and mixtures thereof are known to the skilled person.

The absolute configuration is specified according to the Cahn-Ingold-Prelog system. The configuration at an asymmetric atom is specified by either *R* or *S*. Resolved stereoisomers whose absolute configuration is not known can be designated by (+) or (-) depending on the direction in which they rotate plane polarized light. For instance, resolved enantiomers whose absolute configuration is not known can be designated by (+) or (-) depending on the direction in which they rotate plane polarized light.

When a specific stereoisomer is identified, this means that said stereoisomer is substantially free, i.e. associated with less than 50%, preferably less than 20%, more preferably less than 10%, even more preferably less than 5%, in particular less than 2% and most preferably less than 1%, of the other stereoisomers. Thus, when a compound of Formula (I) is for instance specified as (*R*), this means that the compound is substantially free of the (*S*) isomer; when a compound of Formula (I) is for instance specified as *E*, this means that the compound is substantially free of the *Z* isomer; when a compound of Formula (I) is for instance specified as cis, this means that the compound is substantially free of the trans isomer.

Some of the compounds according to Formula (I) may also exist in their tautomeric form. Such forms in so far as they may exist, although not explicitly indicated in the above Formula (I) are intended to be included within the scope of the present invention. It follows that a single compound may exist in both stereoisomeric and tautomeric form.

Pharmaceutically acceptable salts include acid addition salts and base addition salts. Such salts may be formed by conventional means, for example by reaction of a free acid or a free base form with one or more equivalents of an appropriate base or acid, optionally in a solvent, or in a medium in which the salt is insoluble, followed by removal of said solvent, or said medium, using standard techniques (e.g. *in vacuo*, by freeze-drying or by filtration). Salts may also be

prepared by exchanging a counter-ion of a compound of the invention in the form of a salt with another counter-ion, for example using a suitable ion exchange resin.

The pharmaceutically acceptable salts as mentioned hereinabove or hereinafter are meant to comprise the therapeutically active non-toxic acid and base salt forms which the compounds of Formula (I) and solvates thereof, are able to form.

Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric, nitric, phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic (i.e. ethanedioic), malonic, succinic (i.e. butanedioic acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, cyclamic, salicylic, p-aminosalicylic, pamoic and the like acids. Conversely said salt forms can be converted by treatment with an appropriate base into the free base form.

The compounds of Formula (I) and solvates thereof containing an acidic proton may also be converted into their non-toxic metal or amine salt forms by treatment with appropriate organic and inorganic bases.

Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, cesium, magnesium, calcium salts and the like, salts with organic bases, e.g. primary, secondary and tertiary aliphatic and aromatic amines such as methylamine, ethylamine, propylamine, isopropylamine, the four butylamine isomers, dimethylamine, diethylamine, diethanolamine, dipropylamine, diisopropylamine, di-n-butylamine, pyrrolidine, piperidine, morpholine, trimethylamine, triethylamine, tripropylamine, quinuclidine, pyridine, quinoline and isoquinoline; the benzathine, N-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like. Conversely the salt form can be converted by treatment with acid into the free acid form.

The term “prodrug” includes any compound that, following oral or parenteral administration, in particular oral administration, is metabolised *in vivo* to a (more) active form in an experimentally-detectable amount, and within a predetermined time (e.g. within a dosing interval of between 0.5 and 24 hours, or e.g. within a dosing interval of between 6 and 24 hours (i.e. once to four times daily)). For the avoidance of doubt, the term “parenteral” administration includes all forms of administration other than oral administration, in particular intravenous *(*IV*),* intramuscular (IM), and subcutaneous *(*SC*)* injection.

Prodrugs may be prepared by modifying functional groups present on a compound in such a way that the modifications are cleaved *in vivo* when such prodrug is administered to a mammalian subject. The modifications typically are achieved by synthesising the parent compound with a prodrug substituent. In general, prodrugs include compounds wherein a hydroxyl, amino, sulfhydryl, carboxy or carbonyl group is bonded to any group that may be

cleaved *in vivo* to regenerate the free hydroxyl, amino, sulfhydryl, carboxy or carbonyl group, respectively.

Examples of prodrugs include, but are not limited to, esters and carbamates of hydroxy functional groups, esters groups of carboxyl functional groups, N-acyl derivatives and N-Mannich bases. General information on prodrugs may be found e.g. in Bundegaard, H. "Design of Prodrugs" p. l-92, Elesevier, New York-Oxford (1985).

The term solvate comprises the solvent addition forms as well as the salts thereof, which the compounds of Formula (I) are able to form. Examples of such solvent addition forms are e.g. hydrates, alcoholates and the like.

The compounds of the invention as prepared in the processes described below may be synthesized in the form of mixtures of enantiomers, in particular racemic mixtures of enantiomers, that can be separated from one another following art-known resolution procedures. A manner of separating the enantiomeric forms of the compounds of Formula (I), and pharmaceutically acceptable salts, and solvates thereof, involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound would be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

The term "enantiomerically pure" as used herein means that the product contains at least 80% by weight of one enantiomer and 20% by weight or less of the other enantiomer. Preferably the product contains at least 90% by weight of one enantiomer and 10% by weight or less of the other enantiomer. In the most preferred embodiment the term "enantiomerically pure" means that the composition contains at least 99% by weight of one enantiomer and 1% or less of the other enantiomer.

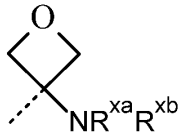
The present invention also embraces isotopically-labeled compounds of the present invention which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature (or the most abundant one found in nature).

All isotopes and isotopic mixtures of any particular atom or element as specified herein are contemplated within the scope of the compounds of the invention, either naturally occurring or synthetically produced, either with natural abundance or in an isotopically enriched form. Exemplary isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C , ^{13}N, ^{15}O, ^{17}O, ^{18}O, ^{32}P, ^{33}P, ^{35}S, ^{18}F, ^{36}Cl, ^{122}I, ^{123}I, ^{125}I, ^{131}I, ^{75}Br, ^{76}Br, ^{77}Br and ^{82}Br. Preferably, the isotope is selected from the group of ^{2}H, ^{3}H, ^{11}C, ^{13}C and ^{18}F. Preferably, the isotope is selected from the group of ^{2}H, ^{3}H, ^{11}C and ^{18}F. More preferably, the

isotope is ^{2}H, ^{3}H or ^{13}C. More preferably, the isotope is ^{2}H or ^{13}C. More preferably, the isotope is ^{2}H. In particular, deuterated compounds and ^{13}C-enriched compounds are intended to be included within the scope of the present invention. In particular, deuterated compounds are intended to be included within the scope of the present invention.

Certain isotopically-labeled compounds of the present invention (e.g., those labeled with ^{3}H and ^{14}C) may be useful for example in substrate tissue distribution assays. Tritiated (^{3}H) and carbon-l4 (^{14}C) isotopes are useful for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased *in vivo* half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Positron emitting isotopes such as ^{15}O, ^{13}N, ^{11}C and ^{18}F are useful for positron emission tomography (PET) studies. PET imaging in cancer finds utility in helping locate and identify tumours, stage the disease and determine suitable treatment. Human cancer cells overexpress many receptors or proteins that are potential disease-specific molecular targets. Radiolabelled tracers that bind with high affinity and specificity to such receptors or proteins on tumour cells have great potential for diagnostic imaging and targeted radionuclide therapy (Charron, Carlie L. et al. Tetrahedron Lett. 2016, 57(37), 4119-4127). Additionally, target-specific PET radiotracers may be used as biomarkers to examine and evaluate pathology, by for example, measuring target expression and treatment response (Austin R. et al. Cancer Letters (2016), doi: 10.1016/j.canlet.2016.05.008).

The present invention relates in particular to compounds of Formula (I) as defined herein, and the tautomers and the stereoisomeric forms thereof, wherein

R^{1a} represents -C(=O)-$NR^{xa}R^{xb}$; Het; or 

;

Het represents a 5- or 6-membered monocyclic aromatic ring containing one, two or three nitrogen atoms and optionally a carbonyl moiety;
wherein said 5- or 6-membered monocyclic aromatic ring is optionally substituted with one or two substituents selected from the group consisting of C_{3-6}cycloalkyl and C_{1-4}alkyl;

R^{xa} and R^{xb} are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl and C_{3-6}cycloalkyl;

R^{1b} represents F or Cl;

Y^{1} represents -$CR^{5a}R^{5b}$-, -O- or -NR^{5c}-;

R^2 is selected from the group consisting of hydrogen, halo, C_{1-4}alkyl, -O-C_{1-4}alkyl, and -$NR^{7a}R^{7b}$;

U represents N or CH;

n1, n2, n3 and n4 are each independently selected from 1 and 2;

X^1 represents CH, and X^2 represents N;

R^4 represents isopropyl;

R^{5a}, R^{5b}, R^{5c}, R^{7a}, and R^{7b}, are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl and C_{3-6}cycloalkyl;

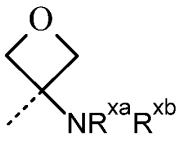
R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$, -C_{1-6}alkyl-C(=O)-$NR^{9a}R^{9b}$, -C_{1-6}alkyl-OH, or -C_{1-6}alkyl-NR^{11}-C(=O)-O-C_{1-4}alkyl-O-C(=O)-C_{1-4}alkyl;
wherein each of the C_{1-4}alkyl or C_{1-6}alkyl moieties in the R^3 definitions independently of each other may be substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo or -O-C_{1-4}alkyl;

R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; -C(=O)-C_{1-4}alkyl; -C(=O)-O-C_{1-4}alkyl; -C(=O)-$NR^{12a}R^{12b}$; and C_{1-6}alkyl substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo, -$S(=O)_2$-C_{1-4}alkyl, -O-C_{1-4}alkyl, and -C(=O)-$NR^{10a}R^{10b}$;

R^{9a}, R^{9b}, R^{10a}, R^{10b}, R^{11}, R^{12a}, and R^{12b} are each independently selected from the group consisting of hydrogen and C_{1-6}alkyl;

and the pharmaceutically acceptable salts and the solvates thereof.

The present invention relates in particular to compounds of Formula (I) as defined herein, and the tautomers and the stereoisomeric forms thereof, wherein

R^{1a} represents -C(=O)-$NR^{xa}R^{xb}$; Het; or 

;

Het represents a 5- or 6-membered monocyclic aromatic ring containing one, two or three nitrogen atoms and optionally a carbonyl moiety;
wherein said 5- or 6-membered monocyclic aromatic ring is optionally substituted with one or two substituents selected from the group consisting of C_{3-6}cycloalkyl and C_{1-4}alkyl;

R^{xa} and R^{xb} are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl and C_{3-6}cycloalkyl;

R^{1b} represents F or Cl;

Y^1 represents $-CR^{5a}R^{5b}-$, -O- or $-NR^{5c}-$;

R^2 is selected from the group consisting of hydrogen, halo, C_{1-4}alkyl, -O-C_{1-4}alkyl, and $-NR^{7a}R^{7b}$;

U represents N or CH;

n1, n2, n3 and n4 are each independently selected from 1 and 2;

X^1 represents CH, and X^2 represents N;

R^4 represents isopropyl;

R^{5a}, R^{5b}, R^{5c}, R^{7a}, and R^{7b}, are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl and C_{3-6}cycloalkyl;

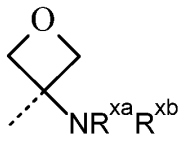
R^3 represents $-C_{1-6}$alkyl-$NR^{8a}R^{8b}$;
wherein the C_{1-6}alkyl moiety in the R^3 definition may be substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo, OH, and -O-C_{1-4}alkyl;

R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; and C_{1-6}alkyl substituted with one, two or three substituents each independently selected from the group consisting of -OH, cyano, halo, $-S(=O)_2-C_{1-4}$alkyl, -O-C_{1-4}alkyl, $-C(=O)-NR^{10a}R^{10b}$, and $-NR^{10c}-C(=O)-C_{1-4}$alkyl;

R^{10a}, R^{10b}, R^{10c} are each independently selected from the group consisting of hydrogen and C_{1-6}alkyl;

and the pharmaceutically acceptable salts and the solvates thereof.

The present invention relates in particular to compounds of Formula (I) as defined herein, and the tautomers and the stereoisomeric forms thereof, wherein

R^{1a} represents $-C(=O)-NR^{xa}R^{xb}$; Het; or 

;

Het represents a 5- or 6-membered monocyclic aromatic ring containing one, two or three nitrogen atoms and optionally a carbonyl moiety;
wherein said 5- or 6-membered monocyclic aromatic ring is optionally substituted with one or two substituents selected from the group consisting of C_{3-6}cycloalkyl and C_{1-4}alkyl;

R^{xa} and R^{xb} are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl and C_{3-6}cycloalkyl;

R^{1b} represents F or Cl;

Y^1 represents $-CR^{5a}R^{5b}-$, -O- or $-NR^{5c}-$;

R^2 is selected from the group consisting of hydrogen, halo, C_{1-4}alkyl, -O-C_{1-4}alkyl, and $-NR^{7a}R^{7b}$;

U represents N or CH;

n1, n2, n3 and n4 are each independently selected from 1 and 2;

X^1 represents CH, and X^2 represents N;

R^4 represents isopropyl;

R^{5a}, R^{5b}, R^{5c}, R^{7a}, and R^{7b}, are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl and C_{3-6}cycloalkyl;

R^3 represents $-C_{1-6}$alkyl-$NR^{8a}R^{8b}$;

wherein the C_{1-6}alkyl moiety in the R^3 definition may be substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo and -O-C_{1-4}alkyl;

R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; and C_{1-6}alkyl substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo, $-S(=O)_2-C_{1-4}$alkyl, -O-C_{1-4}alkyl, and $-C(=O)-NR^{10a}R^{10b}$;

R^{10a} and R^{10b} are each independently selected from the group consisting of hydrogen and C_{1-6}alkyl;

and the pharmaceutically acceptable salts and the solvates thereof.

The present invention relates in particular to compounds of Formula (I) as defined herein, and the tautomers and the stereoisomeric forms thereof, wherein

R^{1a} represents $-C(=O)-NR^{xa}R^{xb}$ or Het;

Het represents a 6-membered monocyclic aromatic ring containing two nitrogen atoms; wherein said 6-membered monocyclic aromatic ring is substituted with one C_{3-6}cycloalkyl;

R^{xa} and R^{xb} represent C_{1-4}alkyl;

R^{1b} represents F;

Y^1 represents -O-;

R^2 represents hydrogen;

U represents N or CH;

n1, n2, n3 and n4 are each independently selected from 1 and 2;

X^1 represents CH, and X^2 represents N;

R^4 represents isopropyl;

R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$, -C_{1-6}alkyl-C(=O)-$NR^{9a}R^{9b}$, -C_{1-6}alkyl-OH, or -C_{1-6}alkyl-NR^{11}-C(=O)-O-C_{1-4}alkyl-O-C(=O)-C_{1-4}alkyl;
wherein each of the C_{1-4}alkyl or C_{1-6}alkyl moieties in the R^3 definitions independently of each other may be substituted with one, two or three substituents each independently selected from the group consisting of -OH and -O-C_{1-4}alkyl;

R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; -C(=O)-C_{1-4}alkyl; -C(=O)-O-C_{1-4}alkyl; -C(=O)-$NR^{12a}R^{12b}$; and C_{1-6}alkyl substituted with one, two or three substituents each independently selected from the group consisting of -OH, cyano, halo, -$S(=O)_2$-C_{1-4}alkyl, -O-C_{1-4}alkyl, -C(=O)-$NR^{10a}R^{10b}$, and -NR^{10c}-C(=O)-C_{1-4}alkyl;

R^{9a}, R^{9b}, R^{10a}, R^{10b}, R^{10c}, R^{11}, R^{12a}, and R^{12b} are each independently selected from the group consisting of hydrogen and C_{1-6}alkyl;

and the pharmaceutically acceptable salts and the solvates thereof.

The present invention relates in particular to compounds of Formula (I) as defined herein, and the tautomers and the stereoisomeric forms thereof, wherein

R^{1a} represents -C(=O)-$NR^{xa}R^{xb}$ or Het;

Het represents a 6-membered monocyclic aromatic ring containing two nitrogen atoms;
wherein said 6-membered monocyclic aromatic ring is substituted with one C_{3-6}cycloalkyl;

R^{xa} and R^{xb} represent C_{1-4}alkyl;

R^{1b} represents F;

Y^1 represents -O-;

R^2 represents hydrogen;

U represents N or CH;

n1, n2, n3 and n4 are each independently selected from 1 and 2;

X^1 represents CH, and X^2 represents N;

R^4 represents isopropyl;

R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$;
wherein the C_{1-6}alkyl moiety in the R^3 definition may be substituted with one, two or three substituents each independently selected from the group consisting of -OH and -O-C_{1-4}alkyl;

R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; and C_{1-6}alkyl substituted with one, two or three substituents each independently selected from the group consisting of -OH, cyano, halo, -S(=O)$_2$-C_{1-4}alkyl, -O-C_{1-4}alkyl, -C(=O)-$NR^{10a}R^{10b}$, and -NR^{10c}-C(=O)-C_{1-4}alkyl;

R^{10a}, R^{10b}, and R^{10c} are each independently selected from the group consisting of hydrogen and C_{1-6}alkyl;

and the pharmaceutically acceptable salts and the solvates thereof.

The present invention relates in particular to compounds of Formula (I) as defined herein, and the tautomers and the stereoisomeric forms thereof, wherein

R^{1a} represents -C(=O)-$NR^{xa}R^{xb}$;

R^{xa} and R^{xb} represent C_{1-4}alkyl;

R^{1b} represents F;

Y^1 represents -O-;

R^2 represents hydrogen;

U represents N or CH;

n1, n2, n3 and n4 are each independently selected from 1 and 2;

X^1 represents CH, and X^2 represents N;

R^4 represents isopropyl;

R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$;
wherein the C_{1-6}alkyl moiety in the R^3 definition may be substituted with one, two or three substituents each independently selected from the group consisting of -OH and -O-C_{1-4}alkyl;

R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; and C_{1-6}alkyl substituted with one, two or three substituents each independently selected from the group consisting of -OH, cyano, halo, -S(=O)$_2$-C_{1-4}alkyl, -O-C_{1-4}alkyl, -C(=O)-$NR^{10a}R^{10b}$, and -NR^{10c}-C(=O)-C_{1-4}alkyl;

R^{10a}, R^{10b}, and R^{10c} are each independently selected from the group consisting of hydrogen and C_{1-6}alkyl;

and the pharmaceutically acceptable salts and the solvates thereof.

The present invention relates in particular to compounds of Formula (I) as defined herein, and the tautomers and the stereoisomeric forms thereof, wherein

R^{1a} represents -C(=O)-$NR^{xa}R^{xb}$ or Het;

Het represents pyrimidinyl substituted with one C_{3-6}cycloalkyl;

R^{xa} and R^{xb} represent C_{1-4}alkyl;

R^{1b} represents F;

Y^1 represents -O-;

R^2 represents hydrogen;

U represents N;

n1, n2, n3 and n4 are each independently selected from 1 and 2;

X^1 represents CH, and X^2 represents N;

R^4 represents isopropyl;

R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$;

wherein the C_{1-6}alkyl moiety in the R^3 definition may be substituted with one -OH;

R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; and C_{1-6}alkyl substituted with one or two substituents each independently selected from the group consisting of halo, -O-C_{1-4}alkyl, and -NR^{10c}-C(=O)-C_{1-4}alkyl;

R^{10a}, R^{10b}, and R^{10c} are each independently selected from the group consisting of hydrogen and C_{1-6}alkyl;

and the pharmaceutically acceptable salts and the solvates thereof.

The present invention relates in particular to compounds of Formula (I) as defined herein, and the tautomers and the stereoisomeric forms thereof, wherein

R^{1a} represents -C(=O)-$NR^{xa}R^{xb}$ or Het;

Het represents pyrimidinyl substituted with one C_{3-6}cycloalkyl;

R^{xa} and R^{xb} represent C_{1-4}alkyl;

R^{1b} represents F;

Y^1 represents -O-;

R^2 represents hydrogen;

U represents N;

n2 is 2;
n1, n3 and n4 are 1;

X^1 represents CH, and X^2 represents N;

R^4 represents isopropyl;

R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$;
wherein the C_{1-6}alkyl moiety in the R^3 definition may be substituted with one -OH;

R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; and C_{1-6}alkyl substituted with one or two substituents each independently selected from the group consisting of halo, -O-C_{1-4}alkyl, and -NR^{10c}-C(=O)-C_{1-4}alkyl;

R^{10a}, R^{10b}, and R^{10c} are each independently selected from the group consisting of hydrogen and C_{1-6}alkyl;

and the pharmaceutically acceptable salts and the solvates thereof.

The present invention relates in particular to compounds of Formula (I) as defined herein, and the tautomers and the stereoisomeric forms thereof, wherein

R^{1a} represents -C(=O)-$NR^{xa}R^{xb}$;

R^{xa} and R^{xb} represent C_{1-4}alkyl;

R^{1b} represents F;

Y^1 represents -O-;

R^2 represents hydrogen;

U represents N;

n2 is 2;
n1, n3 and n4 are 1;

X^1 represents CH, and X^2 represents N;

R^4 represents isopropyl;

R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$;
R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; and C_{1-6}alkyl substituted with one or two substituents each independently selected from the group consisting of halo, -O-C_{1-4}alkyl, and -NR^{10c}-C(=O)-C_{1-4}alkyl;
R^{10a}, R^{10b}, and R^{10c} are each independently selected from the group consisting of hydrogen and C_{1-6}alkyl;

and the pharmaceutically acceptable salts and the solvates thereof.

The present invention relates in particular to compounds of Formula (I) as defined herein, and the tautomers and the stereoisomeric forms thereof, wherein

R^{1a} represents -C(=O)-$NR^{xa}R^{xb}$;

R^{xa} and R^{xb} represent C_{1-4}alkyl;

R^{1b} represents F;

Y^1 represents -O-;

R^2 represents hydrogen;

U represents N;

n2 is 2;
n1, n3 and n4 are 1;

X^1 represents CH, and X^2 represents N;

R^4 represents isopropyl;

R^3 represents -CH_2-CH_2-CH_2-$NR^{8a}R^{8b}$;

R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; and C_{1-6}alkyl substituted with one or two substituents each independently selected from the group consisting of halo, -O-C_{1-4}alkyl, and -NR^{10c}-C(=O)-C_{1-4}alkyl;

R^{10a}, R^{10b}, and R^{10c} are each independently selected from the group consisting of hydrogen and C_{1-6}alkyl;

and the pharmaceutically acceptable salts and the solvates thereof.

The present invention relates in particular to compounds of Formula (I) as defined herein, and the tautomers and the stereoisomeric forms thereof, wherein

R^{1a} represents -C(=O)-$NR^{xa}R^{xb}$;

R^{xa} and R^{xb} represent C_{1-4}alkyl;

R^{1b} represents F;

Y^1 represents -O-;

R^2 represents hydrogen;

U represents N;

n1, n2, n3 and n4 are each independently selected from 1 and 2;

X^1 represents CH, and X^2 represents N;

R^4 represents isopropyl;

R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$;

R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; and C_{1-6}alkyl substituted with one, two or three substituents each independently selected from the group consisting of -OH, cyano, halo, -$S(=O)_2$-C_{1-4}alkyl, -O-C_{1-4}alkyl, and -C(=O)-$NR^{10a}R^{10b}$;

R^{10a} and R^{10b} are each independently selected from the group consisting of hydrogen and C_{1-6}alkyl;

and the pharmaceutically acceptable salts and the solvates thereof.

The present invention relates in particular to compounds of Formula (I) as defined herein, and the tautomers and the stereoisomeric forms thereof, wherein

R^{1a} represents -C(=O)-$NR^{xa}R^{xb}$;

R^{xa} and R^{xb} represent C_{1-4}alkyl;

R^{1b} represents F;

Y^1 represents -O-;

R^2 represents hydrogen;

U represents N;

n1, n2, n3 and n4 are each independently selected from 1 and 2;

X^1 represents CH, and X^2 represents N;

R^4 represents isopropyl;

R^3 represents $-CH_2-CH_2-CH_2-NR^{8a}R^{8b}$;

R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; and C_{1-6}alkyl substituted with one, two or three substituents each independently selected from the group consisting of -OH, cyano, halo, $-S(=O)_2-C_{1-4}$alkyl, $-O-C_{1-4}$alkyl, and $-C(=O)-NR^{10a}R^{10b}$;

R^{10a} and R^{10b} are each independently selected from the group consisting of hydrogen and C_{1-6}alkyl;

and the pharmaceutically acceptable salts and the solvates thereof.

The present invention relates in particular to compounds of Formula (I) as defined herein, and the tautomers and the stereoisomeric forms thereof, wherein

R^{1a} represents $-C(=O)-NR^{xa}R^{xb}$;

R^{xa} and R^{xb} represent hydrogen or C_{1-4}alkyl;

R^{1b} represents F;

Y^1 represents -O-;

R^2 represents hydrogen;

U represents N;

n1, n2, n3 and n4 are each independently selected from 1 and 2;

X^1 represents CH, and X^2 represents N;

R^4 represents isopropyl;

R^3 represents $-CH_2-CH_2-CH_2-NR^{8a}R^{8b}$;

R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; and C_{1-6}alkyl substituted with one, two or three substituents each independently selected from the group consisting of -OH, cyano, halo, $-S(=O)_2-C_{1-4}$alkyl, $-O-C_{1-4}$alkyl, and $-C(=O)-NR^{10a}R^{10b}$;

R^{10a} and R^{10b} are each independently selected from the group consisting of hydrogen and C_{1-6}alkyl;

and the pharmaceutically acceptable salts and the solvates thereof.

The present invention relates in particular to compounds of Formula (I) as defined herein, and the tautomers and the stereoisomeric forms thereof, wherein

R^{1a} represents -C(=O)-$NR^{xa}R^{xb}$;

R^{xa} and R^{xb} represent hydrogen or C_{1-4}alkyl;

R^{1b} represents F;

Y^1 represents -O-;

R^2 represents hydrogen;

U represents N;

n1, n2, n3 and n4 are each independently selected from 1 and 2;

X^1 represents CH, and X^2 represents N;

R^4 represents isopropyl;

R^3 represents -CH_2-CH_2-CH_2-$NR^{8a}R^{8b}$;

R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; and C_{1-6}alkyl substituted with one, two or three substituents each independently selected from the group consisting of -OH and -O-C_{1-4}alkyl;

and the pharmaceutically acceptable salts and the solvates thereof.

The present invention relates in particular to compounds of Formula (I) as defined herein, and the tautomers and the stereoisomeric forms thereof, wherein

R^{1a} represents -C(=O)-$NR^{xa}R^{xb}$;

R^{xa} and R^{xb} represent C_{1-4}alkyl;

R^{1b} represents F;

Y^1 represents -O-;

R^2 represents hydrogen;

U represents N;

n1, n2, n3 and n4 are each independently selected from 1 and 2;

X^1 represents CH, and X^2 represents N;

R^4 represents isopropyl;

R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$;

R^{8a} and R^{8b} are each independently selected from the group consisting of C_{1-6}alkyl; and C_{1-6}alkyl substituted with one -O-C_{1-4}alkyl;

and the pharmaceutically acceptable salts and the solvates thereof.

The present invention relates in particular to compounds of Formula (I) as defined herein, and the tautomers and the stereoisomeric forms thereof, wherein

R^{1a} represents -C(=O)-$NR^{xa}R^{xb}$;

R^{xa} and R^{xb} represent C_{1-4}alkyl;

R^{1b} represents F;

Y^1 represents -O-;

R^2 represents hydrogen;

U represents N;

n1, n2, n3 and n4 are each independently selected from 1 and 2;

X^1 represents CH, and X^2 represents N;

R^4 represents isopropyl;

R^3 represents -CH_2-CH_2-CH_2-$NR^{8a}R^{8b}$;

R^{8a} and R^{8b} are each independently selected from the group consisting of C_{1-6}alkyl; and C_{1-6}alkyl substituted with one -O-C_{1-4}alkyl;

and the pharmaceutically acceptable salts and the solvates thereof.

The present invention relates in particular to compounds of Formula (I) as defined herein, and the tautomers and the stereoisomeric forms thereof, wherein

R^{1a} represents -C(=O)-$NR^{xa}R^{xb}$; or Het;

Het represents a 6-membered monocyclic aromatic ring containing two nitrogen atoms; wherein said 6-membered monocyclic aromatic ring is optionally substituted with one C_{3-6}cycloalkyl;

R^{xa} and R^{xb} represent C_{1-4}alkyl;

R^{1b} represents F;

Y^1 represents -O-;

R^2 is hydrogen;

U represents N;

n1, n2, n3 and n4 are each independently selected from 1 and 2;

X^1 represents CH, and X^2 represents N;

R^4 represents isopropyl;

R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$, -C_{1-6}alkyl-C(=O)-$NR^{9a}R^{9b}$, -C_{1-6}alkyl-OH, or -C_{1-6}alkyl-NR^{11}-C(=O)-O-C_{1-4}alkyl-O-C(=O)-C_{1-4}alkyl;

R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; -C(=O)-C_{1-4}alkyl; -C(=O)-O-C_{1-4}alkyl; -C(=O)-$NR^{12a}R^{12b}$; and C_{1-6}alkyl substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo, -$S(=O)_2$-C_{1-4}alkyl, and -O-C_{1-4}alkyl;

R^{9a}, R^{9b}, R^{12a}, and R^{12b} are each independently selected from the group consisting of hydrogen and C_{1-6}alkyl;

and the pharmaceutically acceptable salts and the solvates thereof.

The present invention relates in particular to compounds of Formula (I) as defined herein, and the tautomers and the stereoisomeric forms thereof, wherein

R^{1a} represents -C(=O)-$NR^{xa}R^{xb}$;

R^{xa} and R^{xb} represent C_{1-4}alkyl;

R^{1b} represents F;

Y^1 represents -O-;

R^2 is hydrogen;

U represents N;

n1, n2, n3 and n4 are each independently selected from 1 and 2;

X^1 represents CH, and X^2 represents N;

R^4 represents isopropyl;

R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$, -C_{1-6}alkyl-C(=O)-$NR^{9a}R^{9b}$, or -C_{1-6}alkyl-OH;

R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; -C(=O)-C_{1-4}alkyl; -C(=O)-O-C_{1-4}alkyl; -C(=O)-$NR^{12a}R^{12b}$; and C_{1-6}alkyl substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo, -$S(=O)_2$-C_{1-4}alkyl, and -O-C_{1-4}alkyl;

R^{9a}, R^{9b}, R^{12a}, and R^{12b} are each independently selected from the group consisting of hydrogen and C_{1-6}alkyl;

and the pharmaceutically acceptable salts and the solvates thereof.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
R^{1b} represents F.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
R^2 represents hydrogen.

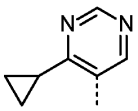
In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein n1 is 1, n2 is 2, n3 is 1, and n4 is 1.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
Y^1 represents -O-.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
Y^1 represents -O-; and
U represents N.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
Y^1 represents -O-;
U represents N;
R^{1b} represents F; and
R^2 represents hydrogen.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het represents



In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het represents a monocyclic 5- or 6-membered aromatic ring containing one or two nitrogen atoms; wherein said monocyclic 5- or 6-membered aromatic ring is substituted with one C_{3-6}cycloalkyl.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het represents a monocyclic 5- or 6-membered aromatic ring containing one or two nitrogen atoms; wherein said monocyclic 5- or 6-membered aromatic ring is substituted with one C_{3-6}cycloalkyl; and
R^{1b} represents F.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het represents a monocyclic 6-membered aromatic ring containing one or two nitrogen atoms; wherein said monocyclic 6-membered aromatic ring is substituted with one C_{3-6}cycloalkyl.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het represents a monocyclic 6-membered aromatic ring containing one or two nitrogen atoms; wherein said monocyclic 6-membered aromatic ring is substituted with one C_{3-6}cycloalkyl; and
R^{1b} represents F.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$;
wherein the C_{1-6}alkyl moiety in the R^3 definition may be substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo and -O-C_{1-4}alkyl.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$;
wherein the C_{1-6}alkyl moiety in the R^3 definition may be substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo, -OH, and -O-C_{1-4}alkyl.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$;
wherein the C_{1-6}alkyl moiety in the R^3 definition may be substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo and -O-C_{1-4}alkyl;
R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; and C_{1-6}alkyl substituted with one, two or three substituents each independently selected from the group consisting of -OH, cyano, halo, -S(=O)$_2$-C_{1-4}alkyl, -O-C_{1-4}alkyl, -C(=O)-$NR^{10a}R^{10b}$, and -NR^{10c}-C(=O)-C_{1-4}alkyl.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$;
wherein the C_{1-6}alkyl moiety in the R^3 definition may be substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo, -OH, and -O-C_{1-4}alkyl;
R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; and C_{1-6}alkyl substituted with one, two or three substituents each independently selected from the group consisting of -OH, cyano, halo, -S(=O)$_2$-C_{1-4}alkyl, -O-C_{1-4}alkyl, -C(=O)-$NR^{10a}R^{10b}$, and -NR^{10c}-C(=O)-C_{1-4}alkyl.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$;
wherein the C_{1-6}alkyl moiety in the R^3 definition may be substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo and -O-C_{1-4}alkyl;
R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; and C_{1-6}alkyl substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo, -$S(=O)_2$-C_{1-4}alkyl, -O-C_{1-4}alkyl, and -C(=O)-$NR^{10a}R^{10b}$.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$;
wherein the C_{1-6}alkyl moiety in the R^3 definition may be substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo and -O-C_{1-4}alkyl;
R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; and C_{1-6}alkyl substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo, -$S(=O)_2$-C_{1-4}alkyl, -O-C_{1-4}alkyl, -C(=O)-$NR^{10a}R^{10b}$, and -NR^{10c}-C(=O)-C_{1-4}alkyl.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$;
wherein the C_{1-6}alkyl moiety in the R^3 definition may be substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo, -OH, and -O-C_{1-4}alkyl;
R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; and C_{1-6}alkyl substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo, -$S(=O)_2$-C_{1-4}alkyl, -O-C_{1-4}alkyl, and -C(=O)-$NR^{10a}R^{10b}$.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$;
wherein the C_{1-6}alkyl moiety in the R^3 definition may be substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo, -OH, and -O-C_{1-4}alkyl;
R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; and C_{1-6}alkyl substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo, -$S(=O)_2$-C_{1-4}alkyl, -O-C_{1-4}alkyl, -C(=O)-$NR^{10a}R^{10b}$, and -NR^{10c}-C(=O)-C_{1-4}alkyl.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
R^3 represents -C_{2-6}alkyl-$NR^{8a}R^{8b}$;
wherein the C_{2-6}alkyl moiety in the R^3 definition may be substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo and -O-C_{1-4}alkyl.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
R^3 represents -C_{2-6}alkyl-$NR^{8a}R^{8b}$;
wherein the C_{2-6}alkyl moiety in the R^3 definition may be substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo, -OH, and -O-C_{1-4}alkyl.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
R^3 represents -C_{2-6}alkyl-$NR^{8a}R^{8b}$;
wherein the C_{2-6}alkyl moiety in the R^3 definition may be substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo and -O-C_{1-4}alkyl;
R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; and C_{1-6}alkyl substituted with one, two or three substituents each independently

selected from the group consisting of -OH, cyano, halo, -S(=O)$_2$-C$_{1-4}$alkyl, -O-C$_{1-4}$alkyl, -C(=O)-NR^{10a}R^{10b}, and -NR^{10c}-C(=O)-C$_{1-4}$alkyl.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
R^3 represents -C$_{2-6}$alkyl-NR^{8a}R^{8b};
wherein the C$_{2-6}$alkyl moiety in the R^3 definition may be substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo, -OH, and -O-C$_{1-4}$alkyl;
R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C$_{1-6}$alkyl; and C$_{1-6}$alkyl substituted with one, two or three substituents each independently selected from the group consisting of -OH, cyano, halo, -S(=O)$_2$-C$_{1-4}$alkyl, -O-C$_{1-4}$alkyl, -C(=O)-NR^{10a}R^{10b}, and -NR^{10c}-C(=O)-C$_{1-4}$alkyl.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
R^3 represents -C$_{2-6}$alkyl-NR^{8a}R^{8b};
wherein the C$_{2-6}$alkyl moiety in the R^3 definition may be substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo, -OH, and -O-C$_{1-4}$alkyl;
R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C$_{1-6}$alkyl; and C$_{1-6}$alkyl substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo, -S(=O)$_2$-C$_{1-4}$alkyl, -O-C$_{1-4}$alkyl, and -C(=O)-NR^{10a}R^{10b}.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
R^3 represents -C$_{2-6}$alkyl-NR^{8a}R^{8b};
wherein the C$_{2-6}$alkyl moiety in the R^3 definition may be substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo and -O-C$_{1-4}$alkyl;
R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C$_{1-6}$alkyl; and C$_{1-6}$alkyl substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo, -S(=O)$_2$-C$_{1-4}$alkyl, -O-C$_{1-4}$alkyl, and -C(=O)-NR^{10a}R^{10b}.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein

R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$;

R^{8a} and R^{8b} are each independently selected from the group consisting of C_{1-6}alkyl; and C_{1-6}alkyl substituted with one, two or three substituents each independently selected from the group consisting of -OH, cyano, halo, -$S(=O)_2$-C_{1-4}alkyl, -O-C_{1-4}alkyl, and -C(=O)-$NR^{10a}R^{10b}$.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein

R^3 represents -C_{2-6}alkyl-$NR^{8a}R^{8b}$;

wherein the C_{2-6}alkyl moiety in the R^3 definition may be substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo, -OH, and -O-C_{1-4}alkyl;

R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; and C_{1-6}alkyl substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo, -$S(=O)_2$-C_{1-4}alkyl, -O-C_{1-4}alkyl, -C(=O)-$NR^{10a}R^{10b}$, and -NR^{10c}-C(=O)-C_{1-4}alkyl.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein

R^3 represents -C_{2-6}alkyl-$NR^{8a}R^{8b}$;

wherein the C_{2-6}alkyl moiety in the R^3 definition may be substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo and -O-C_{1-4}alkyl;

R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; and C_{1-6}alkyl substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo, -$S(=O)_2$-C_{1-4}alkyl, -O-C_{1-4}alkyl, -C(=O)-$NR^{10a}R^{10b}$, and -NR^{10c}-C(=O)-C_{1-4}alkyl.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as

mentioned in any of the other embodiments, wherein
R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$;

R^{8a} and R^{8b} are each independently selected from the group consisting of C_{1-6}alkyl; and C_{1-6}alkyl substituted with one, two or three substituents each independently selected from the group consisting of -OH, cyano, halo, -$S(=O)_2$-C_{1-4}alkyl, -O-C_{1-4}alkyl, -$C(=O)$-$NR^{10a}R^{10b}$, and -NR^{10c}-$C(=O)$-C_{1-4}alkyl.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$;
R^{8a} represents C_{1-6}alkyl; and
R^{8b} represents C_{1-6}alkyl substituted with one -O-C_{1-4}alkyl.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$, -C_{1-6}alkyl-$C(=O)$-$NR^{9a}R^{9b}$, -C_{1-6}alkyl-OH, or -C_{1-6}alkyl-NR^{11}-$C(=O)$-O-C_{1-4}alkyl-O-$C(=O)$-C_{1-4}alkyl;
wherein each of the C_{1-4}alkyl or C_{1-6}alkyl moieties in the R^3 definitions independently of each other may be substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo or -O-C_{1-4}alkyl.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$, -C_{1-6}alkyl-$C(=O)$-$NR^{9a}R^{9b}$, or -C_{1-6}alkyl-NR^{11}-$C(=O)$-O-C_{1-4}alkyl-O-$C(=O)$-C_{1-4}alkyl;
wherein each of the C_{1-4}alkyl or C_{1-6}alkyl moieties in the R^3 definitions independently of each other may be substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo, -OH, and -O-C_{1-4}alkyl.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
R^3 represents -CH_2-CH_2-CH_2-$NR^{8a}R^{8b}$.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein

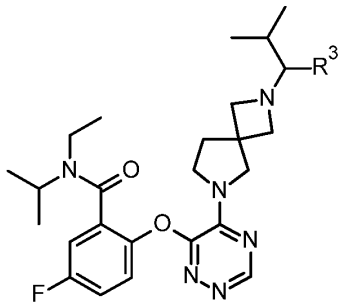
R^3 represents $-CH_2-CH_2-CH_2-NR^{8a}R^{8b}$;

R^{8a} represents methyl; and

R^{8b} represents $-CH_2-CH_2-OCH_3$.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein C_{1-6}alkyl in the R^3 definition $-C_{1-6}$alkyl-$NR^{8a}R^{8b}$ is limited to $-CH_2-CH_2-CH_2-$.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein the compounds of Formula (I) are restricted to compounds of Formula (I-y):



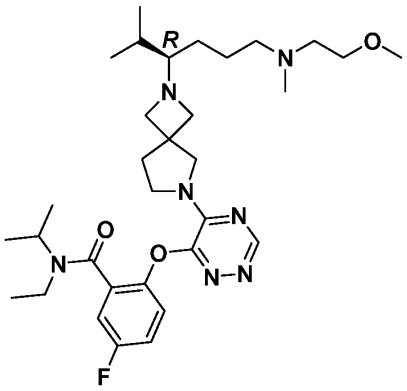
(I-y)

,

wherein R^3 is as defined for the compounds of Formula (I) or any subgroup thereof as mentioned in any of the other embodiments.

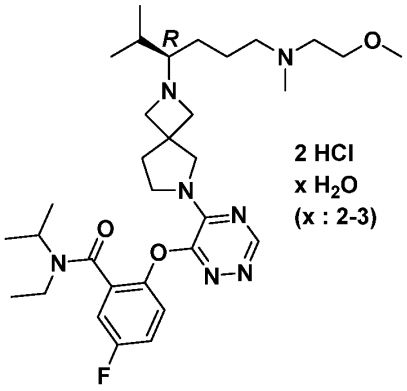
In Formula (I-y) n1 is 1, n2 is 2, n3 is 1, and n4 is 1.

In an embodiment the compound of Formula (I) is



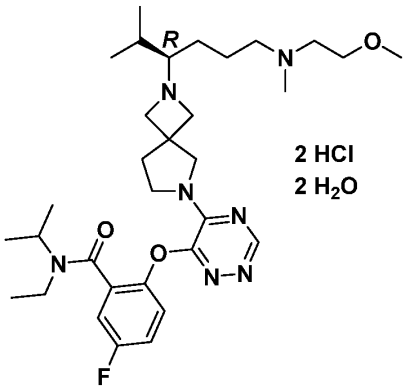
and pharmaceutically acceptable addition salts, and solvates thereof.

In an embodiment the compound of Formula (I) is



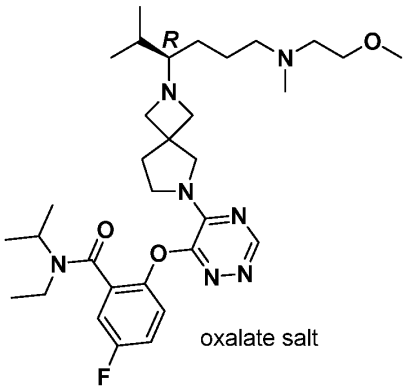
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In an embodiment the compound of Formula (I) is



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In an embodiment the compound of Formula (I) is



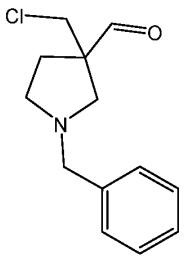
oxalate salt

In an embodiment, the present invention relates to a subgroup of Formula (I) as defined in the general reaction schemes.

In an embodiment the compound of Formula (I) is selected from the group consisting of any of the exemplified compounds,
tautomers and stereoisomeric forms thereof,
and the free bases, any pharmaceutically acceptable salts, and the solvates thereof.

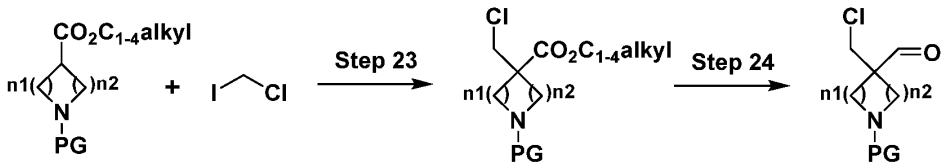
All possible combinations of the above indicated embodiments are considered to be embraced within the scope of the invention.

In another embodiment, the present invention relates to the intermediate



tautomers and stereoisomeric forms thereof,
and any pharmaceutically acceptable salts, and the solvates thereof.

In another embodiment, the present invention relates to a process for the preparation of an intermediate comprising the following steps:



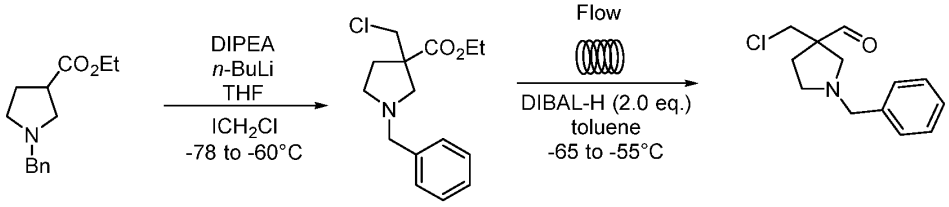
wherein PG is a suitable protecting group such as benzyl;

wherein n1 and n2 are as defined for formula (I);

Step 23: at a suitable temperature such as for example from -78 °C to -25 °C, in the presence of suitable bases such as for example DIEA and n-BuLi, in a suitable solvent such as for example THF;

Step 24: at a suitable temperature such as for example between -55°C and -65 °C, in the presence of suitable reducing agent such as for example DIBAL-H, in a suitable solvent such as for example toluene, conducted in a suitable flow chemistry system.

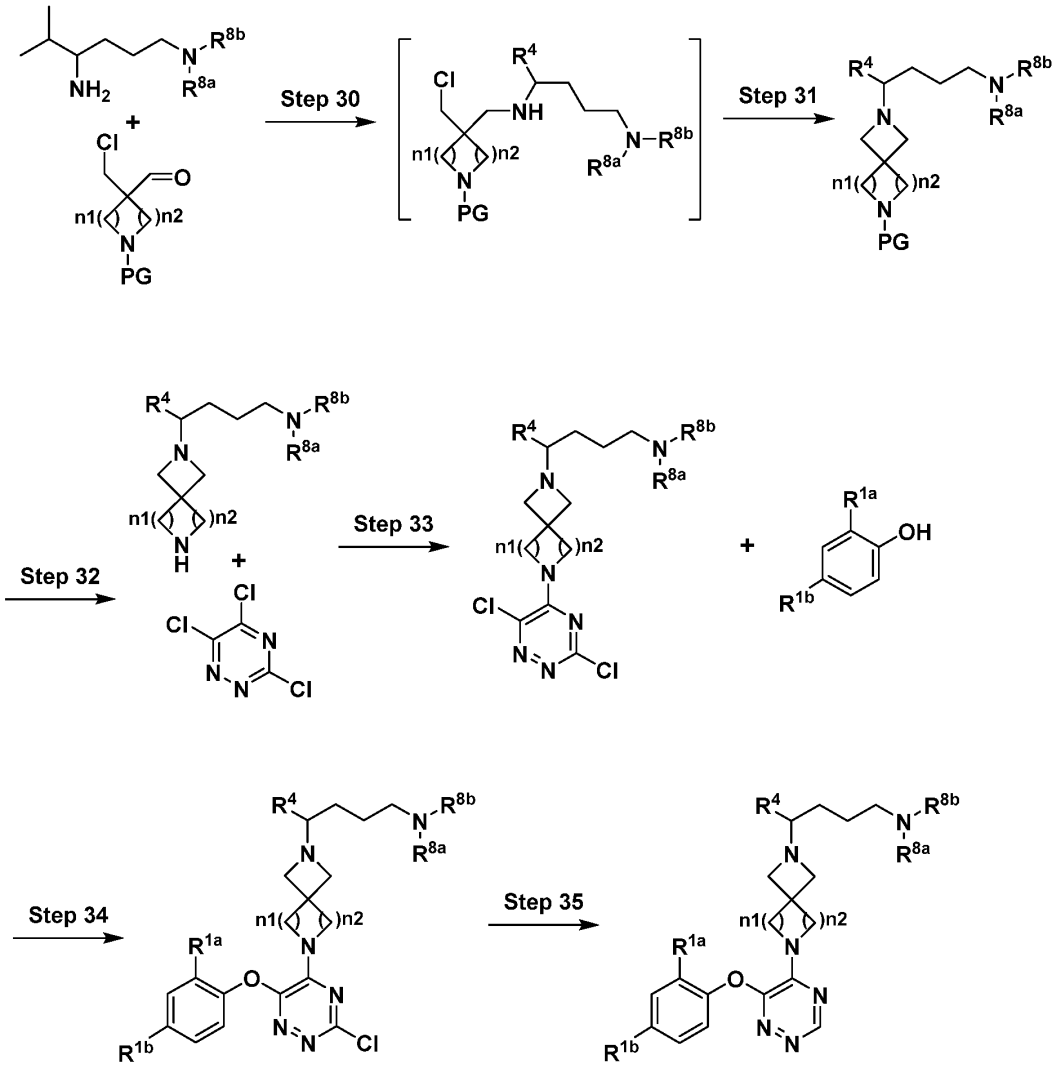
In another embodiment, the present invention relates to a process for the preparation of an intermediate comprising the following steps:



first reaction at a suitable temperature such as for example from -78 °C to -25 °C, in the presence of suitable bases such as for example DIEA and n-BuLi, in a suitable solvent such as for example THF;

then, reaction at a suitable temperature such as for example between -55°C and -65 °C, in the presence of suitable reducing agent such as for example DIBAL-H, in a suitable solvent such as for example toluene, conducted in a suitable flow chemistry system.

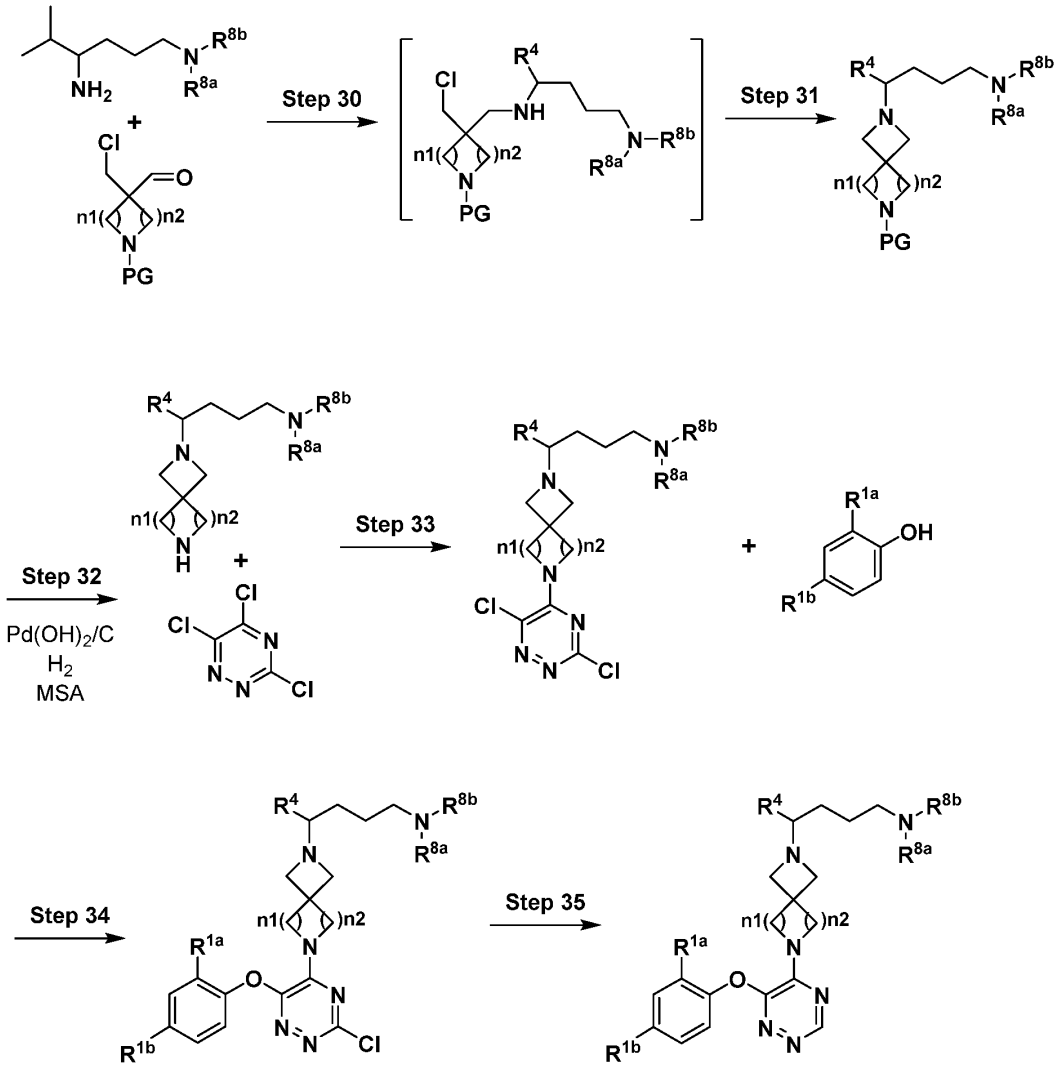
In another embodiment, the present invention relates to a process for the preparation of an intermediate comprising the following steps:



PG is a suitable protecting group such as benzyl;

other variables are as defined for formula (I).

In another embodiment, the present invention relates to a process for the preparation of an intermediate comprising the following steps:



PG is a suitable protecting group such as benzyl;

other variables are as defined for formula (I);

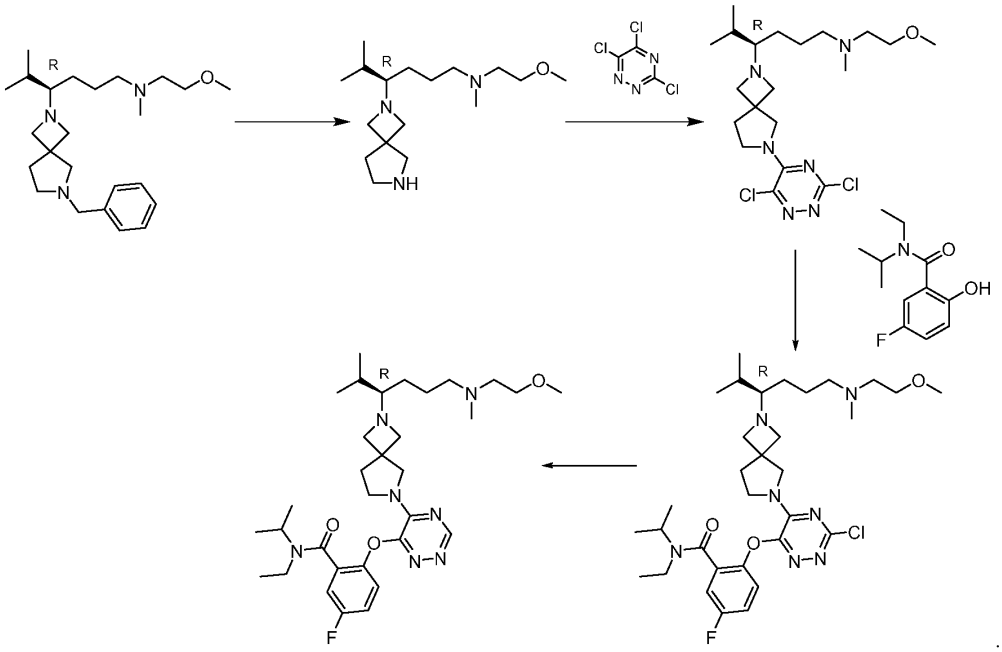
Step 30: at a suitable temperature such as for example from 5 °C to 30 °C, in the presence of a suitable base such as for example TEA, in the presence of suitable reducing agent such as for example $NaBH(OAc)_3$, in a suitable solvent such as for example toluene;

Step 31: at a suitable temperature such as for example from 50 °C to 55 °C, in the presence of a suitable base such as for example K_2HPO_4, in a suitable solvent such as for example H_2O;

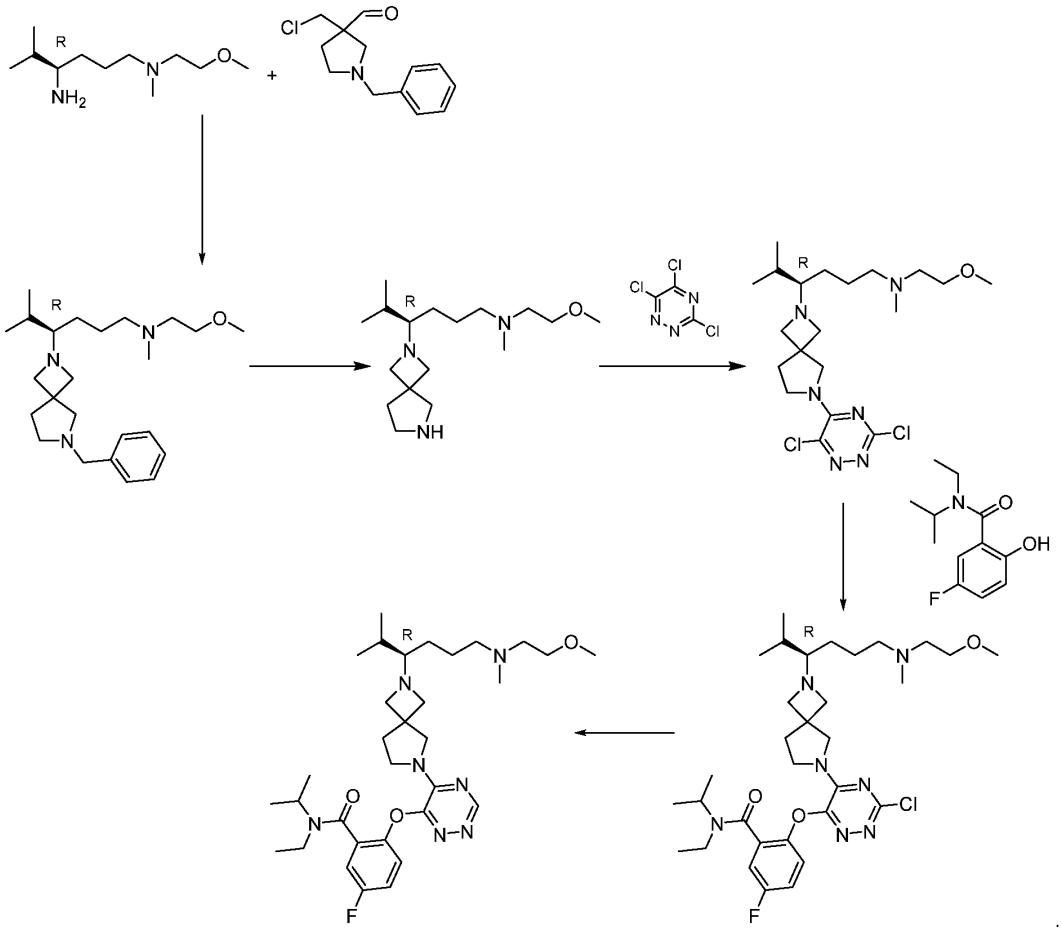
Step 32: at a suitable temperature such as for example from -5 °C to 45 °C, under a hydrogen atmosphere within a suitable pressure range such as for example from 0.27 to 0.40 MPa, in the presence of palladium hydroxide on carbon, in the presence of MSA in a suitable solvent such as EtOH;

Step 33: at a suitable temperature such as for example from -50 °C to -40 °C, in the presence of suitable base such as for example TEA, in a suitable solvent such as 2-methyltetrahydrofuran;
Step 34: at a suitable temperature such as for example from 20 °C to 30 °C, in the presence of suitable base such as for example TMG, in a suitable solvent such as 2-methyltetrahydrofuran;
Step 35: at a suitable temperature such as for example from 20 °C to 30 °C, under a hydrogen atmosphere within a suitable pressure range such as for example from 0.20 to 0.30 Mpa, in the presence of a suitable catalyst such as for example palladium on carbon, in a suitable solvent such as MeOH.

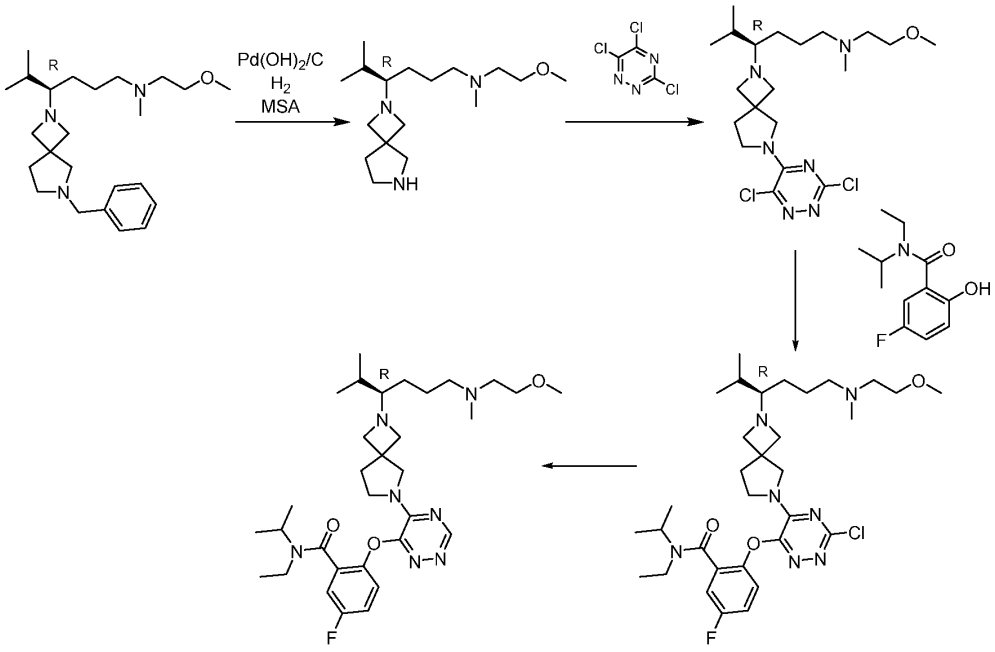
In another embodiment, the present invention relates to a process for the preparation of a compound comprising the following steps:



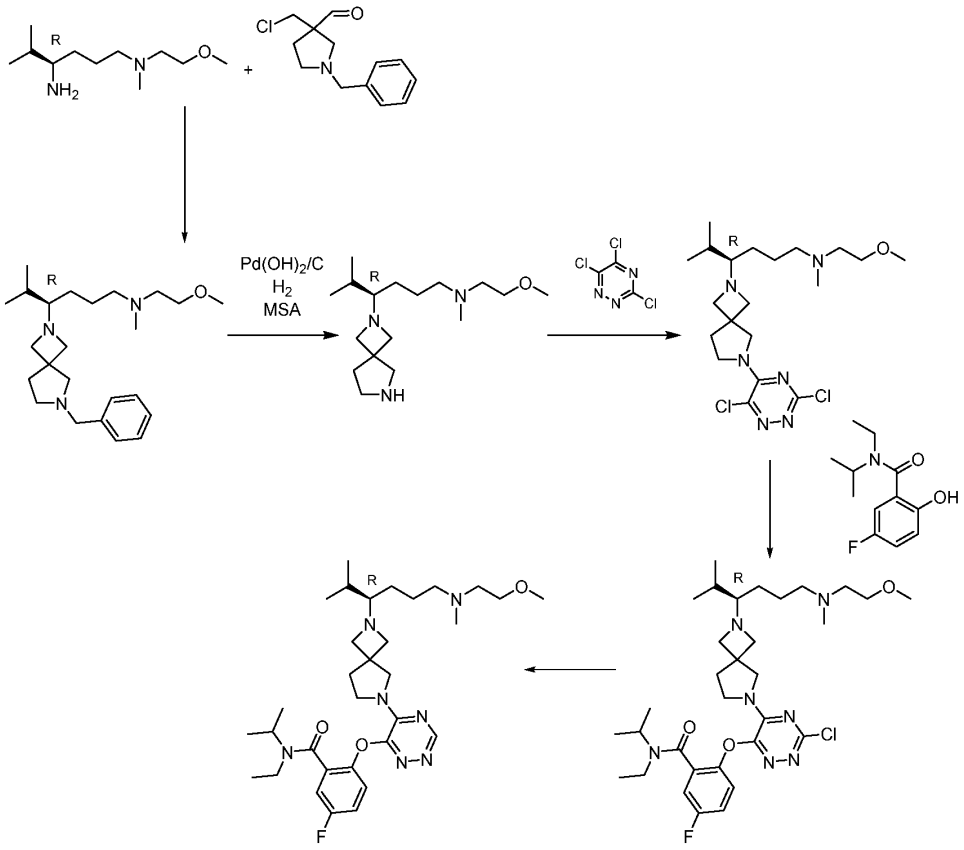
In another embodiment, the present invention relates to a process for the preparation of a compound comprising the following steps:



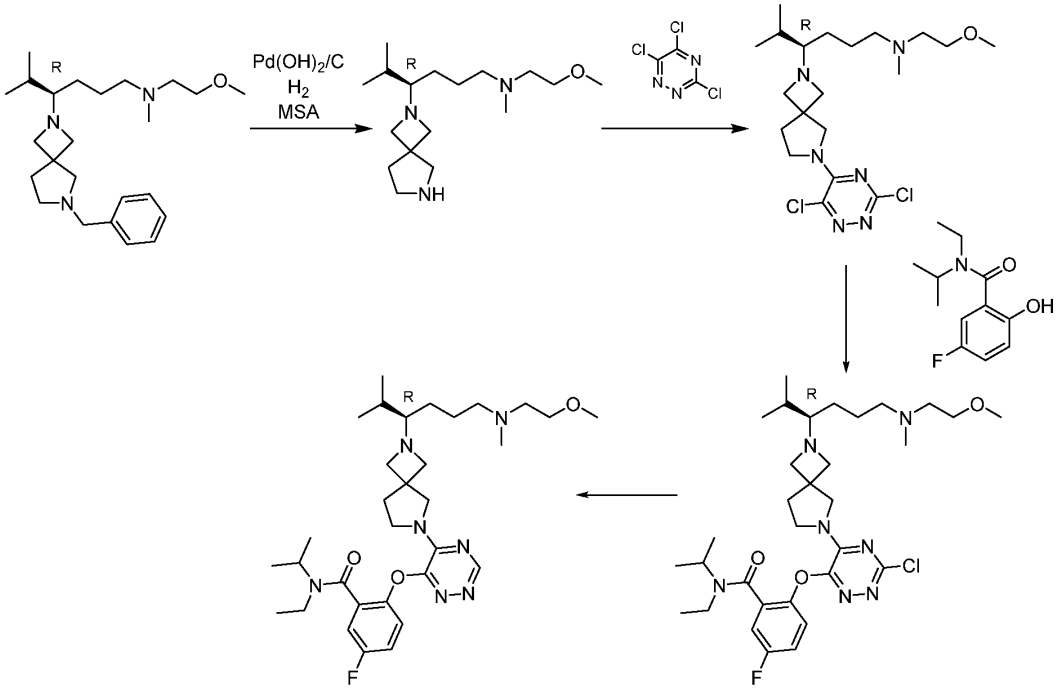
In another embodiment, the present invention relates to a process for the preparation of a compound comprising the following steps:



In another embodiment, the present invention relates to a process for the preparation of a compound comprising the following steps:



In another embodiment, the present invention relates to a process for the preparation of a compound comprising the following steps:



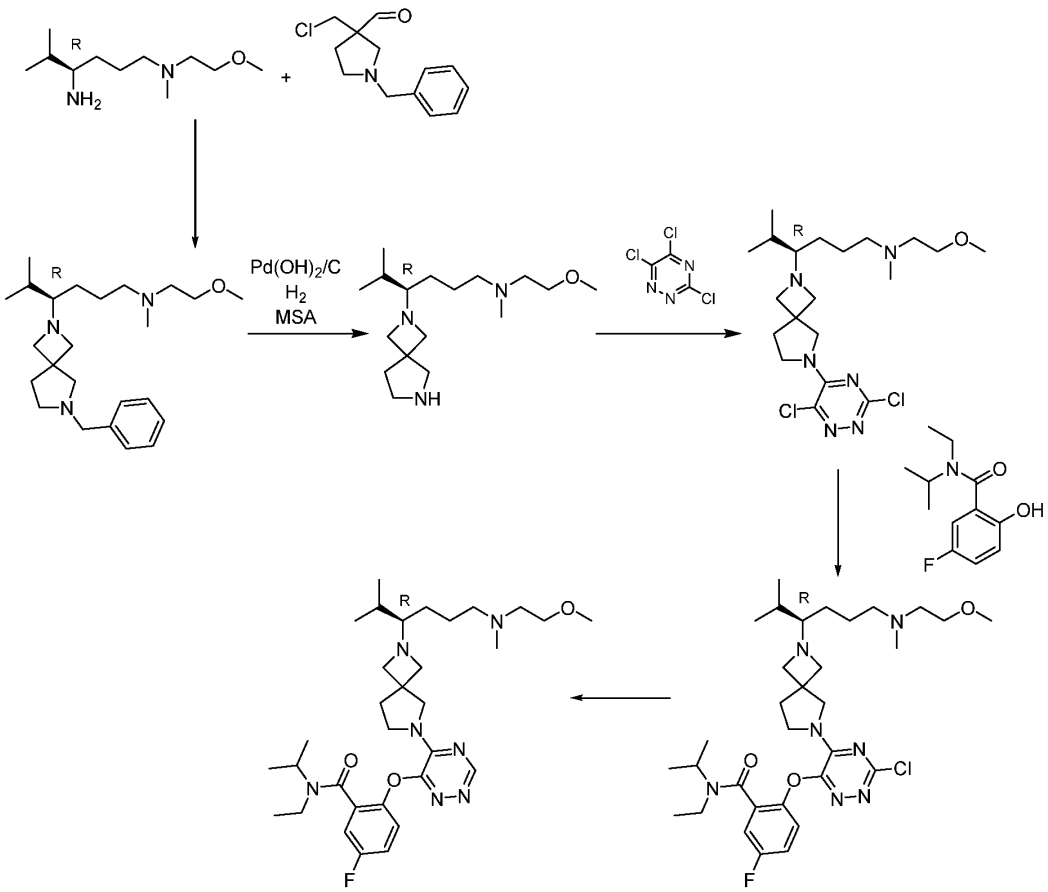
in a first step, at a suitable temperature such as for example from -5 °C to 45 °C, under a hydrogen atmosphere within a suitable pressure range such as for example from 0.27 to 0.40 MPa, in the presence of palladium hydroxide on carbon, in the presence of MSA in a suitable solvent such as EtOH;

in a next step at a suitable temperature such as for example from -50 °C to -40 °C, in the presence of suitable base such as for example TEA, in a suitable solvent such as 2-methyltetrahydrofuran;

in a next step at a suitable temperature such as for example from 20 °C to 30 °C, in the presence of suitable base such as for example TMG, in a suitable solvent such as 2-methyltetrahydrofuran;

in a next step at a suitable temperature such as for example from 20 °C to 30 °C, under a hydrogen atmosphere within a suitable pressure range such as for example from 0.20 to 0.30 Mpa, in the presence of a suitable catalyst such as for example palladium on carbon, in a suitable solvent such as MeOH.

In another embodiment, the present invention relates to a process for the preparation of a compound comprising the following steps:



In a first step first at a suitable temperature such as for example from 5 °C to 30 °C, in the presence of a suitable base such as for example TEA, in the presence of suitable reducing agent such as for example $NaBH(OAc)_3$, in a suitable solvent such as for example toluene; and then at a suitable temperature such as for example from 50 °C to 55 °C, in the presence of a suitable base such as for example K_2HPO_4, in a suitable solvent such as for example H_2O;

in a next step, at a suitable temperature such as for example from -5 °C to 45 °C, under a hydrogen atmosphere within a suitable pressure range such as for example from 0.27 to 0.40 MPa, in the presence of palladium hydroxide on carbon, in the presence of MSA in a suitable solvent such as EtOH;

in a next step at a suitable temperature such as for example from -50 °C to -40 °C, in the presence of suitable base such as for example TEA, in a suitable solvent such as 2-methyltetrahydrofuran;

in a next step at a suitable temperature such as for example from 20 °C to 30 °C, in the presence of suitable base such as for example TMG, in a suitable solvent such as 2-methyltetrahydrofuran;

in a next step at a suitable temperature such as for example from 20 °C to 30 °C, under a hydrogen atmosphere within a suitable pressure range such as for example from 0.20 to 0.30

Mpa, in the presence of a suitable catalyst such as for example palladium on carbon, in a suitable solvent such as MeOH.

METHODS FOR THE PREPARATION OF COMPOUNDS OF FORMULA (I)

In this section, as in all other sections unless the context indicates otherwise, references to Formula (I) also include all other sub-groups and examples thereof as defined herein.

The general preparation of some typical examples of the compounds of Formula (I) is described hereunder and in the specific examples, and are generally prepared from starting materials which are either commercially available or prepared by standard synthetic processes commonly used by those skilled in the art of organic chemistry. The following schemes are only meant to represent examples of the invention and are in no way meant to be a limit of the invention.

Alternatively, compounds of the present invention may also be prepared by analogous reaction protocols as described in the general schemes below, combined with standard synthetic processes commonly used by those skilled in the art.

The skilled person will realize that in the reactions described in the Schemes, although this is not always explicitly shown, it may be necessary to protect reactive functional groups (for example hydroxy, amino, or carboxy groups) where these are desired in the final product, to avoid their unwanted participation in the reactions. In general, conventional protecting groups (PG) can be used in accordance with standard practice. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The skilled person will realize that in the reactions described in the Schemes, it may be advisable or necessary to perform the reaction under an inert atmosphere, such as for example under N_2-gas atmosphere.

It will be apparent for the skilled person that it may be necessary to cool the reaction mixture before reaction work-up (refers to the series of manipulations required to isolate and purify the product(s) of a chemical reaction such as for example quenching, column chromatography, extraction).

The skilled person will realize that heating the reaction mixture under stirring may enhance the reaction outcome. In some reactions microwave heating may be used instead of conventional heating to shorten the overall reaction time.

The skilled person will realize that another sequence of the chemical reactions shown in the Schemes below, may also result in the desired compound of Formula (I).

The skilled person will realize that intermediates and final compounds shown in the Schemes below may be further functionalized according to methods well-known by the person skilled in the art. The intermediates and compounds described herein can be isolated in free form or as a

salt, or a solvate thereof. The intermediates and compounds described herein may be synthesized in the form of mixtures of tautomers and stereoisomeric forms that can be separated from one another following art-known resolution procedures.

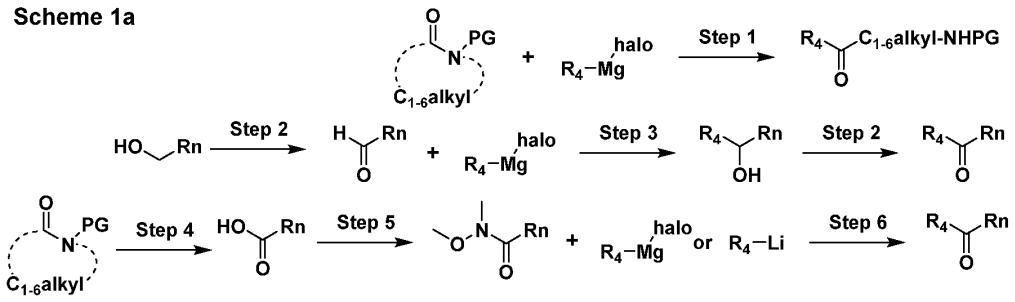
General Synthetic Schemes

All abbreviations used in the general schemes are as defined in the Table in the part Examples. Variables are as defined in the scope or as specifically defined in the general Schemes.

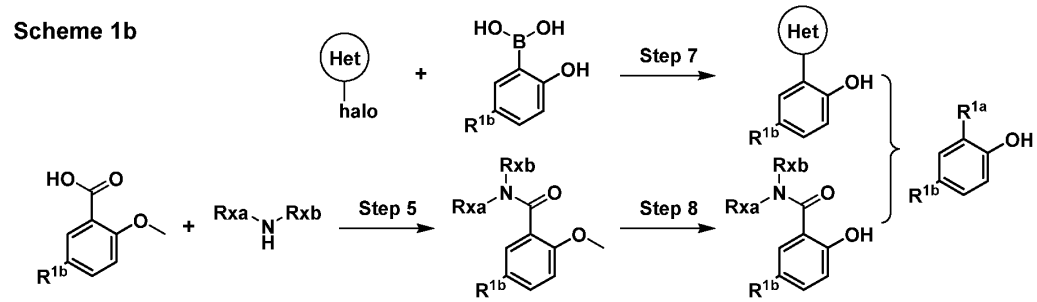
Part A) Schemes 1a, 1b, 1c, 2a, 2b and 3

Rn = C_{1-6}alkyl-NR^{8a}PG or C_{1-6}alkyl-OPG or C_{1-6}alkyl-C(=O)OR^{9a}, PG = protecting group

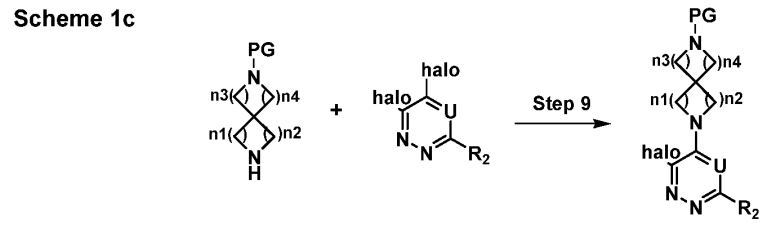
Scheme 1a



Scheme 1b



Scheme 1c



In Scheme 1a, 1b and 1c the following reaction conditions apply:

Step 1: at a suitable temperature such as for example -70°C, in the presence of a suitable base such as for example TMEDA and a suitable organometallic reagent such as for example isopropylmagnesium bromide, in a suitable solvent such as for example THF;

Step 2: at a suitable temperature such as for example from 0 °C to RT, in the presence of a suitable oxidative reagent such as for example DMP, in a suitable solvent such as for example DCM;

Step 3: at a suitable temperature such as for example from -20°C to RT, in the presence of a suitable organometallic reagent such as for example isopropylmagnesium bromide, in a suitable solvent such as for example THF;

Step 4: at a suitable temperature such as for example 80°C, in the presence of a suitable base such as for example NaOH, in suitable solvents such as for example THF and H_2O;

Step 5: at a suitable temperature such as for example RT, in the presence of suitable amide condensation reagents such as for example EDCI and HOBt, in the presence of a suitable base such as for example NMM, in a suitable solvent such as for example DCM;

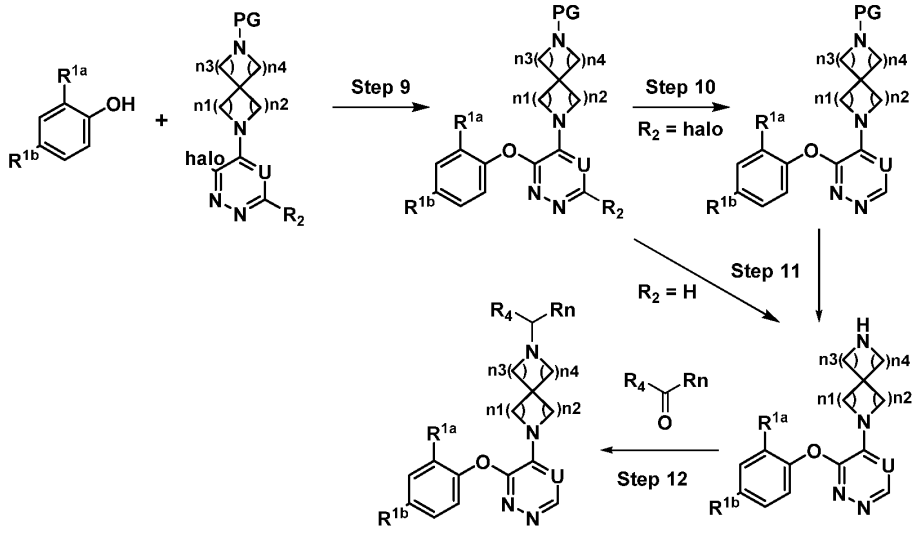
Step 6: at a suitable temperature such as for example -70°C, in the presence of a suitable organometallic reagent such as for example isopropyllithium, in a suitable solvent such as for example THF;

Step 7: at a suitable temperature such as for example 90 °C, in the presence of a suitable organometallic catalyst such as for example $Pd(dppf)Cl_2$, in the presence of a suitable base such as for example Na_2CO_3, in suitable solvents such as for example 1,4-dioxane and H_2O;

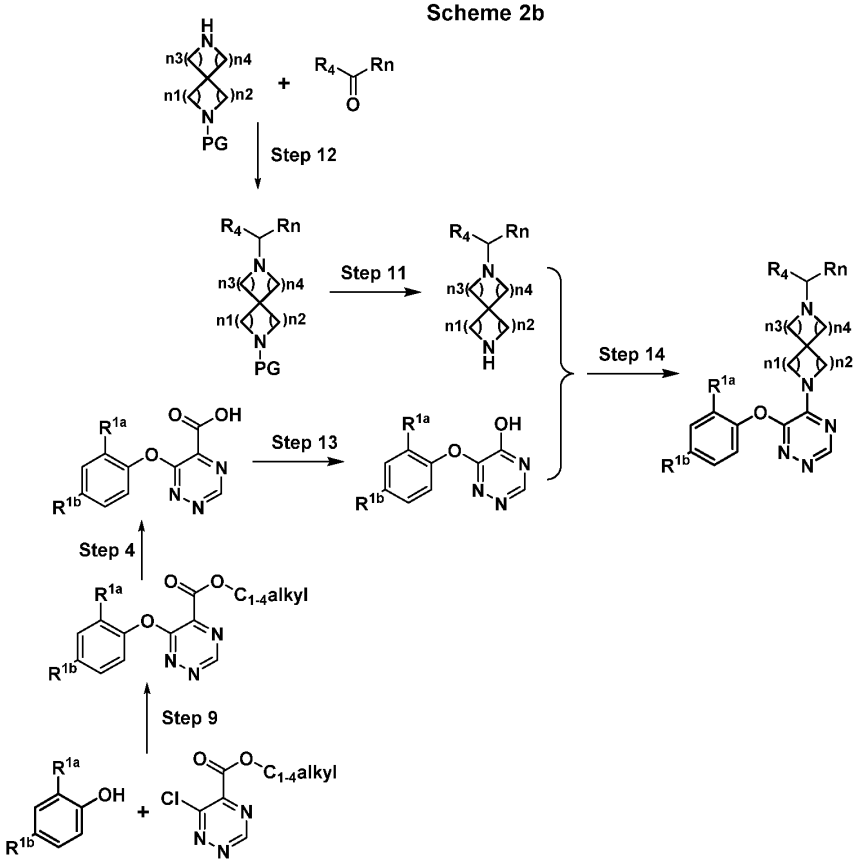
Step 8: at a suitable temperature such as for example from 0 °C to RT, in the presence of a suitable Lewis acid such as for example BBr_3, in a suitable solvent such as for example DCM;

Step 9: at a suitable temperature such as for example from -78 °C to 40 °C, in particular from 0 °C to RT, in the presence of a suitable base such as for example TEA, DBU or K_2CO_3, in a suitable solvent such as for example DCM, THF or DMF;

Scheme 2a



Scheme 2b



In Scheme 2a and 2b, the following reaction conditions apply:

Step 9: See Step 9 in Scheme 1;

Step 10: at a suitable temperature such as for example RT, in the presence of a suitable catalyst such as for example Pd/C, in the presence of a suitable reductive reagent such as for example H_2, optionally in the presence of a suitable base such as for example TEA, in a suitable solvent such as for example THF;

Alternatively, at a suitable temperature such as RT, in the presence of a suitable catalyst such as for example Pd(dppf)Cl_2·DCM complex, a suitable reducing agent such $NaBH_4$, a suitable base such as for example TMEDA, in a suitable solvent such as for example THF.

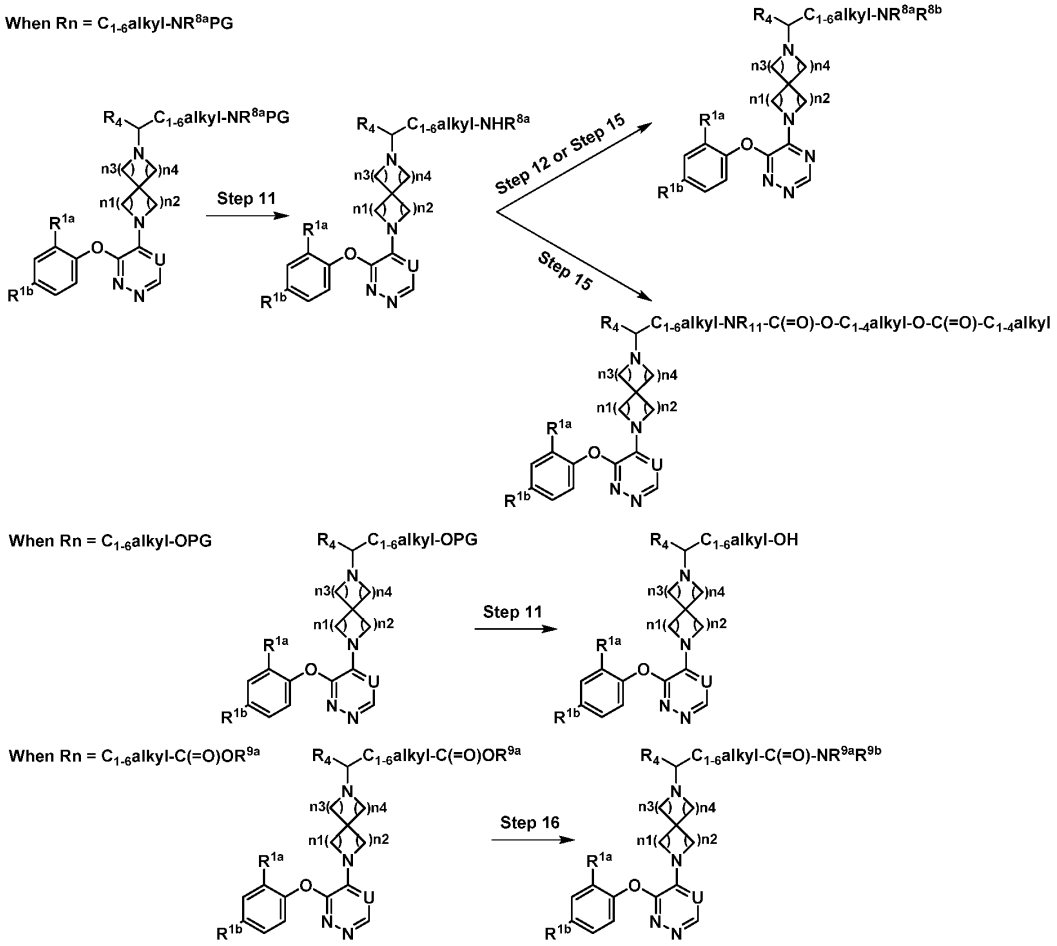
Step 11: for N deprotection, at a suitable temperature such as for example RT, in the presence of a suitable acid as for example TFA, in a suitable solvent such as for example DCM; for O deprotection, at a suitable temperature such as for example RT, in the presence of a suitable acid as for example 4-methylbenzenesulfonic acid, in a suitable solvent such as for example MeOH;

Step 12: at a suitable temperature such as for example 80 °C, optionally in the presence of a suitable Lewis acid such as for example $ZnCl_2$, in the presence of a suitable reductive reagent such as for example $NaBH_3CN$, in a suitable solvent such as for example MeOH;

Step 13: at a suitable temperature such as for example RT, in the presence of a suitable organometallic catalyst such as for example $Ag(Phen)_2OTf$, in the presence of a suitable brominating reagent such as for example 1,3-dibromo-1,3,5-triazinane-2,4,6-trione, in a suitable solvent such as for example DCE;

Step 14: at a suitable temperature such as for example RT, in the presence of a suitable chlorinating reagent such as for example oxalyl chloride, in the presence of DMF, in a suitable solvent such as for example DCM.

Scheme 3



In Scheme 3, the following reaction conditions apply:

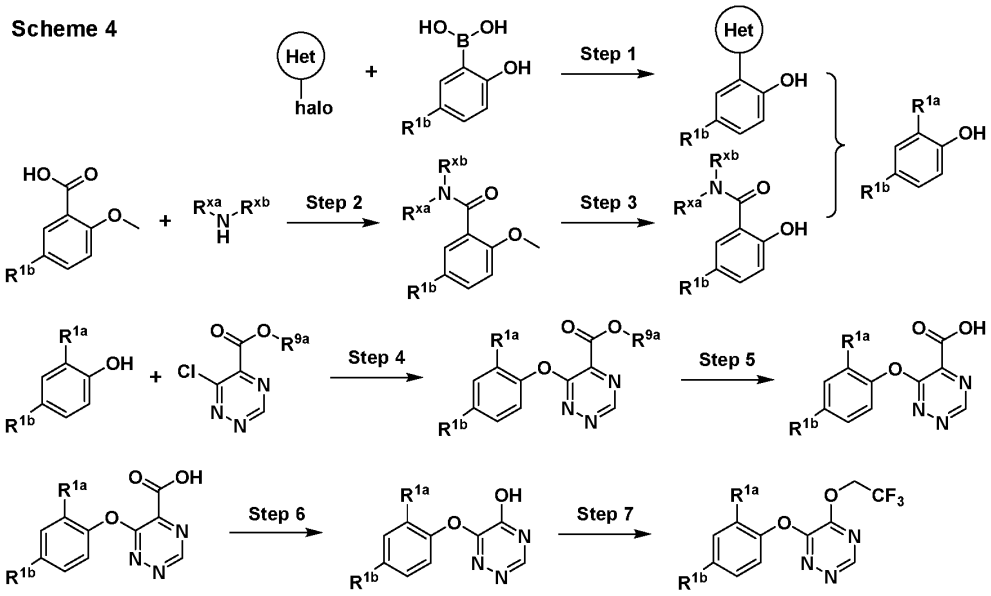
Step 11-12: See Step 11-12 in Scheme 2;

Step 15: at a suitable temperature such as for example 80 °C, in the presence of a suitable base such as for example Cs_2CO_3, in suitable solvent such as for example DMF;

Step 16: at a suitable temperature such as for example 40 °C, in the presence of a suitable base such as for example ammonia, in suitable solvent such as for example 1,4-dioxane.

Part B) Schemes 4, 5, 6, 7, 8, 9, 10, 11 and 12

Scheme 4



In Scheme 4, the following reaction conditions apply:

Step 1: at a suitable temperature such as for example 90 °C, in the presence of a suitable organometallic catalyst such as for example $Pd(dppf)Cl_2$, in the presence of a suitable base such as for example Na_2CO_3, in suitable solvents such as for example 1,4-dioxane and H_2O;

Step 2: at a suitable temperature such as for example RT, in the presence of suitable amide condensation reagent such as for example HATU, in the presence of a suitable base such as for example DIEA, in a suitable solvent such as for example DCM;

Step 3: at a suitable temperature such as for example from -78 °C to RT, in the presence of a suitable Lewis acid such as for example BBr_3, in a suitable solvent such as for example DCM;

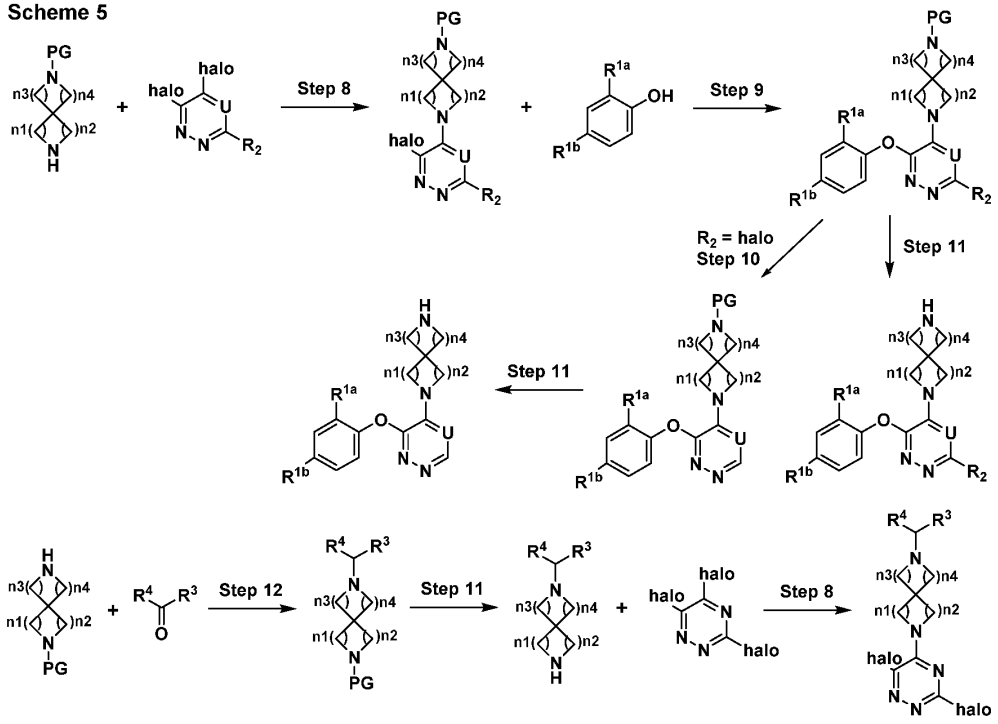
Step 4: at a suitable temperature such as for example from -78 °C to 40 °C, in particular from 0 °C to RT, in the presence of a suitable base such as for example TEA, DBU or K_2CO_3, in a suitable solvent such as for example DCM, THF or DMF;

Step 5: at a suitable temperature such as for example RT, in the presence of a suitable base such as for example $LiOH{\cdot}H_2O$, in suitable solvents such as for example THF and H_2O;

Step 6: at a suitable temperature such as for example RT, in the presence of a suitable organometallic catalyst such as for example $Ag(Phen)_2OTf$, in the presence of a suitable brominating reagent such as for example 1,3-dibromo-1,3,5-triazinane-2,4,6-trione, in a suitable solvent such as for example DCE;

Step 7: at a suitable temperature such as for example RT, in the presence of a suitable brominating reagent such as 1,3-dibromo-1,3,5-triazinane-2,4,6-trione, in the presence of 2,2,2-trifluoroethan-1-ol as solvent.

Scheme 5



In Scheme 5, the following reaction conditions apply:

Step 8: at a suitable temperature such as for example from -78 °C to 40 °C, in particular from 0 °C to RT, in the presence of a suitable base such as for example TEA, DBU or K_2CO_3, in a suitable solvent such as for example DCM, THF or DMF;

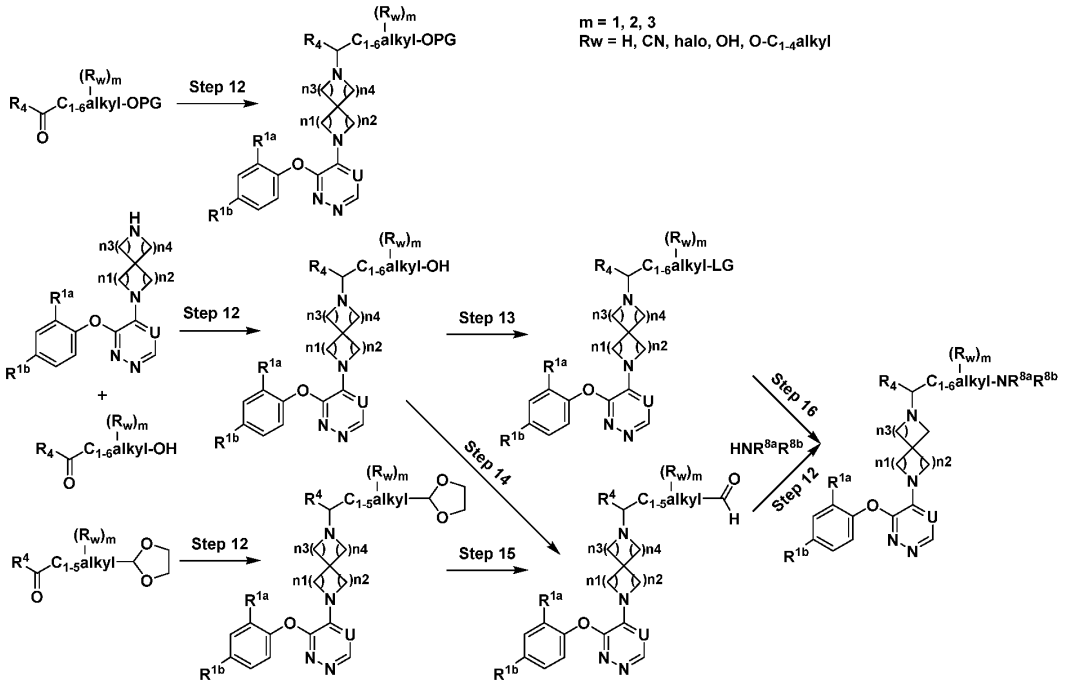
Step 9: at a suitable temperature such as for example from -78 °C to 40 °C, in particular from 0 °C to RT, in the presence of a suitable base such as for example TEA, DBU or K_2CO_3, in a suitable solvent such as for example DCM, THF or DMF;

Step 10: at a suitable temperature such as for example RT, in the presence of a suitable organometallic catalyst as for example Pd/C and a suitable base as for example TEA, in a suitable solvent such as for example MeOH under H_2 atmosphere;

Step 11: When PG is Boc, at a suitable temperature such as for example RT, in the presence of a suitable acid as for example TFA, in a suitable solvent such as for example DCM.

Scheme 6

m = 1, 2, 3
Rw = H, CN, halo, OH, O-C1-4alkyl



In Scheme 6, the following reaction conditions apply:

Step 12: reductive amination condition, at a suitable temperature such as for example from RT to 80 °C, in the presence or absence of a suitable Lewis acid such as for example $ZnCl_2$ or an acid for example AcOH, in the presence of a suitable reducing agent such as for example $NaBH_3CN$, in a suitable solvent such as for example MeOH;

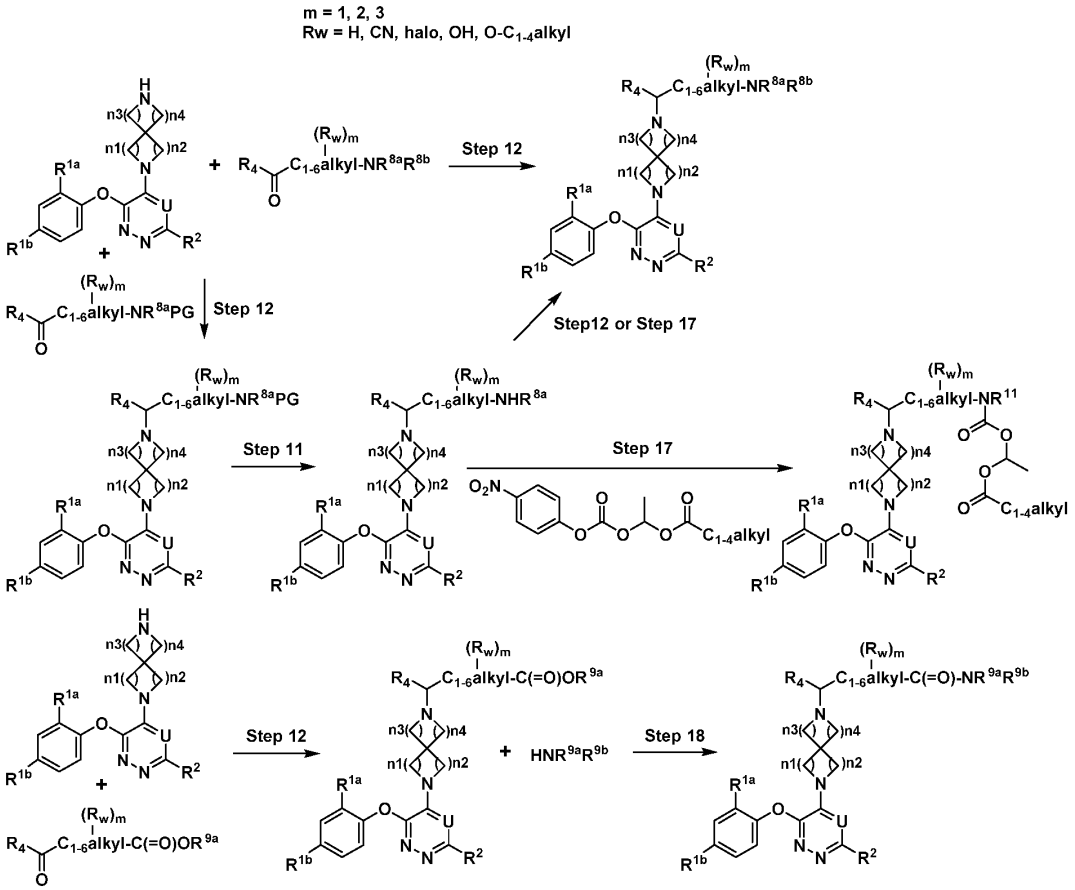
Step 13: at a suitable temperature such as for example 0 °C, in the presence of a suitable electrophile as for example MsCl, in the presence of a suitable base such as for example TEA, in a suitable solvent such as for example DCM;

Step 14: at a suitable temperature such as for example from 0 °C to RT, in the presence of a suitable oxidizing agent as for example DMP, in a suitable solvent such as for example DCM;

Step 15: at a suitable temperature such as for example 50 °C, in the presence of a suitable acid as for example HCl, in a suitable solvent such as for example ACN;

Step 16: at a suitable temperature such as for example RT, in the presence or absence of a suitable base as for example TEA, in a suitable solvent such as for example THF.

Scheme 7



In Scheme 7, the following reaction conditions apply:

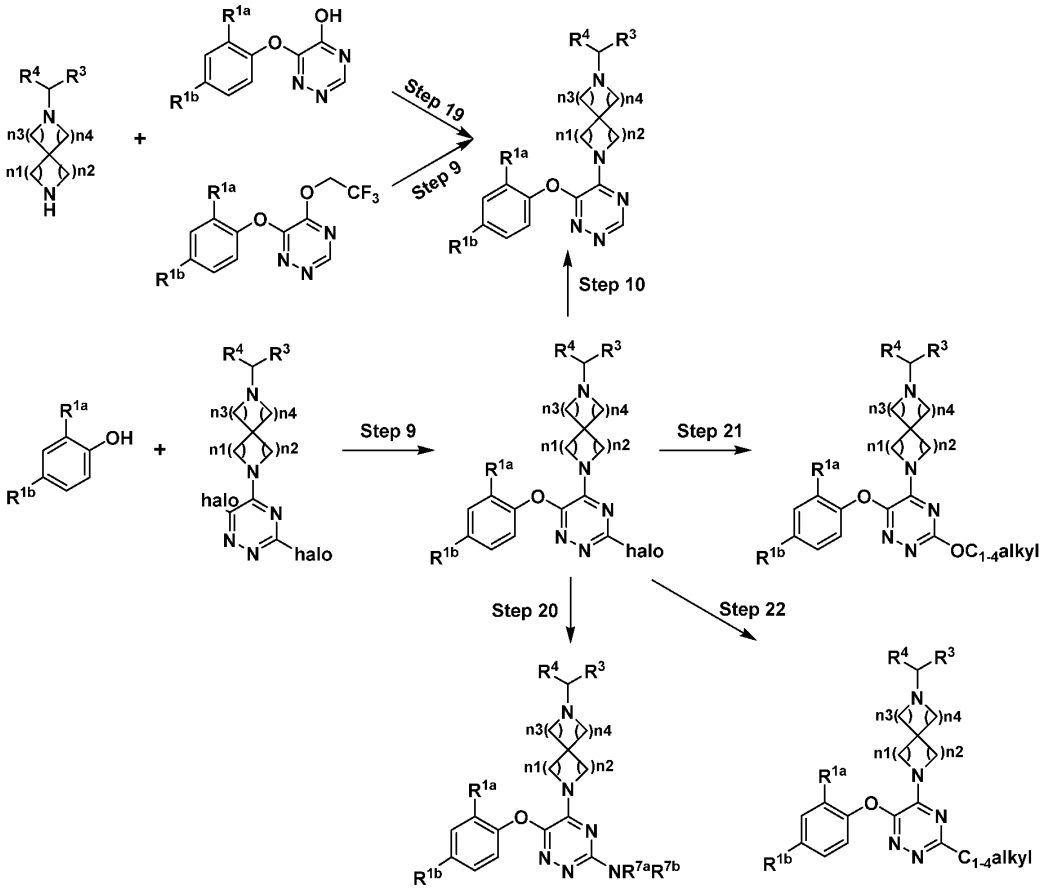
Step 11: When PG is Boc, at a suitable temperature such as for example RT, in the presence of a suitable acid as for example TFA, in a suitable solvent such as for example DCM;

Step 12: reductive amination condition, at a suitable temperature such as for example from RT to 80 °C, in the presence or absence of a suitable Lewis acid such as for example $ZnCl_2$ or an acid for example AcOH, in the presence of a suitable reducing agent such as for example $NaBH_3CN$, in a suitable solvent such as for example MeOH;

Step 17: at a suitable temperature such as for example from RT to 80 °C, in the presence of a suitable base such as for example DIEA or Cs_2CO_3, in suitable solvent such as for example DCM or DMF;

Step 18: at a suitable temperature such as for example 40 °C, in the presence of a suitable base such as for example ammonia, in suitable solvent such as for 1,4-dioxane.

Scheme 8



In Scheme 8, the following reaction conditions apply:

Step 9: at a suitable temperature such as for example from -78 °C to 40 °C, in particular from 0 °C to RT, in the presence of a suitable base such as for example TEA, DBU or K_2CO_3, in a suitable solvent such as for example DCM, THF or DMF;

Step 10: at a suitable temperature such as for example RT, in the presence of a suitable organometallic catalyst as for example Pd/C, optionally in the presence of a suitable base as for example TEA, in a suitable solvent such as for example MeOH under H_2 atmosphere;

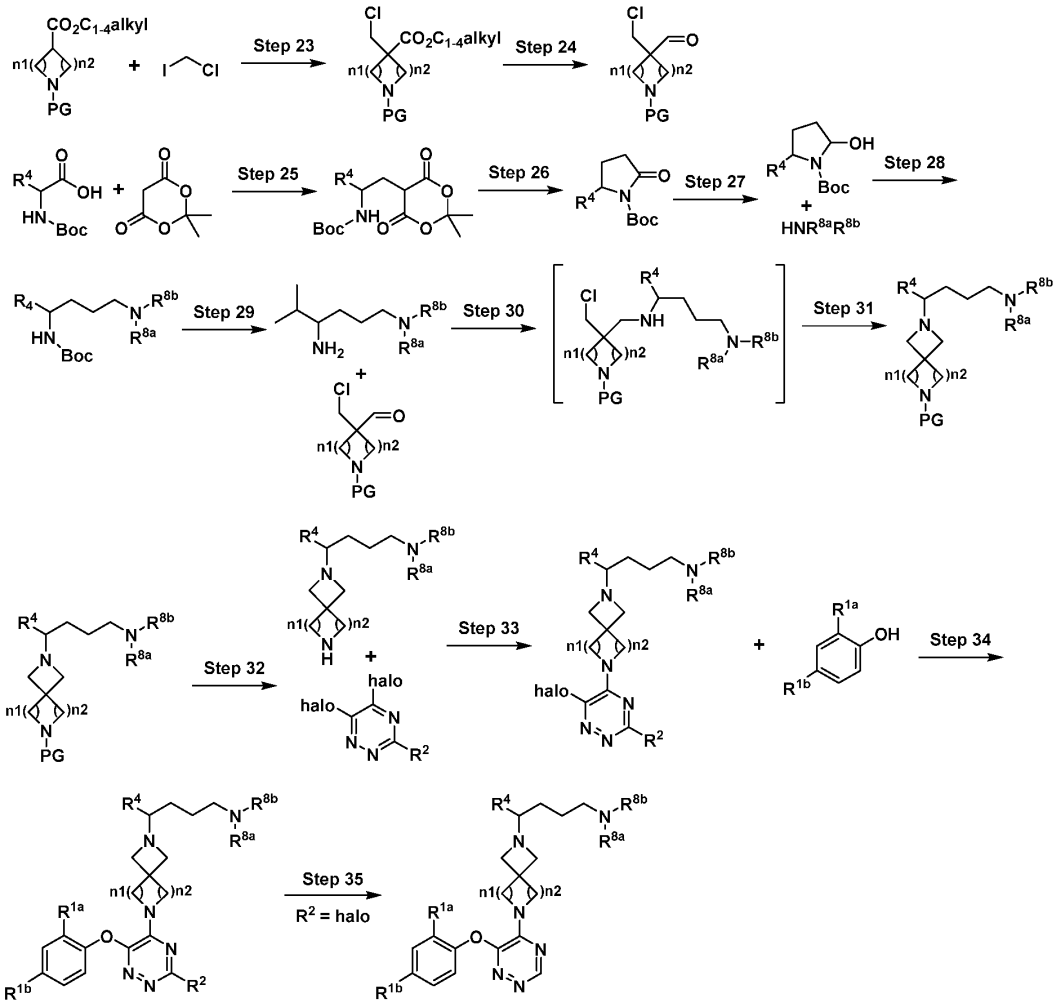
Step 19: at a suitable temperature such as for example RT, in the presence of a suitable chlorinating reagent such as for example oxalyl chloride, in the presence of DMF, in a suitable solvent such as for example DCM;

Step 20: at a suitable temperature such as for example 90 °C, in the presence of a suitable nucleophilic amine, in a suitable solvent such as for example EtOH;

Step 21: at a suitable temperature such as for example RT, in the presence of a suitable acid such as for example HCl in dioxane, in a suitable solvent such as for example MeOH;

Step 22: at a suitable temperature such as for example 110 °C, in the presence of a suitable boron reagent such as for example trimethylboroxine, in the presence of a suitable organometallic catalyst such as for example tetrakis(triphenylphosphine)palladium(0), in the presence of a suitable base such as for example K_2CO_3, in a suitable solvent such as for example 1,4-dioxane;

Scheme 9



In Scheme 9, the following reaction conditions apply:

Step 23: at a suitable temperature such as for example from -78 °C to -25 °C, in the presence of suitable bases such as for example DIEA and n-BuLi, in a suitable solvent such as for example THF;s

Step 24: at a suitable temperature such as for example between -65 °C and – 55°C, in the presence of suitable reducing agent such as for example DIBAL-H, in a suitable solvent such as for example toluene, preferably conducted in a suitable flow chemistry system;

Step 25: first at a suitable temperature such as for example from -10 °C to 10 °C, in the presence of a suitable base such as for example DMAP, in the presence of a suitable condensation agent such as for example DCC, in a suitable solvent such as for example DCM; then at a suitable temperature such as for example from -10 °C to 0 °C, in the presence of a suitable acid such as for example AcOH, in the presence of a suitable reducing agent such as for example $NaBH_4$, in a suitable solvent such as for example DCM;

Step 26: in a suitable solvent such as for example toluene and heated to reflux;

Step 27: at a suitable temperature such as for example from -5 °C to 5 °C, in the presence of suitable reducing agent such as for example $LiBH_4$, in a suitable solvent such as for example 2-methyltetrahydrofuran;

Step 28: at a suitable temperature such as for example from 15 °C to 25 °C, in the presence of a suitable reducing agent such as for example $NaBH(OAc)_3$, in a suitable solvent such as for example DCM;

Step 29: at a suitable temperature such as for example from 15 °C to 25 °C, in the presence of a suitable acid such as for HCl, in a suitable solvent such as for example IPA;

Step 30: at a suitable temperature such as for example from 5 °C to 30 °C, in the presence of a suitable base such as for example TEA, in the presence of suitable reducing agent such as for example $NaBH(OAc)_3$, in a suitable solvent such as for example toluene;

Step 31: at a suitable temperature such as for example from 50 °C to 55 °C, in the presence of a suitable base such as for example K_2HPO_4, in a suitable solvent such as for example H_2O;

Step 32: When PG is Bn at a suitable temperature such as for example from -5 °C to 45 °C, under a hydrogen atmosphere within a suitable pressure range such as for example from 0.27 to 0.40 MPa, in the presence of a suitable catalyst such as for example palladium hydroxide on carbon, in the presence of a suitable acid as for example MSA in a suitable solvent such as EtOH;

Step 33: at a suitable temperature such as for example from -50 °C to -40 °C, in the presence of suitable base such as for example TEA, in a suitable solvent such as 2-methyltetrahydrofuran;

Step 34: at a suitable temperature such as for example from 20 °C to 30 °C, in the presence of suitable base such as for example TMG, in a suitable solvent such as 2-methyltetrahydrofuran;

Step 35: at a suitable temperature such as for example from 20 °C to 30 °C, under a hydrogen atmosphere within a suitable pressure range such as for example from 0.20 to 0.30 Mpa, in the

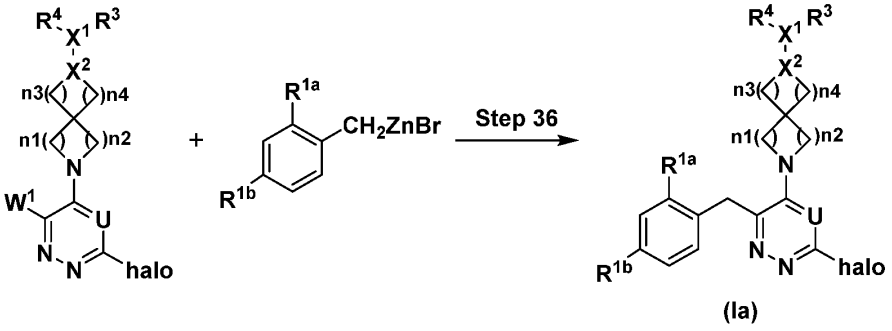
presence of a suitable catalyst such as for example palladium on carbon, in a suitable solvent such as MeOH;

alternatively, at a suitable temperature such as room temperature, in the presence of a suitable catalyst such as for example 1,1'-Bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex, a suitable reducing agent such sodium borohydride , a suitable base such as for example *N,N,N',N'*-tetramethylethylenediamine, in a suitable solvent such as for example tetrahydrofuran.

SCHEME 10

In general, compounds of Formula (I) wherein Y^1 is limited to -CH_2-, and R^2 is limited to W^1, hereby named compounds of Formula (Ia), can be prepared according to the following reaction Scheme 10. In Scheme 10, W^1 represents chloro, bromo or iodo; all other variables are defined according to the scope of the present invention.

Scheme 10



(Ia)

In Scheme 10, the following reaction conditions apply:

Step 36: at a suitable temperature ranged from 60 °C to 100 °C, in presence of a suitable catalyst such as palladium acetate ($Pd(OAc)_2$) or tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) or tetrakis(triphenylphosphine)palladium(0), in a suitable solvent such as for example tetrahydrofuran or dioxane.

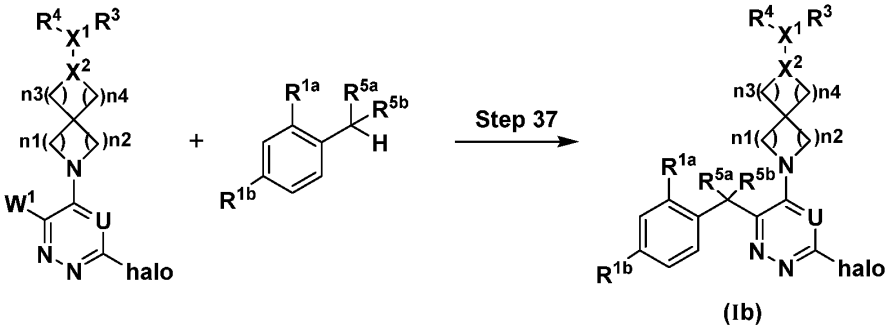
The skilled person will realize that starting from compound (Ia), analogous chemistry as reported in step 10 in scheme 5 and in steps 20, 21 and 22 in scheme 8 could be performed.

SCHEME 11

In general, compounds of Formula (I) wherein Y^1 is limited to -$CR^{5a}R^{5b}$- and R^2 is limited to W^1, hereby named compounds of Formula (Ib), can be prepared according to the following

reaction Scheme 11. In Scheme 11 at least one of R^{5a} and R^{5b} is other than hydrogen. All other variables are defined according to the scope of the present invention.

Scheme 11



(Ib)

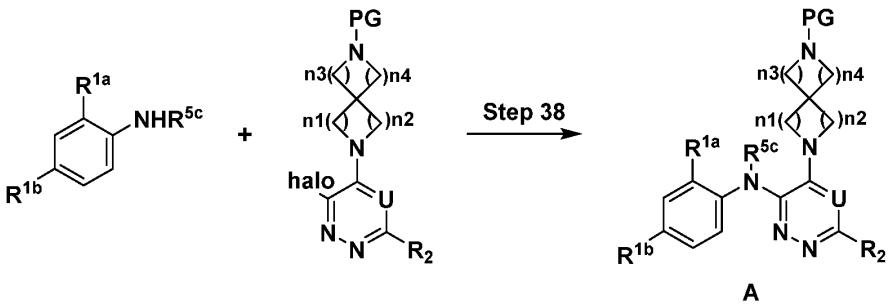
In Scheme 11, the following reaction condition apply:

Step 37: at a suitable temperature ranged from 80°C to 200°C, in presence of a suitable catalyst such as palladium acetate ($Pd(OAc)_2$), in the presence of a suitable ligand such as for example triphenylphosphine or tricyclohexylphosphine, in a suitable solvent such as for example dioxane, preferably in sealed conditions, optionally under microwave irradiation.

The skilled person will realize that starting from compound (Ib), analogous chemistry as reported in step 10 in scheme 5 and in steps 20, 21 and 22 in scheme 8 could be performed.

SCHEME 12

Scheme 12



In Scheme 12, the following reaction condition apply:

Step 38: at a suitable temperature such as for example from RT to 80 °C, in the presence of a suitable base such as for example DIEA, Cs_2CO_3 or DBU, in suitable solvent such as for example DCM, THF or DMF;

Alternatively, at a suitable temperature such as for example RT to 100 °C, in the presence of a suitable catalyst such as for example Pd_2dba_3, in the presence of a suitable ligand such as for example Xantphos, in the presence of a suitable base such as Cs_2CO_3 or Na_2CO_3, in a suitable solvent such dioxane or a mixture of dioxane and water

The skilled person will realize that starting from intermediate A, analogous chemistry as reported in case Y^1 represents O can be performed.

It will be appreciated that where appropriate functional groups exist, compounds of various formulae or any intermediates used in their preparation may be further derivatized by one or more standard synthetic methods employing condensation, substitution, oxidation, reduction, or cleavage reactions. Particular substitution approaches include conventional alkylation, arylation, heteroarylation, acylation, sulfonylation, halogenation, nitration, formylation and coupling procedures.

The compounds of Formula (I) may be synthesized in the form of racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. The racemic compounds of Formula (I) containing a basic nitrogen atom may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali. An alternative manner of separating the enantiomeric forms of the compounds of Formula (I) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically.

In the preparation of compounds of the present invention, protection of remote functionality (e.g., primary or secondary amine) of intermediates may be necessary. The need for such protection will vary depending on the nature of the remote functionality and the conditions of the preparation methods. Suitable amino-protecting groups (NH-Pg) include acetyl, trifluoroacetyl, t-butoxycarbonyl (Boc), benzyloxycarbonyl (CBz) and 9-fluorenylmethyleneoxycarbonyl (Fmoc). The need for such protection is readily determined by one skilled in the art. For a general description of protecting groups and their use, see T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, 4th ed., Wiley, Hoboken, New Jersey, 2007.

PHARMACOLOGY

It has been found that the compounds of the present invention block the interaction of menin with MLL proteins and oncogenic MLL fusion proteins per se, or can undergo metabolism to a (more) active form in vivo (prodrugs). Therefore the compounds according to the present invention and the pharmaceutical compositions comprising such compounds may be useful for the treatment or prevention, in particular treatment, of diseases such as cancer, including but not limited to leukemia, myelodysplastic syndrome (MDS), and myeloproliferative neoplasms (MPN); and diabetes.

In particular, the compounds according to the present invention and the pharmaceutical compositions thereof may be useful in the treatment or prevention of cancer. According to one embodiment, cancers that may benefit from a treatment with menin/MLL inhibitors of the invention comprise leukemias, lymphomas, myelomas or solid tumor cancers (e.g. prostate cancer, lung cancer, breast cancer, pancreatic cancer, colon cancer, liver cancer, melanoma and glioblastoma, etc.). In some embodiments, the leukemias include acute leukemias, chronic leukemias, myeloid leukemias, myelogeneous leukemias, lymphoblastic leukemias, lymphocytic leukemias, Acute myelogeneous leukemias (AML), Chronic myelogenous leukemias (CML), Acute lymphoblastic leukemias (ALL), Chronic lymphocytic leukemias (CLL), T cell prolymphocytic leukemias (T-PLL), Large granular lymphocytic leukemia, Hairy cell leukemia (HCL), MLL-rearranged leukemias, MLL-PTD leukemias, MLL amplified leukemias, MLL-positive leukemias, leukemias exhibiting *HOX/MEIS1* gene expression signatures etc.

In particular, the compounds according to the present invention and the pharmaceutical compositions thereof may be useful in the treatment or prevention of myelodysplastic syndrome (MDS) or myeloproliferative neoplasms (MPN).

In particular, compounds according to the present invention and the pharmaceutical compositions thereof may be useful in the treatment or prevention of leukemias, in particular nucleophosmin (NPM1)-mutated leukemias, e.g. NPM1c.

In particular, compounds according to the present invention and the pharmaceutical compositions thereof may be useful in the treatment or prevention of AML, in particular nucleophosmin (NPM1)-mutated AML (i.e., $NPM1^{mut}$ AML), more in particular abstract NPM1-mutated AML.

In particular, compounds according to the present invention and the pharmaceutical compositions thereof may be useful in the treatment or prevention of MLL-rearranged leukemias, in particular MLL-rearranged AML or ALL.

In particular, compounds according to the present invention and the pharmaceutical compositions thereof may be useful in the treatment or prevention of leukemias with MLL gene alterations, in particular AML or ALL with MLL gene alterations.

In particular, compounds according to the present invention and the pharmaceutical compositions thereof may be suitable for Q.D. dosing (once daily).

In particular, compounds according to the present invention and the pharmaceutical compositions thereof may be useful in the treatment or prevention of hematological cancer in a subject exhibiting NPM1 gene mutations and/or mixed lineage leukemia gene (*MLL*; *MLL1*; *KMT2A*) alterations, mixed lineage leukemia (MLL), MLL-related leukemia, MLL-associated leukemia, MLL-positive leukemia, MLL-induced leukemia, rearranged mixed lineage leukemia, leukemia associated with a MLL, rearrangement/alteration or a rearrangement/alteration of the MLL gene, acute leukemia, chronic leukemia, myelodysplastic syndrome (MDS), myeloproliferative neoplasms (MPN), insulin resistance, pre-diabetes, diabetes, or risk of diabetes, hyperglycemia, chromosomal rearrangement on chromosome 11q23, type-1 diabetes, type-2 diabetes; promoting proliferation of a pancreatic cell, where pancreatic cell is an islet cell, beta cell, the beta cell proliferation is evidenced by an increase in beta cell production or insulin production; and for inhibiting a menin-MLL interaction, where the MLL fusion protein target gene is HOX or MEIS1 in human.

Hence, the invention relates to compounds of Formula (I), the tautomers and the stereoisomeric forms thereof, and the pharmaceutically acceptable salts, and the solvates thereof, for use as a medicament.

The invention also relates to the use of a compound of Formula (I), a tautomer or a stereoisomeric form thereof, or a pharmaceutically acceptable salt, or a solvate thereof, or a pharmaceutical composition according to the invention, for the manufacture of a medicament.

The present invention also relates to a compound of Formula (I), a tautomer or a stereoisomeric form thereof, or a pharmaceutically acceptable salt, or a solvate thereof, or a pharmaceutical composition according to the invention, for use in the treatment, prevention, amelioration, control or reduction of the risk of disorders associated with the interaction of menin with MLL proteins and oncogenic MLL fusion proteins in a mammal, including a human, the treatment or prevention of which is affected or facilitated by blocking the interaction of menin with MLL proteins and oncogenic MLL fusion proteins.

Also, the present invention relates to the use of a compound of Formula (I), a tautomer or a stereoisomeric form thereof, or a pharmaceutically acceptable salt, or a solvate thereof, or a pharmaceutical composition according to the invention, for the manufacture of a medicament for treating, preventing, ameliorating, controlling or reducing the risk of disorders associated

with the interaction of menin with MLL proteins and oncogenic MLL fusion proteins in a mammal, including a human, the treatment or prevention of which is affected or facilitated by blocking the interaction of menin with MLL proteins and oncogenic MLL fusion proteins.

The invention also relates to a compound of Formula (I), a tautomer or a stereoisomeric form thereof, or a pharmaceutically acceptable salt, or a solvate thereof, for use in the treatment or prevention of any one of the diseases mentioned hereinbefore.

The invention also relates to a compound of Formula (I), a tautomer or a stereoisomeric form thereof, or a pharmaceutically acceptable salt, or a solvate thereof, for use in treating or preventing any one of the diseases mentioned hereinbefore.

The invention also relates to the use of a compound of Formula (I), a tautomer or a stereoisomeric form thereof, or a pharmaceutically acceptable salt, or a solvate thereof, for the manufacture of a medicament for the treatment or prevention of any one of the disease conditions mentioned hereinbefore.

The compounds of the present invention can be administered to mammals, preferably humans, for the treatment or prevention of any one of the diseases mentioned hereinbefore.

In view of the utility of the compounds of Formula (I), the tautomers and the stereoisomeric forms thereof, and the pharmaceutically acceptable salts, and the solvates thereof, there is provided a method of treating warm-blooded animals, including humans, suffering from any one of the diseases mentioned hereinbefore.

Said method comprises the administration, i.e. the systemic or topical administration, of a therapeutically effective amount of a compound of Formula (I), a tautomer or a stereoisomeric form thereof, or a pharmaceutically acceptable salt, or a solvate thereof, to warm-blooded animals, including humans.

Therefore, the invention also relates to a method for the treatment or prevention of any one of the diseases mentioned hereinbefore comprising administering a therapeutically effective amount of compound according to the invention to a patient in need thereof.

One skilled in the art will recognize that a therapeutically effective amount of the compounds of the present invention is the amount sufficient to have therapeutic activity and that this amount varies *inter alias*, depending on the type of disease, the concentration of the compound in the therapeutic formulation, and the condition of the patient. An effective therapeutic daily amount would be from about 0.005 mg/kg to 100 mg/kg. The amount of a compound according to the present invention, also referred to herein as the active ingredient, which is required to achieve a therapeutically effect may vary on case-by-case basis, for example with the particular compound, the route of administration, the age and condition of the recipient, and the particular disorder or disease being treated. A method of treatment may also include administering the active ingredient on a regimen of between one and four intakes per day. In these methods of

treatment the compounds according to the invention are preferably formulated prior to administration.

The present invention also provides compositions for preventing or treating the disorders referred to herein. Said compositions comprising a therapeutically effective amount of a compound of Formula (I), a tautomer or a stereoisomeric form thereof, or a pharmaceutically acceptable salt, or a solvate thereof, and a pharmaceutically acceptable carrier or diluent.

While it is possible for the active ingredient to be administered alone, it is preferable to present it as a pharmaceutical composition. Accordingly, the present invention further provides a pharmaceutical composition comprising a compound according to the present invention, together with a pharmaceutically acceptable carrier or diluent. The carrier or diluent must be "acceptable" in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipients thereof.

The pharmaceutical compositions may be prepared by any methods well known in the art of pharmacy, for example, using methods such as those described in Gennaro et al. Remington's Pharmaceutical Sciences (18^{th} ed., Mack Publishing Company, 1990, see especially Part 8 : Pharmaceutical preparations and their Manufacture).

The compounds of the present invention may be administered alone or in combination with one or more additional therapeutic agents. Combination therapy includes administration of a single pharmaceutical dosage formulation which contains a compound according to the present invention and one or more additional therapeutic agents, as well as administration of the compound according to the present invention and each additional therapeutic agent in its own separate pharmaceutical dosage formulation.

Therefore, an embodiment of the present invention relates to a product containing as first active ingredient a compound according to the invention and as further active ingredient one or more anticancer agent, as a combined preparation for simultaneous, separate or sequential use in the treatment of patients suffering from cancer.

The one or more other medicinal agents and the compound according to the present invention may be administered simultaneously (e.g. in separate or unitary compositions) or sequentially in either order. In the latter case, the two or more compounds will be administered within a period and in an amount and manner that is sufficient to ensure that an advantageous or synergistic effect is achieved. It will be appreciated that the preferred method and order of administration and the respective dosage amounts and regimes for each component of the combination will depend on the particular other medicinal agent and compound of the present invention being administered, their route of administration, the particular condition, in particular tumour, being treated and the particular host being treated.

The following examples further illustrate the present invention.

EXAMPLES

Several methods for preparing the compounds of this invention are illustrated in the following examples. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification, or alternatively can be synthesized by a skilled person by using well-known methods.

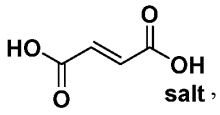
Abbreviation	Meaning
$Ag(Phen)_2OTf$	silver triflate–bis(1,10-phenanthroline) complex
2-MeTHF	2-methyltetrahydrofuran
ACN	acetonitrile
AcCl	acetyl chloride
AcOH	acetic acid
Ac_2O	acetic anhydride
aq.	aqueous
Ar	argon
BBr_3	tribromoborane
bn	benzyl
Boc	*tert*-butyloxycarbonyl
Boc_2O	di-*tert*-butyl dicarbonate
***n*-BuLi**	*n*-butyllithium
Cbz	benzyloxycarbonyl
CD_3OD	Methanol-d_4
$CHCl_3$	chloroform
Cs_2CO_3	cesium carbonate
conc.	concentrated
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCE	dichloroethane
DCM	dichloromethane
DDQ	4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile
DEA	diethylamine

Abbreviation	Meaning
DIBAL-H	diisobutylaluminum hydride
DIEA or DIPEA	*N*,*N*-diisopropylethylamine
DMAP	*N*,*N*-dimethylpyridin-4-amine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dppf	1,1′-ferrocenediyl-bis(diphenylphosphine)
EDCI	*N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride
EA or EtOAc	ethyl acetate
EtOH	ethanol
eq.	equivalent(s)
FA	formic acid
FCC	flash column chromatography
h	hour(s)
H_2	hydrogen
HATU	1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
H_2O	water
HCl	hydrochloric acid
HOBt	1-Hydroxybenzotriazole
HPLC	high performance liquid chromatography
ICH_2Cl	chloroiodomethane
IPA	isopropyl alcohol
IPAc	isopropyl acetate
K_2CO_3	potassium carbonate
KI	potassium iodide
K_2HPO_4	dipotassium phosphate
K_3PO_4	tripotassium phosphate
$LiAlD_4$	lithium aluminum deuteride
LAH	lithium aluminum hydride
$LiBH_4$	lithium borohydride

Abbreviation	Meaning
LDA	lithium diisopropylamide
LiCl	lithium chloride
LG	leaving group
Me	methyl
MeOH	methanol
2-MeTHF	2-methyltetrahydrofuran
min	minute(s)
mL	milliliters
mmol	millimoles
mg	milligram
$MgSO_4$	magnesium sulfate
MSA	methanesulfonic acid
MsCl	methanesulfonyl chloride
MS	molecular sieve
MTBE	methyl *tert*-butyl ether
N_2	nitrogen
NA	not available
$NaBH_3CN$	sodium cyanoborohydride
$NaBH(OAc)_3$	sodium triacetoxyborohydride
$NaBD_3CN$	sodium cyanoborodeuteride
Na_2CO_3	sodium carbonate
NaH	sodium hydride
$NaHCO_3$	sodium bicarbonate
NaI	sodium iodide
NaOAc	sodium acetate
NaOH	sodium hydroxide
Na_2SO_3	sodium sulfite
Na_2SO_4	sodium sulfate
NH_4Cl	ammonium chloride
NMM	1-4-Methylmorpholine
Pd_2dba_3	tris(dibenzylideneacetone)dipalladium(0)

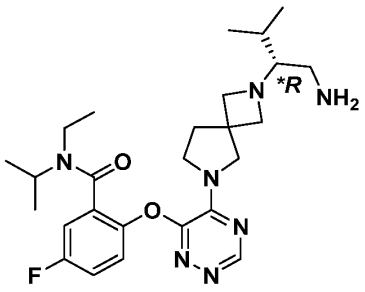
Abbreviation	Meaning
$Pd(dppf)Cl_2 \cdot DCM$	[1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium(0)
PE	petroleum ether
PG	protecting group
Phen	phenanthroline
psi	pound per square inch
***p*-TsOH**	*p*-toluenesulfonic acid
***p*-$TsOH \cdot H_2O$**	*p*-toluenesulfonic acid monohydrate
R_t	retention time
Rochelle's salt	potassium sodium tartrate tetrahydrate
RT	room temperature
sat.	saturated
SFC	supercritical fluid chromatography
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
***t*-BuOK**	potassium *tert*-butoxide
TEA	triethylamine
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
$Ti(OiPr)_4$	titanium(IV) isopropoxide
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TMG	1,1,3,3-tetramethylguanidine
TMSI	iodotrimethylsilane
Ts	*p*-toluenesulfonyl
TsCl	*p*-toluenesulfonyl chloride
v/v	volume per volume

Abbreviation	Meaning
vol.	volume(s)
wt	weight
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

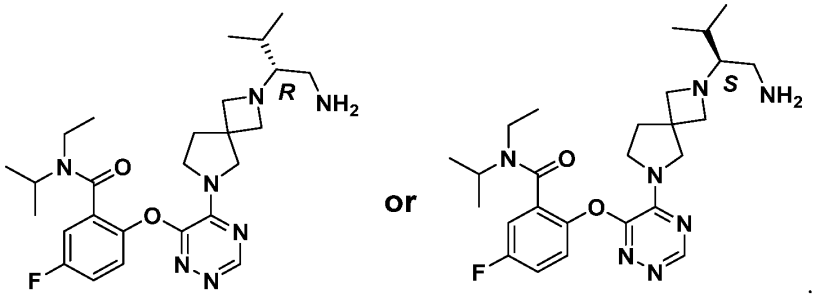
As understood by a person skilled in the art, compounds synthesized using the protocols as indicated may exist as a solvate e.g. hydrate, and/or contain residual solvent or minor impurities. Compounds or intermediates isolated as a salt form, may be integer stoichiometric i.e. mono- or di-salts, or of intermediate stoichiometry. When an intermediate or compound in the experimental part below is indicated as 'HCl salt' without indication of the number of equivalents of HCl, this means that the number of equivalents of HCl was not determined. The same principle will also apply to all other salt forms referred to in the experimental part, such as e.g. 'oxalate salt', 'formate salt' or ''.

The stereochemical configuration for centers in some compounds may be designated "*R*" or "*S*" when the mixture(s) was separated and absolute stereochemistry was known, or when only one enantiomer was obtained and absolute stereochemistry was known; for some compounds, the stereochemical configuration at indicated centers has been designated as "**R*" (first eluted from the column in case the column conditions of the separation are described in the synthesis protocol and when only one stereocenter present or indicated) or "**S*" (second eluted from the column in case the column conditions of the separation are described in the synthesis protocol and when only one stereocenter present or indicated) when the absolute stereochemistry is undetermined (even if the bonds are drawn stereo specifically) although the compound itself has been isolated as a single stereoisomer and is enantiomerically pure. In case a compound designated as "*R" is converted into another compound, the "*R" indication of the resulting compound is derived from its starting material.

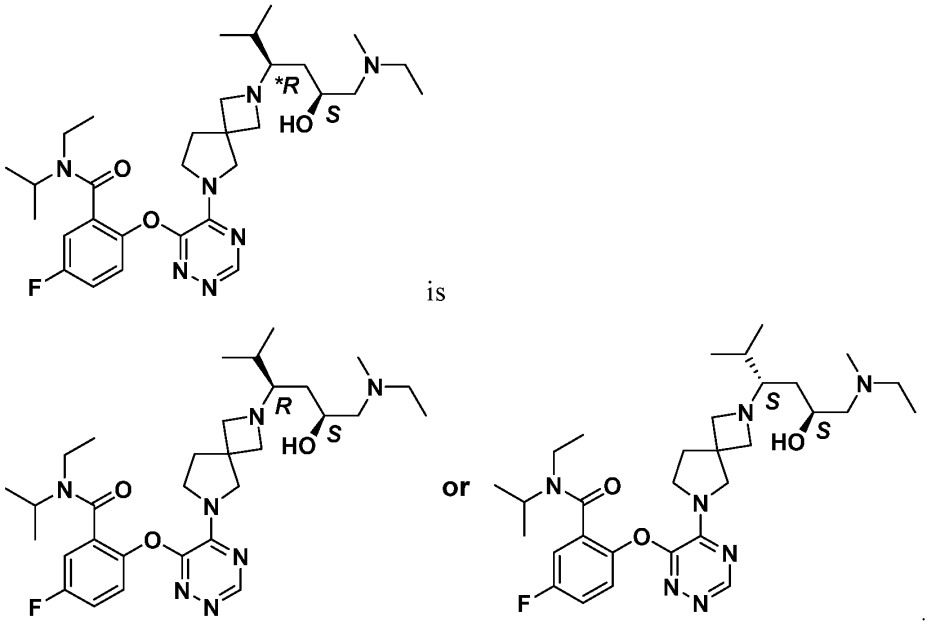
For example, it will be clear that Compound 25



is

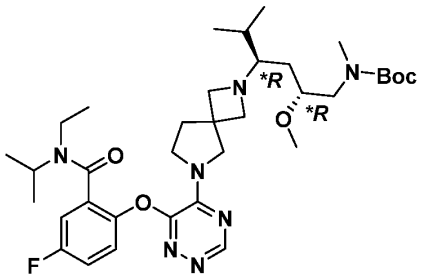


When "*R" or "*S" occurs together with a 2nd stereocentre which is designated "R" or "S" (known absolute stereochemistry for 2nd stereocentre) in the same molecule, the absolute stereochemistry of the stereocentre designated "*R" or "*S" is undetermined (even if the bonds are drawn stereo specifically) although the compound itself has been isolated as a single stereoisomer and is enantiomerically pure. "*R" or "*S" is assigned randomly for such molecules. For example, it will be clear that Compound 340

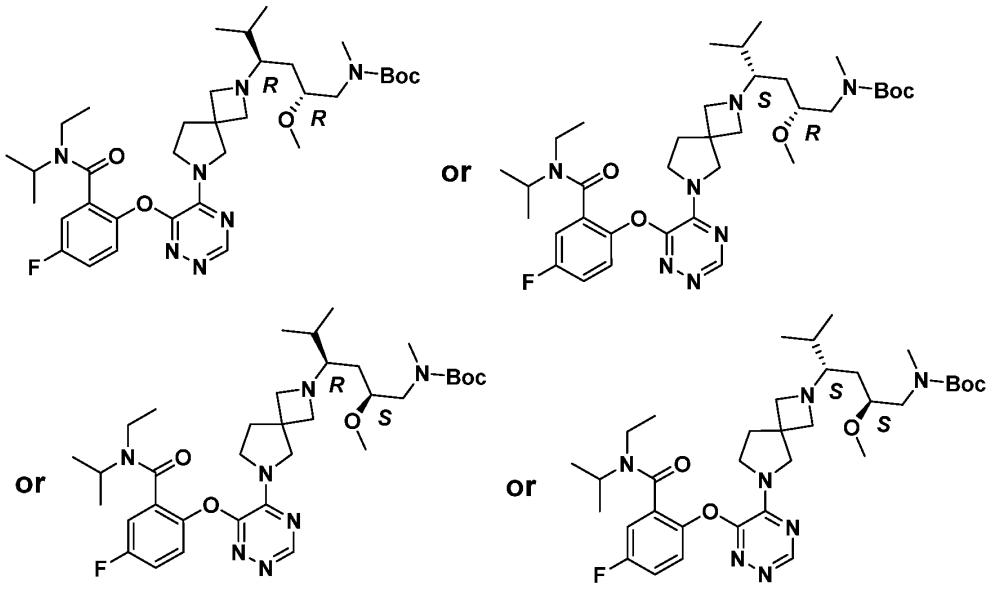


For compounds wherein the stereochemical configuration of two stereocentres is indicated by * (e.g. *R or *S), the absolute stereochemistry of the stereocentres is undetermined (even if the bonds are drawn stereospecifically), although the compound itself has been isolated as a single stereoisomer and is enantiomerically pure. In this case, the configuration of the first stereocentre is independent of the configuration of the second stereocentre in the same compound. "*R" or "*S" is assigned randomly for such molecules.

For example, for Compound 306



this means that the compound is



A skilled person will realize that the paragraphs above about stereochemical configurations, also apply to intermediates.

A skilled person will realize that, even where not mentioned explicitly in the experimental protocols below, typically after a column chromatography purification, the desired fractions were collected and the solvent was evaporated.

In case no stereochemistry is indicated, this means it is a mixture of stereoisomers, unless otherwise is indicated or is clear from the context.

When a stereocenter is indicated with 'RS' this means that a racemic mixture was obtained at the indicated centre, unless otherwise indicated.

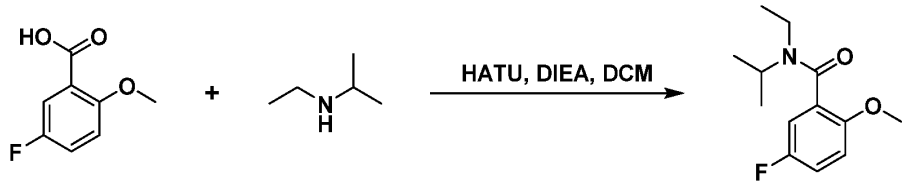
Preparation of intermediates

For intermediates that were used in a next reaction step as a crude or as a partially purified

intermediate, in some cases no mol amounts are mentioned for such intermediate in the next reaction step or alternatively estimated mol amounts or theoretical mol amounts for such intermediate in the next reaction step are indicated in the reaction protocols described below.

Preparation of intermediate 27

***N*-ethyl-5-fluoro-*N*-isopropyl-2-methoxybenzamide**



To the mixture of 5-fluoro-2-methoxybenzoic acid (8.00 g, 47.0 mmol) and *N*-ethylpropan-2-amine (8.19 g, 94.0 mmol) in dry DCM (150 mL) cooled at 0 °C, were slowly added HATU (21.5 g, 56.5 mmol) and DIEA (9.10 g, 70.4 mmol) in portions. The resulting mixture was slowly warmed to RT and stirred for 8 h. The organic layer was washed with water (20 mL x 3) and dried over anhydrous Na_2SO_4. After filtration, the solvent was removed under reduced pressure and the crude product was purified by FCC (EtOAc/PE = 0% to 20%) to afford the title intermediate (12.0 g, 96% yield) as a white solid.

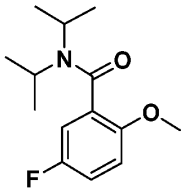
Preparation of intermediate 67, 235, 246

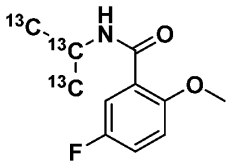
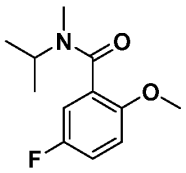
5-fluoro-*N*,*N*-diisopropyl-2-methoxybenzamide

5-fluoro-2-methoxy-*N*-(propan-2-yl-$^{13}C_3$)benzamide

5-fluoro-*N*-isopropyl-2-methoxy-*N*-methylbenzamide

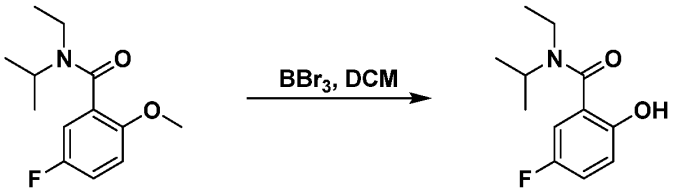
The following intermediate was synthesized by an analogous method as described above for intermediate 27

Int. No.	Structure	Starting Materials
67		5-fluoro-2-methoxybenzoic acid, diisopropylamine

Int. No.	Structure	Starting Materials
235		5-fluoro-2-methoxybenzoic acid, propan-2-amine-1,2,3-$^{13}C_3$
246		5-fluoro-2-methoxybenzoic acid, *N*-methylpropan-2-amine

Preparation of intermediate 28

***N*-ethyl-5-fluoro-2-hydroxy-*N*-isopropylbenzamide**



To the solution of *N*-ethyl-5-fluoro-*N*-isopropyl-2-methoxybenzamide (**intermediate 27**) (12.0 g, 50.1 mmol) in dry DCM (100 mL) cooled at -78 °C was slowly added BBr_3 (14.4 mL, 152 mmol), the resulting mixture was slowly warmed to RT and stirred for 8 h. The mixture was cooled to -78 °C again and MeOH (5 mL) was added dropwise to quench the reaction. The resulting mixture was slowly warmed to RT and the pH value was adjusted to about 8 by adding sat. aq. $NaHCO_3$ solution. The aqueous layer was extracted by DCM (50 mL x 3) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product which was purified by FCC (EtOAc/PE = 0% to 20%) to afford the title intermediate (9.0 g, 78% yield) as a white solid.

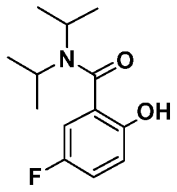
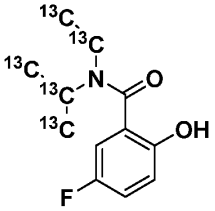
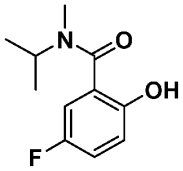
Preparation of intermediate 68, 237, 247

5-fluoro-2-hydroxy-*N*,*N*-diisopropylbenzamide

***N*-(ethyl-$^{13}C_2$)-5-fluoro-2-hydroxy-*N*-(propan-2-yl-$^{13}C_3$)benzamide**

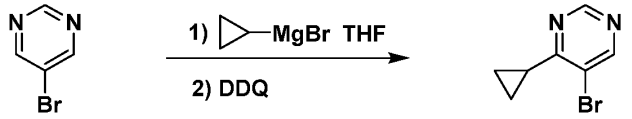
5-fluoro-2-hydroxy-*N*-isopropyl-*N*-methylbenzamide

The following intermediate was synthesized by an analogous method as described above for intermediate 28

Int. No.	Structure	Starting Materials
68		intermediate 67
237		intermediate 236
247		intermediate 246

Preparation of intermediate 60

5-bromo-4-cyclopropylpyrimidine

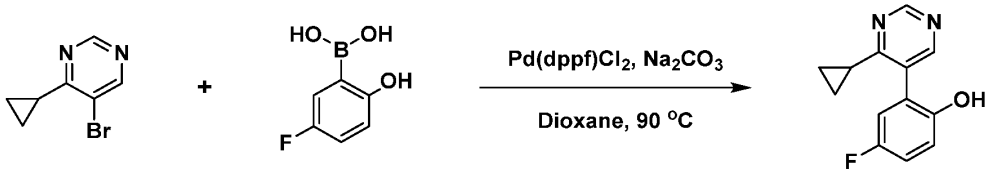


To a solution of 5-bromopyrimidine (30 g, 189 mmol) in THF (1000 mL) was added cyclopropylmagnesium bromide (396 mL, 198 mmol, 0.5 M in THF) at 0 °C under N_2 atmosphere. After addition, the reaction mixture was stirred at RT for 4 h, then a solution of DDQ (42.8 g, 189 mmol) in THF (500 mL) was added dropwise into the reaction mixture at 0 °C. After addition, the reaction mixture was stirred at RT for 16 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between EtOAc (200 mL) and water (200 mL), and the aqueous layer was extracted by EtOAc (200 mL x 3). The combined organic layers were washed with 1N NaOH (200 mL x 2), brine (200 mL), dried over

Na_2SO_4, filtered. The filtrate was concentrated *in vacuo* and the residue was purified by FCC (EtOAc/PE = 0% to 15%) to afford the title intermediate (21.4 g, 55% yield) as white solid.

Preparation of intermediate 61

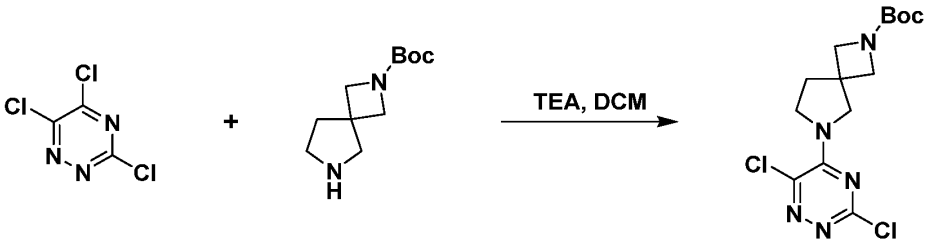
2-(4-cyclopropylpyrimidin-5-yl)-4-fluorophenol



The mixture of 5-bromo-4-cyclopropylpyrimidine (**intermediate 60**) (20.0 g, 100 mmol), (5-fluoro-2-hydroxyphenyl)boronic acid (18.7 g, 120 mmol), $Pd(dppf)Cl_2$ (3.68 g, 5.03 mmol) and Na_2CO_3 (2 M in H_2O, 101 mL, 202 mmol) in 1,4-dioxane (350 mL) was heated at 90 °C for 12 h under N_2 atmosphere. After cooled to RT, the reaction mixture was filtered through a celite pad, the filtrate was suspended into water (400 mL) and further extracted with EtOAc (200 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product, which was purified by FCC on silica gel (PE/EtOAc = 1:0 to 3:1) to afford the title intermediate (24.0 g, 95% purity, 98.6% yield) as a brown solid.

Preparation of intermediate 13

***tert*-butyl 6-(3,6-dichloro-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octane-2-carboxylate**

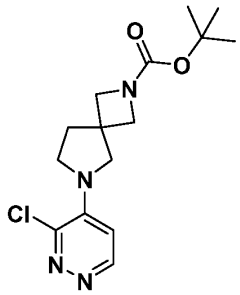


To the solution of 3,5,6-trichloro-1,2,4-triazine (10.0 g, 54.2 mmol) and TEA (15.2 mL, 109 mmol) in DCM (100 mL) cooled at 0 °C was added *tert*-butyl 2,6-diazaspiro[3.4]octane-2-carboxylate (9.21 g, 43.4 mmol), the mixture was warmed to RT and stirred for 1 h. The mixture was diluted with water (20 mL) and extracted with DCM (30 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product which was purified by FCC on silica gel (PE/EtOAc = 1:0 to 3:1) to afford the title intermediate (12.0 g, 58% yield) as a yellow solid.

Preparation of intermediate 69

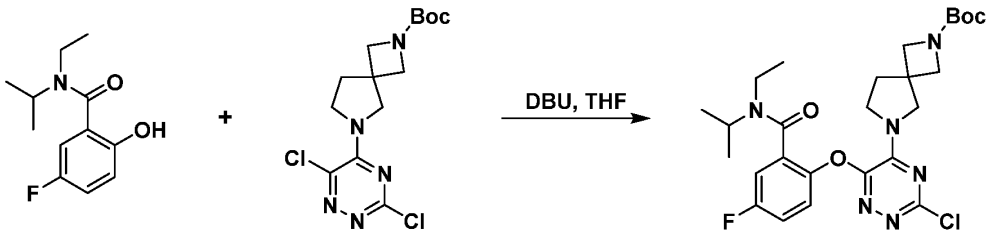
***tert*-butyl 6-(3-chloropyridazin-4-yl)-2,6-diazaspiro[3.4]octane-2-carboxylate**

The following intermediate was synthesized by an analogous method as described above for intermediate 13

Int. No.	Structure	Starting Materials
69		3,4-dichloropyridazine, *tert*-butyl 2,6-diazaspiro[3.4]octane-2-carboxylate

Preparation of intermediate 14

***tert*-butyl 6-(3-chloro-6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octane-2-carboxylate**



The mixture of *tert*-butyl 6-(3,6-dichloro-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octane-2-carboxylate (**intermediate 13**) (12.0 g, 33.3 mmol), *N*-ethyl-5-fluoro-2-hydroxy-*N*-isopropylbenzamide (**intermediate 28**) (7.5 g, 33.3 mmol) and DBU (6.1 g, 40.1 mmol) in THF (120 mL) was stirred at 25 °C for 8 h. The mixture was diluted with water (30 mL) and extracted with DCM (30 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product which was purified by FCC (PE/EtOAc = 1:0 to 3:1) to afford the title intermediate (14.0 g, 73% yield) as green solid.

Preparation of intermediates 57, 74, 70, and 83

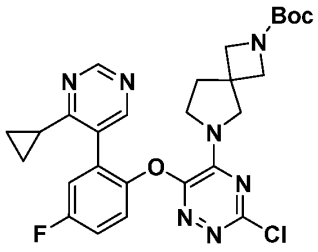
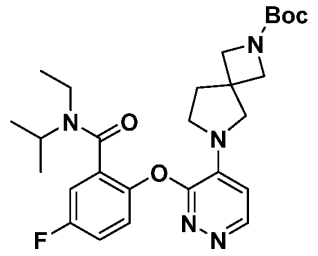
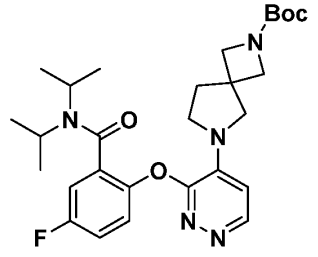
***tert*-butyl 6-(3-chloro-6-(2-(4-cyclopropylpyrimidin-5-yl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octane-2-carboxylate**

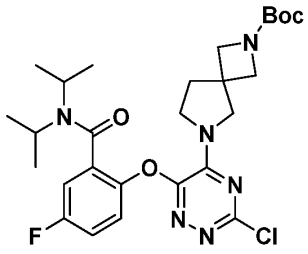
***tert*-butyl 6-(3-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyridazin-4-yl)-2,6-diazaspiro[3.4]octane-2-carboxylate**

***tert*-butyl 6-(3-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)pyridazin-4-yl)-2,6-diazaspiro[3.4]octane-2-carboxylate**

***tert*-butyl 6-(3-chloro-6-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octane-2-carboxylate**

The following intermediates were synthesized by an analogous method as described above for intermediate 14

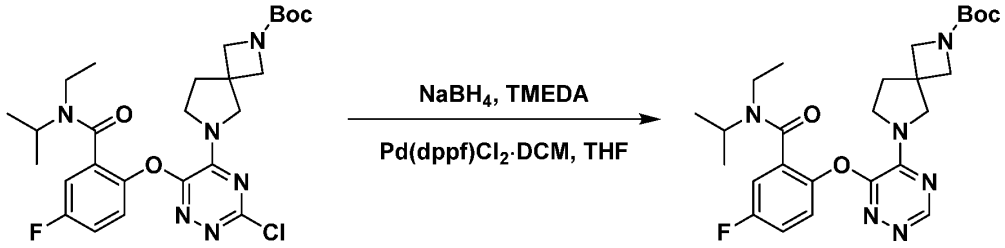
Int. No.	Structure	Starting Materials
57		intermediate 61, intermediate 13
74		intermediate 28, intermediate 69
70		intermediate 68, intermediate 69

Int. No.	Structure	Starting Materials
83		intermediate 68, intermediate 13

Preparation of intermediate 2

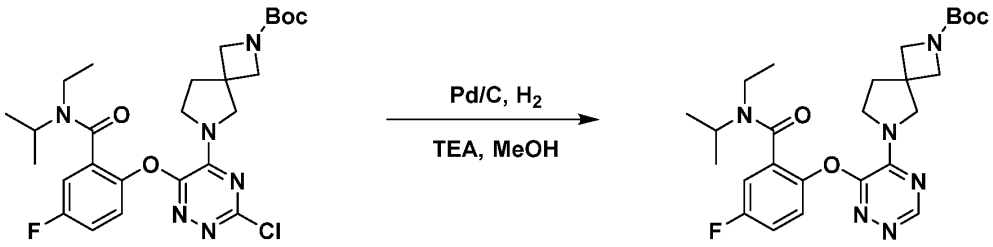
***tert*-butyl 6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octane-2-carboxylate**

Method A:



To the mixture of *tert*-butyl 6-(3-chloro-6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octane-2-carboxylate (**intermediate 14**) (20 g, 36.4 mmol), $NaBH_4$ (2.48 g, 65.7 mmol) and TMEDA (8.54 g, 73.5 mmol) in THF (500 mL) was added $Pd(dppf)Cl_2$·DCM (1.70 g, 2.08 mmol) under N_2 atmosphere. After addition, the reaction mixture was stirred at 25 °C for 14 h. The reaction mixture was filtered and the filtrate was concentrated, the residue was purified by FCC on silica gel (EtOAc) to afford the title intermediate (15 g, 93% purity, 74% yield) as brown solid.

Method B:



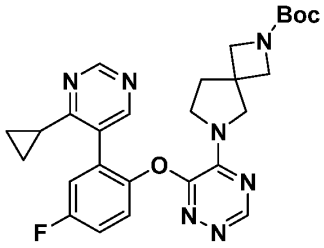
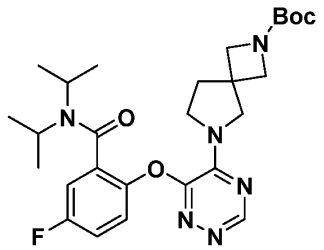
To the solution of *tert*-butyl 6-(3-chloro-6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octane-2-carboxylate (**intermediate 14**) (22.0 g, 40.1 mmol), TEA (15 mL) in MeOH (100 mL) was added Pd/C (wet, 5.0 g, 10%) The resulting mixture was stirred under H_2 atmosphere (30 psi) at 25 °C for 8 h. The reaction mixture was filtered through a celite pad and the filtrate was concentrated *in vacuo* to afford the title intermediate (25.0 g, crude), which was used directly in next step without further purification.

Preparation of intermediate 58, 84

***tert*-butyl 6-(6-(2-(4-cyclopropylpyrimidin-5-yl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octane-2-carboxylate**

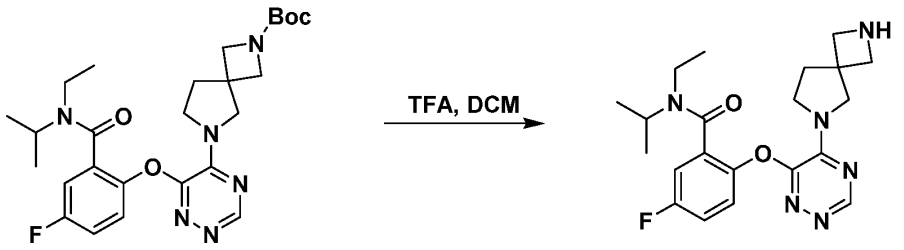
***tert*-butyl 6-(6-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octane-2-carboxylate**

The following intermediates were synthesized by an analogous method described above for intermediate 2

Int. No.	Structure	Starting Material	Conditions
58		intermediate 57	$NaBH_4$, TMEDA, $Pd(dppf)Cl_2$·DCM, THF
84		intermediate 83	Pd/C, H_2, TEA, MeOH

Preparation of intermediate 3

2-((5-(2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide



To the solution of *tert*-butyl 6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octane-2-carboxylate (**intermediate 2**) (300 mg, 0.583 mmol) in DCM (5 mL) was added TFA (0.5 mL, 6.4 mmol), the resulting mixture was stirred at RT for 3 h. Then 10% NaOH (5 mL) solution was slowly added into the mixture to adjust the pH value to about 12, the resulting mixture was extracted with DCM (10 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford the title intermediate (220 mg, 90% yield) as a white solid.

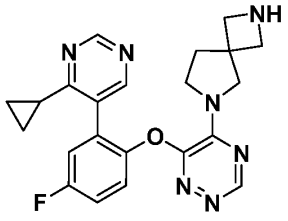
Preparation of intermediate 59, 75, 85

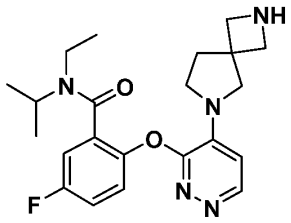
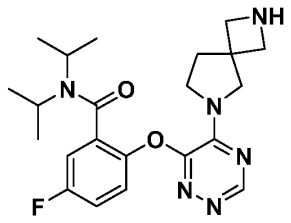
6-(6-(2-(4-cyclopropylpyrimidin-5-yl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octane

2-((4-(2,6-diazaspiro[3.4]octan-6-yl)pyridazin-3-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

2-((5-(2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide

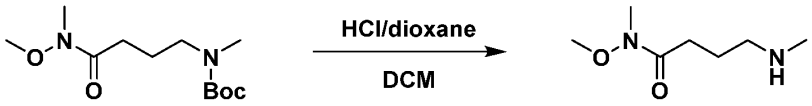
The following intermediates were synthesized by an analogous method described above for intermediate 3

Int. No.	Structure	Starting Material
59		intermediate 58

Int. No.	Structure	Starting Material
75		intermediate 74
85		intermediate 84

Preparation of intermediate 160

***N*-methoxy-*N*-methyl-4-(methylamino)butanamide hydrochloride**



To a solution of *tert*-butyl (4-(methoxy(methyl)amino)-4-oxobutyl)(methyl)carbamate (**intermediate 8**) (220 g, crude) in DCM (200 mL) was slowly added HCl/1,4-dioxane (750 mL, 3 mol) at 0 °C. The resulting mixture was slowly warmed to RT and stirred at this temperature for 2 h. The mixture was concentrated *in vacuo* to afford the title intermediate (197 g, crude) which was used directly in next step without further purification.

Intermediate 164, 238, 243, 244

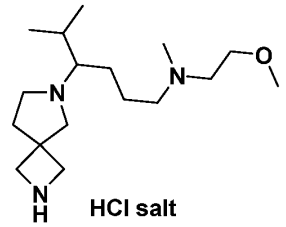
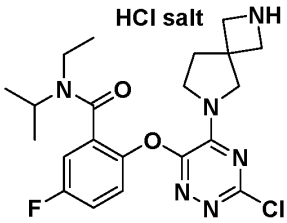
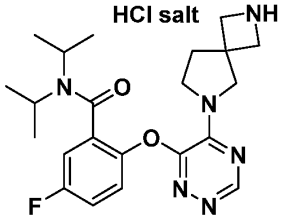
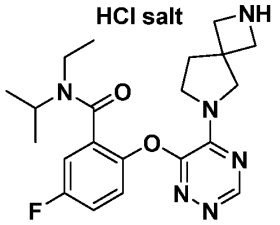
***N*-(2-methoxyethyl)-*N*,5-dimethyl-4-(2,6-diazaspiro[3.4]octan-6-yl)hexan-1-amine hydrochloride**

2-((3-chloro-5-(2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride

2-((5-(2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide hydrochloride

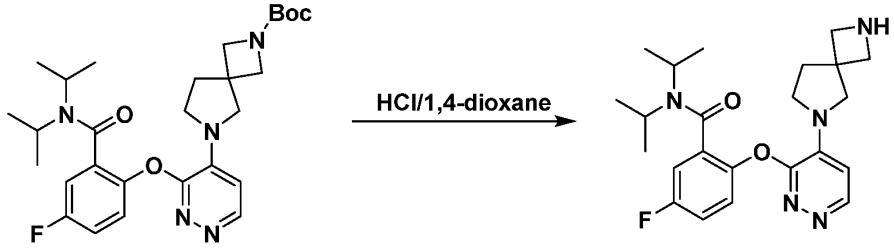
2-((5-(2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride

The following intermediates were synthesized by an analogous method described above for intermediate 160

Int. No.	Structure	Starting Material
164		intermediate 163
238		intermediate 14
243		intermediate 84
244		intermediate 2

Preparation of intermediate 71

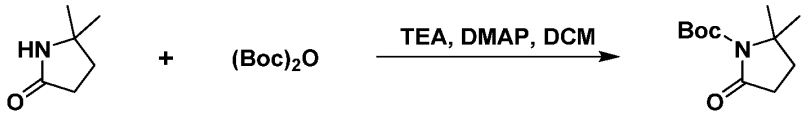
2-((4-(2,6-diazaspiro[3.4]octan-6-yl)pyridazin-3-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide



To the solution of *tert*-butyl 6-(3-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)pyridazin-4-yl)-2,6-diazaspiro[3.4]octane-2-carboxylate (**intermediate 70**) (5.0 g, 9.4 mmol) in 1,4-dioxane (30 mL) cooled at 0 °C was slowly added HCl in 1.4-dioxane (20 mL, 4 M, 80 mmol) The resulting mixture was stirred at RT for 2 h. Then, the mixture was concentrated and the residue was re-dissolved in DCM (50 mL), to which 1 M NaOH (20 mL) was slowly added and the pH value was adjusted to 12, the resulting mixture was extracted by DCM (30 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford the title intermediate (4 g, crude) as a yellow solid, which was used in the next step without further purification.

Preparation of intermediate 29

***tert*-butyl 2,2-dimethyl-5-oxopyrrolidine-1-carboxylate**



To a solution of 5,5-dimethylpyrrolidin-2-one (3.00 g, 26.5 mmol) in DCM (30 mL) were added TEA (8.10 g, 80.0 mmol) and DMAP (325 mg, 2.66 mmol), and followed by addition of di-*tert*-butyl dicarbonate (8.70 g, 39.8 mmol). The reaction was stirred at 40 °C overnight. After cooled to RT, the reaction mixture was washed with brine (30 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a crude product. The crude product was further purified by FCC on silica gel (PE/EtOAc = 100:0 to 3:1) to afford the title intermediate (2.8 g, 50% yield) as a yellow powder.

Preparation of intermediate 1

***tert*-butyl (5-methyl-4-oxohexyl)carbamate**



To a solution of *tert*-butyl 2-oxopyrrolidine-1-carboxylate (5.0 g, 27 mmol) and TMEDA (5.0 mL, 33 mmol) in THF (60 mL) cooled at -70 °C was slowly added isopropylmagnesium bromide solution (19 mL, 55 mmol, 2.9 M in 2-methyltetrahydrofuran), the resulting mixture was slowly warmed to RT and stirred for 12 h. The mixture was poured into sat. aq. NH_4Cl (50 mL) solution and extracted with EtOAc (50 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the

crude product, which was further purified by FCC (PE/EtOAc = 1:0 to 100:1) to afford the title intermediate (3.7 g, 60% yield) as a yellow oil.

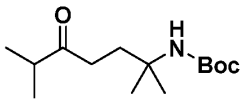
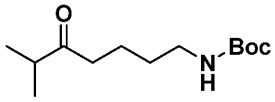
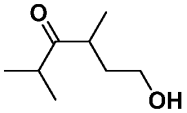
Preparation of intermediate 30, 110, 141

***tert*-butyl (2,6-dimethyl-5-oxoheptan-2-yl)carbamate**

***tert*-butyl (6-methyl-5-oxoheptyl)carbamate**

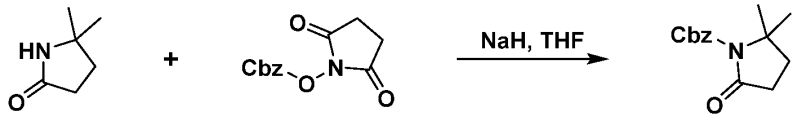
6-hydroxy-2,4-dimethylhexan-3-one

The following intermediates were synthesized by an analogous method described above for intermediate 1

Int. No.	Structure	Starting Materials
30		isopropylmagnesium bromide, intermediate 29
110		isopropylmagnesium bromide, *tert*-butyl 2-oxopiperidine-1-carboxylate
141		isopropylmagnesium chloride, 3-methyldihydrofuran-2(3*H*)-one

Preparation of intermediate 34

benzyl 2,2-dimethyl-5-oxopyrrolidine-1-carboxylate

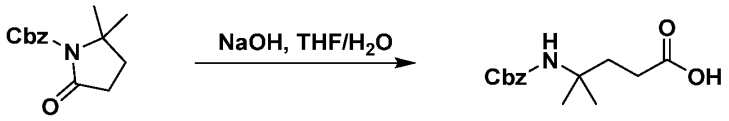


To a solution of 5,5-dimethylpyrrolidin-2-one (5.00 g, 44.2 mmol) in THF (150 mL) cooled at 0 °C was added NaH (1.94 g, 48.5 mmol, 60%), the resulting mixture was stirred at this temperature for 30 min. Subsequently *N*-(benzyloxycarbonyloxy)succinimide (12.1 g, 48.6 mmol) was added and the reaction mixture was slowly warmed to RT and stirred for additional 16 h. The solvent was evaporated under reduced pressure, sat. aq. NH_4Cl solution (30 mL) was added and extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, filtered, and concentrated under reduced

pressure to afford the crude product, which was further purified by FCC (PE/EtOAc = 1:0 to 3: 1) to afford the title intermediate (5.16 g, 39% yield) as colorless oil.

Preparation of intermediate 35

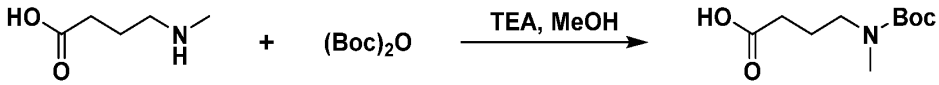
4-(((benzyloxy)carbonyl)amino)-4-methylpentanoic acid



NaOH (4.18 g, 16.9 mmol) was added to a solution of benzyl 2,2-dimethyl-5-oxopyrrolidine-1-carboxylate (**intermediate 34**) (5.16 g, 20.9 mmol) in THF (60 mL) and H_2O (15 mL). The mixture was stirred at 80 °C for 16 h. The reaction mixture was cooled to 25 °C and acidified by 1 M HCl to adjust the pH value to about 3, then the mixture was extracted by EtOAc (20 x 2 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the title intermediate (4.48 g, crude) as colorless oil, which was used directly in next step without further purification.

Preparation of intermediate 7

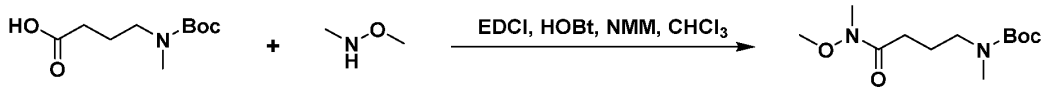
4-((*tert*-butoxycarbonyl)(methyl)amino)butanoic acid



To a solution of 4-(methylamino)butanoic acid hydrochloride (3.0 g, 19.5 mmol) and TEA (7.78 mL, 58.6 mmol) in MeOH (30 mL) was added Boc_2O (4.69 g, 21.5 mmol) dropwise. The mixture was stirred at RT for 2 h. The mixture was concentrated under reduced pressure and the residue was diluted with EtOAc (100 mL), washed with cooled 0.1 N HCl (70 mL x 2), H_2O (50 mL x 2) and brine (50 mL), dried over Na_2SO_4, filtered and concentrated to afford the title intermediate (1.80 g, crude) as colorless oil.

Preparation of intermediate 8

***tert*-butyl (4-(methoxy(methyl)amino)-4-oxobutyl)(methyl)carbamate**



To a solution of 4-((*tert*-butoxycarbonyl)(methyl)amino)butanoic acid (**intermediate 7**) (1.80 g, crude) in $CHCl_3$ (30 mL) was added *N*,*O*-dimethylhydroxylamine hydrochloride (960 mg, 9.84 mmol), HOBt (1.24 g, 9.18 mmol) and NMM (2.80 mL, 25.1 mmol). And, then EDCI

(2.23 g, 11.6 mmol) was added and the reaction mixture was stirred at RT for 4 h. The reaction mixture was diluted with DCM (100 mL), washed with 1N HCl (30 mL x 3), sat. aq. $NaHCO_3$ (30 mL x 3) and brine (30 mL), dried over Na_2SO_4, filtered and concentrated under *in vacuo* to afford the title intermediate (1.70 g, crude) as colorless oil.

Preparation of intermediates 19, 36, 189, 190, 203, 204

***tert*-butyl (3-(methoxy(methyl)amino)-3-oxopropyl)carbamate**

benzyl (5-(methoxy(methyl)amino)-2-methyl-5-oxopentan-2-yl)carbamate

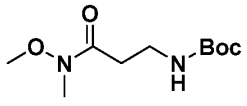
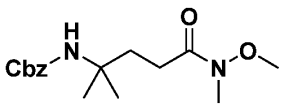
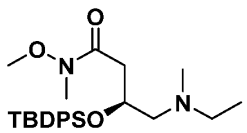
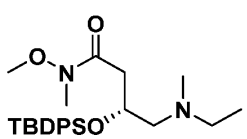
(*S*)-3-((*tert*-butyldiphenylsilyl)oxy)-4-(ethyl(methyl)amino)-*N*-methoxy-*N*-methylbutanamide

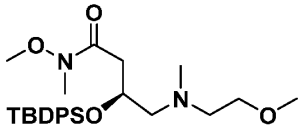
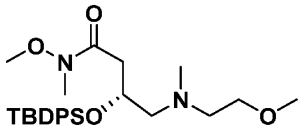
(*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-4-(ethyl(methyl)amino)-*N*-methoxy-*N*-methylbutanamide

(*S*)-3-((*tert*-butyldiphenylsilyl)oxy)-*N*-methoxy-4-((2-methoxyethyl)(methyl)amino)-*N*-methylbutanamide

(*R*)-3-((tert-butyldiphenylsilyl)oxy)-*N*-methoxy-4-((2-methoxyethyl)(methyl)amino)-*N*-methylbutanamide

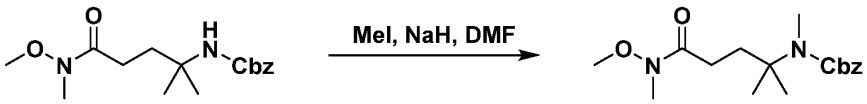
The following intermediates were synthesized by an analogous method described above for intermediate 8

Int. No.	Structure	Starting Materials
19		3-((*tert*-butoxycarbonyl)amino)propanoic acid *N*,*O*-dimethylhydroxylamine hydrochloride
36		intermediate 35 *N*,*O*-dimethylhydroxylamine hydrochloride
189		intermediate 187, *N*,*O*-dimethylhydroxylamine hydrochloride
190		intermediate 188, *N*,*O*-dimethylhydroxylamine hydrochloride

Int. No.	Structure	Starting Materials
203		intermediate 201, *N*,*O*-dimethylhydroxylamine hydrochloride
204		intermediate 202, *N*,*O*-dimethylhydroxylamine hydrochloride

Preparation of intermediate 37

benzyl (5-(methoxy(methyl)amino)-2-methyl-5-oxopentan-2-yl)(methyl)carbamate

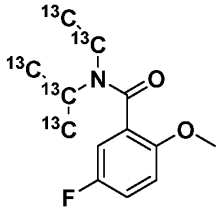


To a solution of benzyl (5-(methoxy(methyl)amino)-2-methyl-5-oxopentan-2-yl)carbamate (**intermediate 36**) (2.30 g, 7.46 mmol) in DMF (30 mL) cooled at 0 °C under N_2 atmosphere was added NaH (358 mg, 8.95 mmol, 60%). Then, MeI (8.87 g, 62.5 mmol) was added and the mixture was stirred at 25 °C for 12 h. The mixture was quenched with sat. aq. NH_4Cl (30 mL) and extracted with EtOAc (30 mL x 2). The combined organic layers washed with brine (40 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product, which was further purified by FCC on silica gel (PE/EtOAc = 1:0 to 3:1) to afford the title intermediate (2.15 g, 76% yield) as yellow oil.

Preparation of intermediate 236

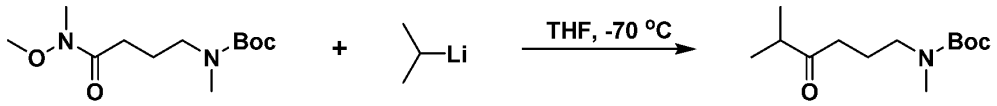
***N*-(ethyl-$^{13}C_2$)-5-fluoro-2-methoxy-*N*-(propan-2-yl-$^{13}C_3$)benzamide**

The following intermediate was synthesized by an analogous method as described above for intermediate 37

Int. No.	Structure	Starting Materials	Conditions
236		intermediate 235, iodoethane-1,2-$^{13}C_2$	NaH, DMF, from 0 °C to 90 °C

Preparation of intermediate 9

***tert*-butyl methyl(5-methyl-4-oxohexyl)carbamate**



To a solution of *tert*-butyl (4-(methoxy(methyl)amino)-4-oxobutyl)(methyl)carbamate (**intermediate 8**) (200 mg, crude) in THF (5 mL) cooled at -70°C under N_2 atmosphere was added dropwise isopropyllithium (3.2 mL, 2.24 mmol, 0.7M in pentane). The resulting mixture was stirred at -70 °C for 2 h. The mixture was quenched with sat. aq. NH_4Cl (15 mL), extracted with EtOAc (30 mL x 2). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a crude product. The crude product was further purified by FCC (PE/EtOAc = 10 : 1) to afford the title intermediate (60 mg) as colorless oil.

Preparation of intermediates 20, 38, 162, 191, 192, 205, 206

***tert*-butyl (4-methyl-3-oxopentyl)carbamate**

benzyl (2,6-dimethyl-5-oxoheptan-2-yl)(methyl)carbamate

6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-one

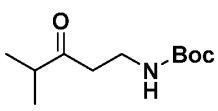
(*S*)-5-((*tert*-butyldiphenylsilyl)oxy)-6-(ethyl(methyl)amino)-2-methylhex-1-en-3-one

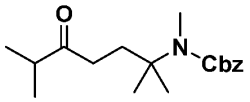
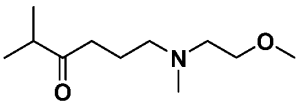
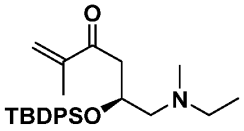
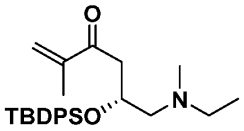
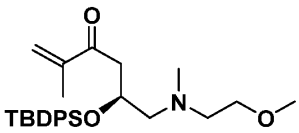
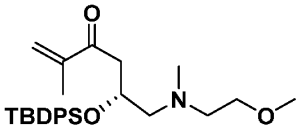
(*R*)-5-((*tert*-butyldiphenylsilyl)oxy)-6-(ethyl(methyl)amino)-2-methylhex-1-en-3-one

(*S*)-5-((*tert*-butyldiphenylsilyl)oxy)-6-((2-methoxyethyl)(methyl)amino)-2-methylhex-1-en-3-one

(*R*)-5-((*tert*-butyldiphenylsilyl)oxy)-6-((2-methoxyethyl)(methyl)amino)-2-methylhex-1-en-3-one

The following intermediates were synthesized by an analogous method described above for intermediate 9

Int. No.	Structure	Starting Materials
20		intermediate 19, isopropylmagnesium chloride

Int. No.	Structure	Starting Materials
38		intermediate 37 isopropylmagnesium chloride
162		intermediate 161, isopropyllithium
191		intermediate 189, isopropenylmagnesium bromide
192		intermediate 190, isopropenylmagnesium bromide
205		intermediate 203, isopropenylmagnesium bromide
206		intermediate 204, isopropenylmagnesium bromide

Preparation of intermediate 15

2-(3-methyl-2-oxobutyl)isoindoline-1,3-dione

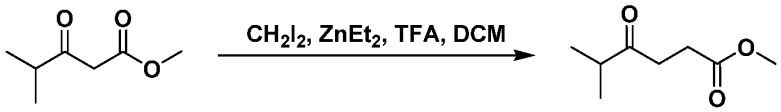


To the solution of 1-bromo-3-methylbutan-2-one (200 mg, 1.21 mmol) in DMF (4 mL) was added potassium phthalimide (1.12 g, 6.05 mmol) and the mixture was stirred at 80 °C for 12 h. After cooled to RT, water (15 mL) was added and the mixture was extracted with EtOAc (40 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product, which was further purified

by preparative TLC (PE/EtOAc = 3:1) to afford the title intermediate (200 mg, 69% yield) as a white solid.

Preparation of intermediate 46

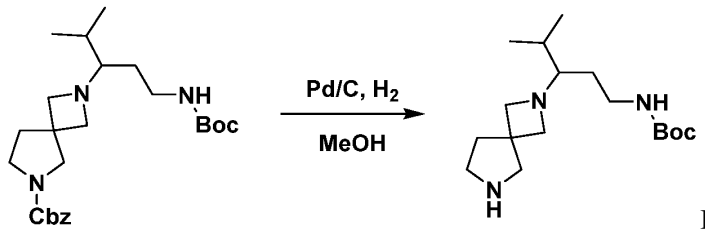
methyl 5-methyl-4-oxohexanoate



To a solution of $ZnEt_2$ (104 mL, 104 mmol) in DCM (150 mL) at 0 °C under N_2 was added dropwise TFA (11.9 g, 104 mmol) slowly via syringe and the mixture was stirred at 0 °C for 30 min. Then, methylene iodide (27.9 g, 104 mmol) was added dropwise with stirring and the suspension was stirred for another 30 min. And, then methyl 4-methyl-3-oxopentanoate (5.00 g, 34.7 mmol) was added rapidly by syringe and the resulting mixture was stirred at RT for 16 h and refluxed at 50 °C for 20 h. After cooled to RT, the reaction mixture was quenched with sat. aq. NH_4Cl (50 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to an oil residue which was purified by FCC (PE/EtOAc = 1:0 to 20:1) to afford the title intermediate (300 mg, 5% yield) as a yellow oil.

Preparation of intermediate 22

***tert*-butyl (4-methyl-3-(2,6-diazaspiro[3.4]octan-2-yl)pentyl)carbamate hydrochloride**

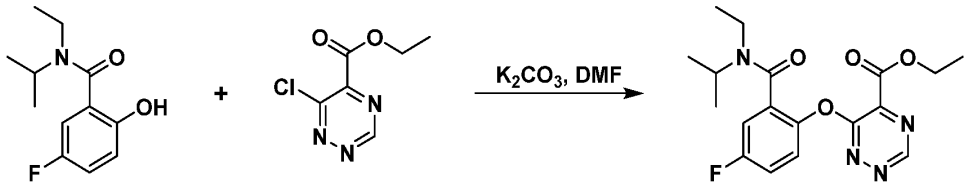


HCl salt

To a solution of benzyl 2-(1-((*tert*-butoxycarbonyl)amino)-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octane-6-carboxylate (**intermediate 21**) (0.580 g, 1.30 mmol) in MeOH (50 mL) were added 1,1,2-trichloroethane (0.260 g, 1.95 mmol) and Pd/C (0.05 g, 10%) under Ar and the reaction was stirred at 35 °C for 8 h under H_2 (15 psi) atmosphere. The reaction mixture was filtered. The filtrate was concentrated *in vacuo* to afford the title intermediate (280 mg, crude) as colorless oil.

Preparation of intermediate 23

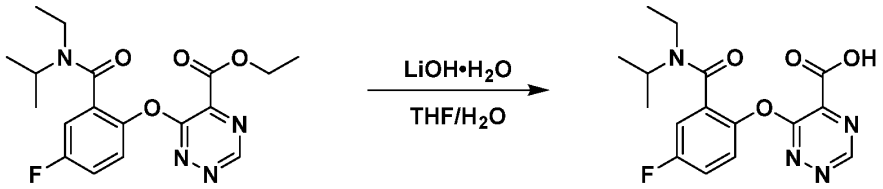
ethyl 6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazine-5-carboxylate



To the mixture of ethyl 6-chloro-1,2,4-triazine-5-carboxylate (13 g, 69 mmol) and *N*-ethyl-5-fluoro-2-hydroxy-*N*-isopropylbenzamide (**intermediate 28**) (15.6 g, 69.3 mmol) in DMF (150 mL) was added K_2CO_3 (28.6 g, 204 mmol). The resulting mixture was stirred at RT for 2 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give the crude residue, which was diluted with water (100 mL) and extracted with EtOAc (100 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product, which was further purified by FCC (PE/EtOAc = 1:0 to 1:1) to afford the title intermediate (30 g, 81% purity, 92% yield) as a yellow solid.

Preparation of intermediate 24

6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazine-5-carboxylic acid



To the mixture of ethyl 6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazine-5-carboxylate (**intermediate 23**) (8.6 g, 23 mmol) in THF (100 mL) and H_2O (25 mL) was added LiOH•H_2O (2.0 g, 48 mmol) and the reaction mixture was stirred at RT for 1 h. The mixture was acidified with 0.5M HCl to adjust the pH value to 5~6, and further extracted with EtOAc (150 mL). The aqueous phase was purified by preparative HPLC over Boston Prime (column: C18 150x30 mm 5 um; eluent: ACN/H_2O (0.225% FA) from 19% to 49%, v/v) to afford the title intermediate (5.0 g, 62% yield).

Preparation of intermediates 187, 188, 201, 202

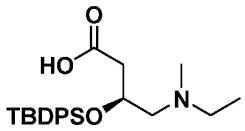
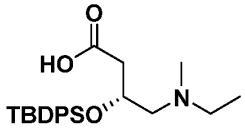
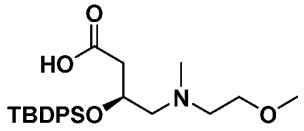
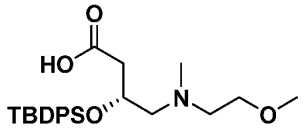
(*S*)-3-((*tert*-butyldiphenylsilyl)oxy)-4-(ethyl(methyl)amino)butanoic acid

(*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-4-(ethyl(methyl)amino)butanoic acid

(*S*)-3-((*tert*-butyldiphenylsilyl)oxy)-4-((2-methoxyethyl)(methyl)amino)butanoic acid

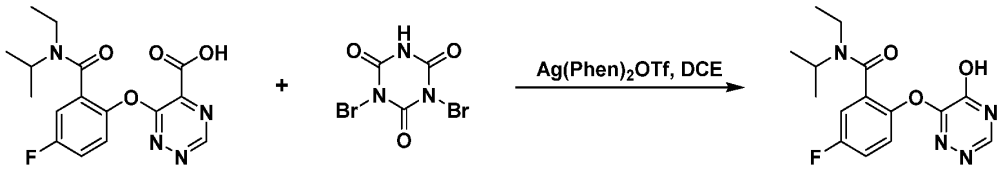
(*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-4-((2-methoxyethyl)(methyl)amino)butanoic acid

The following intermediates were synthesized by an analogous method as described above for intermediate 24

Int. No.	Structure	Starting Material	Conditions
187		intermediate 185	NaOH, THF/MeOH/H_2O, RT
188		intermediate 186	NaOH, THF/MeOH/H_2O, RT
201		intermediate 199	NaOH, THF/EtOH/H_2O, RT
202		intermediate 200	NaOH, THF/MeOH/H_2O, RT

Preparation of intermediate 25

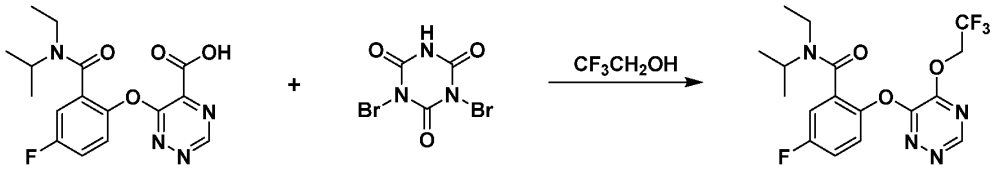
***N*-ethyl-5-fluoro-2-((5-hydroxy-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide**



To the solution of 6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazine-5-carboxylic acid (**intermediate 24**) (50 mg, 0.14 mmol) and 1,3-dibromo-1,3,5-triazinane-2,4,6-trione (50 mg, 0.17 mmol) in DCE (1 mL) was added $Ag(Phen)_2OTf$ (30 mg, 0.049 mmol) and the resulting mixture was stirred at RT for 2 h. The reaction mixture was filtered through a celite pad and washed with ACN (10 mL). The filtrate was concentrated under reduced pressure to afford the crude product, which was further purified by preparative HPLC using a Xtimate (column: C18 150x40 mm 10 μm; eluent: ACN/H_2O (0.2% FA) from 20% to 50% v/v) to afford the title intermediate (20 mg, 41%) as a white solid.

Preparation of intermediate 159

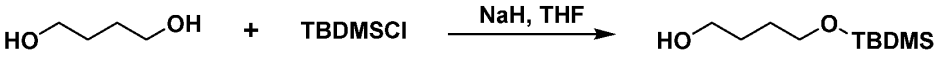
***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2,2,2-trifluoroethoxy)-1,2,4-triazin-6-yl)oxy)benzamide**



4Å molecular sieve (8 g) was added to the mixture of 6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazine-5-carboxylic acid (**intermediate 24**) (8.0 g, 23.0 mmol) in 2,2,2-trifluoroethan-1-ol (100 mL). The resulting mixture was stirred under N_2 atmosphere at 70 °C for 1 h. Then cooled to RT and 1,3-dibromo-1,3,5-triazinane-2,4,6-trione (13.1 g, 45.7 mmol) was added to above mixture. The resulting mixture was further stirred under N_2 atmosphere at RT overnight. The reaction mixture was filtered over a celite pad. The filtrate was concentrated under reduced pressure and the crude residue was purified by FCC (PE : EtOAc from 1:0 to 2:1) to afford the title intermediate (3.1 g, purity 84%, yield 28%) as a yellow solid.

Preparation of intermediate 51

4-((*tert*-butyldimethylsilyl)oxy)butan-1-ol



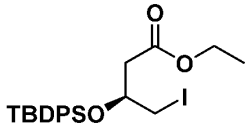
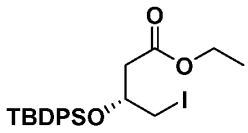
To the solution of butane-1,4-diol (5.00 g, 55.5 mmol) in THF (100 mL) cooled at 0 °C was added NaH (1.55 g, 38.8 mmol, 60%), the resulting mixture was stirred at 0 °C for 20 min. Then TBDMSCl (5.85 g, 38.8 mmol) was added to the reaction mixture and the reaction was further stirred at 0 °C for additional 1 h. The mixture was quenched with water (80 mL) and extracted with EtOAc (80 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product which was further purified by FCC (PE/EtOAc = 1:0 to 10:1) to afford the title intermediate (7.2 g, 63%) as a colorless liquid.

Preparation of intermediates 183, 184

ethyl (*S*)-3-((*tert*-butyldiphenylsilyl)oxy)-4-iodobutanoate

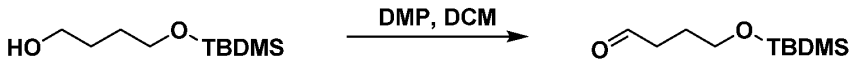
ethyl (*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-4-iodobutanoate

The following intermediates were synthesized by an analogous method as described above for intermediate 51

Int. No.	Structure	Starting Materials	Conditions
183		TBDPSCl, intermediate 181	imidazole, DCM, RT
184		TBDPSCl, intermediate 182	imidazole, DCM, RT

Preparation of intermediate 52

4-((*tert*-butyldimethylsilyl)oxy)butanal



To the solution of 4-((*tert*-butyldimethylsilyl)oxy)butan-1-ol (**intermediate 51**) (7.20 g, 35.2 mmol) in DCM (200 mL) cooled at 0 °C was added DMP (22.4 g, 52.8 mmol) and the reaction mixture was slowly warmed to RT and stirred for 2 h. The reaction mixture was diluted with DCM (100 mL) and stirred with of sat. aq. ($NaHCO_3$/Na_2SO_3 = 1/1, 100 mL) for 2 min, the separated organic layer was washed with brine (100 mL x 3), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product which was further purified by FCC (PE/EtOAc = 1:0 to 12:1) to afford the title intermediate (2.95 g, 41%) as a colorless liquid.

Preparation of intermediate 54, 145, 146, 158

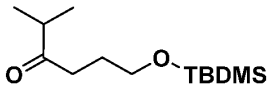
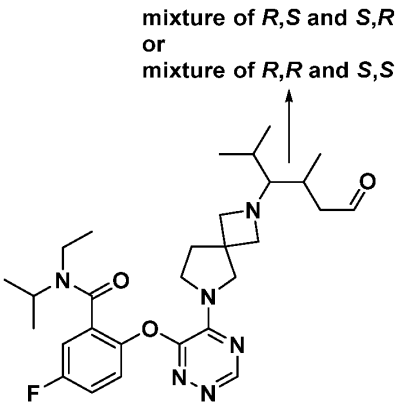
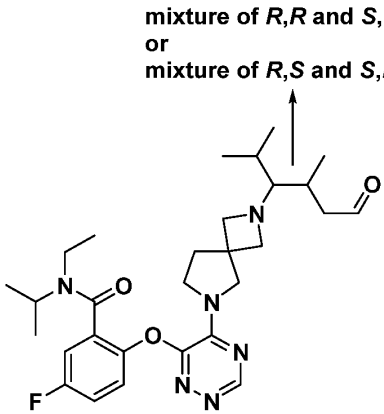
6-((*tert*-butyldimethylsilyl)oxy)-2-methylhexan-3-one

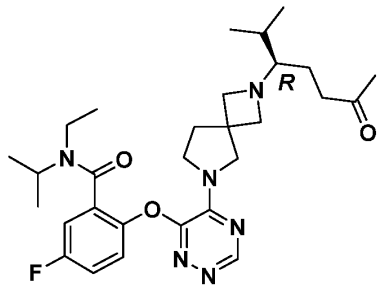
2-((5-(2-(2,4-dimethyl-6-oxohexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (mixture of *R*,*S* and *S*,*R*; or mixture of *R*,*R* and *S*,*S*)

2-((5-(2-(2,4-dimethyl-6-oxohexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (mixture of *R*,*R* and *S*,*S*; or mixture of *R*,*S* and *S*,*R*)

(*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(2-methyl-6-oxoheptan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide

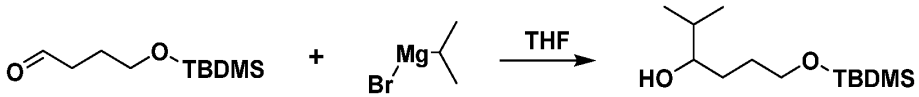
The following intermediates were synthesized by an analogous method described above for intermediate 52

Int. No.	Structure	Starting Material
54		intermediate 53
145		Compound 261
146		Compound 262

Int. No.	Structure	Starting Material
158		Compound 298

Preparation of intermediate 53

6-((*tert*-butyldimethylsilyl)oxy)-2-methylhexan-3-ol



To the solution of 4-((*tert*-butyldimethylsilyl)oxy)butanal (**intermediate 52**) (1.00 g, 4.94 mmol) in THF (4.9 mL) cooled at -20 °C under N_2 atmosphere was added dropwise isopropylmagnesium bromide (4.94 mL, 14.8 mmol, 3 M in THF) and the reaction mixture was slowly warmed to RT and stirred for 2 h. The mixture was quenched with sat. aq. NH_4Cl (20 mL), and extracted with EtOAc (50 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give the crude product which was further purified by FCC (PE/EtOAc = 1:0 to 20:1) to afford the title intermediate (580 mg, 48%) as a white oil.

Preparation of intermediates 16, 21, 39, 47, 55, 94, 98, 161, 163

2-((5-(2-(1-(1,3-dioxoisoindolin-2-yl)-3-methylbutan-2-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

benzyl 2-(1-((*tert*-butoxycarbonyl)amino)-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octane-6-carboxylate

benzyl (5-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-2,6-dimethylheptan-2-yl)(methyl)carbamate

methyl 4-(6-(6-(2-(4-cyclopropylpyrimidin-5-yl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-5-methylhexanoate

2-((5-(2-(6-((*tert*-butyldimethylsilyl)oxy)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

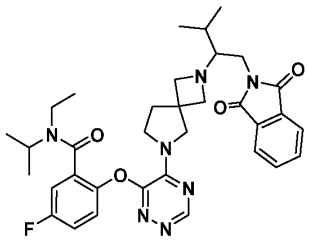
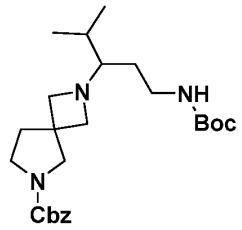
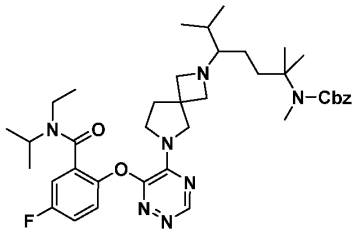
2-((5-(2-(1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

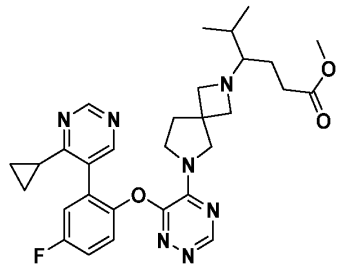
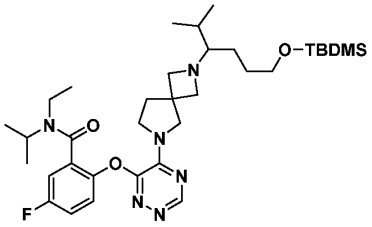
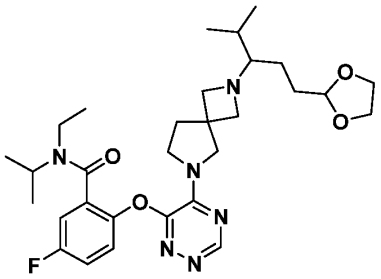
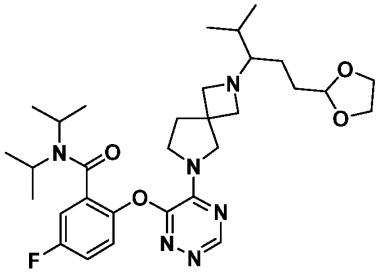
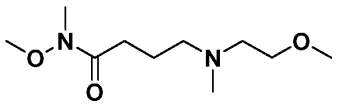
2-((5-(2-(1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide

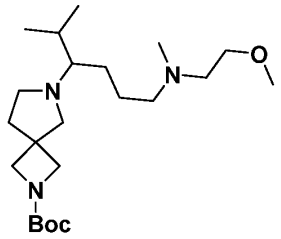
5 *N*-methoxy-4-((2-methoxyethyl)(methyl)amino)-*N*-methylbutanamide

***tert*-butyl 6-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octane-2-carboxylate**

The following intermediates were synthesized by an analogous method as described for 10 Compound 60 and Compound 61

Int. No.	Structure	Starting Materials	Conditions
16		intermediate 3, intermediate 15	$ZnCl_2$, $NaBH_3CN$, MeOH, 65 °C
21		intermediate 20, benzyl 2,6-diazaspiro[3.4]octane-6-carboxylate	AcOH, $NaBH_3CN$, MeOH, 45 °C
39		intermediate 3, intermediate 38	$ZnCl_2$, $NaBH_3CN$, MeOH, 65 °C

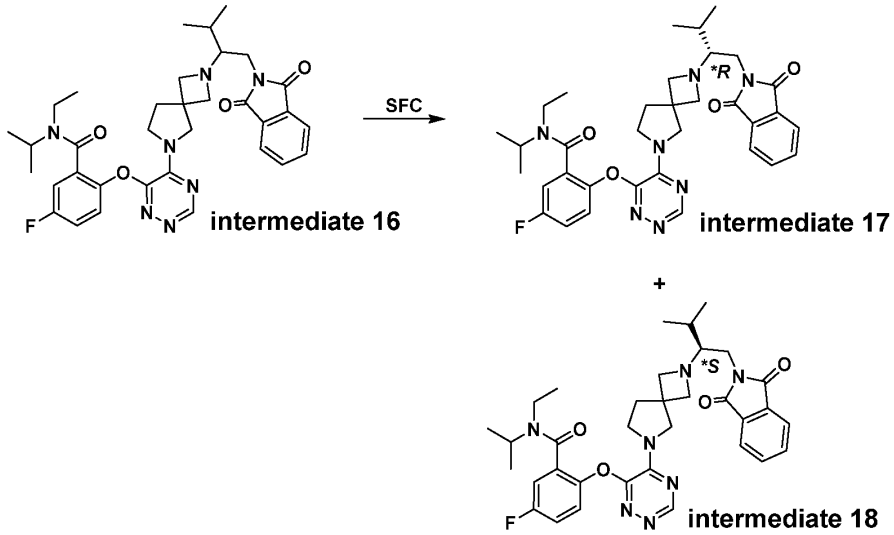
Int. No.	Structure	Starting Materials	Conditions
47		intermediate 59 intermediate 46	$ZnCl_2$, $NaBH_3CN$, MeOH, 80 °C
55		intermediate 3, intermediate 54	$ZnCl_2$, $NaBH_3CN$, MeOH, 80 °C
94		intermediate 3, intermediate 93	AcOH, $NaBH_3CN$, MeOH, 45 °C
98		intermediate 85, intermediate 93	AcOH, $NaBH_3CN$, MeOH, 60 °C
161		intermediate 160, 1,1,2-trimethoxyethane, HCl	AcOH, $NaBH_3CN$, EtOH, RT

Int. No.	Structure	Starting Materials	Conditions
163		intermediate 162, *tert*-butyl 2,6-diazaspiro[3.4]octane-2-carboxylate	NaOAc, $NaBH_3CN$, MeOH, 55 °C

Preparation of intermediate 17 and 18

(*R)-2-((5-(2-(1-(1,3-dioxoisoindolin-2-yl)-3-methylbutan-2-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

(*S)-2-((5-(2-(1-(1,3-dioxoisoindolin-2-yl)-3-methylbutan-2-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

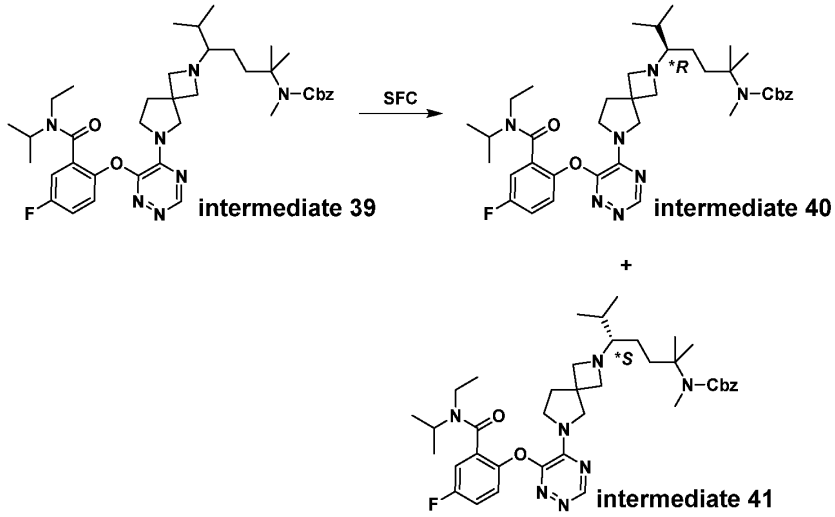


2-((5-(2-(1-(1,3-dioxoisoindolin-2-yl)-3-methylbutan-2-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (**intermediate 16**) (200 mg, 0.254 mmol) was purified by SFC over DAICEL CHIRALCEL OD (column: 250x50 mm 10μm; Mobile phase: A: Supercritical CO_2, B: IPA (0.1% ammonia), A:B =65:35 at 70 mL/min; Column Temp: 38 °C; Nozzle Pressure: 100 Bar; Nozzle Temp: 60 °C; Evaporator Temp: 20 °C; Trimmer Temp: 25 °C; Wavelength: 220 nm) to afford the title intermediates **intermediate 17** (100 mg, 95% purity, 42% yield) and **intermediate 18** (100 mg, 99% purity, 44% yield) both as colorless oil.

Preparation of intermediate 40 and 41

benzyl (*R)-(5-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-2,6-dimethylheptan-2-yl)(methyl)carbamate

benzyl (*S)-(5-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-2,6-dimethylheptan-2-yl)(methyl)carbamate

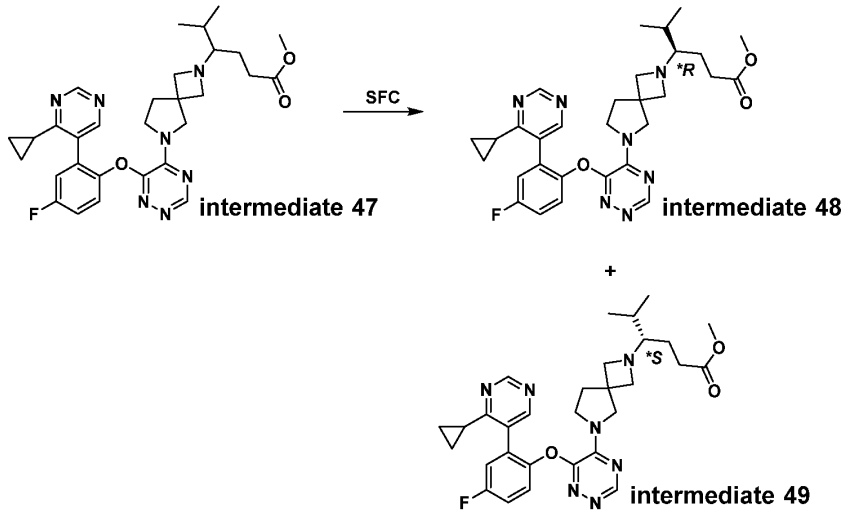


benzyl (5-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-2,6-dimethylheptan-2-yl)(methyl)carbamate (**intermediate 39**) (650 mg, 0.923 mmol) was separated by SFC over DAICEL CHIRALPAK AD-H (column: 250x30mm 5μm; eluent: 30% (v/v) super critical CO_2 in EtOH (0.1% ammonia), flow rate: 60 mL/min) to afford the title intermediates **intermediate 40** (250 mg, 96% purity, 37% yield) and **intermediate 41** (220 mg, 99.9% purity, 34% yield) both as a colorless oil.

Preparation of intermediate 48 and 49

methyl (*R)-4-(6-(6-(2-(4-cyclopropylpyrimidin-5-yl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-5-methylhexanoate

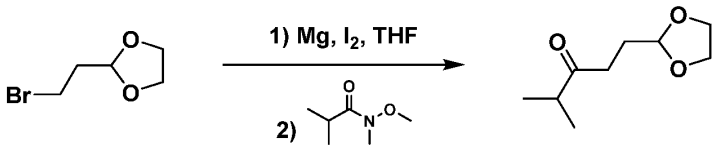
methyl (*S)-4-(6-(6-(2-(4-cyclopropylpyrimidin-5-yl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-5-methylhexanoate



methyl 4-(6-(6-(2-(4-cyclopropylpyrimidin-5-yl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-5-methylhexanoate (**intermediate 47**) (360 mg, 0.513 mmol) was purified by SFC over Phenomenex-Cellulose-2 (column: 250x30mm, 10μm; eluent: 35% (v/v) supercritical CO_2 in MeOH with 0.1% ammonia) to afford the title intermediates **intermediate 48** (110 mg, 35% yield) and **intermediate 49** (90 mg, 31% yield) both as white solid.

Preparation of intermediate 93

1-(1,3-dioxolan-2-yl)-4-methylpentan-3-one

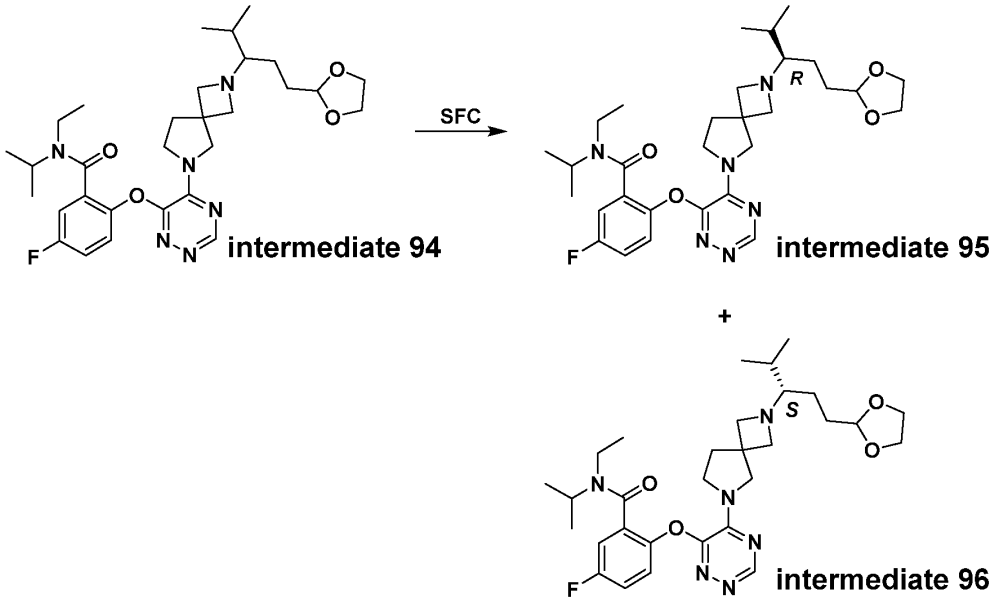


To the mixture of magnesium (6.0 g, 247 mmol) and iodine (100 mg, 0.394 mmol) in THF (70 mL) at 25 °C was slowly added a solution of 2-(2-bromoethyl)-1,3-dioxolane (20.0 g, 110 mmol) in THF (30 mL), the resulting mixture was stirred at 25 °C for 1 h. Then, the mixture was slowly added to the solution of *N*-methoxy-*N*-methylisobutyramide (10 g, 76.2 mmol) in THF (100 mL) cooled at 0 °C. The reaction mixture was slowly warmed to 25 °C and stirred at this temperature for 8 h. The mixture was quenched by sat. aq. NH_4Cl (300 mL), extracted with MTBE (200 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product, which was purified by FCC (PE:EtOAc = 1:0 to 20:1) to afford the title intermediate (13 g, crude) as colorless oil which was used directly in next step without further purification.

Preparation of intermediate 95 and 96

(*R*)-2-((5-(2-(1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

(*S*)-2-((5-(2-(1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

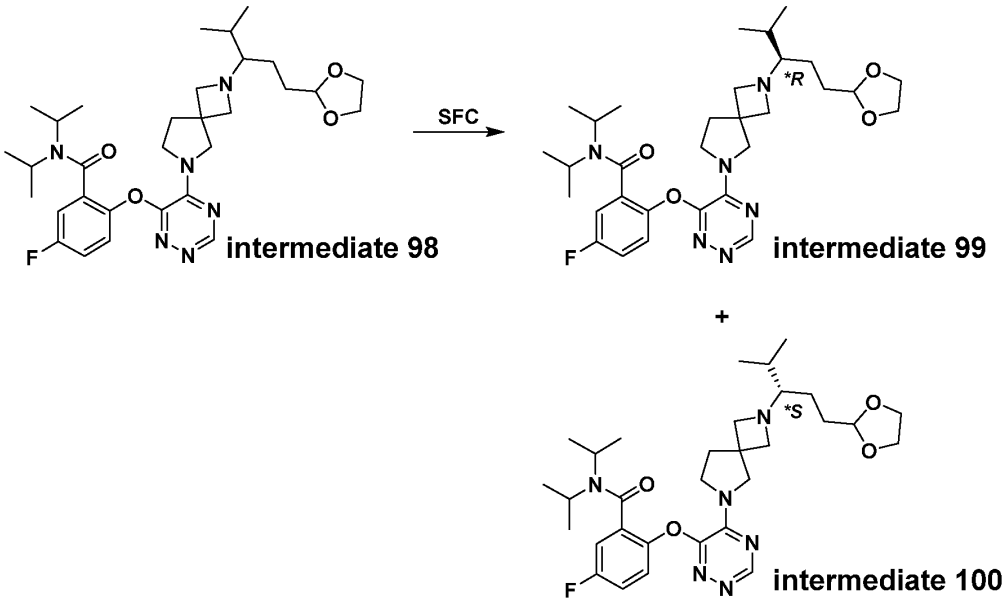


2-((5-(2-(1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (**intermediate 94**) (4.00 g, 7.01 mmol) separated by SFC over DAICEL CHIRALCEL OD (column: 250x50mm 10um; Mobile phase: A: Supercritical CO_2, B: MeOH (0.1% ammonia), A:B = 75:25 at 200 mL/min; Column Temp: 38 °C; Nozzle Pressure: 100 Bar; Nozzle Temp: 60 °C; Evaporator Temp: 20 °C; Trimmer Temp: 25 °C; Wavelength: 220 nm) to afford the title intermediates **intermediate 95** (1.72 g, 98.76% purity, 42.5% yield) and **intermediate 96** (1.57 g, 98.09% purity, 38.5% yield) as white solid.

Preparation of intermediate 99 and 100

(R*)-2-((5-(2-(1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide**

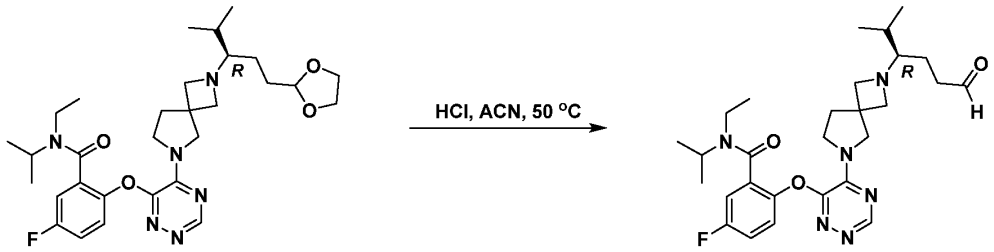
(S*)-2-((5-(2-(1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide**



2-((5-(2-(1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide (**intermediate 98**) (6.5 g) was separated by SFC over DAICEL CHIRALPAK IG (column: 250x50mm 10um; Mobile phase: A: Supercritical CO_2, B: MeOH (0.1% ammonia), A:B = 65:35 at 200 mL/min; Column Temp: 38 ; Nozzle Pressure: 100Bar; Nozzle Temp: 60 °C; Evaporator Temp: 20 °C; Trimmer Temp: 25 °C; Wavelength: 220nm) to afford the title intermediates **intermediate 99** (2.7 g) and **intermediate 100** (2.8 g).

Preparation of intermediate 97

(*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(2-methyl-6-oxohexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide



To a solution of (*R*)-2-((5-(2-(1-(1,3-dioxolan-2-yl)-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (**intermediate 95**) (1.00 g, 1.75 mmol) in ACN (10 mL) was added 1M HCl (10.0 mL, 10.0 mmol) and the resulting mixture was stirred at 50 °C for 1 h. After cooling to RT, the reaction mixture was concentrated under reduced pressure. The resulting residue was diluted with

DCM (50 mL) and basified to pH = 14 by 10% aq. NaOH. The mixture was further extracted by DCM (30 mL x 3) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford the title intermediate (900 mg, 87% purity, 85% yield) as a white solid, which was used directly in next step without further purification.

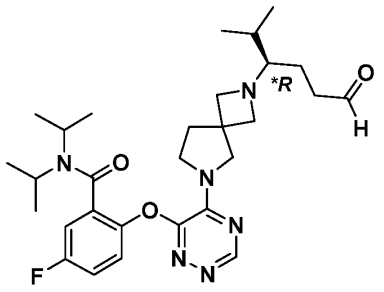
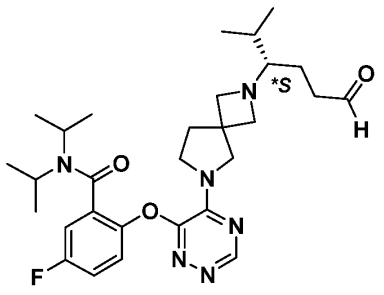
Preparation of intermediates 101, 102, 103

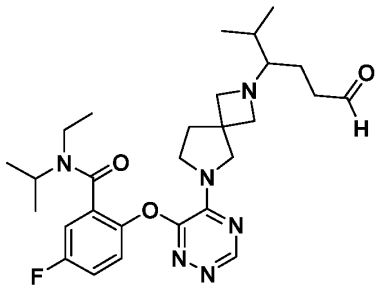
(*R)-5-fluoro-*N*,*N*-diisopropyl-2-((5-(2-(2-methyl-6-oxohexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide

(*S)-5-fluoro-*N*,*N*-diisopropyl-2-((5-(2-(2-methyl-6-oxohexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide

***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(2-methyl-6-oxohexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide**

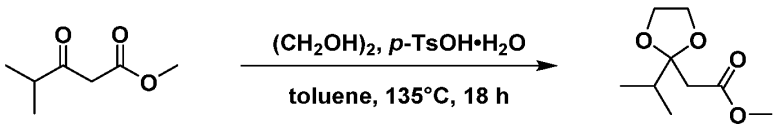
The following intermediates were synthesized by an analogous method as described for intermediate 97

Int. No.	Structure	Starting Material
101		intermediate 99
102		intermediate 100

Int. No.	Structure	Starting Material
103		intermediate 94

Preparation of intermediate 114

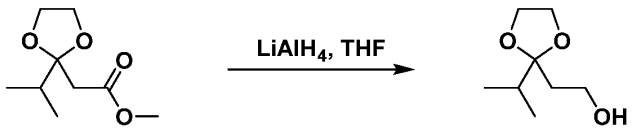
methyl 2-(2-isopropyl-1,3-dioxolan-2-yl)acetate



In a 1000 mL flask equipped with a Dean–Stark apparatus, methyl 4-methyl-3-oxopentanoate (50 g, 347 mmol) was added to a solution consisting of ethane-1,2-diol (43 g, 693 mmol), *p*-toluenesulfonic acid monohydrate (597 mg, 3.47 mmol) and toluene (500 mL). The mixture was stirred at 135°C for 18 h. After cooling to RT, 1M Na_2CO_3 (300 mL) aqueous solution was added to the reaction mixture. The organic layer was separated and washed with H_2O (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford the title intermediate (41 g, crude) as a yellow oil which was used directly in next step without further purification.

Preparation of intermediate 115

2-(2-isopropyl-1,3-dioxolan-2-yl)ethan-1-ol

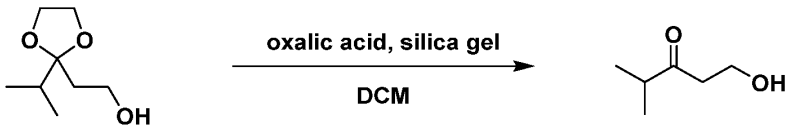


$LiAlH_4$ (2.5 g, 66 mmol) was added in portions to THF (250 mL) cooled at 0°C under N_2 atmosphere. A solution of methyl 2-(2-isopropyl-1,3-dioxolan-2-yl)acetate (**intermediate 114**) (10 g, crude) in THF (20 mL) was added drop-wise to above mixture at 0°C under N_2 atmosphere. The resulting mixture was slowly warmed to RT and stirred at this temperature for 18 h under N_2 atmosphere. Then 2.5 mL H_2O was slowly added to above mixture, followed with addition of aq. NaOH solution (15%, 7.5 mL). The resulting mixture was

stirred at RT for 0.5 h. Then anhydrous $MgSO_4$ was added to above mixture. The suspension was filtered through a celite pad and washed with THF (200 mL). The filtrate was concentrated *in vacuo* to afford the title intermediate (6.8 g, crude) as a yellow oil which was used directly in next step without further purification.

Preparation of intermediate 116

1-hydroxy-4-methylpentan-3-one



Oxalic acid (4.2 mL, 10% in water, 4.7 mmol) was added to a mixture of silica gel (27 g, 449 mmol) in DCM (230 mL). Once the aqueous layer vanished, a solution of 2-(2-isopropyl-1,3-dioxolan-2-yl)ethan-1-ol (**intermediate 115**) (3.7 g, crude) in DCM (7 mL) was added and the reaction mixture was stirred at RT for 5 h. Then $NaHCO_3$ (800 mg) was added. The resulting mixture was filtered and washed with DCM (50 mL x 3). The filtrate was concentrated *in vacuo* to afford the title intermediate (2.4 g, crude) as a colorless oil which was used directly in next step without further purification.

Preparation of intermediate 124

(*R)-3-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-4-methylpentyl methanesulfonate



MsCl (250 mg, 2.18 mmol) was added dropwise to a solution of *N*-ethyl-5-fluoro-2-((5-(2-(1-hydroxy-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide (**Compound 213**) (500 mg, 0.972 mmol) and TEA (0.27 mL, 1.9 mmol) in DCM (10 mL) cooled at 0 °C under N_2 atmosphere. The resulting mixture was stirred at 0 °C under N_2 for 45 min. Then the reaction mixture was quenched with H_2O (5 mL) and extracted with DCM (10 mL x 3). The combined organic layers were washed with brine (5

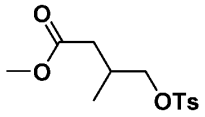
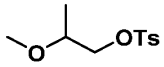
mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford the title intermediate (400 mg, crude) as a yellow oil which was used directly in next step without further purification.

Preparation of intermediate 130, 139

methyl 3-methyl-4-(tosyloxy)butanoate

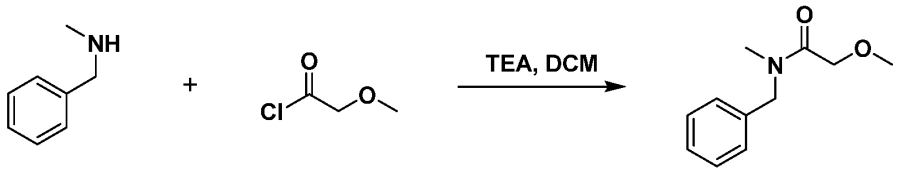
2-methoxypropyl 4-methylbenzenesulfonate

The following intermediates were synthesized by an analogous method as described above for intermediate 124

Int. No.	Structure	Starting Materials	Conditions
130		intermediate 129, TsCl	DMAP, TEA, DCM, RT
139		2-methoxypropan-1-ol, TsCl	DMAP, TEA, DCM, RT

Preparation of intermediate 125

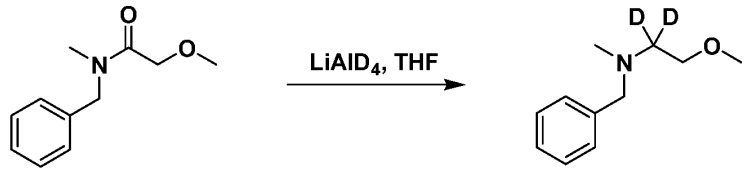
***N*-benzyl-2-methoxy-*N*-methylacetamide**



To a solution of *N*-methyl-1-phenylmethanamine (5.5 g, 45.4 mmol) and TEA (14g, 138.4 mmol) in DCM (60 mL) cooled at 0 °C was dropwise added 2-methoxyacetyl chloride (5 g, 46.073 mmol). The resulting mixture was slowly warmed to 25 °C and stirred at this temperature for 1 h. Then, aq. sat. $NaHCO_3$ solution (50 mL) was added to above mixture and extracted with DCM (50 mL x 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* give a crude residue which was purified by FCC (EA:PE = from 0 to 80%) to afford the title intermediate (3.4 g, 34% yield) as a colorless oil.

Preparation of intermediate 126

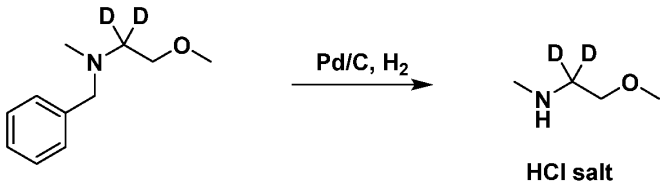
***N*-benzyl-2-methoxy-*N*-methylethan-1-amine-1,1-d_2**



To the mixture of $LiAlD_4$ (1.5 g, 35.732 mmol) in THF (25 mL) cooled at 0 °C under N_2 atmosphere was added dropwise a solution of *N*-benzyl-2-methoxy-*N*-methylacetamide (**intermediate 125**) (3.4 g, 17.6 mmol) in THF (25 mL). The reaction mixture was first stirred at 25 °C for 1 h and at 50 °C for additional 2 h. Then the reaction mixture was cooled to 0 °C and quenched with aq. NaOH (1 M, 10 mL) dropwise. The resulting mixture was filtered and the filter cake was washed with EtOAc (100 mL). The filtrate was washed with H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4, and filtered. The solvent was concentrated under reduced pressure to afford a residue which was purified by FCC (EtOAc:PE = from 0 to 100%) to afford the title intermediate (2.0 g, 60% yield) as a colorless oil.

Preparation of intermediate 127

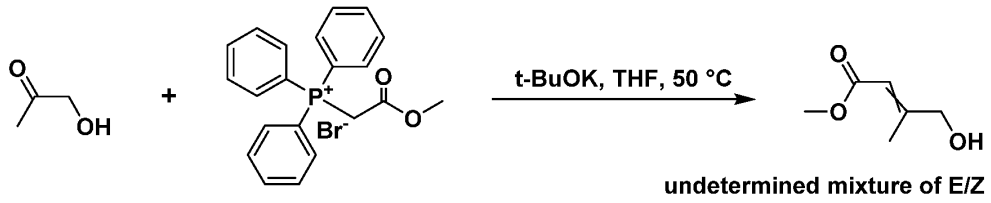
2-methoxy-*N*-methylethan-1,1-d_2-1-amine, hydrochloride



To the solution of *N*-benzyl-2-methoxy-*N*-methylethan-1-amine-1,1-d_2 (800 mg, 4.413 mmol) in MeOH (20 mL) and THF (60 mL) was added 1,1,2-trichloroethane (1.2 g, 9.0 mmol) and Pd/C (wet, 10%, 0.5 g). The resulting mixture was stirred under H_2 atmosphere (50 psi) at 50 °C for 18 h. After cooling to RT, the reaction mixture was filtered by celite and the filtrate was concentrated *in vacuo* to afford the title intermediate (600 mg, crude) as yellow oil which was used directly in next step without further purification.

Preparation of intermediate 128

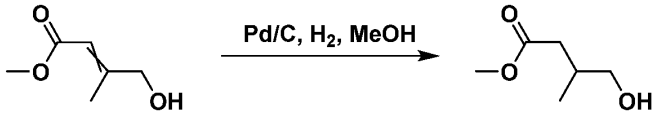
methyl 4-hydroxy-3-methylbut-2-enoate



t-BuOK (16.0 g, 143 mmol) was added to a solution of (2-methoxy-2-oxoethyl)triphenylphosphonium bromide (59.0 g, 142 mmol) in THF (220 mL). The resulting mixture was stirred at 50 °C for 1 h. Then 1-hydroxypropan-2-one (7.2 g, 97 mmol) in THF (30 mL) was added to above mixture and the reaction mixture was stirred at 50 °C for another 16 h. After cooling to RT, H_2O (200 mL) was added and the mixture was extracted with EtOAc (200 mL x 3). The combined organic layers were washed with H_2O (300 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated to *in vacuo* to afford a crude compound which was purified by FCC (PE: EtOAc = 1:0 to 1:1) to afford the title intermediate (3.4 g, 27% yield) as a light yellow oil.

Preparation of intermediate 129

methyl 4-hydroxy-3-methylbutanoate



To the solution of methyl 4-hydroxy-3-methylbut-2-enoate (**intermediate 128**) (3.4 g, 26 mmol) in MeOH (100 mL) was added dry Pd/C (500 mg, 10%) and the suspension was stirred at RT under H_2 (15 psi) atmosphere for 4 h. Then the reaction mixture was filtered through a celite pad and washed with MeOH (200 mL). The filtrate was concentrated *in vacuo* afford the title intermediate (2.3 g, 67% yield) as a yellow oil which was used directly in the next step without further purification.

Preparation of intermediates 193, 194, 207, 208

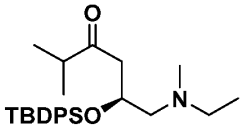
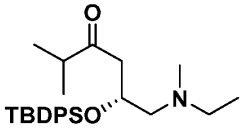
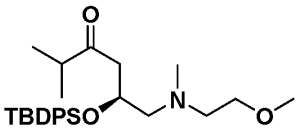
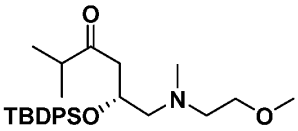
(*S*)-5-((*tert*-butyldiphenylsilyl)oxy)-6-(ethyl(methyl)amino)-2-methylhexan-3-one

(*R*)-5-((*tert*-butyldiphenylsilyl)oxy)-6-(ethyl(methyl)amino)-2-methylhexan-3-one

(*S*)-5-((*tert*-butyldiphenylsilyl)oxy)-6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-one

(*R*)-5-((*tert*-butyldiphenylsilyl)oxy)-6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-one

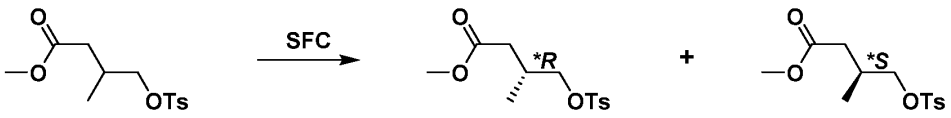
The following intermediates were synthesized by an analogous method as described for intermediate 129

Int. No.	Structure	Starting Material
193		intermediate 191
194		intermediate 192
207		intermediate 205
208		intermediate 206

Preparation of intermediate 131 and 132

methyl (*R)-3-methyl-4-(tosyloxy)butanoate

methyl (*S)-3-methyl-4-(tosyloxy)butanoate

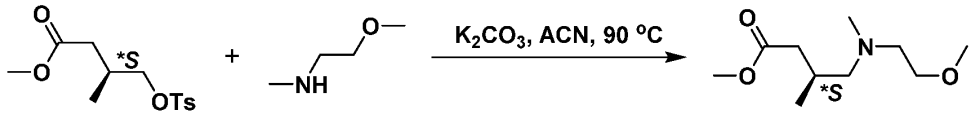


intermediate 130 **intermediate 131** **intermediate 132**

Methyl 3-methyl-4-(tosyloxy)butanoate (**intermediate 130**) (3.3 g) was purified by SFC over DAICEL CHIRALPAK AY-H (column: 250x30mm 5um; Mobile phase: A: Supercritical CO_2, B: EtOH (0.1% ammonia), A:B = 90:10 at 60 mL/min) to afford the title intermediates (**intermediate 131**) (1.28 g, 97% purity, 36 % yield) and (**intermediate 132**) (1.27 g, 85% purity, 33 % yield) both as white solid.

Preparation of intermediate 134

methyl (*S)-4-((2-methoxyethyl)(methyl)amino)-3-methylbutanoate



A mixture of methyl (*S)-3-methyl-4-(tosyloxy)butanoate (**intermediate 132**) (1.27 g, 4.44 mmol), 2-methoxy-*N*-methylethan-1-amine (593 mg, 6.65 mmol), and K_2CO_3 (1.23 mg, 8.87 mmol) in ACN (5 mL) was stirred at 90 °C overnight. After cooling to RT, the reaction mixture was filtered and the filtrate was concentrated *in vacuo* to afford the title intermediate (670 mg, crude) as a brown oil which was used directly in next step without further purification.

Preparation of intermediates 133, 185, 186, 199, 200, 219

methyl (*R)-4-((2-methoxyethyl)(methyl)amino)-3-methylbutanoate

ethyl (*S*)-3-((*tert*-butyldiphenylsilyl)oxy)-4-(ethyl(methyl)amino)butanoate

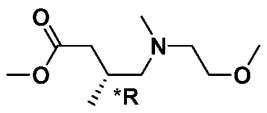
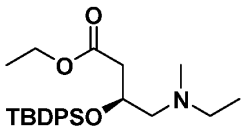
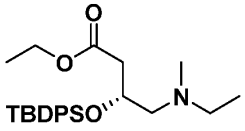
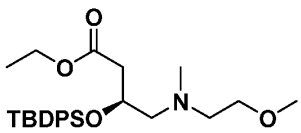
ethyl (*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-4-(ethyl(methyl)amino)butanoate

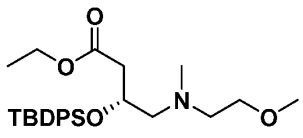
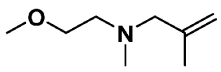
ethyl (*S*)-3-((*tert*-butyldiphenylsilyl)oxy)-4-((2-methoxyethyl)(methyl)amino)butanoate

ethyl (*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-4-((2-methoxyethyl)(methyl)amino)butanoate

***N*-(2-methoxyethyl)-*N*,2-dimethylprop-2-en-1-amine**

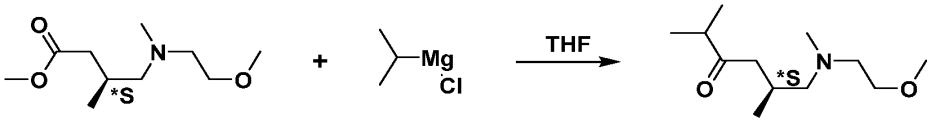
The following intermediates were synthesized by an analogous method as described for intermediate 134

Int. No.	Structure	Starting Materials	Conditions
133		intermediate 131, 2-methoxy-*N*-methylethan-1-amine	K_2CO_3, ACN, 90 °C
185		intermediate 183, *N*-methylethanamine	K_2CO_3, ACN, 80 °C
186		intermediate 184, *N*-methylethanamine	K_2CO_3, ACN, 80 °C
199		intermediate 183, 2-methoxy-*N*-methylethan-1-amine	K_2CO_3, ACN, 85 °C

Int. No.	Structure	Starting Materials	Conditions
200		intermediate 184, 2-methoxy-*N*-methylethan-1-amine	K_2CO_3, ACN, 85 °C
219		3-bromo-2-methylprop-1-ene, 2-methoxy-*N*-methylethan-1-amine	K_2CO_3, H_2O, RT

Preparation of intermediate 136

(*S)-6-((2-methoxyethyl)(methyl)amino)-2,5-dimethylhexan-3-one

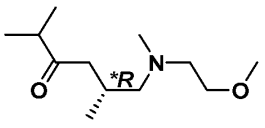


To the solution of methyl (*S)-4-((2-methoxyethyl)(methyl)amino)-3-methylbutanoate (**intermediate 134**) (670 mg, crude) in THF (5 mL) cooled at 0 °C under N_2 was added dropwise isopropylmagnesium chloride (4.94 mL, 9.88 mmol, 2 M, in THF). The resulting mixture was stirred at 50 °C for 5 h under N_2. After cooling to RT, the reaction mixture was quenched with sat. aq. NH_4Cl solution (1.5 mL) and filtered. The filtrate was concentrated *in vacuo* to afford the title intermediate (507.1 mg, crude) as a yellow oil which was used directly in next step without further purification.

Preparation of intermediate 135

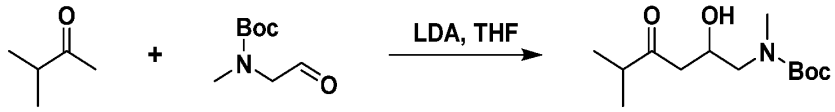
(*R)-6-((2-methoxyethyl)(methyl)amino)-2,5-dimethylhexan-3-one

The following intermediate was synthesized by an analogous method as described for intermediate 136

Int. No.	Structure	Starting Materials	Conditions
135		intermediate 133, isopropylmagnesium chloride	THF, 50 °C

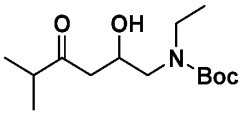
Preparation of intermediate 165

***tert*-butyl (2-hydroxy-5-methyl-4-oxohexyl)(methyl)carbamate**



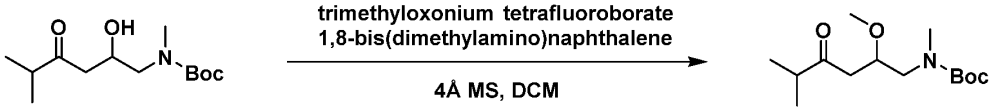
To the solution of 3-methylbutan-2-one (6.0 g, 70.0 mmol) in THF (150 mL) cooled at -40 °C under N_2 atmosphere was added dropwise LDA (40 mL, 2 M in THF, 80.0 mmol). The resulting mixture was stirred at -40 °C for 1 h. Then a solution of *tert*-butyl methyl(2-oxoethyl)carbamate (8.0 g, 46.2 mmol) in THF (50 mL) was added dropwise to above mixture and the reaction was further stirred at -40 °C for 2 h. The reaction was quenched by the dropwise addition of H_2O (20 mL) at -40 °C. Then the mixture was warmed to RT and concentrated under reduced pressure. The crude residue was diluted with H_2O (200 mL) and extracted with EtOAc (200 mL × 2). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by FCC (PE/EtOAc = 20/1 to 3/1) to afford the title intermediate (8.8 g, 85% purity, 62% yield) as colorless oil.

The following intermediate was synthesized by an analogous method as described for intermediate 165

Int. No.	Structure	Starting Materials
174		3-methylbutan-2-one, *tert*-butyl ethyl(2-oxoethyl)carbamate

Preparation of intermediate 166

***tert*-butyl (2-methoxy-5-methyl-4-oxohexyl)(methyl)carbamate**



To a solution of *tert*-butyl (2-hydroxy-5-methyl-4-oxohexyl)(methyl)carbamate (**intermediate 165**) (4.00 g, 15.4 mmol) in DCM (200 mL) was added 4 Å molecular sieve (4 g) under N_2 atmosphere and the mixture was stirred at 25 °C for 10 min. Then 1,8-bis(dimethylamino)naphthalene (8.26 g, 38.6 mmol) was added and the mixture was cooled to 0 °C, followed with addition of trimethyloxonium tetrafluoroborate (5.93 g, 40.1 mmol). The reaction mixture was first stirred at 0 °C for 2 h, then warmed up to 25 °C and stirred at this

temperature for additional 16 h. The suspension was filtered and washed with DCM (40 mL × 2). The filtrate was concentrated *in vacuo* and the residue was purified by FCC (PE/EtOAc = 5/1 to 4/1) to afford the title intermediate (2.00 g, 44% yield) as colorless oil.

Preparation of intermediate 181

ethyl (*S*)-3-hydroxy-4-iodobutanoate

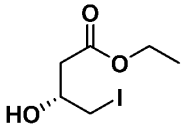


To a solution of (*S*)-4-hydroxydihydrofuran-2(3*H*)-one (5 g, 50.0 mmol) in EtOH (8.6 mL) in DCM (20 mL) under N_2 atmosphere was slowly added TMSI (14.8 g, 74.0 mmol). The resulting mixture was stirred at RT for 16 h. A solution of sat. Na_2SO_3 (40 mL) was added. The organic layer was separated and concentrated *in vacuo* to afford the title intermediate (8.8 g, crude) as yellow oil which was used directly in next step without further purification.

Preparation of intermediate 182

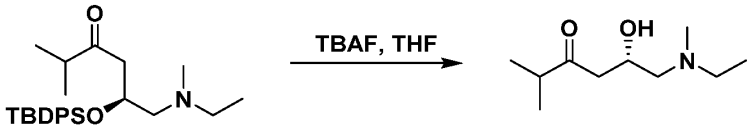
ethyl (*R*)-3-hydroxy-4-iodobutanoate

The following intermediate was synthesized by an analogous method as described above for intermediate 181

Int. No.	Structure	Starting Material
182		(*R*)-4-hydroxydihydrofuran-2(3*H*)-one

Preparation of intermediate 195

(*S*)-6-(ethyl(methyl)amino)-5-hydroxy-2-methylhexan-3-one



To a solution of (*S*)-5-((*tert*-butyldiphenylsilyl)oxy)-6-(ethyl(methyl)amino)-2-methylhexan-3-one (**intermediate 193**) (2.33 g, 5.04 mmol) in THF (3 mL) was added TBAF (0.65 mL, 1.0 M in THF, 0.65 mmol) under N_2 atmosphere. The resulting mixture was stirred at RT for 16 h. The reaction mixture was concentrated under reduced pressure and the crude residue

was diluted with H_2O (25 mL) and extracted with DCM (60 mL × 3). The combined organic layers were washed with brine (40 mL × 2), dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford the title intermediate (2.2 g, crude) as yellow oil which was used directly in next step without further purification.

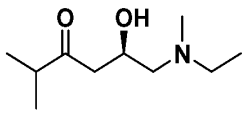
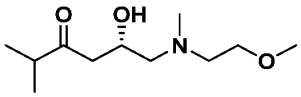
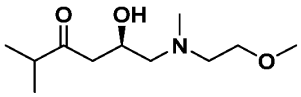
Preparation of intermediate 196, 209, 210

(*R*)-6-(ethyl(methyl)amino)-5-hydroxy-2-methylhexan-3-one

(*S*)-5-hydroxy-6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-one

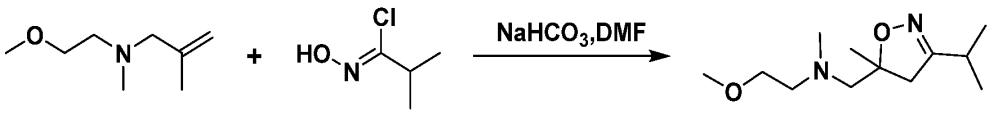
(*R*)-5-hydroxy-6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-one

The following intermediates were synthesized by an analogous method as described above for intermediate 195

Int. No.	Structure	Starting Material
196		intermediate 194
209		intermediate 207
210		intermediate 208

Preparation of intermediate 220

***N*-((3-isopropyl-5-methyl-4,5-dihydroisoxazol-5-yl)methyl)-2-methoxy-*N*-methylethan-1-amine**

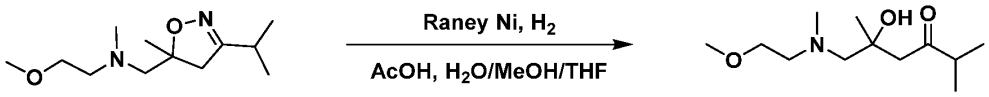


To a solution of *N*-(2-methoxyethyl)-*N*,2-dimethylprop-2-en-1-amine (**intermediate 219**) (2.90 g, 20.2 mmol) in DMF (50 mL) cooled at 0 °C were added $NaHCO_3$ (6.82 g, 81.2 mmol) and (*Z*)-*N*-hydroxyisobutyrimidoyl chloride (2.47 g, 20.3 mmol). The reaction mixture was stirred at 0 °C for 30 min and then at RT for 16 h. The reaction mixture was quenched by

H_2O (50 mL) and extracted with EtOAc (30 mL × 2). The combined organic layers were washed with sat. aq. LiCl solution (50 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to give the crude product, which was purified by FCC (MeOH: DCM = 1:10) to afford the title intermediate (1.20 g, 89.9% purity, 25.9% yield) as brown oil.

Preparation of intermediate 221

5-hydroxy-6-((2-methoxyethyl)(methyl)amino)-2,5-dimethylhexan-3-one

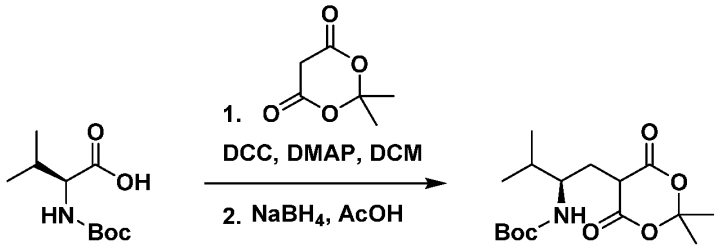


To a solution of *N*-((3-isopropyl-5-methyl-4,5-dihydroisoxazol-5-yl)methyl)-2-methoxy-*N*-methylethan-1-amine (**intermediate 220**) (1.20 g, 5.26 mmol) in MeOH and THF (40 mL, MeOH/THF = 1/2) were added AcOH (3.15 g, 52.5 mmol) and H_2O (9.50 mL, 572.3 mmol). Raney-Ni (750 mg) was added to the solution under N_2 atmosphere at 0 °C. The suspension was degassed and purged with H_2 for 3 times and the mixture was stirred under H_2 atmosphere (30 Psi) at 25 °C overnight.

The reaction mixture was filtered through a celite pad and the filtrate was extracted with DCM. The combined organic layers were washed with $NaHCO_3$ (20 mL × 2) and brine (20 mL × 2), dried over Na_2SO_4 and filtered. The filtrate was concentrated in vacuo to afford the title intermediate (1.10 g, crude) as brown oil, which was used directly in next step without further purification.

Preparation of intermediate 227

***tert*-butyl (*R*)-(1-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-3-methylbutan-2-yl)carbamate**

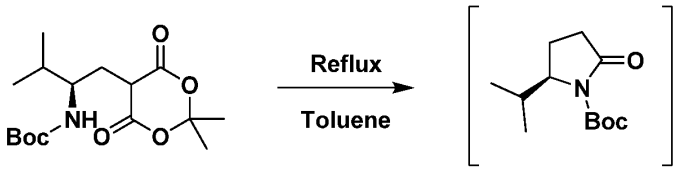


Boc-L-valine (44.9 kg), 2,2-dimethyl-1,3-dioxane-4,6-dione (32.9 kg) and DMAP (35.5 kg) in DCM (607 kg) pre-cooled at -10 to 0°C were added to a solution of DCC (55.5 kg) in DCM (613 kg) over 3 h and aged for 16 h at -10 to 0°C. 10% citric acid aqueous solution (449 kg) was added whilst maintaining a temperature below 10°C. The resulting slurry was aged for 2 h

at 0 to 10°C. then filtered. The filter cake was washed with DCM (91 kg). The filtrate was separated and the organic layer was washed with 10% citric acid aqueous solution (two times 450 kg) and 10% NaCl aqueous solution (449 kg). To organic phase (1200 kg), was added acetic acid (75.0 kg) whilst maintaining a temperature between -10 to 0°C. Sodium Borohydride (18.0 kg) was added in portions over 5 h whilst maintaining a temperature in the range -10 to 0°C and then resulting mixture was aged at -10 to 0°C for an additional 16 h. The mixture was warmed to 15 to 25°C, and aged for 2 h. The mixture was then washed with 14% NaCl aqueous solution (450 kg) followed by a second wash with 14% NaCl aqueous solution (432 kg) and a final water wash (444 kg). The organic phase was concentrated under reduced pressure to 2-4 vol. Iso-propanol (143 kg) was added to the residue and concentrated to 4-5 vol. under reduced pressure. After cooling to -10 to 0°C and aging for 8 h, the resulting slurry was filtered, washed with IPA (38 kg) and dried to afford the title intermediate (46.7 kg, 69% yield) as a white solid.

Preparation of intermediate 228

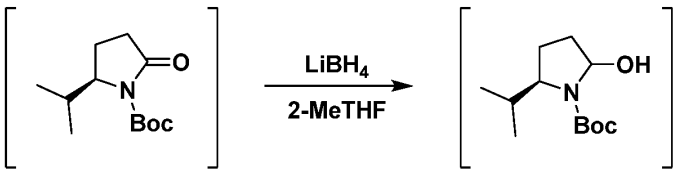
***tert*-butyl (*R*)-2-isopropyl-5-oxopyrrolidine-1-carboxylate**



tert-butyl (*R*)-(1-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-3-methylbutan-2-yl)carbamate (**intermediate 227**) (46.7 kg) in toluene (333 kg) was heated to reflux and aged for 4 h. The mixture was cooled to ambient temperature, filtered and washed with toluene (20 kg). The combined filtrates were concentrated to dryness at reduced pressure to afford the desired compound (31.05 kg, 96% yield) as an oil which was used directly without further purification.

Preparation of intermediate 229

***tert*-butyl (5*R*)-2-hydroxy-5-isopropylpyrrolidine-1-carboxylate**

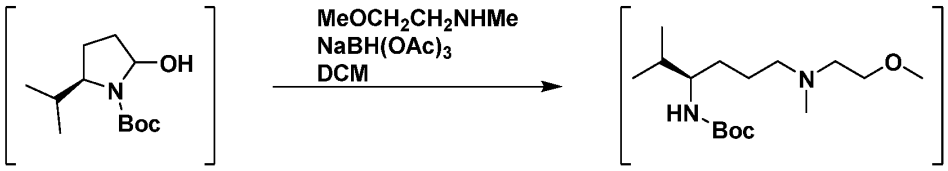


tert-butyl (*R*)-2-isopropyl-5-oxopyrrolidine-1-carboxylate (**intermediate 228**) (30.9 kg) in 2-MeTHF (26.7 kg) was cooled to -5 to 5°C. A solution of $LiBH_4$ in 2-MeTHF (1M, 45.2 kg,

54.4 mol) was added over 3 h and the mixture was aged for 4 h. A cold aqueous solution of 5% $NaHCO_3$ (163 kg) was added at -5 to 5°C over 3h and aged for an additional 2 h. The mixture was warmed to ambient temperature and aged for a further 2 h. The aqueous layer was separated and the organic layer was washed with 10% NaCl aqueous solution (170 kg) and water (155 kg). During the water wash, an emulsion formed and solid NaCl (3.1 kg) was added to affect the separation. After removal of the aqueous layer, the organic layer was concentrated under reduced pressure to dryness to afford the desired compound (28.5 kg, 91% yield) as an oil, which was used directly without further purification.

Preparation of intermediate 230

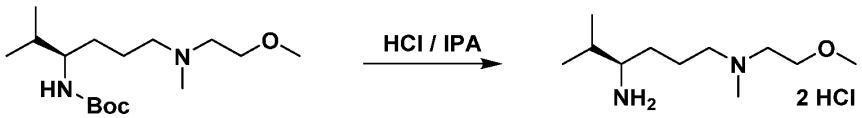
***tert*-butyl (*R*)-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)carbamate**



tert-butyl (5*R*)-2-hydroxy-5-isopropylpyrrolidine-1-carboxylate (**intermediate 229**) (28.55 kg) in DCM (344 kg), at 15 to 25°C was treated with 2-methoxy-*N*-methylethan-1-amine (12.3 kg, 138.0 mol) and the resulting mixture was aged for 1 h. Sodium triacetoxyborohydride (40.12 kg) was added in portions over 5h whilst maintaining a temperature between 15 to 25°C and the resulting mixture was aged for 48 h. The reaction mixture was quenched by the addition of 8% NaOH aqueous solution (184 kg) over 2 h whilst maintaining a temperature between 15 to 25°C and the mixture was aged for a further 2 h. The water layer was separated, and the organic layer was washed with water (169 kg). The organic layer was then concentrated under reduced pressure to dryness to afford the title intermediate (33.26 kg, 88% yield) as an oil which was used directly without further purification.

Preparation of intermediate 231

(*R*)-N^1-(2-methoxyethyl)-N^1,5-dimethylhexane-1,4-diamine, dihydrochloride

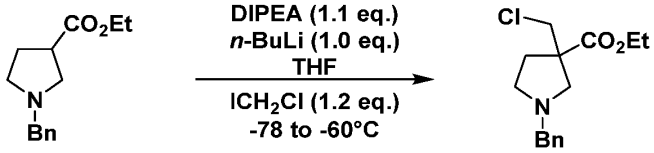


To 4 molar solution of HCl in iso-propanol (84.80 kg) at ambient temperature was added a solution of *tert*-butyl (*R*)-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)carbamate (**intermediate 230**) (32.38 kg) in iso-propanol (25.6 kg) over 3 h and the mixture was aged at

ambient temperature for an additional 19 h. Methyl *tert*-butyl ether (95.25 kg) was then added over 1 h and the mixture was aged for 2.5 h. The resulting slurry was filtered and washed with MTBE (53 kg). The filter cake was dried to afford the title compound (23.92 kg, 81% yield) as a white solid.

Preparation of intermediate 232

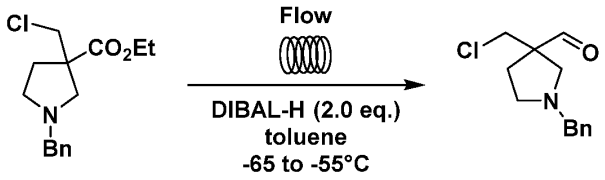
ethyl 1-benzyl-3-(chloromethyl)pyrrolidine-3-carboxylate



To a solution of DIPEA (952 g, 1.1 eq.) in THF (6 L) which was cooled to -35 to -25°C was added *n*-BuLi (2.33 kg, 2.5 M in hexane, 1.0 eq.) whilst maintaining a temperature below -25°C. The resulting mixture was aged at -35 to -25°C for an additional 30 min then cooled to between -78 to -60°C. A solution of ethyl 1-benzylpyrrolidine-3-carboxylate (2 kg, 1.0 eq.) in THF (2 L) at -78 to -60°C was added and stirred for an addition 30 min. Chloroiodomethane (1.81 kg, 1.2 eq.) was then charged at -78 to -60°C. The reaction mixture was aged at -60 to -40°C for 2 h. To the reaction mixture was added to citric acid aqueous solution (660 g in 6 L H_2O) at a temperature between 0 to 10°C and the resulting mixture was aged at 20 to 30°C for an additional 20 min. After separating the layers, the aqueous layer was extracted with EtOAc (6 L) and the combined organic layers washed with brine (6 L) then warmed to 50 to 60°C. Oxalic acid (2.22 kg) was charged at 50 to 60°C. The resulting mixture was stirred at 50 to 60°C for 3 h then cooled to 20 to 30°C and aged overnight. The resulting solid was filtered and the cake was washed with ethyl acetate (2 L). The wet cake was added to toluene (4 L), H_2O (8 L) and K_3PO_4 (1.5 eq.) and the resulting mixture was aged at 20 to 30°C for 20 min. After separating the layers, the aqueous layer was extracted with toluene (2 L). The organic layers were combined and washed twice with water (2 L). The organic phase was concentrated under reduced pressure to afford 4.2 kg of the desired compound as a toluene solution (46 wt % by assay, giving an assay yield of 80%).

Preparation of intermediate 233

1-benzyl-3-(chloromethyl)pyrrolidine-3-carbaldehyde

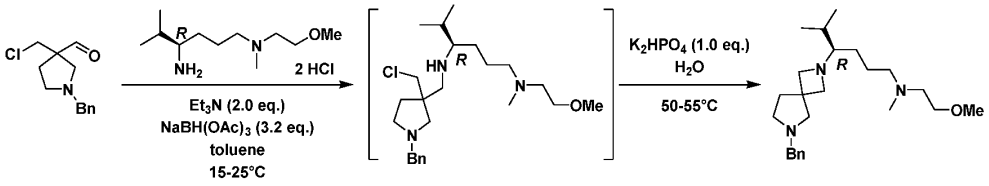


Reaction conducted in a flow chemistry system: A solution of ethyl 1-benzyl-3-(chloromethyl)pyrrolidine-3-carboxylate (**intermediate 232**) (4.4 kg) in toluene (26 L) was pumped at 26.7 mL/min and cooled to -60°C. After cooling, it was then mixed with a cooled solution of DIBAL-H (28.1 mol) in toluene at -60°C (28 L) with a pumping rate of 32.1 mL/min. The mixture was passed through a Perfluoroalkoxy (PFA) coil tube reactor at –60°C (total flow rate of 58.8 mL/min with a residence time of 5 seconds). The resulting mixture was mixed with cooled MeOH (-60°C) which was pumped at the rate of 15.2 mL/min. This mixed solution was pumped to another PFA coil tube reactor at –60°C (total flow rate of 74 mL/min with a residence time of 5 seconds). The resulting mixture was collected into a receiver which contained 20 wt % aq. solution Rochelle's salt (20 V). The layers were separated, and the organic phase was twice washed with water (2 x 44 L). The organic phase was combined with another 3.0 kg batch prepared in an analogous manner and concentrated under reduced pressure to afford 20.8 kg of a toluene solution of the desired compound (25.5 wt % assay by HPLC, giving an assay yield of 85%) which was used directly without further purification.

^{1}H NMR (300 MHz, Chloroform-d): δ 9.62 (s, 1H), 7.39 - 7.20 (m, 5H), 3.83 - 3.57 (m, 4H), 2.96 (d, J = 10.2 Hz, 1H), 2.80 - 2.55 (m, 3H), 2.17 (ddd, J = 13.9, 7.9, 6.1 Hz, 1H), 1.83 (ddd, J = 13.4, 7.8, 5.5 Hz, 1H).

Preparation of intermediate 234

(*R*)-4-(6-benzyl-2,6-diazaspiro[3.4]octan-2-yl)-*N*-(2-methoxyethyl)-*N*,5-dimethylhexan-1-amine



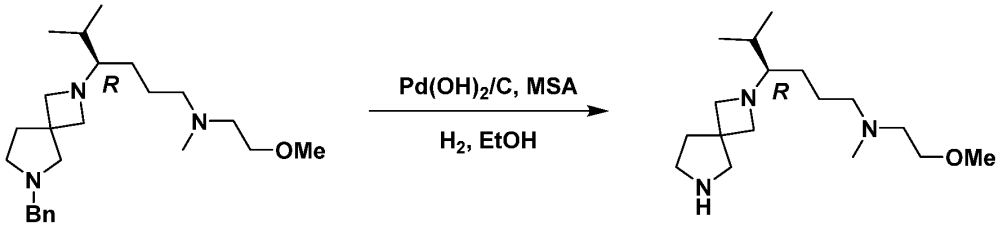
To a solution of 1-benzyl-3-(chloromethyl)pyrrolidine-3-carbaldehyde (**intermediate 233**) in toluene (3.0 kg, 10 wt %) diluted with toluene (30 L) and (*R*)-N^1-(2-methoxyethyl)-N^1,5-dimethylhexane-1,4-diamine, dihydrochloride (**intermediate 231**) (3.47 kg) was added triethylamine (2.55 kg, 25.2 mol) at 20 to 30°C. The resulting mixture was aged for 2 h at 20 to 30°C. Then sodium triacetoxyborohydride (9.0 kg) was charged at 20 to 30°C and the mixture was aged for 12 h. The reaction mixture was cooled to 5 to 15°C and 25 wt % NaOH

aqueous solution (25 L, ~16.75 eq.) was added maintaining a temperature below 35°C. The resulting mixture was aged at 20 to 30°C for 25 mins and the layers were separated. The organic layer was washed with 15 wt % aq. NaCl (10 L) and the layers were again separated and water (18 L) was charged to the organic phase. The pH of the aqueous phase was adjusted to 6~7 with 4M aq. HCl whilst maintaining an internal temperature below 35°C. The organic phase was then discarded and the aqueous phase was separated and basified to pH 8~9 with K_2HPO_4.

The resulting mixture was warmed to 50 to 55°C and aged for 3 h. The reaction mixture was then cooled to ambient temperature and combined with other two batches (2.4 kg + 3.0 kg). The combined streams were washed with methyl *tert*-butyl ether three times (3 x 40 L). To the resulting aqueous layer was added additional methyl *tert*-butyl ether (83 L) and the aqueous phase was basified to pH 9~10 using 8 wt % aq. NaOH whilst maintaining a temperature between 15 to 35°C. The aqueous layer was separated, and the organic layer was washed with three times water (3 x 30 L). The organic layer was then concentrated under reduced pressure to approximately 3 volumes and then flushed with methanol three times (3 x 30 L) and concentrated to dryness to afford the desired compound (12.4 kg, 90% isolated yield) as light-yellow oil, which was used directly without further purification.

Preparation of intermediate 224

(*R*)-*N*-(2-methoxyethyl)-*N*,5-dimethyl-4-(2,6-diazaspiro[3.4]octan-2-yl)hexan-1-amine

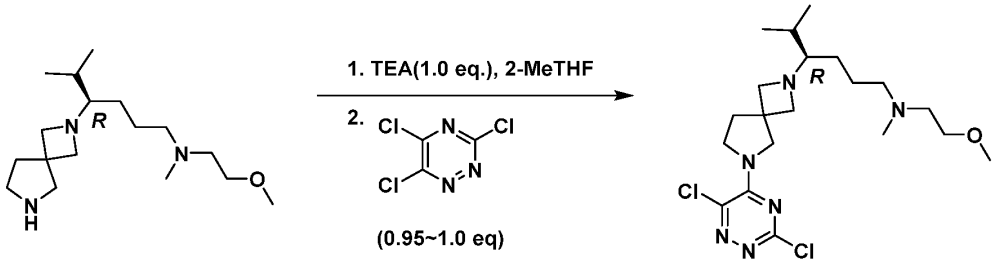


To palladium hydroxide on carbon (1.2kg) in EtOH (1.47 kg) cooled to -5 to 5°C were added methanesulfonic acid (MSA) (11kg), (*R*)-4-(6-benzyl-2,6-diazaspiro[3.4]octan-2-yl- *N*-(2-methoxyethyl)-*N*,5-dimethylhexan-1-amine (**intermediate 234**) (10kg) and EtOH (250L). The mixture was warmed to 35-45°C and stirred under a hydrogen atmosphere (0.27 to 0.40 MPa) for 16-20h. The mixture was filtered over diatomite (20kg) and the pad was washed with EtOH (24L). The filtrate was concentrated under reduced pressure (<40°C) to 2~3 vol. and then flushed twice with 2-MeTHF (73kg and 47kg) to give a 2~3 vol. solution. After dilution with 2-MeTHF (65kg), 10% aq. sodium sulfate (30kg) was added and the mixture was cooled to 0 to 10°C, followed by the addition of 16% aq. NaOH (50kg) to adjust the pH to 13~14. The temperature was adjusted to 15 to 25°C and stirred for 30 to 60 min. The

aqueous layer was separated and extracted twice with 2-MeTHF (47kg x 2). The combined organic layers were concentrated under reduced pressure (<40°C) to 3~4 vol. and 2-MeTHF (950g) was added. After concentration under reduced pressure (<40°C) to 3~4 vol., the resulting solution was diluted with 2-MeTHF (30kg), dried by passing through 4A molecular sieves (25kg) and washed with 2-MeTHF (30kg). The final solution was concentrated to afford the desired compound (6.7kg) as an oil with 90.1% assay purity in a 79% corrected yield.

Preparation of intermediate 225

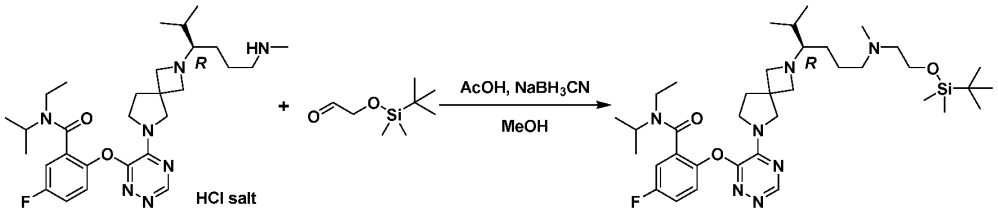
(*R*)-4-(6-(3,6-dichloro-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-*N*-(2-methoxyethyl)-*N*,5-dimethylhexan-1-amine



To (*R*)-*N*-(2-methoxyethyl)-*N*,5-dimethyl-4-(2,6-diazaspiro[3.4]octan-2-yl)hexan-1-amine (**intermediate 224**) (100 g) was added 2-MeTHF (430 g) and TEA (68 g) and the mixture was cooled to -50 to -40°C. 3,5,6-trichloro-1,2,4-triazine (62 g) in 2-MeTHF (172 g) was added and the mixture was stirred for 1 to 3 h. The resulting mixture was warmed to -20 to -10°C and a 7% $NaHCO_3$ aqueous solution was added, the mixture was warmed to 20 to 30°C and stirred for 30 to 60 min. The aqueous layer was removed and the organic layer was washed with 10% Na_2SO_4 (500 g). The organic layer was dried by passing through 4Å molecular sieves (220 g) and washed with 2-MeTHF (180 g). The title intermediate was afforded in 90% assay yield as a solution 14.8 wt% in 2-MeTHF.

Preparation of intermediate 245

(*R*)-2-((5-(2-(6-((2-((*tert*-butyldimethylsilyl)oxy)ethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

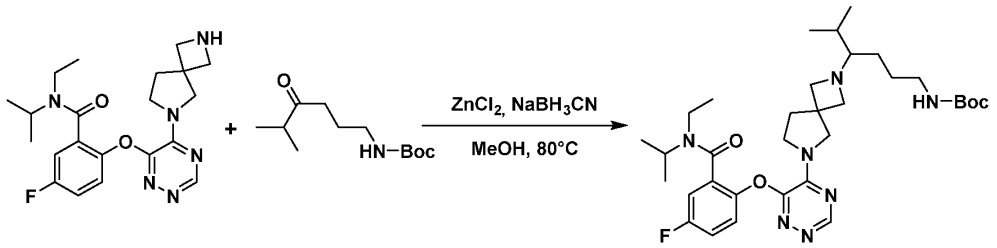


$NaBH_3CN$ (23.2 mg, 0.37 mmol) was added to a solution of (*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(2-methyl-6-(methylamino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide hydrochloride (**Compound 19**) (100 mg, 0.18 mmol), 2-((*tert*-butyldimethylsilyl)oxy)acetaldehyde (71 µL, 0.37 mmol) and AcOH (11 µL, 0.18 mmol) in MeOH (2 mL). Then, the reaction mixture was stirred at RT for 24 h. The reaction mixture was poured into water, basified with an aqueous solution of K_2CO_3 and DCM was added. The organic layer was separated, dried over $MgSO_4$, filtered and evaporated till dryness to give a crude (152 mg) which was purified by silica gel chromatography (Stationary phase: irregular bare silica 4g, Mobile phase: 0.5% NH4OH, 95% DCM, 5% MeOH). The fractions containing the product were mixed and concentrated to afford the title intermediate (46 mg, 36% yield).

Preparation of Compounds

Preparation of Compound 61

***tert*-butyl (4-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-5-methylhexyl)carbamate**



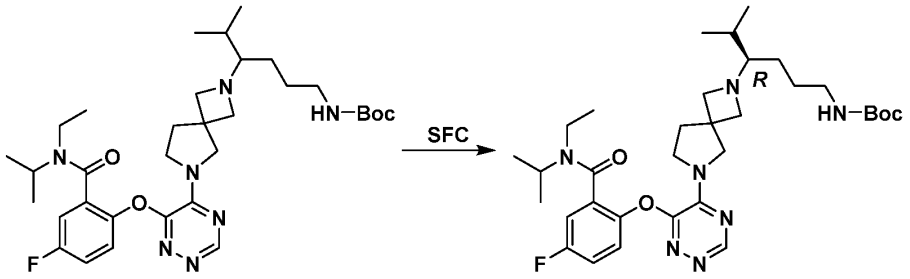
The mixture 2-((5-(2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (**intermediate 3**) (1.0 g, 2.4 mmol), *tert*-butyl (5-methyl-4-oxohexyl)carbamate (**intermediate 1**) (830 mg, 3.62 mmol) and $ZnCl_2$ (660 mg, 4.84 mmol) in MeOH (15 mL) was stirred at 80 °C for 0.5 h. Then $NaBH_3CN$ (310 mg, 4.93 mmol) was added and the resulting mixture was stirred at 80 °C for 6 h. After cooled to RT, the mixture was concentrated under reduced pressure to give the crude product, which was further purified by preparative HPLC using a Waters Xbridge Prep OBD (column: C18 150x40 mm

10 um; eluent: ACN/H_2O (0.05% ammonia) from 45% to 75% v/v) to afford the title compound (700 mg, 46% yield) as colorless oil.

Preparation of Compounds 62 and 63

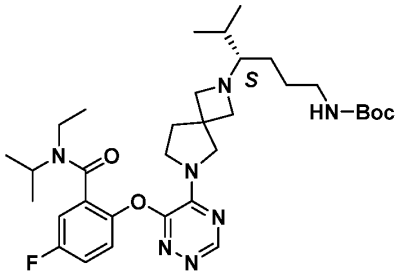
***tert*-butyl (*R*)-(4-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-5-methylhexyl)carbamate**

***tert*-butyl (*S*)-(4-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-5-methylhexyl)carbamate**



Compound 61 **Compound 62**

+



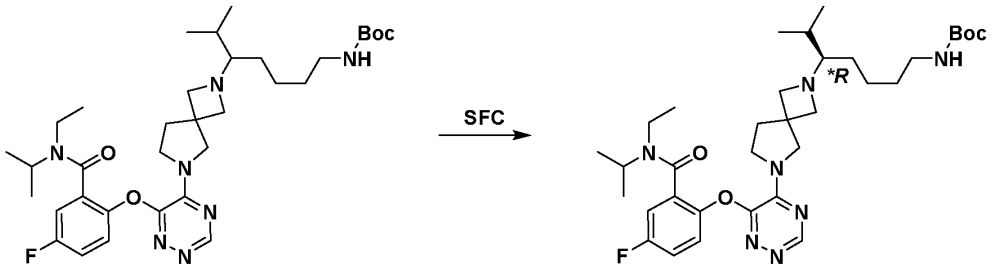
Compound 63

tert-butyl (4-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-5-methylhexyl)carbamate (**Compound 61**) (200 mg, 0.319 mmol) was purified by SFC over DAICEL CHIRALPAK IG (column: 250x30 mm 10 um; isocratic elution: EtOH (containing 0.1% of 25% ammonia): supercritical CO_2, 40% : 60% (v/v)) to afford the title compounds (**Compound 62**) (85 mg, 42% yield) and (**Compound 63**) (80 mg, 40% yield) both as light yellow oil.

Compound 207 and 208

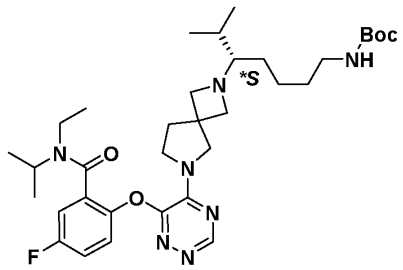
***tert*-butyl (*R)-(5-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-6-methylheptyl)carbamate**

***tert*-butyl (*S)-(5-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-6-methylheptyl)carbamate**



Compound 206 **Compound 207**

+



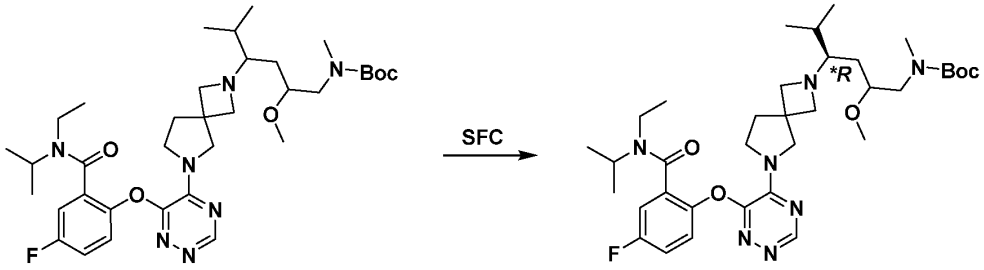
Compound 208

Tert-butyl (5-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-6-methylheptyl)carbamate (**Compound 206**) (1.4 g) was purified by SFC over DAICEL CHIRALPAK IG (column: 250×30 mm, 10 μm; Mobile phase: A: Supercritical CO_2, B: MeOH (0.1% ammonia), A:B = 55:45 at 200 mL/min) to afford the title compounds (**Compound 207**) (700 mg) and (**Compound 208**) (700 mg) both as white solid.

Compound 304 and 305

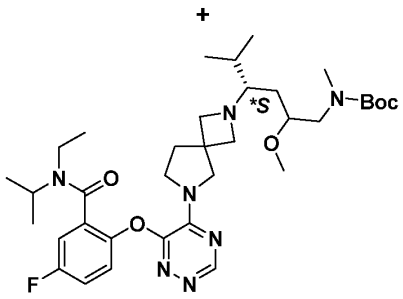
***tert*-butyl ((4*R)-4-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-2-methoxy-5-methylhexyl)(methyl)carbamate**

***tert*-butyl ((4*S)-4-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-2-methoxy-5-methylhexyl)(methyl)carbamate**



Compound 303 **Compound 304**

\+



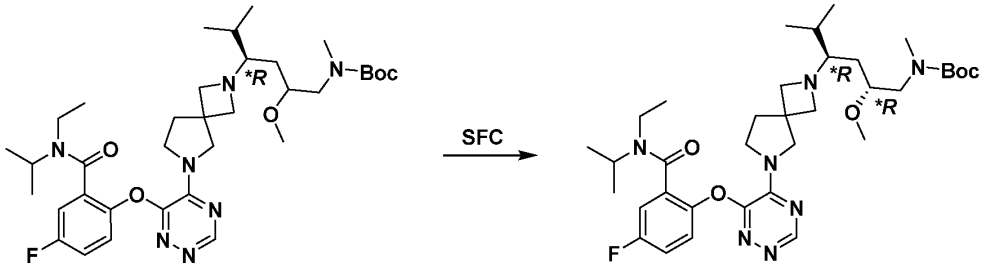
Compound 305

tert-butyl (4-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-2-methoxy-5-methylhexyl)(methyl)carbamate (**Compound 303**) (250 mg) was separated by SFC over DAICEL CHIRALPAK IG (column: 250×30 mm, 10 μm; Mobile phase: A: Supercritical CO_2, B: MeOH (0.1% ammonia), A:B = 60:40; Flow rate: 80 mL/min) to afford the title compounds (**Compound 304**) (124 mg) and (**Compound 305**) (124 mg) both as colorless sticky oil.

Compound 306 and 307

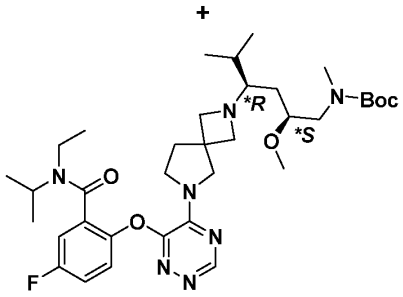
***tert*-butyl ((2*R,4*R)-4-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-2-methoxy-5-methylhexyl)(methyl)carbamate**

***tert*-butyl ((2*S,4*R)-4-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-2-methoxy-5-methylhexyl)(methyl)carbamate**



Compound 304 **Compound 306**

+



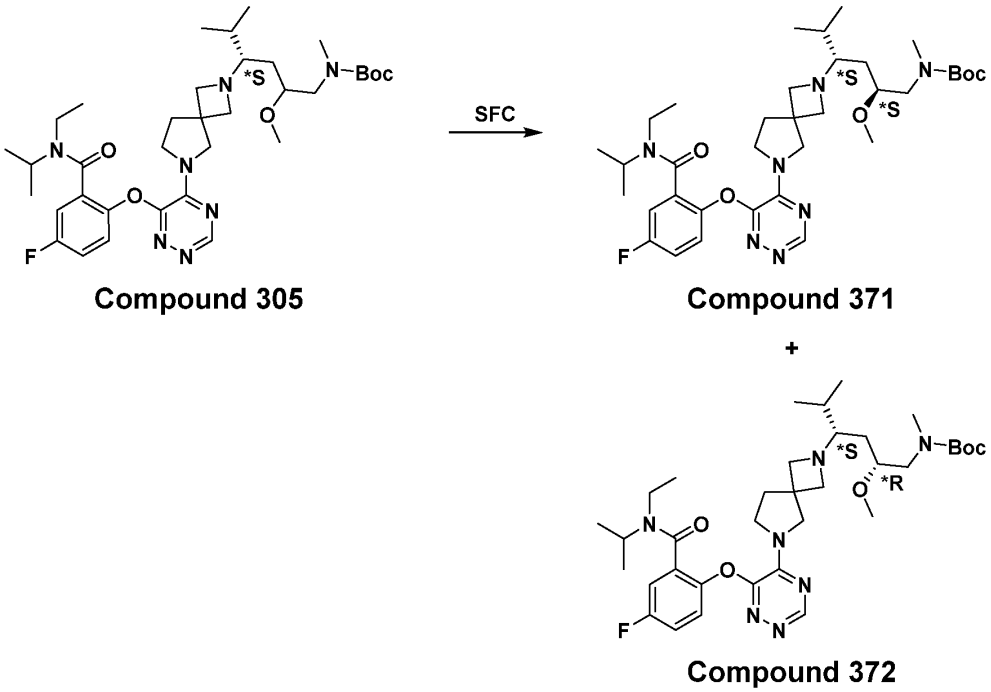
Compound 307

Tert-butyl ((4*R)-4-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-2-methoxy-5-methylhexyl)(methyl)carbamate (**Compound 304**) (120 mg) was separated by SFC over DAICEL CHIRALPAK IG (column: 250×30 mm,10 um; Mobile phase: A: Supercritical CO_2, B: MeOH (0.1% ammonia), A:B = 70:30 at 80 mL/min) to afford the title compounds (**Compound 306**) (45 mg) and (**Compound 307**) (46 mg) both as colorless sticky oil.

Compound 371 and 372

***tert*-butyl ((2*S,4*S)-4-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-2-methoxy-5-methylhexyl)(methyl)carbamate**

***tert*-butyl ((2*R,4*S)-4-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-2-methoxy-5-methylhexyl)(methyl)carbamate**

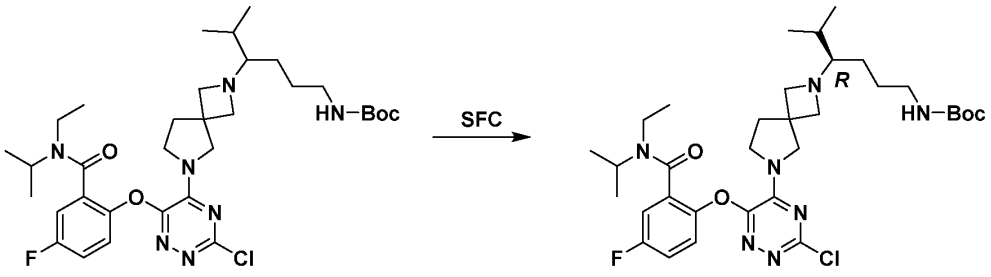


Tert-butyl ((4*S*)-4-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-2-methoxy-5-methylhexyl)(methyl)carbamate (**Compound 305**) (120 mg) was separated by SFC over DAICEL CHIRALPAK IG (column: 250×30 mm, 10 μm; Mobile phase: A: Supercritical CO_2, B: IPA (0.1% ammonia), A:B = 60:40; Flow rate: 80 mL/min) to afford the title compounds (**Compound 371**) (45 mg) and (**Compound 372**) (46 mg) both as colorless sticky oil.

Compound 404 and 405

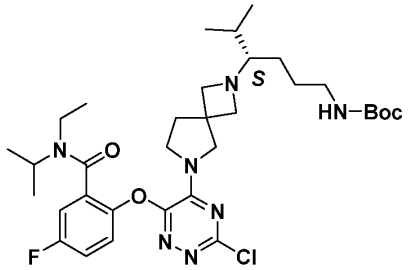
***tert*-butyl (*R*)-(4-(6-(3-chloro-6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-5-methylhexyl)carbamate**

***tert*-butyl (*S*)-(4-(6-(3-chloro-6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-5-methylhexyl)carbamate**



Compound 403 **Compound 404**

+

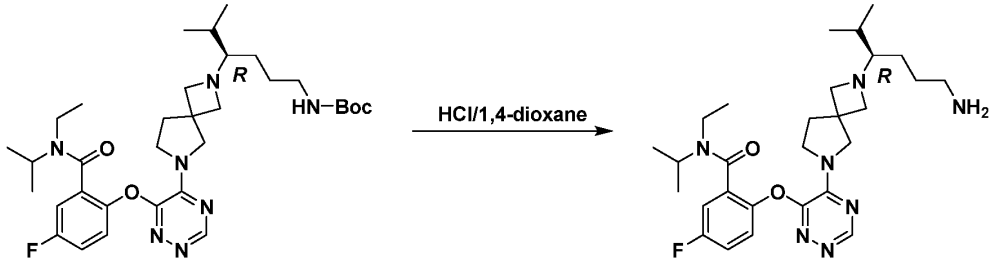


Compound 405

Tert-butyl (4-(6-(3-chloro-6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-5-methylhexyl)carbamate (**Compound 403**) (19.5 g) was separated by SFC over DAICEL CHIRALPAK IG (column: 250×30 mm, 10 um; Mobile phase: A: Supercritical CO_2, B: MeOH (0.1% ammonia), A:B =55:45 at 80 mL/min; Column Temp: 38 °C; Nozzle Pressure: 100 Bar; Nozzle Temp: 60 °C; Evaporator Temp: 20 °C; Trimmer Temp: 25 °C; Wavelength: 220 nm) to afford the title compounds (**Compound 404**) (8.00 g) and (**Compound 405**) (7.00 g) both as sticky oil.

Compound 1

(*R*)-2-((5-(2-(6-amino-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide formate



formate salt

HCl/1,4-dioxane (0.5 mL, 2.0 mmol) was added to a solution of *tert*-butyl (*R*)-(4-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-5-methylhexyl)carbamate (**Compound 62**) (85 mg, 0.14 mmol) in 1,4-dioxane (2 mL). The reaction mixture was sitrred at RT for 4 h. The mixture was concentrated under reduced pressure and the residue was first neutralized by ammonia (5 mL) and further purified by preparative HPLC using a Welch Xtimate C18 (column: 150x25 mm 5μm; eluent: ACN/H_2O (0.225%FA) from 1% to 31% (v/v)) to afford the title compound (32 mg, 41% yield) as a colorless oil.

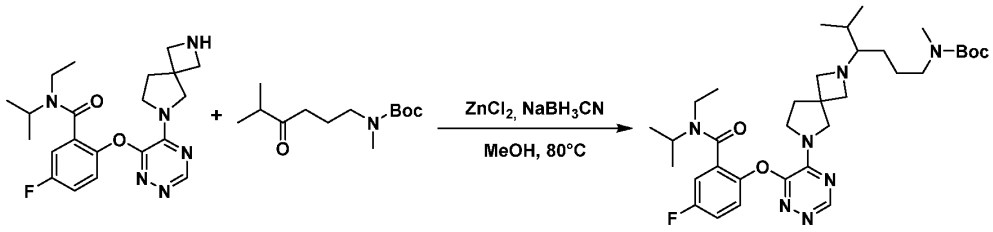
^{1}H NMR (400 MHz, Methanol-d_4): δ = 8.45-8.41 (m, 3H), 7.48-7.13 (m, 3H), 4.50-4.01 (m, 6H), 3.98-3.66 (m, 3H), 3.56-3.38 (m, 1H), 3.25-3.12 (m, 1H), 3.10-3.01 (m, 1H), 2.99-2.87 (m, 2H), 2.43-2.18 (m, 2H), 2.13-1.96 (m, 1H), 1.84-1.44 (m, 4H), 1.25-0.92 (m, 13H), 0.87-0.69 (m, 2H).

LC-MS (ESI) (Method 1): R_t = 2.957 min, m/z found 528.3 $[M+H]^+$.

SFC (Method 12): R_t = 1.151 min.

Preparation of Compound 60

***tert*-butyl (4-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-5-methylhexyl)(methyl)carbamate**

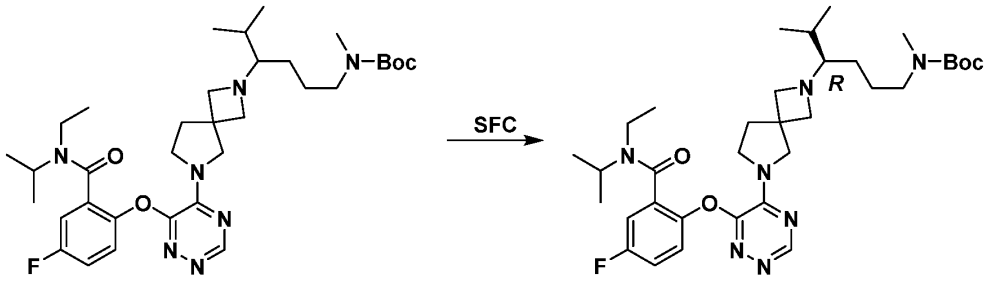


To a solution of 2-((5-(2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (**intermediate 3**) (600 mg, 1.45 mmol) and *tert*-butyl methyl(5-methyl-4-oxohexyl)carbamate (**intermediate 9**) (330 mg, 1.37 mmol) in MeOH (50 mL) was added $ZnCl_2$ (789 mg, 5.79 mmol). The resulting mixture was stirred at 80 °C for 2 h. Then $NaBH_3CN$ (729 mg, 11.6 mmol) was added and the reaction mixture was stirred at 80°C overnight. After cooling to RT, the mixture was concentrated under reduced pressure to give a crude residue, which was diluted with DCM (50 mL), quenched with sat. aq. NH_4Cl (50 mL) and extracted with DCM (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a crude product which was further purified by FCC (DCM/MeOH = 10:1) to afford the title compound (400 mg, 42% yield) as white solid.

Compound 56 and 57

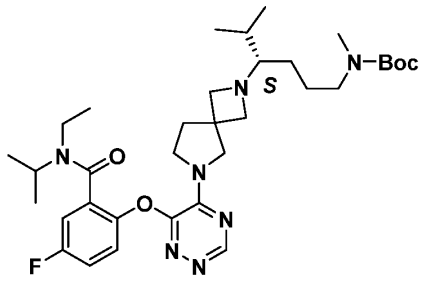
***tert*-butyl (*R*)-(4-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-5-methylhexyl)(methyl)carbamate**

***tert*-butyl (*S*)-(4-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-5-methylhexyl)(methyl)carbamate**



Compound 60 **Compound 56**

+

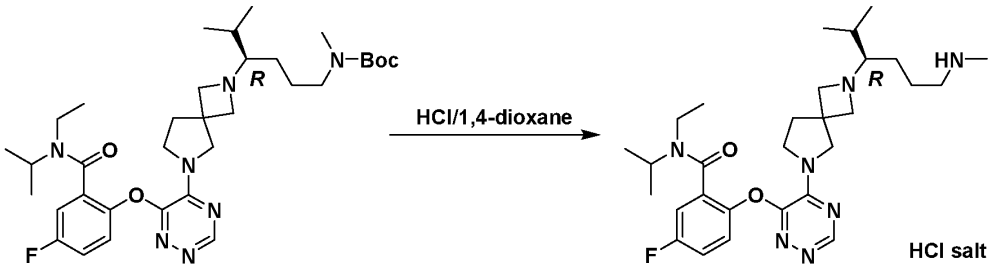


Compound 57

Tert-butyl (4-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-5-methylhexyl)(methyl)carbamate (**Compound 60**) (419 mg, 0.653 mmol) was purified by SFC over DAICEL CHIRALPAK AD (column: 250x30 mm 10 µm; Mobile phase: A: Supercritical CO_2, B: IPA (0.1% ammonia), A:B = 80:20 at 60 mL/min; Column Temp: 38 °C; Nozzle Pressure: 100 Bar; Nozzle Temp: 60 °C; Evaporator Temp: 20 °C; Trimmer Temp: 25 °C; Wavelength: 220 nm) to afford the title compounds (**Compound 56**) (146 mg, 34% yield) and (**Compound 57**) (149 mg, 36% yield) both as white solid.

Compound 19

(*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(2-methyl-6-(methylamino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide hydrochloride



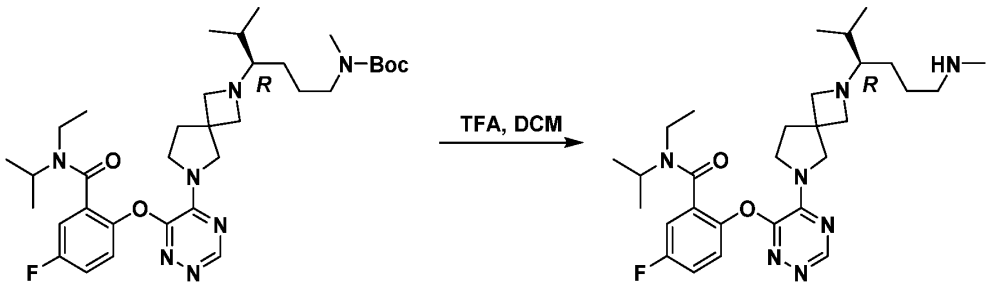
To a solution of *tert*-butyl (*R*)-(4-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-5-methylhexyl)(methyl)carbamate (**Compound 56**) (130 mg, 0.203 mmol) in 1,4-dioxane (3 mL) was added HCl/1,4-dioxane (5 mL, 20.0 mmol), and the reaction mixture was stirred at RT for 1 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by preparative HPLC over Phenomenex Gemini-NX (column: 150x30 mm 5um, Mobile Phase A: water (0.05%HCl), Mobile Phase B: ACN, Flow rate: 25 mL/min, gradient condition B/A from 0% B to 26% (0% B to 26% B)) to afford the title compound (105 mg, 84% yield) as colorless oil.

LC-MS (ESI) (Method 1): R_t = 2.939 min, m/z found 542.4 $[M+H]^+$.

SFC (Method 1): R_t = 1.201 min.

Compound 398

(*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(2-methyl-6-(methylamino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide



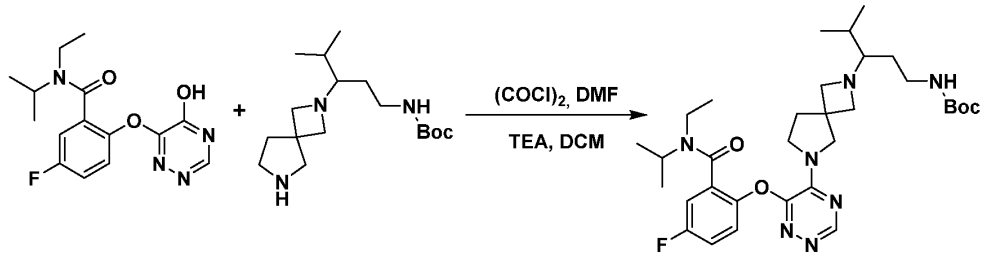
At 5 °C, TFA (0.51 mL, 6.7 mmol) was added dropwise to a solution of *tert*-butyl (*R*)-(4-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-5-methylhexyl)(methyl)carbamate (**Compound 56**) (287 mg, 0.45 mmol) in DCM (7.5 mL) and the reaction mixture was stirred overnight. The reaction mixture was evaporated to dryness to give a crude mixture (540 mg) which was purified by silica gel chromatography (Stationary phase: irregular bare silica 12g, Mobile phase: Gradient from 95% DCM, 5% MeOH (+10% NH_4OH) to 90% DCM, 10% MeOH (+10% NH_4OH)). The

pure fractions were mixed and concentrated to afford 173 mg of an intermediate fractions which was freeze-dried with ACN/H_2O (20/80, v/v) to afford of the title compound (170 mg, 70% yield).

LC-MS (ESI) (Method 4): R_t = 2.08 min, m/z found 542.6 $[M+H]^+$.

Compound 51

***tert*-butyl (3-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-4-methylpentyl)carbamate**

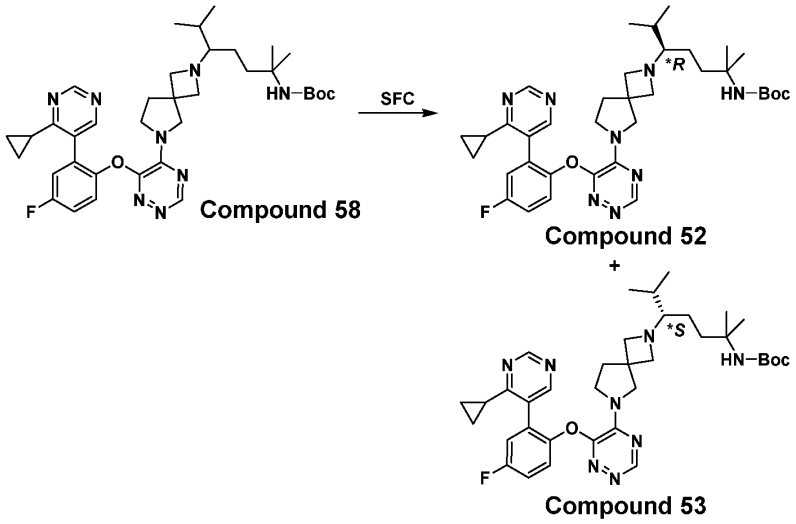


To a solution of *N*-ethyl-5-fluoro-2-((5-hydroxy-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide (**intermediate 25**) (0.100 g, 0.312 mmol) in DCM (12 mL) was added oxalyl chloride (0.079 g, 0.624 mmol), followed by DMF (0.046 g, 0.624 mmol) at RT. The mixture was stirred at this temperature for 1 h. Then the mixture was added to a solution of *tert*-butyl (4-methyl-3-(2,6-diazaspiro[3.4]octan-2-yl)pentyl)carbamate hydrochloride (**intermediate 22**) (0.272 g, crude) and TEA (0.158 g, 1.56 mmol) in DCM (3 mL). The resulting mixture was stirred at 25 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between DCM (35 mL) and H_2O (35 mL), extracted with DCM (35 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by FCC (PE/EtOAc (0.5% ammonia) = 1/1) to afford the title compound (100 mg, 89% purity, 46% yield) as colorless oil.

Compound 52 and 53

***tert*-butyl (*R)-(5-(6-(6-(2-(4-cyclopropylpyrimidin-5-yl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-2,6-dimethylheptan-2-yl)carbamate**

***tert*-butyl (*S)-(5-(6-(6-(2-(4-cyclopropylpyrimidin-5-yl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-2,6-dimethylheptan-2-yl)carbamate**

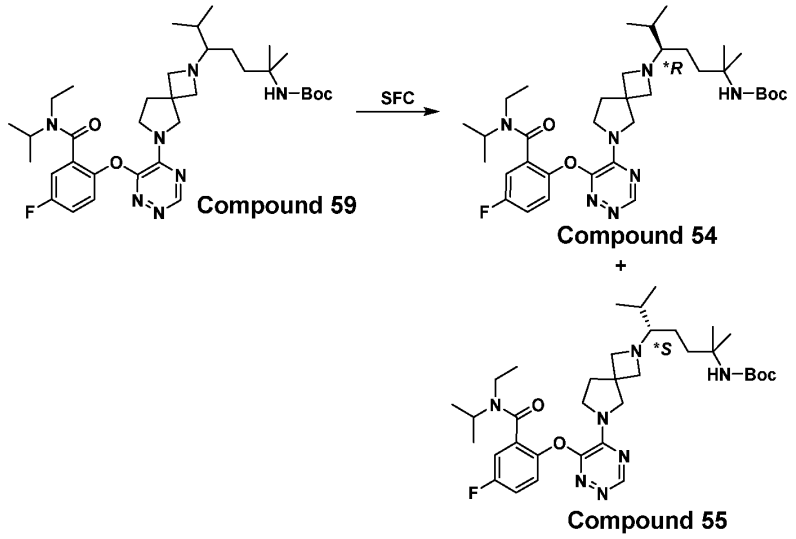


tert-butyl (5-(6-(6-(2-(4-cyclopropylpyrimidin-5-yl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-2,6-dimethylheptan-2-yl)carbamate (**Compound 58**) (150 mg, 0.227 mmol) was purified by SFC over DAICEL CHIRALPAK AD-H (column: 250x30 mm 5 μm; Mobile phase: A: Supercritical CO_2, B: IPA (0.1% ammonia), A: B = 4:1 at 60 mL/min) to afford the title compounds **Compound 52** (47 mg, 96.3% purity, 30.2% yield) and **Compound 53** (56 mg, 97.7% purity, 36.5% yield) both as white solids.

Compound 54 and 55

tert-butyl (*_R_)-(5-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-2,6-dimethylheptan-2-yl)carbamate

tert-butyl (*_S_)-(5-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-2,6-dimethylheptan-2-yl)carbamate

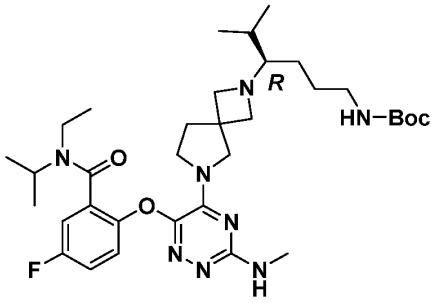


tert-butyl (5-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-2,6-dimethylheptan-2-yl)carbamate (**Compound 59**) (1.70 g, 2.59 mmol) was separated by SFC over DAICEL CHIRALPAK IG (column: 250x50 mm 10 μm)); Mobile phase: A: Supercritical CO_2, B: EtOH (0.1% ammonia), A: B = 3:2 at 150 mL/min) to afford the title compounds **Compound 54** (700 mg, 90% purity, 37% yield) and **Compound 55** (700 mg, purity: 96% purity, 40% yield) both as a white solid.

Compound 408

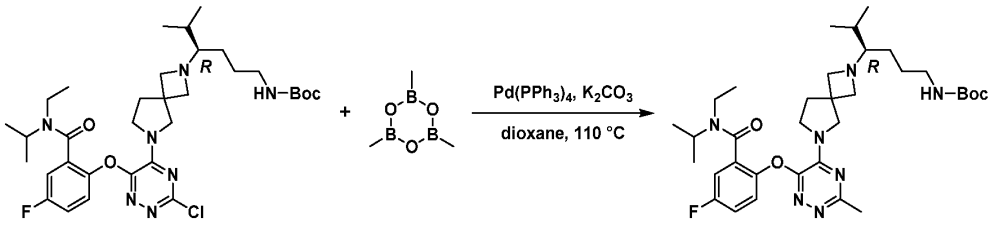
***tert*-butyl (*R*)-(4-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-3-(methylamino)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-5-methylhexyl)carbamate**

The following compounds was synthesized by an analogous method as described above for Compound 395

Co. No.	Structure	Starting Material	Conditions
408		Compound 404	methanamine in EtOH (33%), 90 °C, 1 h

Compound 412

***tert*-butyl (*R*)-(4-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-3-methyl-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-5-methylhexyl)carbamate**



To the mixture of *tert*-butyl (*R*)-(4-(6-(3-chloro-6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-5-methylhexyl)carbamate (**Compound 404**) (50.0 mg, 0.076 mmol), 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (76.0

mg, 0.303 mmol, 50% in THF) and K_2CO_3 (21.0 mg, 0.152 mmol) in anhydrous dioxane (1 mL) was added $Pd(PPh_3)_4$ (8.7 mg, 0.008 mmol) and the resulting mixture was stirred at 110 °C for 8 h under N_2 atmosphere. After cooled to RT, the mixture was diluted with H_2O (40 mL) and extracted with EtOAc (20 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to give the crude product which was purified by preparative TLC (DCM/MeOH = 10/1) to afford the title compound (30.0 mg, 59.7% yield) as yellow solid.

Compounds 2, 3, 20, 30, 31, 37, 38, 26, 80, 209, 210, 218, 220, 221, 308, 309, 317, 328, 359, 373, 374, 409, 413

(*S*)-2-((5-(2-(6-amino-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide formate

2-((5-(2-(6-amino-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide formate

(*S*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(2-methyl-6-(methylamino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide hydrochloride

(R*)-2-((5-(2-(6-amino-2,6-dimethylheptan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide**

(S*)-2-((5-(2-(6-amino-2,6-dimethylheptan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide**

(R*)-5-(6-(6-(2-(4-cyclopropylpyrimidin-5-yl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-2,6-dimethylheptan-2-amine**

(S*)-5-(6-(6-(2-(4-cyclopropylpyrimidin-5-yl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-2,6-dimethylheptan-2-amine**

2-((5-(2-(1-amino-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

***N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(2-(2-methyl-6-(methylamino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)pyridazin-3-yl)oxy)benzamide**

(R*)-2-((5-(2-(7-amino-2-methylheptan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide formate**

(S*)-2-((5-(2-(7-amino-2-methylheptan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide**

(R*)-2-((5-(2-(1-amino-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide**

(*R)-2-((5-(2-(1-amino-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride

(*S)-2-((5-(2-(1-amino-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride

5 *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((3*R,5*R)-5-methoxy-2-methyl-6-(methylamino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide hydrochloride

***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((3*R,5*S)-5-methoxy-2-methyl-6-(methylamino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-**

10 yl)oxy)benzamide hydrochloride

***N*-ethyl-5-fluoro-2-((5-(2-(5-hydroxy-2-methyl-6-(methylamino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide hydrochloride**

***N*-ethyl-2-((5-(2-(6-(ethylamino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide**

15 hydrochloride

5-fluoro-2-((5-(2-(5-hydroxy-2-methyl-6-(methylamino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*,*N*-diisopropylbenzamide hydrochloride

***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((3*S,5*S)-5-methoxy-2-methyl-6-**

20 (methylamino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide hydrochloride

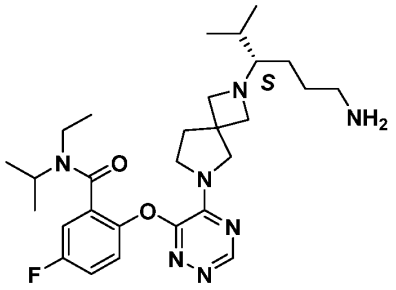
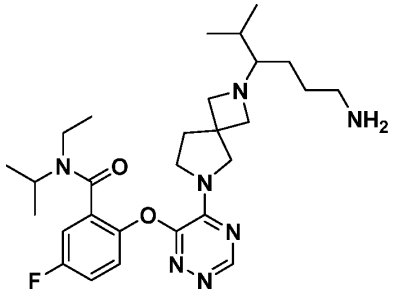
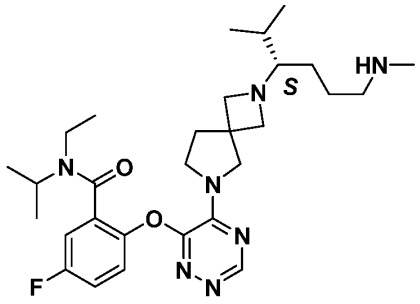
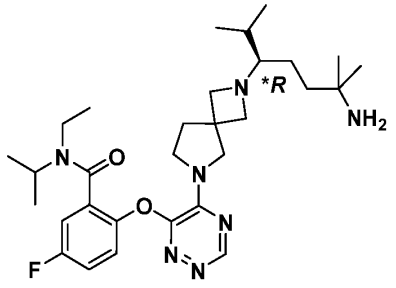
***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((3*S,5*R)-5-methoxy-2-methyl-6-(methylamino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide hydrochloride**

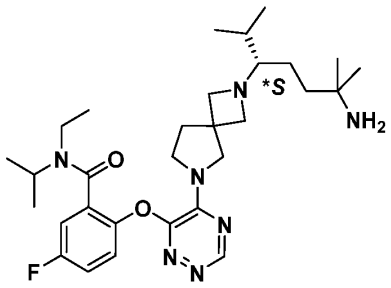
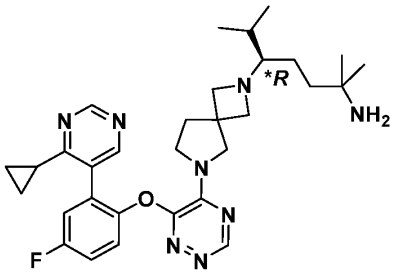
25 (*R*)-2-((5-(2-(6-amino-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-3-(methylamino)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride

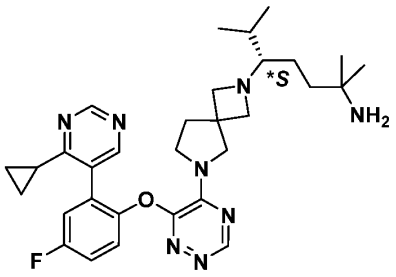
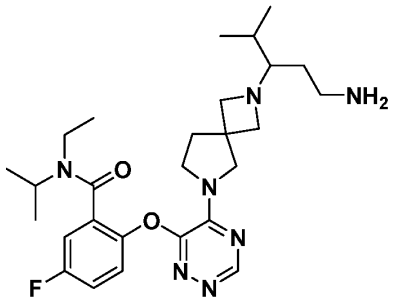
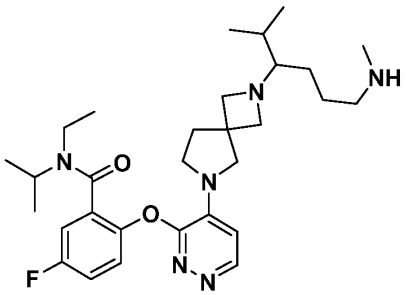
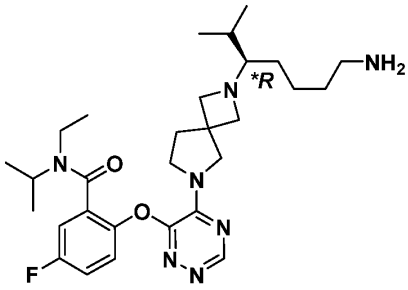
(*R*)-2-((5-(2-(6-amino-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-3-methyl-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide formate

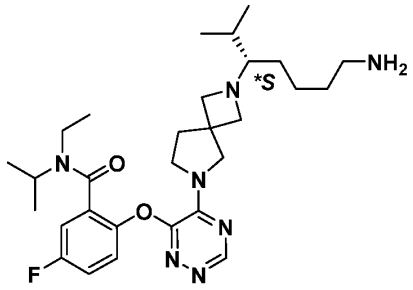
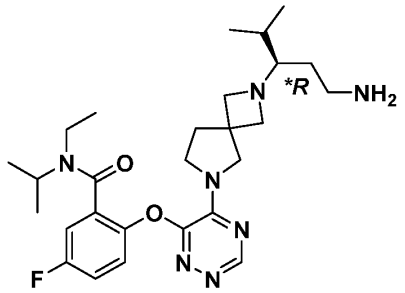
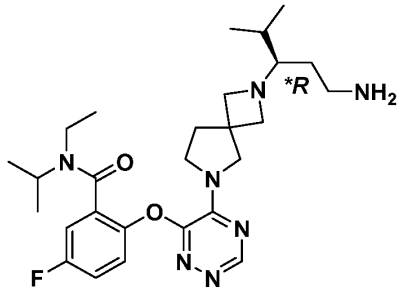
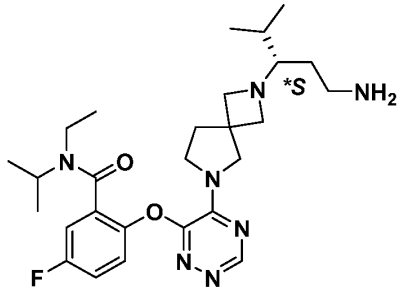
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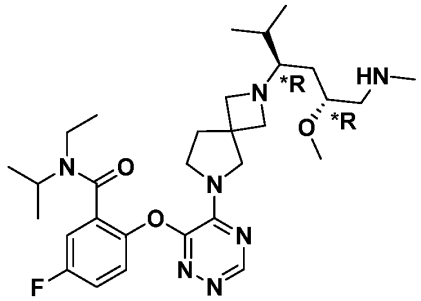
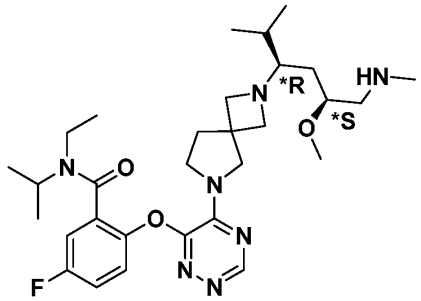
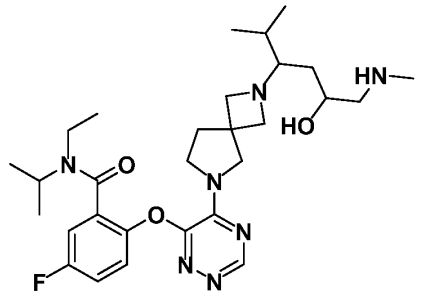
The following Compounds were synthesized by an analogous method described above for Compound 1 and 19

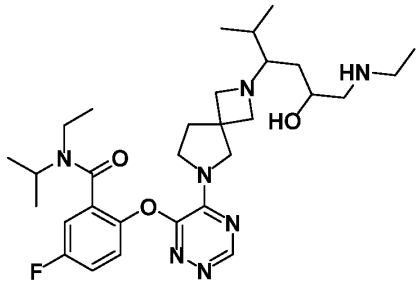
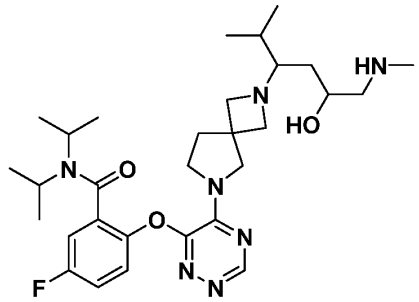
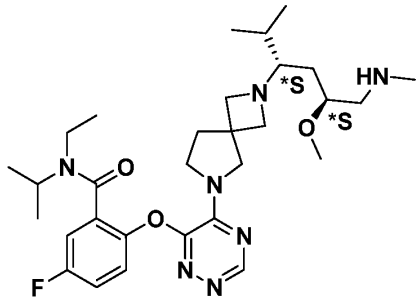
Co. No.	Structure	Starting Material	Conditions	Spectra Details
2	 formate salt	Compound 63	HCl 1,4-dioxane	**LC-MS (ESI) (Method 1)**: R_t = 3.028 min, m/z found 528.3 $[M+H]^+$. **SFC (Method 12):** R_t = 1.502 min.
3	 formate salt	Compound 61	HCl 1,4-dioxane	**LC-MS (ESI) (Method 1):** R_t = 2.977 min, m/z found 528.4 $[M+H]^+$.
20	 HCl salt	Compound 57	HCl 1,4-dioxane	**LC-MS (ESI) (Method 1):** R_t = 2.890 min, m/z found 542.3 $[M+H]^+$. **SFC (Method 1):** R_t = 1.697 min.
30		Compound 54	TFA DCM	**LC-MS (ESI) (Method 1**): R_t = 2.931 min, m/z found 556.3 $[M+H]^+$. **SFC (Method 2)**: R_t = 4.431 min.

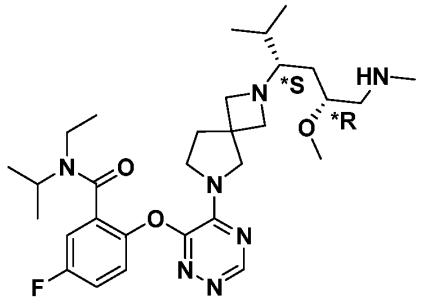
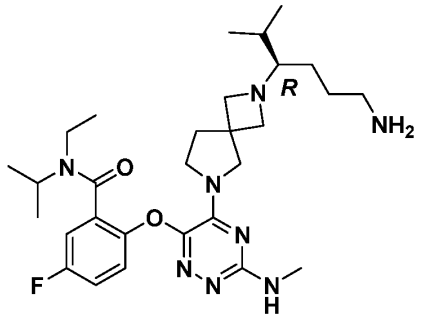
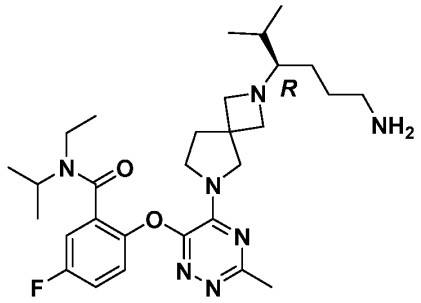
Co. No.	Structure	Starting Material	Conditions	Spectra Details
31		Compound 55	TFA DCM	**LC-MS (ESI) (Method 1)**: R_t = 2.897 min, m/z found 556.3 $[M+H]^+$. **SFC (Method 2)**: R_t = 4.997 min.
37		Compound 52	TFA DCM	**^{1}H NMR (400 MHz, Methanol-d_4):** δ 8.88 (brs, 1H), 8.46-8.36 (m, 2H), 7.58-7.45 (m, 1H), 7.44-7.26 (m, 2H), 4.07-3.52 (m, 4H), 3.31-3.11 (m, 4H), 2.24-2.02 (m, 3H), 1.99-1.78 (m, 2H), 1.55-1.38 (m, 3H), 1.37-1.20 (m, 2H), 1.14-1.06 (m, 8H), 0.99-0.83 (m, 7H). **LC-MS (ESI) (Method 1)**: Rt = 3.21 min, m/z found 561.3 $[M+H]^+$. **SFC (Method 3)**: R_t = 5.566 min.

Co. No.	Structure	Starting Material	Conditions	Spectra Details
38		Compound 53	TFA DCM	**LC-MS (ESI) (Method 1)**: R_t = 3.26 min, m/z found 561.3 $[M+H]^+$. **SFC (Method 3)**: R_t = 5.929 min.
26		Compound 51	TFA DCM	**LC-MS (ESI) (Method 1)**: R_t = 2.98 min, m/z found 514.4 $M+H]^+$.
80		Compound 79	TFA DCM	
209	 formate salt	Compound 207	HCl 1,4-dioxane	**LC-MS (ESI) (Method 1):** R_t = 2.950 min, m/z found 542.3 $[M+H]^+$. **SFC (Method 18):** R_t = 2.021 min.

Co. No.	Structure	Starting Material	Conditions	Spectra Details
210		Compound 208	HCl 1,4-dioxane	**LC-MS (ESI) (Method 1):** R_t = 2.919 min, m/z found 542.3 $[M+H]^+$. **SFC (Method 18):** R_t = 2.201 min.
218		Compound 216	TFA DCM	
220	 HCl salt	Compound 216	HCl 1,4-dioxane	
221	 HCl salt	Compound 217	HCl 1,4-dioxane	

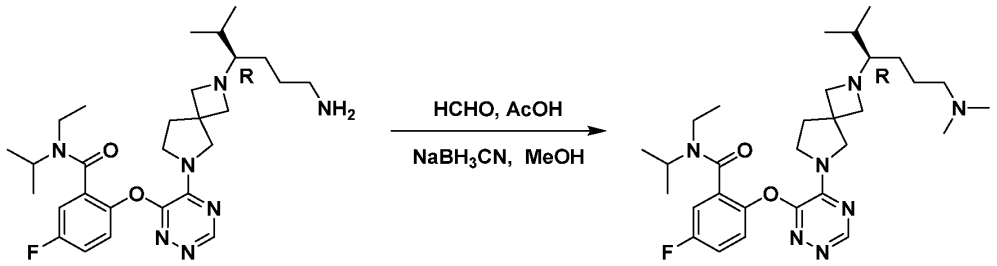
Co. No.	Structure	Starting Material	Conditions	Spectra Details
308	 HCl salt	Compound 306	HCl/1,4-dioxane, MeOH	
309	 HCl salt	Compound 307	HCl/1,4-dioxane, MeOH	
317	 HCl salt	Compound 316	HCl/1,4-dioxane, MeOH	

Co. No.	Structure	Starting Material	Conditions	Spectra Details
328	 HCl salt	Compound 327	HCl/1,4-dioxane, MeOH	
359	 HCl salt	Compound 358	HCl/1,4-dioxane, MeOH	
373	 HCl salt	Compound 371	HCl/1,4-dioxane, MeOH	

Co. No.	Structure	Starting Material	Conditions	Spectra Details
374	 HCl salt	Compound 372	HCl/1,4-dioxane, MeOH	
409	 HCl salt	Compound 408	HCl/1,4-dioxane, ACN	**LC-MS (ESI) (Method 2)**: R_t = 1.94 min, m/z found 557.3 $[M+H]^+$. **SFC (Method 13)**: R_t = 2.75 min.
413	 formate salt	Compound 412	HCl/1,4-dioxane, MeOH	**LC-MS (ESI) (Method 1)**: R_t = 2.885 min, m/z found 542.3 $[M+H]^+$. **SFC (Method 13)**: R_t = 2.347 min.

Compound 4

(*R*)-2-((5-(2-(6-(dimethylamino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide



To the mixture of (*R*)-2-((5-(2-(6-amino-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride (**Compound 65**) (180 mg, crude), formaldehyde (0.085 mL, 1.1 mmol) and AcOH (0.043 mL, 0.76 mmol) in MeOH (10 mL) was added $NaBH_3CN$ (72.0 mg, 1.14 mmol), the resulting mixture was stirred at RT for 2 h. The mixture was filtered and the filtrate was purified by preparative HPLC over Welch Xtimate (column: C18 150x30mm 5um; eluent: ACN/H_2O (0.225% FA) from 5% to 25%, v/v) and the desired fractions were collected and freeze dried. The resulting solid was further neutralized by 25% ammonia (15 mL) and extracted with DCM (20 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue, which was further dissolved in ACN/water and freeze dried to afford the title compound (37.65 mg) as yellow solid.

LC-MS (ESI) (Method 1): R_t = 2.95 min, m/z found 556.3 $[M+H]^+$.

SFC (Method 4): R_t = 1.772 min.

Compound 5, 32, 33, 74, 81, 101, 211, 212, 222, 224, 231, 410
(*S*)-2-((5-(2-(6-(dimethylamino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide formate
(R*)-2-((5-(2-(6-(dimethylamino)-2,6-dimethylheptan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide**
(S*)-2-((5-(2-(6-(dimethylamino)-2,6-dimethylheptan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide**
2-((4-(2-(6-(dimethylamino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)pyridazin-3-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide
2-((4-(2-(6-(dimethylamino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)pyridazin-3-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide
2-((5-(2-(6-(dimethylamino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide

(*R)-2-((5-(2-(7-(dimethylamino)-2-methylheptan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

(*S)-2-((5-(2-(7-(dimethylamino)-2-methylheptan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

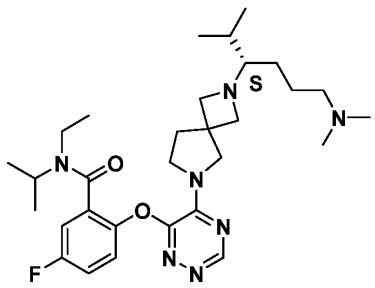
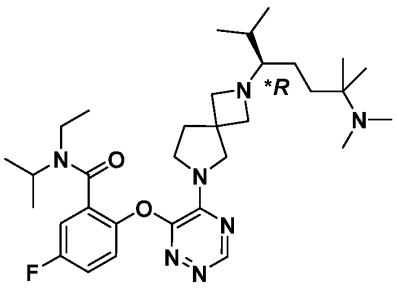
(*R)-2-((5-(2-(1-(dimethylamino)-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

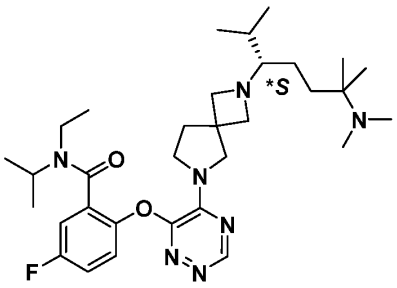
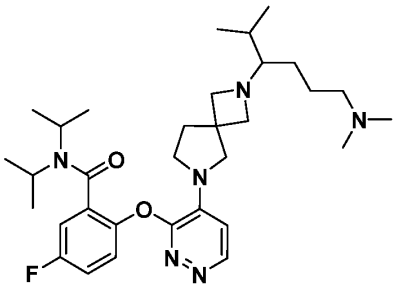
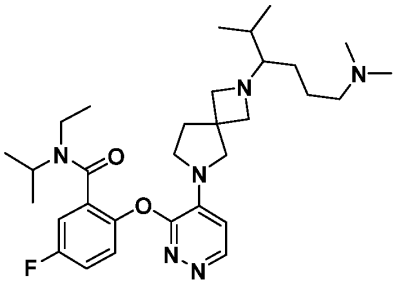
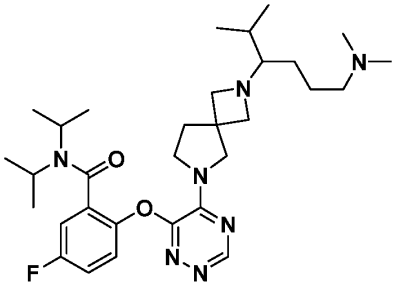
(*S)-2-((5-(2-(1-(dimethylamino)-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

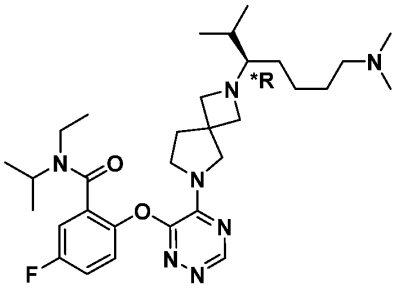
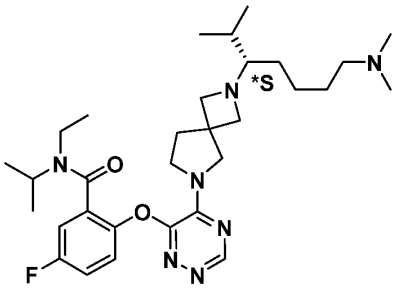
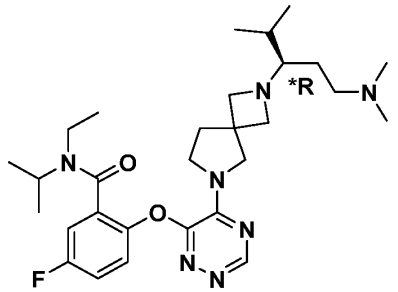
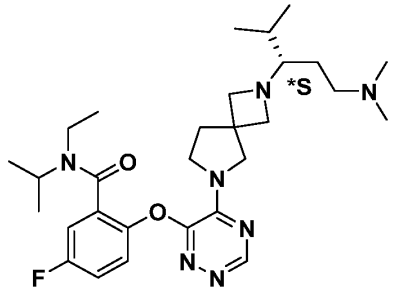
(*R)-2-((5-(2-(1-((2-amino-2-oxoethyl)(methyl)amino)-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

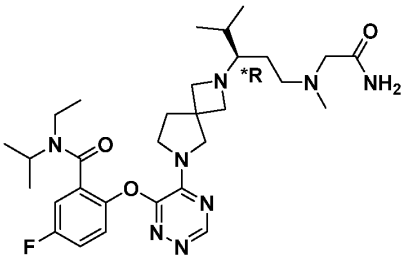
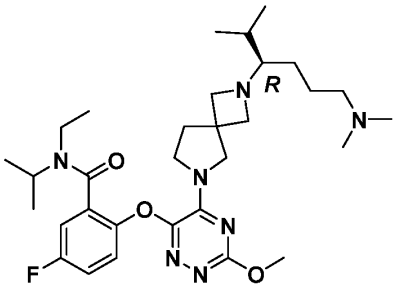
(*R*)-2-((5-(2-(6-(dimethylamino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-3-methoxy-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide formate

The following Compounds were synthesized by an analogous method described above for Compound 4

Co. No.	Structure	Starting Materials	Spectra Details
5	 formate salt	Compound 66	**LC-MS (Method 1):** R_t = 2.977 min, m/z found 556.4 $[M+H]^+$. **SFC (Method 4):** R_t = 1.402 min.
32		Compound 30	**LC-MS (ESI) (Method 2):** R_t = 2.043 min, m/z found 584.3 $[M+H]^+$. **SFC (Method 2):** R_t = 4.431 min.

Co. No.	Structure	Starting Materials	Spectra Details
33		Compound 31	**LC-MS (ESI) (Method 2):** R_t = 2.008 min, *m/z* found 584.3 $[M+H]^+$. **SFC (Method 2):** R_t = 4.997 min.
74		Compound 73	**LC-MS (ESI) (Method 2):** R_t = 1.933 min, m/z found 569.4 $[M+H]^+$.
81		Compound 80	
101		Compound 97	

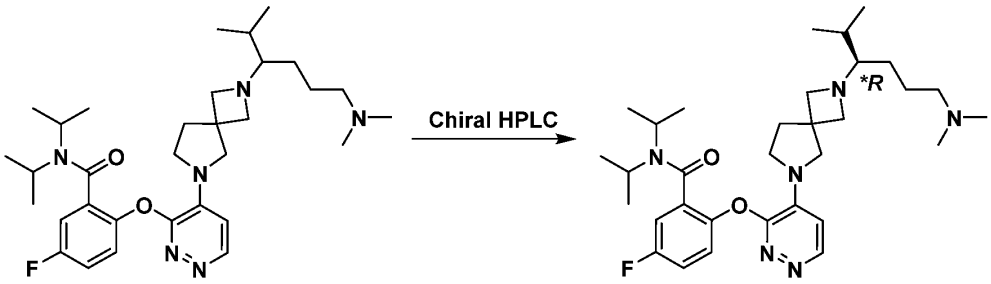
Co. No.	Structure	Starting Materials	Spectra Details
211		Compound 209	**LC-MS (ESI) (Method 2):** R_t = 1.946 min, m/z found 570.3 $[M+H]^+$. **SFC (Method 8):** R_t = 2.243 min.
212		Compound 210	**LC-MS (ESI) (Method 1):** R_t = 3.021 min, m/z found 570.3 $[M+H]^+$. **SFC (Method 8):** R_t = 2.431 min.
222		Compound 220	
224		Compound 221	

Co. No.	Structure	Starting Materials	Spectra Details
231		Compound 230	**LC-MS (ESI) (Method 1):** R_t = 2.858 min, m/z found 585.3 $[M+H]^+$. **SFC (Method 6):** R_t = 1.454 min.
410	 formate salt	Compound 407	**LC-MS (ESI) (Method 2):** R_t = 2.066 min, m/z found 586.3 $[M+H]^+$. **SFC (Method 14):** R_t = 2.582 min.

Compound 75, 76

(*_R_)-2-((4-(2-(6-(dimethylamino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)pyridazin-3-yl)oxy)-5-fluoro-_N_,_N_-diisopropylbenzamide

(*_S_)-2-((4-(2-(6-(dimethylamino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)pyridazin-3-yl)oxy)-5-fluoro-_N_,_N_-diisopropylbenzamide



Compound 74 **Compound 75** + **Compound 76**

2-((4-(2-(6-(dimethylamino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)pyridazin-3-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide (**Compound 74**) (600 mg) was separated by chiral HPLC over DAICEL CHIRALPAK IG (column: 250x30mm 10um; Mobile phase: A: Heptane, B: EtOH, A:B from 20% to 70% (v/v); flowrate: 25 mL/min) to afford the title compounds **Compound 75** (92 mg, 15%) and **Compound 76** (84 mg) as white solid.

Compound 75

LC-MS (ESI) (Method 2): R_t = 1.915 min, m/z found 569.3 $[M+H]^+$.

Chiral HPLC (Method 4): R_t = 4.842 min.

Compound 76

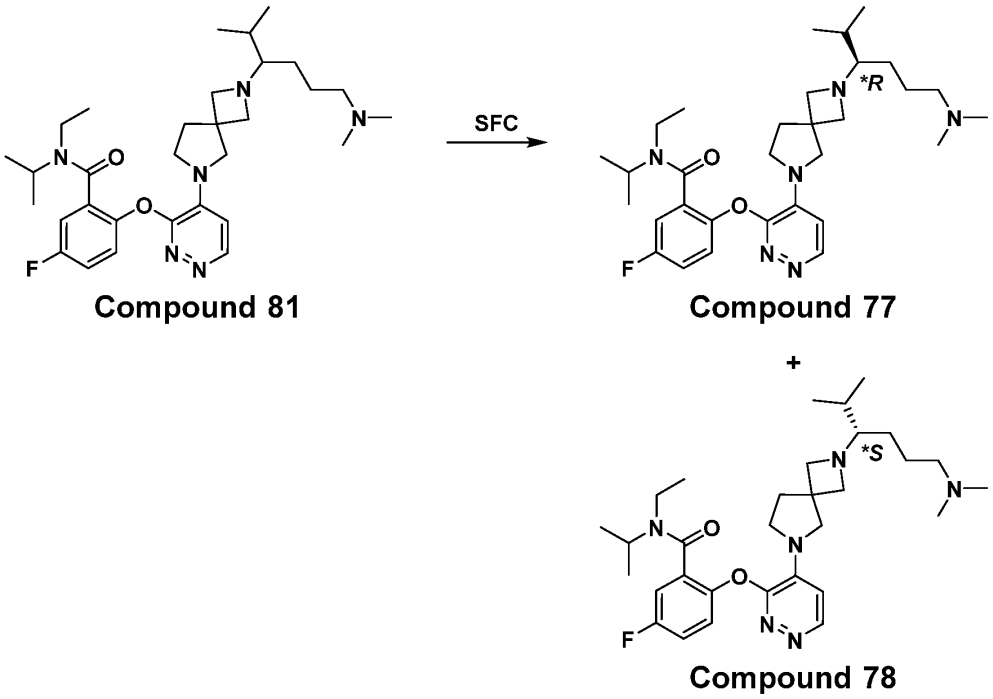
LC-MS (ESI) (Method 2): R_t = 1.924 min, m/z found 569.3 $[M+H]^+$.

Chiral HPLC (Method 4): R_t = 6.200 min.

Compound 77, 78

(R*)-2-((4-(2-(6-(dimethylamino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)pyridazin-3-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide**

(S*)-2-((4-(2-(6-(dimethylamino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)pyridazin-3-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide**



2-((4-(2-(6-(dimethylamino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)pyridazin-3-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (**Compound 81**) (31.0 mg) was separated by SFC over DAICEL CHIRALPAK IE (column: 250x30mm 10um; eluent: 100% MeOH (0.1% ammonia); flowrate: 25 mL/min) to afford the title compounds **Compound 77** (4.2 mg) and **Compound 78** (1.3 mg) as white solid.

Compound 77

LC-MS (ESI) (Method 3): R_t = 5.039 min, m/z found 555.3 $[M+H]^+$.

Chiral HPLC (Method 2): R_t = 7.719 min.

Compound 78

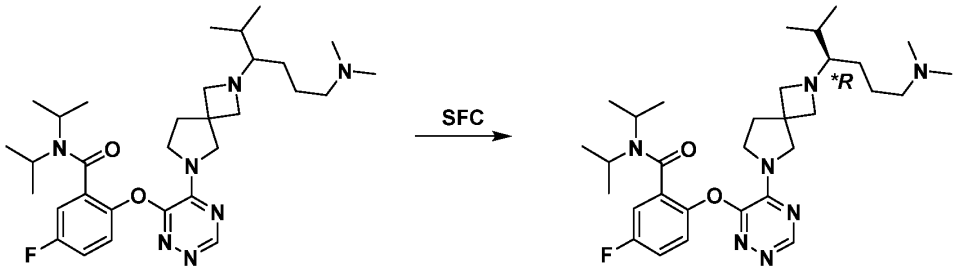
LC-MS (ESI) (Method 3): R_t = 4.870 min, m/z found 555.3 $[M+H]^+$.

Chiral HPLC (Method 2): R_t = 8.754 min.

Compound 105, 106

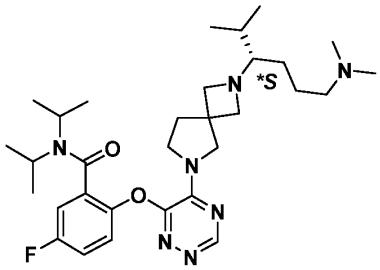
(R*)-2-((5-(2-(6-(dimethylamino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide**

(S*)-2-((5-(2-(6-(dimethylamino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide**



Compound 101 **Compound 105**

+

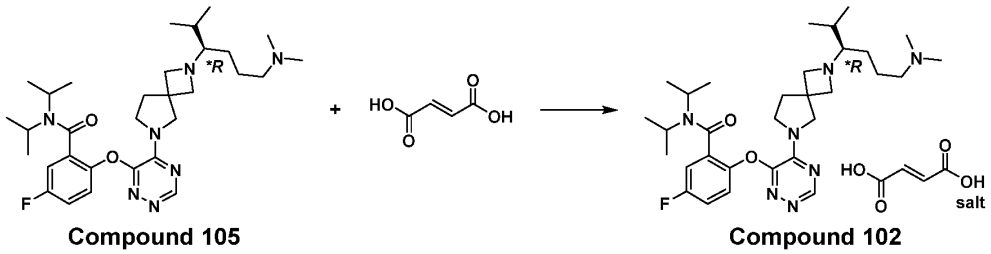


Compound 106

2-((5-(2-(6-(dimethylamino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide (**Compound 101**) (1.5 g) was obtained by SFC over DAICEL CHIRALPAK IG (column: 250x50mm 10um; Mobile phase: A: Supercritical CO_2, B: MeOH (0.1% ammonia), A:B = 55:45 at 200 mL/min; Column Temp: 38 ; Nozzle Pressure: 100Bar; Nozzle Temp: 60 ; Evaporator Temp: 20 ; Trimmer Temp: 25 ; Wavelength: 220nm) to afford the title compounds **Compound 105** (600 mg, 40.0 % yield) and **Compound 106** (600 mg, 40.0 % yield) as white solid.

Compound 102

(*R)-2-((5-(2-(6-(dimethylamino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide fumarate



Compound 105 **Compound 102**

To a solution of (**R*)-2-((5-(2-(6-(dimethylamino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide (**Compound 105**) (300 mg, 0.527 mmol) in ACN (12 mL) and water (4 mL) was added

fumaric acid (123 mg, 1.06 mmol). After a clear solution was formed, the mixture was concentrated under reduced pressure, the resulting residue was added to a mixture of ACN (3 mL) and water (10 mL). The mixture was lyophilized to dryness to afford the title compound (422 mg) as a white solid.

^{1}H NMR (400 MHz, Methanol-d_4): δ = 8.50 (s, 1H), 7.50-7.15 (m, 3H), 6.72 (s, 4H), 4.51-3.89 (m, 7H), 3.86-3.69 (m, 2H), 3.61-3.49 (m, 1H), 3.25-3.07 (m, 3H), 2.88 (s, 6H), 2.50-2.20 (m, 2H), 2.19-2.06 (m, 1H), 1.97-1.77 (m, 2H), 1.75-1.57 (m, 2H), 1.51 (d, *J*=6.8 Hz, 3H), 1.37-1.14 (m, 6H), 1.11-0.97 (m, 6H), 0.78 (d, *J*=6.0 Hz, 3H).

LC-MS (ESI) (Method 2): R_t = 2.08 min, m/z found 570.3 $[M+H]^+$.

SFC (Method 4): Rt = 1.284 min.

Compound 103, 112, 114, 122, 123, 127, 128, 132, 133, 135, 137, 140, 142, 145, 146, 148, 150, 152, 154, 157, 159, 161, 165, 167, 170, 172, 176, 177, 179, 181, 184, 185, 188, 189, 191, 193, 195, 197, 199, 201, 203, 205, 219, 223, 225, 227, 233, 240, 241, 242, 243, 245, 256, 265, 266, 268, 270, 278, 280, 283, 259, 104, 229, 300, 302, 314, 315, 323, 324, 325, 326, 334, 335, 336, 337, 342, 343, 346, 352, 353, 356, 357, 365, 366, 369, 370, 377, 378, 382, 386, 387, 391, 392, 394, 397

(S*)-2-((5-(2-(6-(dimethylamino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide fumarate**

***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((*R*)-6-(((*R*)-1-methoxypropan-2-yl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide fumarate**

(*R*)-2-((5-(2-(6-((3,3-difluoropropyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide fumarate

(R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(6-(isopropyl(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide fumarate**

(S*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(6-(isopropyl(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide fumarate**

(R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(2-methyl-6-(methyl(propyl)amino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide fumarate**

(S*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(2-methyl-6-(methyl(propyl)amino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide fumarate**

(*R)-*N*-ethyl-2-((5-(2-(6-(ethyl(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide fumarate

(*S)-*N*-ethyl-2-((5-(2-(6-(ethyl(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide fumarate

(*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(6-((2-methoxy-2-methylpropyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide fumarate

(*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(6-((2-methoxy-2-methylpropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide fumarate

(*R*)-*N*-ethyl-5-fluoro-2-((5-(2-(6-((2-hydroxy-2-methylpropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide fumarate

(*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(6-((3-methoxypropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide fumarate

(*R)-2-((5-(2-(6-((3-(dimethylamino)-3-oxopropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide fumarate

(*S)-2-((5-(2-(6-((3-(dimethylamino)-3-oxopropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide fumarate

(*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(2-methyl-6-(methyl(2-(*N*-methylacetamido)ethyl)amino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide fumarate

(*R*)-2-((5-(2-(6-((2,2-dimethoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide fumarate

(*R*)-2-((5-(2-(6-((4-(dimethylamino)-4-oxobutyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide fumarate

***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((*R*)-6-(((*R*)-1-methoxypropan-2-yl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide fumarate**

***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((*R*)-6-(((*S*)-1-methoxypropan-2-yl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide fumarate**

(*R*)-2-((5-(2-(6-((1,3-dimethoxypropan-2-yl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide fumarate

(*R*)-2-((5-(2-(6-((1,3-dimethoxypropan-2-yl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide fumarate

***N*-ethyl-5-fluoro-2-((5-(2-((*R*)-6-(((*R*)-1-hydroxy-3-methoxypropan-2-yl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide fumarate**

***N*-ethyl-5-fluoro-2-((5-(2-((*R*)-6-(((*S*)-1-hydroxy-3-methoxypropan-2-yl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide fumarate**

***N*-ethyl-5-fluoro-2-((5-(2-((3*R*)-6-((3-hydroxy-2-methoxypropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide fumarate**

2-((5-(2-((3*R*)-6-((2,3-dimethoxypropyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide fumarate

2-((5-(2-((*R*)-6-(((R*)-2,3-dimethoxypropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide fumarate**

2-((5-(2-((*R*)-6-(((S*)-2,3-dimethoxypropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide fumarate**

2-((5-(2-((3*R*)-6-((4-(dimethylamino)-4-oxobutan-2-yl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide fumarate

2-((5-(2-((3*R*)-6-((3-(dimethylamino)-2-methyl-3-oxopropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide fumarate

2-((5-(2-((*R*)-6-(((R*)-4-(dimethylamino)-4-oxobutan-2-yl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide fumarate**

2-((5-(2-((*R*)-6-(((S*)-4-(dimethylamino)-4-oxobutan-2-yl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide fumarate**

2-((5-(2-((*R*)-6-(((R*)-3-(dimethylamino)-2-methyl-3-oxopropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide fumarate**

2-((5-(2-((*R*)-6-(((S*)-3-(dimethylamino)-2-methyl-3-oxopropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide fumarate**

***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((*R*)-2-methyl-6-(methyl((*R*)-4-(methylamino)-4-oxobutan-2-yl)amino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide fumarate**

***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((*R*)-2-methyl-6-(methyl((*S*)-4-(methylamino)-4-oxobutan-2-yl)amino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide fumarate**

***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((*R*)-2-methyl-6-(methyl((*R*)-2-methyl-3-(methylamino)-3-oxopropyl)amino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide fumarate**

***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((*R*)-2-methyl-6-(methyl((*S*)-2-methyl-3-(methylamino)-3-oxopropyl)amino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide fumarate**

2-((5-(2-((R*)-6-(((*R*)-4-amino-4-oxobutan-2-yl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide fumarate**

2-((5-(2-((R*)-6-(((S)-4-amino-4-oxobutan-2-yl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide fumarate**

2-((5-(2-((*R*)-6-(((*R*)-3-amino-2-methyl-3-oxopropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide fumarate

2-((5-(2-((*R*)-6-(((S)-3-amino-2-methyl-3-oxopropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide fumarate

(R*)-2-((5-(2-(1-amino-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide fumarate**

(R*)-2-((5-(2-(1-(dimethylamino)-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide fumarate**

(S*)-2-((5-(2-(1-(dimethylamino)-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide fumarate**

(R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(1-((2-methoxyethyl)amino)-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide fumarate**

(*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(6-((2-methoxyethyl-1,1-d_2)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide fumarate

***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((3**R*,5**R*)-6-((2-methoxyethyl)(methyl)amino)-2,5-dimethylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide fumarate**

***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((3**S*,5**R*)-6-((2-methoxyethyl)(methyl)amino)-2,5-dimethylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide fumarate**

***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((3**R*,5**S*)-6-((2-methoxyethyl)(methyl)amino)-2,5-dimethylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide fumarate**

***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((3**S*,5**S*)-6-((2-methoxyethyl)(methyl)amino)-2,5-dimethylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide fumarate**

(*R*)-2-((5-(2-(6-((2-acetamidoethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide fumarate

(*R*)-2-((5-(2-(6-((1,3-dihydroxypropan-2-yl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide fumarate

_N_-ethyl-5-fluoro-_N_-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2,4-dimethylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide (mixture of _R_,_S_ and _S_,_R_; or mixture of _R_,_R_ and _S_,_S_) fumarate

_N_-ethyl-5-fluoro-_N_-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2,4-dimethylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide (mixture of _R_,_R_ and _S_,_S_; or mixture of _R_,_S_ and _S_,_R_) fumarate

(*_R_)-_N_-ethyl-5-fluoro-2-((5-(2-(1-((2-hydroxyethyl)amino)-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-_N_-isopropylbenzamide fumarate

(*_R_)-_N_-ethyl-5-fluoro-2-((5-(2-(1-((2-hydroxyethyl)(methyl)amino)-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-_N_-isopropylbenzamide fumarate

(*_R_)-2-((5-(2-(1-((3-amino-3-oxopropyl)amino)-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-_N_-ethyl-5-fluoro-_N_-isopropylbenzamide fumarate

(*_R_)-2-((5-(2-(1-((3-amino-3-oxopropyl)(methyl)amino)-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-_N_-ethyl-5-fluoro-_N_-isopropylbenzamide fumarate

_N_-ethyl-5-fluoro-2-((5-(2-((_R_)-6-(((_R_)-2-hydroxy-3-methoxypropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-_N_-isopropylbenzamide fumarate

(_R_)-_N_-ethyl-5-fluoro-2-((5-(2-(6-((2-hydroxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-_N_-isopropylbenzamide fumarate

(_R_)-2-((5-(2-(6-((2,2-dimethoxyethyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-_N_-ethyl-5-fluoro-_N_-isopropylbenzamide fumarate

(*_R_)-_N_-ethyl-5-fluoro-_N_-isopropyl-2-((5-(2-(1-(isopropylamino)-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide fumarate

_N_-ethyl-5-fluoro-_N_-isopropyl-2-((5-(2-((3_R_)-6-((2-methoxyethyl)(methyl)amino)-2-methylheptan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide fumarate

_N_-ethyl-5-fluoro-_N_-isopropyl-2-((5-(6-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide fumarate

2-((5-(2-((3*_R_,5*_R_)-6-(dimethylamino)-5-methoxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-_N_-ethyl-5-fluoro-_N_-isopropylbenzamide fumarate

2-((5-(2-((3*_R_,5*_S_)-6-(dimethylamino)-5-methoxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-_N_-ethyl-5-fluoro-_N_-isopropylbenzamide fumarate

_N_-ethyl-5-fluoro-2-((5-(2-((3*_R_,5*_R_)-5-hydroxy-6-(isopropyl(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-_N_-isopropylbenzamide fumarate

_N_-ethyl-5-fluoro-2-((5-(2-((3*_S_,5*_S_)-5-hydroxy-6-(isopropyl(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-_N_-isopropylbenzamide fumarate

_N_-ethyl-5-fluoro-2-((5-(2-((3*_R_,5*_S_)-5-hydroxy-6-(isopropyl(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-_N_-isopropylbenzamide fumarate

_N_-ethyl-5-fluoro-2-((5-(2-((3*_S_,5*_R_)-5-hydroxy-6-(isopropyl(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-_N_-isopropylbenzamide fumarate

2-((5-(2-((3*_R_,5*_R_)-6-(diethylamino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-_N_-ethyl-5-fluoro-_N_-isopropylbenzamide fumarate

2-((5-(2-((3*_S_,5*_S_)-6-(diethylamino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-_N_-ethyl-5-fluoro-_N_-isopropylbenzamide fumarate

2-((5-(2-((3*_S_,5*_R_)-6-(diethylamino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-_N_-ethyl-5-fluoro-_N_-isopropylbenzamide fumarate

2-((5-(2-((3*_R_,5*_S_)-6-(diethylamino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-_N_-ethyl-5-fluoro-_N_-isopropylbenzamide fumarate

_N_-ethyl-2-((5-(2-((3*_R_,5_S_)-6-(ethyl(methyl)amino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-_N_-isopropylbenzamide fumarate

_N_-ethyl-2-((5-(2-((3*_S_,5_S_)-6-(ethyl(methyl)amino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-_N_-isopropylbenzamide fumarate

_N_-ethyl-2-((5-(2-((3*_R_,5_R_)-6-(ethyl(methyl)amino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-_N_-isopropylbenzamide fumarate

_N_-ethyl-5-fluoro-2-((5-(2-((3*_R_,5_S_)-5-hydroxy-6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-_N_-isopropylbenzamide fumarate

_N_-ethyl-5-fluoro-2-((5-(2-((3*_S_,5_S_)-5-hydroxy-6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-_N_-isopropylbenzamide fumarate

_N_-ethyl-5-fluoro-2-((5-(2-((3*_R_,5_R_)-5-hydroxy-6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-_N_-isopropylbenzamide fumarate

_N_-ethyl-5-fluoro-2-((5-(2-((3*_S_,5_R_)-5-hydroxy-6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-_N_-isopropylbenzamide fumarate

2-((5-(2-((3*_R_,5*_R_)-6-(dimethylamino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-_N_,_N_-diisopropylbenzamide fumarate

2-((5-(2-((3*_R_,5*_S_)-6-(dimethylamino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-_N_,_N_-diisopropylbenzamide fumarate

2-((5-(2-((3*_S_,5*_S_)-6-(dimethylamino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-_N_,_N_-diisopropylbenzamide fumarate

2-((5-(2-((3*_S_,5*_R_)-6-(dimethylamino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-_N_,_N_-diisopropylbenzamide fumarate

2-((5-(2-((3*S*,5*S*)-6-(dimethylamino)-5-methoxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide fumarate

2-((5-(2-((3*S*,5*R*)-6-(dimethylamino)-5-methoxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide fumarate

***N*-ethyl-5-fluoro-2-((5-(2-(5-hydroxy-6-((2-methoxyethyl)(methyl)amino)-2,5-dimethylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide fumarate**

***N*-ethyl-5-fluoro-2-((5-(2-((3*R*,5*R*)-5-hydroxy-2-methyl-6-(methyl(propyl)amino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide fumarate**

***N*-ethyl-5-fluoro-2-((5-(2-((3*S*,5*S*)-5-hydroxy-2-methyl-6-(methyl(propyl)amino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide fumarate**

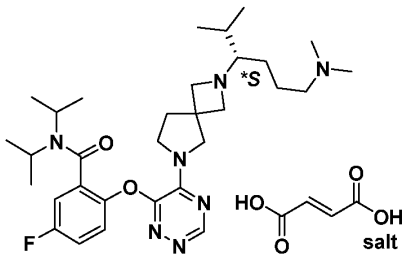
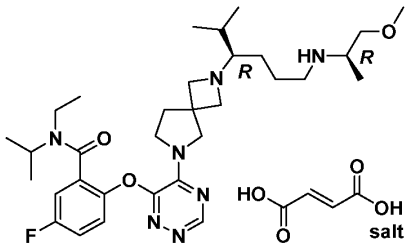
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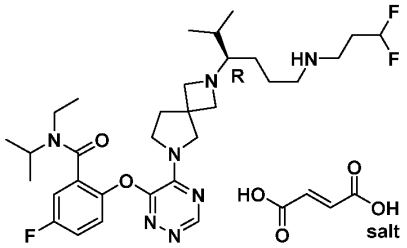
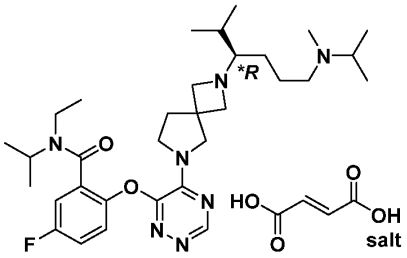
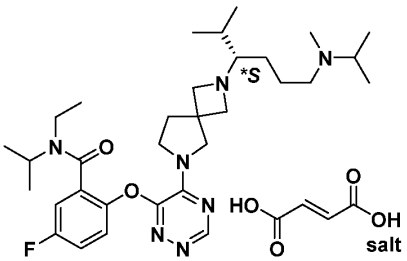
2-((5-(2-((3*S*,5*S*)-6-(ethyl(methyl)amino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide fumarate

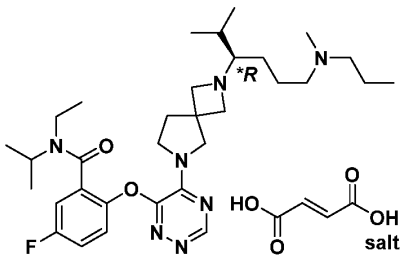
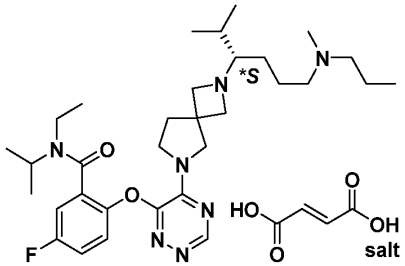
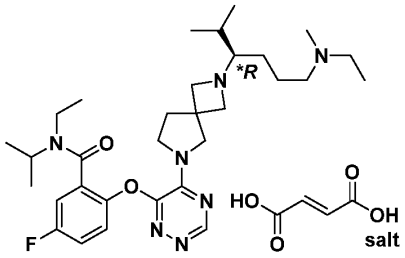
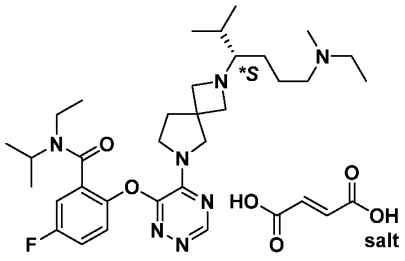
(*R*)-2-((3-chloro-5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide fumarate

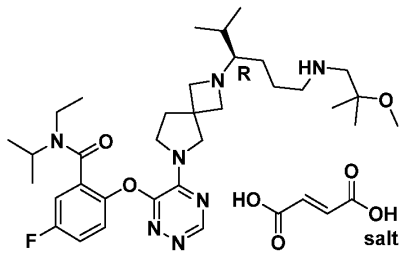
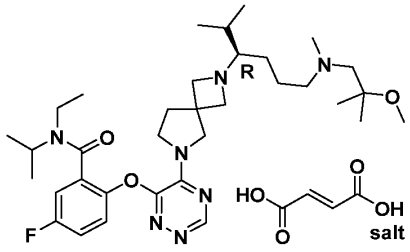
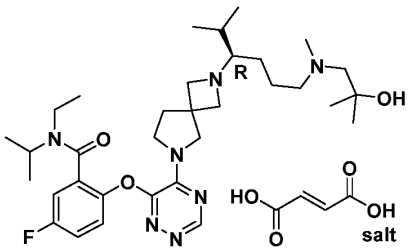
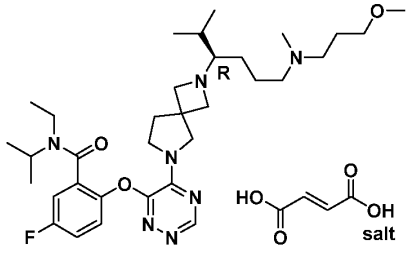
(*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(6-((2-methoxyethyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide fumarate

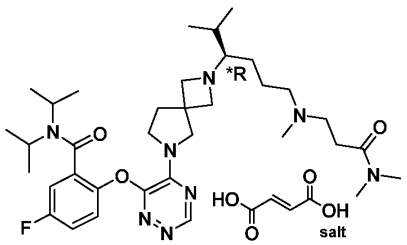
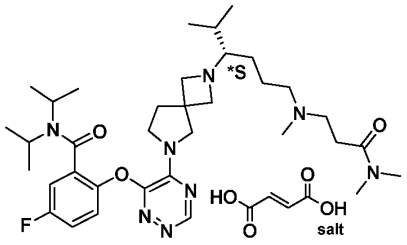
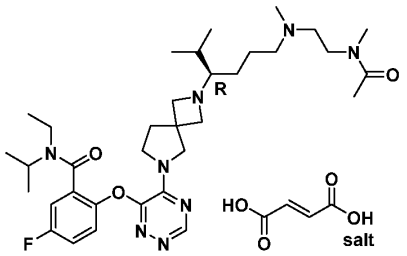
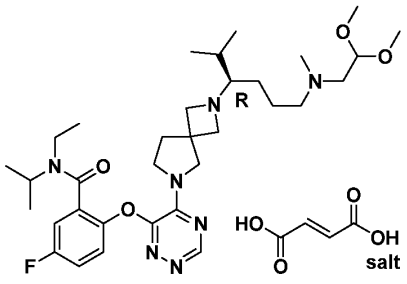
The following Compounds were synthesized by an analogous method described above for Compound 102

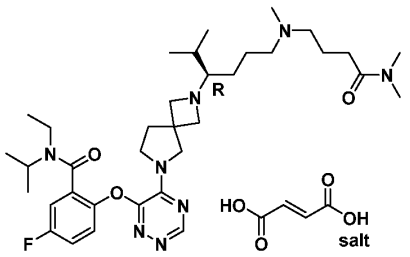
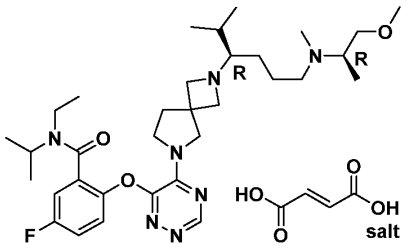
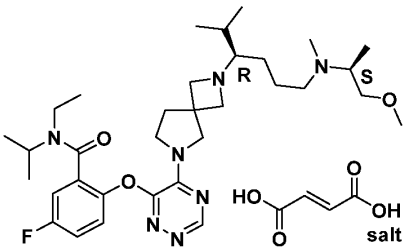
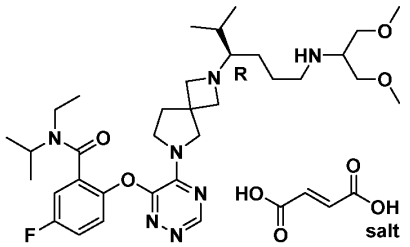
Co. No.	Structure	Starting Materials	Spectra Details
103		Compound 106, fumaric acid	**LC-MS (ESI) (Method 2):** R_t = 2.041 min, m/z found 570.3 $[M+H]^+$. **SFC (Method 13):** R_t = 1.722 min.
112		Compound 111, fumaric acid	**^{1}H NMR (400 MHz, Methanol-d_4):** δ = 8.49 (s, 1H), 7.45-7.22 (m, 3H), 6.71 (s, 4H), 4.20-3.63 (m, 9H), 3.51-3.40 (m, 6H), 3.31-2.95 (m, 5H), 2.47-2.23 (m, 2H), 2.19-1.98 (m, 1H), 1.94-1.54 (m, 4H), 1.35 (d, *J*=5.6 Hz, 3H), 1.19-0.98 (m, 13H), 0.89-0.73 (m, 2H). **LC-MS (ESI) (Method 1):** R_t = 3.063 min, m/z found 600.5 $[M+H]^+$. **SFC (Method 6):** R_t = 1.214 min.

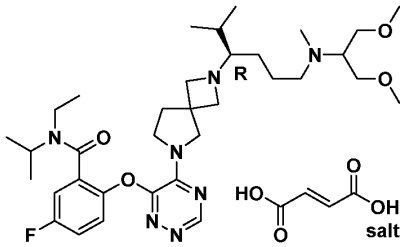
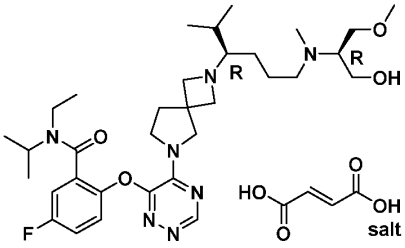
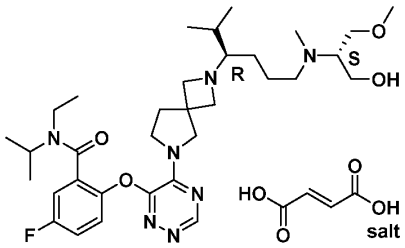
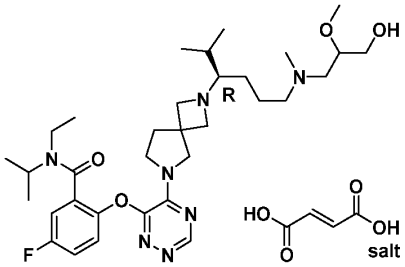
Co. No.	Structure	Starting Materials	Spectra Details
114		Compound 113, fumaric acid	**^{1}H NMR (400 MHz, Methanol-d_4):** δ = 8.47 (s, 1H), 7.52-7.07 (m, 3H), 6.69 (s, 4H), 6.30-5.90 (m, 1H), 4.50-3.39 (m, 10H), 3.25-2.83 (m, 6H), 2.43-1.99 (m, 5H), 1.90-1.49 (m, 4H), 1.23-0.71 (m, 15H). **LC-MS (ESI) (Method 1):** R_t = 3.056 min, m/z found 606.3 $[M+H]^+$. **SFC (Method 13):** R_t = 1.944 min.
122		Compound 120, fumaric acid	**LC-MS (ESI) (Method 2):** R_t = 2.030 min, m/z found 584.3 $[M+H]^+$. **SFC (Method 18):** R_t = 2.312 min.
123		Compound 121, fumaric acid	**LC-MS (ESI) (Method 2):** R_t = 2.020 min, m/z found 584.3 $[M+H]^+$. **SFC (Method 18):** R_t = 2.557 min.

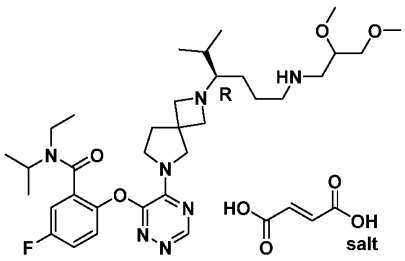
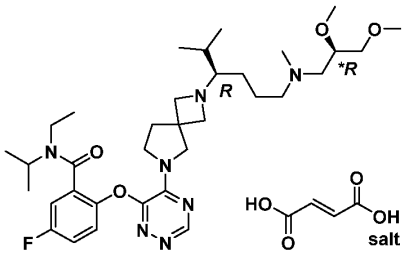
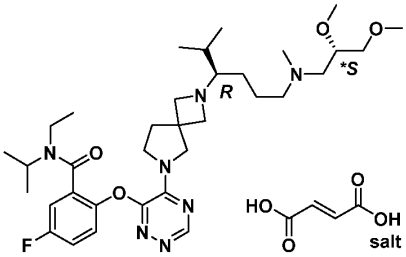
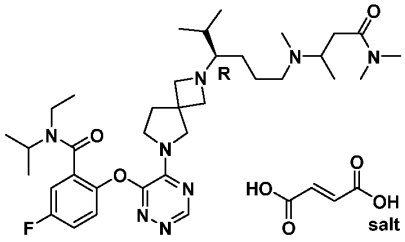
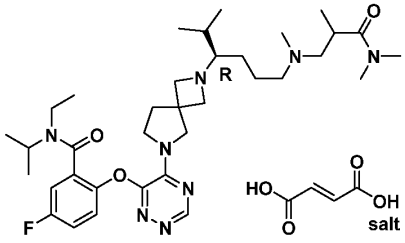
Co. No.	Structure	Starting Materials	Spectra Details
127		Compound 125, fumaric acid	**LC-MS (ESI) (Method 2):** R_t = 2.065 min, m/z found 584.3 $[M+H]^+$. **Chiral HPLC (Method 7):** R_t = 3.197 min.
128		Compound 126, fumaric acid	**LC-MS (ESI) (Method 2):** R_t = 2.074 min, m/z found 584.3 $[M+H]^+$. **Chiral HPLC (Method 7):** R_t = 3.805 min.
132		Compound 130, fumaric acid	**LC-MS (ESI) (Method 2):** R_t = 1.954 min, m/z found 570.3 $[M+H]^+$. **Chiral HPLC (Method 7):** R_t = 3.702 min.
133		Compound 131, fumaric acid	**LC-MS (ESI) (Method 2):** R_t = 1.955 min, m/z found 570.3 $[M+H]^+$. **Chiral HPLC (Method 7):** R_t = 4.808 min.

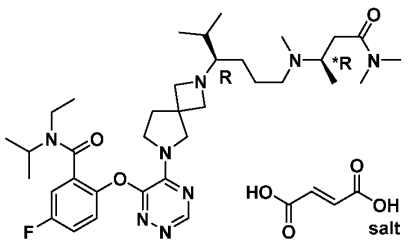
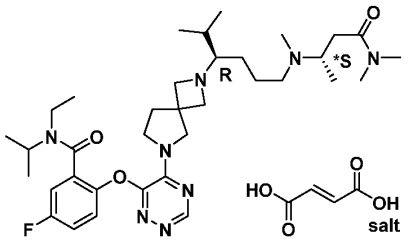
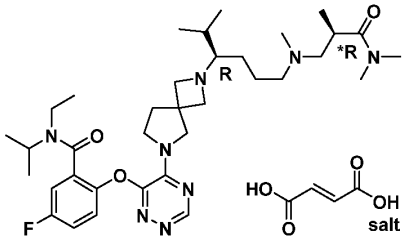
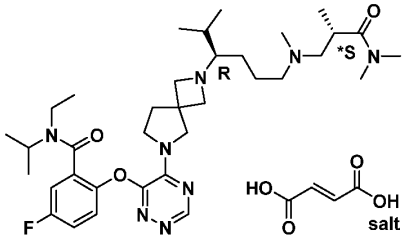
Co. No.	Structure	Starting Materials	Spectra Details
135		Compound 134, fumaric acid	**LC-MS (ESI) (Method 2):** R_t = 2.083 min, m/z found 614.4 $[M+H]^+$. **SFC (Method 6):** R_t = 1.346 min.
137		Compound 136, fumaric acid	**LC-MS (ESI) (Method 2):** R_t = 2.115 min, m/z found 628.4 $[M+H]^+$. **SFC (Method 6):** R_t = 0.938 min.
140		Compound 139, fumaric acid	**LC-MS (ESI) (Method 2):** R_t = 1.986 min, m/z found 614.4 $[M+H]^+$. **SFC (Method 13):** R_t = 1.749 min.
142		Compound 141, fumaric acid	**LC-MS (ESI) (Method 2):** R_t = 2.039 min, m/z found 614.4 $[M+H]^+$. **SFC (Method 6):** R_t = 1.171 min.

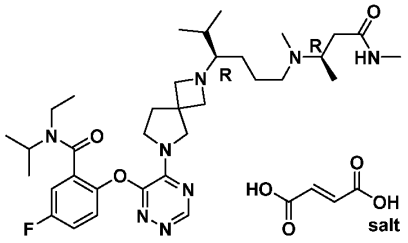
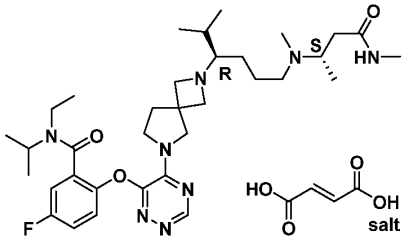
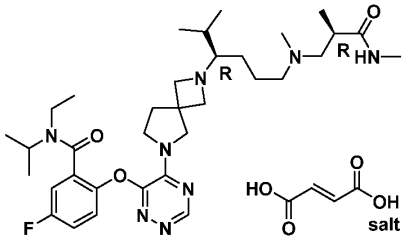
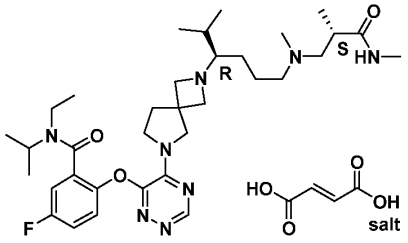
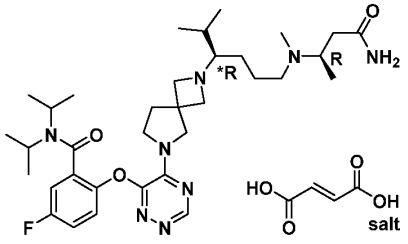
Co. No.	Structure	Starting Materials	Spectra Details
145		Compound 143, fumaric acid	**LC-MS (ESI) (Method 2):** R_t = 2.096 min, m/z found 655.6 $[M+H]^+$. **SFC (Method 19):** R_t = 3.861 min.
146		Compound 144, fumaric acid	**LC-MS (ESI) (Method 2):** R_t = 2.096 min, m/z found 655.6 $[M+H]^+$. **SFC (Method 19):** R_t = 4.578 min.
148		Compound 147, fumaric acid	**LC-MS (ESI) (Method 3):** R_t = 4.480 min, m/z found 641.6 $[M+H]^+$. **SFC (Method 6):** R_t = 1.356 min.
150		Compound 149, fumaric acid	**LC-MS (ESI) (Method 3):** R_t = 4.836 min, m/z found 630.4 $[M+H]^+$. **SFC (Method 6):** R_t = 1.067 min.

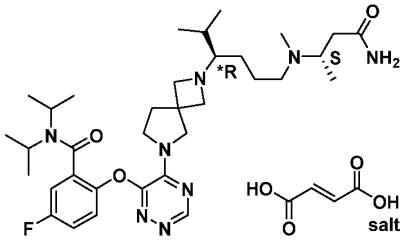
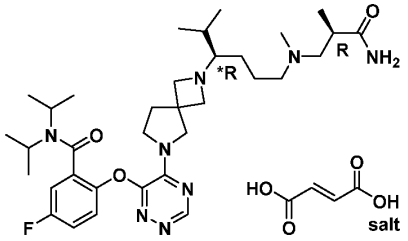
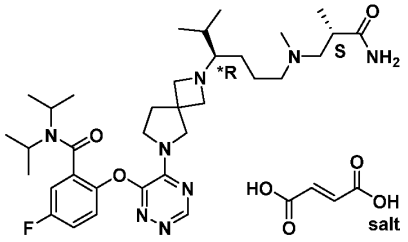
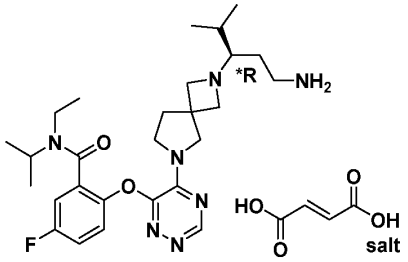
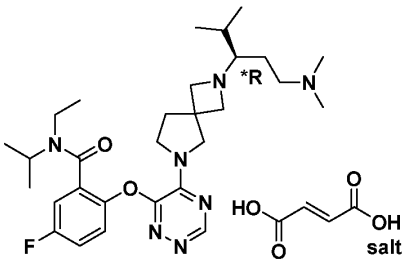
Co. No.	Structure	Starting Materials	Spectra Details
152		Compound 151, fumaric acid	**LC-MS (ESI) (Method 2):** R_t = 2.332 min, m/z found 655.5 $[M+H]^+$. **SFC (Method 6):** R_t = 1.449 min.
154		Compound 153, fumaric acid	**LC-MS (ESI) (Method 2):** R_t = 2.022 min, m/z found 614.4 $[M+H]^+$. **SFC (Method 6):** R_t = 1.137 min.
157		Compound 156, fumaric acid	**LC-MS (ESI) (Method 2):** R_t = 2.049 min, m/z found 614.4 $[M+H]^+$. **SFC (Method 20):** R_t = 1.001 min.
159		Compound 158, fumaric acid	**LC-MS (ESI) (Method 1):** R_t = 3.102 min, m/z found 630.4 $[M+H]^+$. **SFC (Method 6):** R_t = 1.194 min.

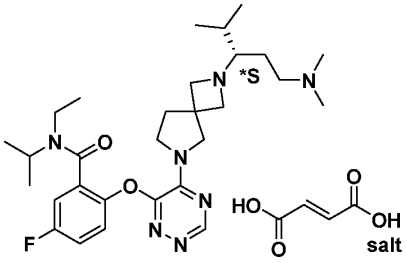
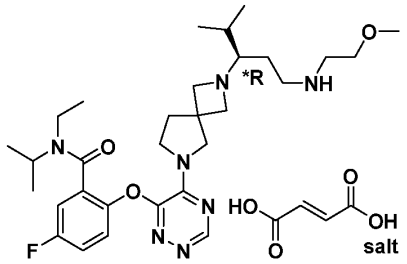
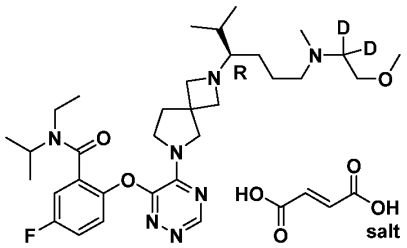
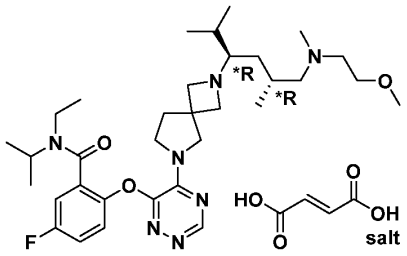
Co. No.	Structure	Starting Materials	Spectra Details
161		Compound 160, fumaric acid	**LC-MS (ESI) (Method 2):** R_t = 2.112 min, m/z found 644.3 $[M+H]^+$. **SFC (Method 6):** R_t = 1.073 min.
165		Compound 164, fumaric acid	**LC-MS (ESI) (Method 3):** R_t = 4.766 min, m/z found 630.3 $[M+H]^+$. **SFC (Method 6):** R_t = 1.271 min.
167		Compound 166, fumaric acid	**LC-MS (ESI) (Method 3):** R_t = 4.730 min, m/z found 630.3 $[M+H]^+$. **SFC (Method 6):** R_t = 1.373 min.
170		Compound 169, fumaric acid	**LC-MS (ESI) (Method 3):** R_t = 4.652 min, m/z found 630.4 $[M+H]^+$.

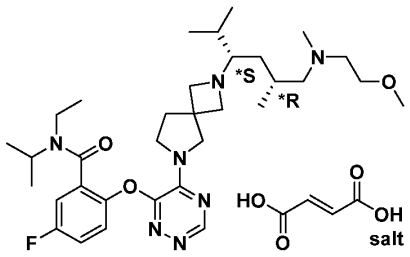
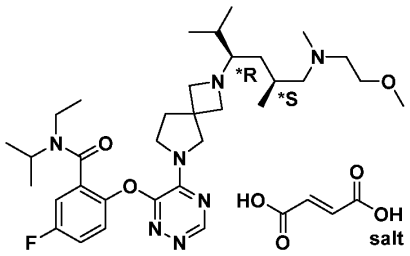
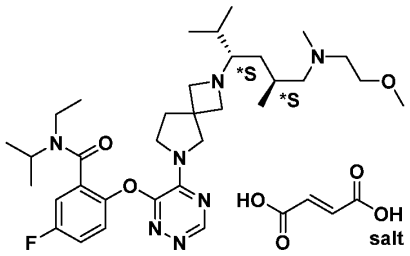
Co. No.	Structure	Starting Materials	Spectra Details
172		Compound 171, fumaric acid	**LC-MS (ESI) (Method 3):** R_t = 5.073 min, m/z found 630.4 $[M+H]^+$.
176		Compound 174, fumaric acid	**LC-MS (ESI) (Method 3):** R_t = 5.035 min, m/z found 644.5 $[M+H]^+$. **SFC (Method 23):** R_t = 4.662 min.
177		Compound 175, fumaric acid	**LC-MS (ESI) (Method 3):** R_t = 5.031 min, m/z found 644.5 $[M+H]^+$. **SFC (Method 23):** R_t = 4.977 min.
179		Compound 178, fumaric acid	**LC-MS (ESI) (Method 5):** R_t = 1.72 min, m/z found 655.5 $[M+H]^+$.
181		Compound 180, fumaric acid	**LC-MS (ESI) (Method 5):** R_t = 1.61 min, m/z found 655.5 $[M+H]^+$.

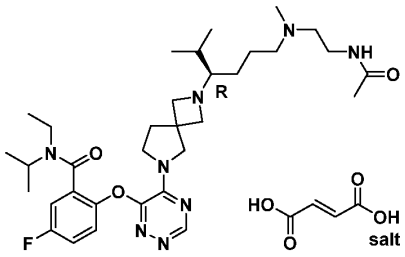
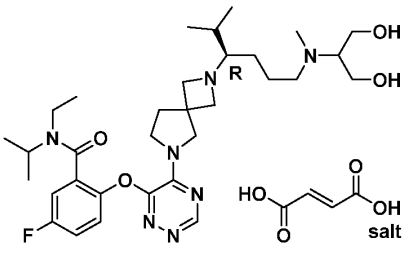
Co. No.	Structure	Starting Materials	Spectra Details
184		Compound 182, fumaric acid	**LC-MS (ESI) (Method 2):** R_t = 2.041 min, m/z found 655.4 $[M+H]^+$. **SFC (Method 8):** R_t = 2.752 min.
185		Compound 183, fumaric acid	**LC-MS (ESI) (Method 2):** R_t = 2.058 min, m/z found 655.4 $[M+H]^+$. **SFC (Method 8):** R_t = 3.09 min.
188		Compound 186, fumaric acid	**LC-MS (ESI) (Method 3):** R_t = 4.940 min, m/z found 655.4 $[M+H]^+$. **SFC (Method 23):** R_t = 5.055 min.
189		Compound 187, fumaric acid	**LC-MS (ESI) (Method 3):** R_t = 4.907 min, m/z found 655.4 $[M+H]^+$. **SFC (Method 23):** R_t = 5.287 min.

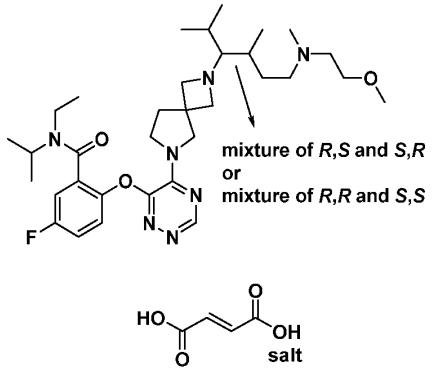
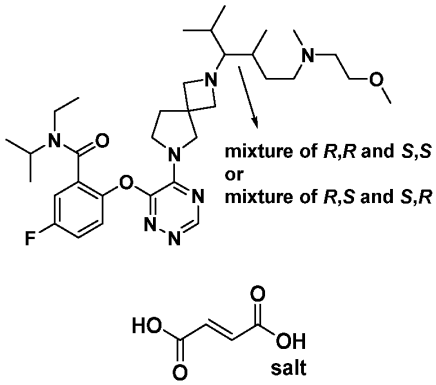
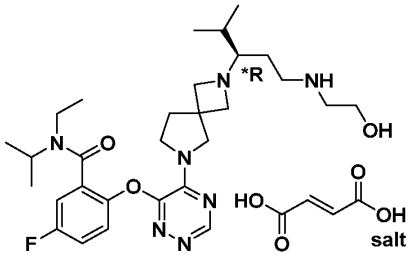
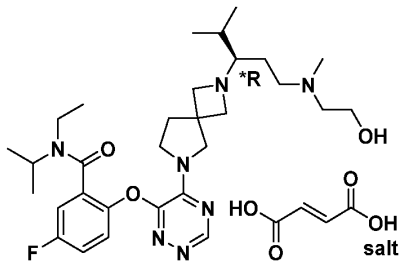
Co. No.	Structure	Starting Materials	Spectra Details
191		Compound 190, fumaric acid	**LC-MS (ESI) (Method 5):** R_t = 1.66 min, m/z found 641.3 $[M+H]^+$.
193		Compound 192, fumaric acid	**LC-MS (ESI) (Method 5):** R_t = 1.70 min, m/z found 641.3 $[M+H]^+$.
195		Compound 194, fumaric acid	**LC-MS (ESI) (Method 5):** R_t = 1.67 min, m/z found 641.3 $[M+H]^+$.
197		Compound 196, fumaric acid	**LC-MS (ESI) (Method 5):** R_t = 1.85 min, m/z found 641.3 $[M+H]^+$.
199		Compound 198, fumaric acid	**LC-MS (ESI) (Method 5):** R_t = 1.62 min, m/z found 641.3 $[M+H]^+$.

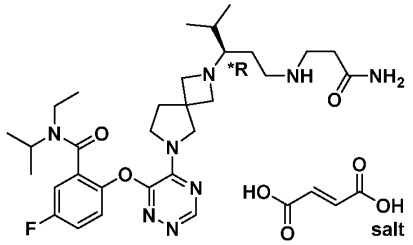
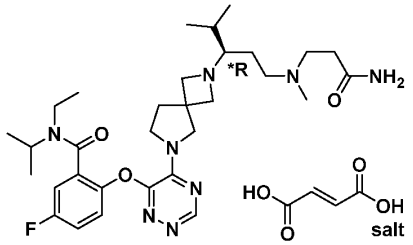
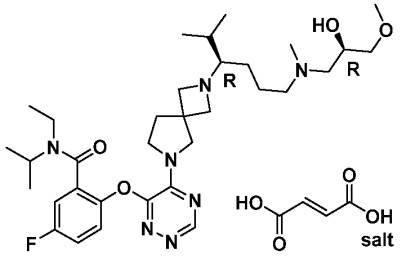
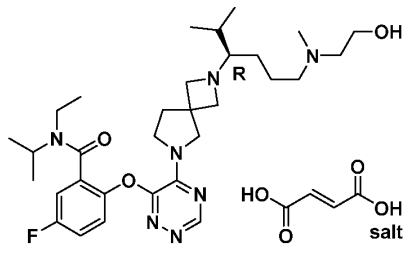
Co. No.	Structure	Starting Materials	Spectra Details
201		Compound 200, fumaric acid	**LC-MS (ESI) (Method 5):** R_t = 1.63 min, m/z found 641.3 $[M+H]^+$.
203		Compound 202, fumaric acid	**LC-MS (ESI) (Method 5):** R_t = 1.72 min, m/z found 641.3 $[M+H]^+$.
205		Compound 204, fumaric acid	**LC-MS (ESI) (Method 5):** R_t = 1.66 min, m/z found 641.2 $[M+H]^+$.
219		Compound 218, fumaric acid	**LC-MS (ESI) (Method 6):** R_t = 2.67 min, m/z found 514.2 $[M+H]^+$.
223		Compound 222, fumaric acid	**LC-MS (ESI) (Method 3):** R_t = 5.047 min, m/z found 542.3 $[M+H]^+$. **SFC (Method 18):** R_t = 1.991 min.

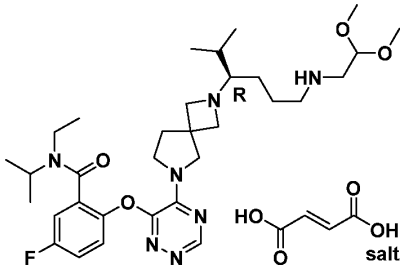
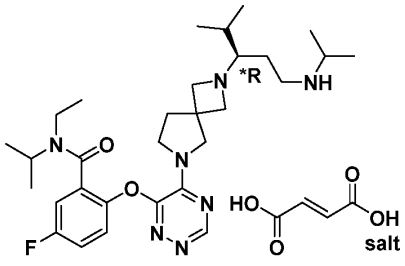
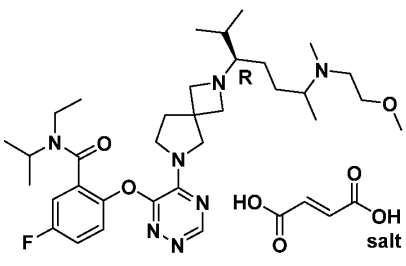
Co. No.	Structure	Starting Materials	Spectra Details
225		Compound 224, fumaric acid	**LC-MS (ESI) (Method 3):** R_t = 4.890 min, m/z found 542.3 $[M+H]^+$. **SFC (Method 18):** R_t = 2.189 min.
227		Compound 226, fumaric acid	**LC-MS (ESI) (Method 6):** R_t = 3.00 min, m/z found 572.3 $[M+H]^+$.
233		Compound 232, fumaric acid	**LC-MS (ESI) (Method 1):** R_t = 3.031 min, m/z found 602.3 $[M+H]^+$. **SFC (Method 6):** R_t = 1.134 min.
240		Compound 236, fumaric acid	**LC-MS (ESI) (Method 3):** R_t = 5.301 min, m/z found 614.4 $[M+H]^+$. **SFC (Method 4):** R_t = 1.241 min.

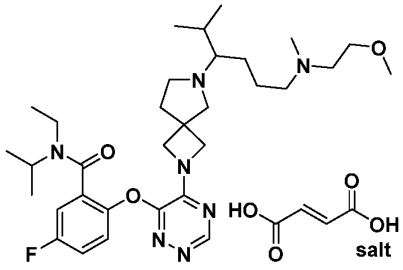
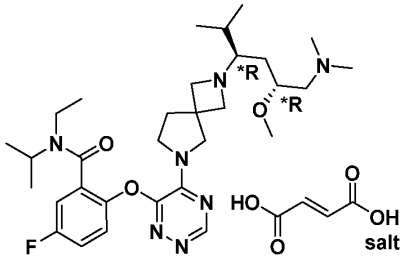
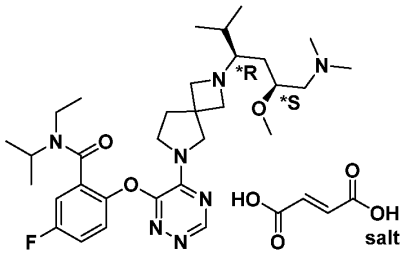
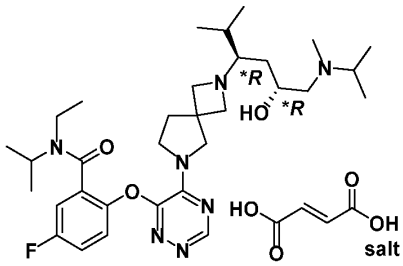
Co. No.	Structure	Starting Materials	Spectra Details
241		Compound 237, fumaric acid	**LC-MS (ESI) (Method 3):** R_t = 5.194 min, m/z found 614.4 $[M+H]^+$. **SFC (Method 4):** R_t = 1.347 min.
242		Compound 238, fumaric acid	**LC-MS (ESI) (Method 3):** R_t = 5.284 min, m/z found 614.4 $[M+H]^+$. **SFC (Method 14):** R_t = 2.358 min.
243		Compound 239, fumaric acid	**LC-MS (ESI) (Method 3):** R_t = 5.244 min, m/z found 614.4 $[M+H]^+$. **SFC (Method 14):** R_t = 2.450 min.

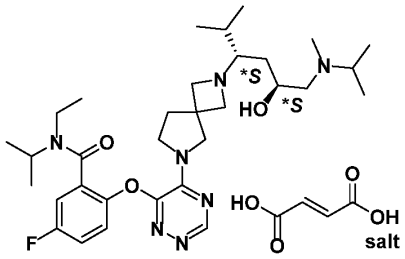
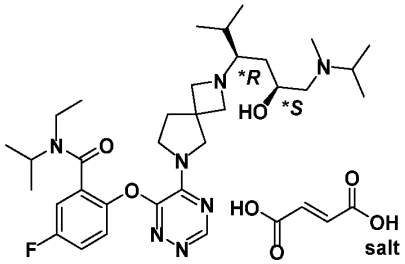
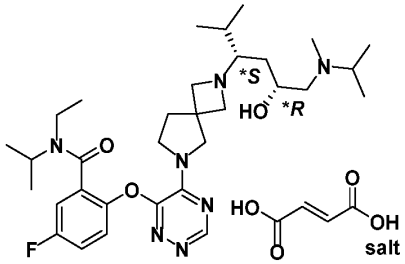
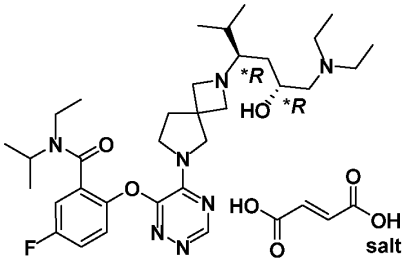
Co. No.	Structure	Starting Materials	Spectra Details
245		Compound 244, fumaric acid	**^{1}H NMR (400 MHz, Methanol-d_4):** δ = 8.51 (brs, 1H), 7.56-7.16 (m, 3H), 6.74 (s, 4H), 4.57-3.67 (m, 9H), 3.63-3.40 (m, 3H), 3.30-3.08 (m, 6H), 2.87 (s, 3H), 2.48-2.28 (m, 2H), 2.20-2.07 (m, 1H), 1.98 (s, 3H), 1.92-1.79 (m, 2H), 1.76-1.52 (m, 2H), 1.26-0.94 (m, 13H), 0.89-0.74 (m, 2H). **LC-MS (ESI) (Method 1):** R_t = 2.916 min, m/z found 627.4 $[M+H]^+$. **SFC (Method 25):** R_t = 1.707 min.
256		Compound 255, fumaric acid	**LC-MS (ESI) (Method 1):** R_t = 2.932 min, m/z found 616.3 $[M+H]^+$. **SFC (Method 6):** R_t = 1.383 min.

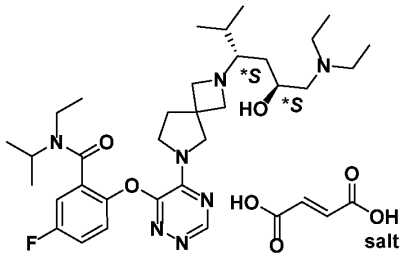
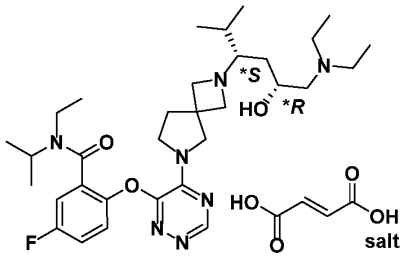
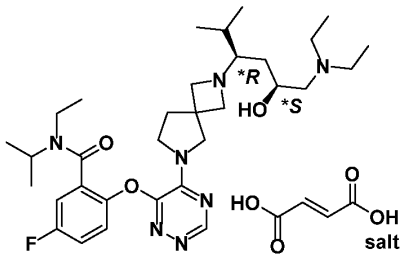
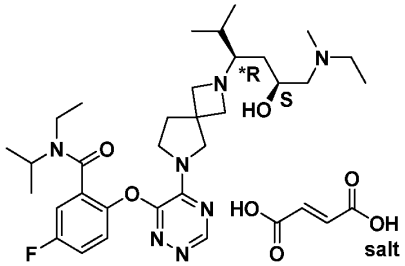
Co. No.	Structure	Starting Materials	Spectra Details
265		Compound 263, fumaric acid	**LC-MS (ESI) (Method 2):** R_t = 2.043 min, m/z found 614.3 $[M+H]^+$.
266		Compound 264, fumaric acid	**LC-MS (ESI) (Method 2):** R_t = 1.988 min, m/z found 614.5 $[M+H]^+$.
268		Compound 267, fumaric acid	**LC-MS (ESI) (Method 5):** R_t = 1.45 min, m/z found 558.2 $[M+H]^+$.
270		Compound 269, fumaric acid	**LC-MS (ESI) (Method 5):** R_t = 1.49 min, m/z found 572.3 $[M+H]^+$.

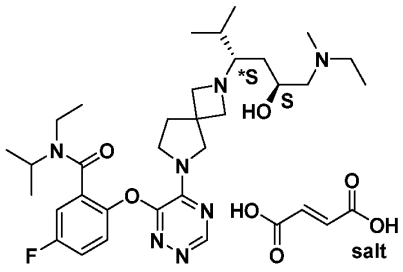
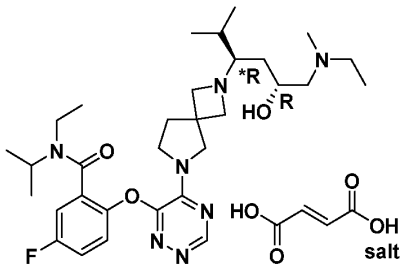
Co. No.	Structure	Starting Materials	Spectra Details
278		Compound 277, fumaric acid	**LC-MS (ESI) (Method 5):** R_t = 1.54 min, m/z found 585.2 $[M+H]^+$.
280		Compound 279, fumaric acid	**LC-MS (ESI) (Method 5):** R_t = 1.54 min, m/z found 599.3 $[M+H]^+$.
283		Compound 282, fumaric acid	**LC-MS (ESI) (Method 1):** R_t = 2.605 min, m/z found 630.3 $[M+H]^+$. **SFC (Method 6):** R_t = 1.303 min.
259		Compound 286, fumaric acid	**LC-MS (ESI) (Method 1):** R_t = 2.900 min, m/z found 586.6 $[M+H]^+$. **SFC (Method 6):** R_t = 1.301 min.

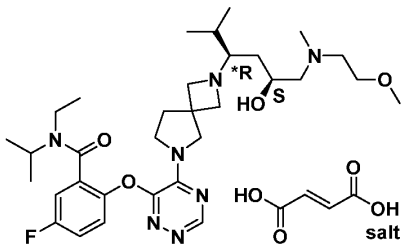
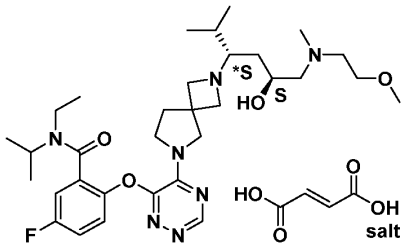
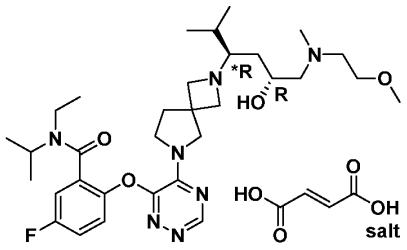
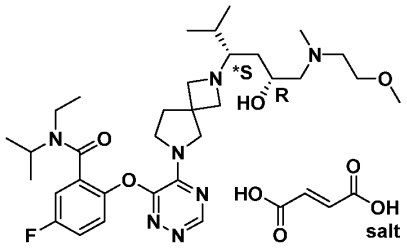
Co. No.	Structure	Starting Materials	Spectra Details
104		Compound 287, fumaric acid	**^{1}H NMR (400 MHz, Methanol-d_4):** δ = 8.45 (s, 1H), 7.50-7.09 (m, 3H), 6.67 (s, 4H), 4.48-3.60 (m, 10H), 3.45 (s, 6H), 3.23-2.87 (m, 6H), 2.44-2.18 (m, 2H), 2.16-1.96 (m, 1H), 1.89-1.50 (m, 4H), 1.29-0.91 (m, 14H), 0.87-0.70 (m, 2H). **LC-MS (ESI) (Method 1)**: R_t = 3.025 min, m/z found 616.3 $[M+H]^+$. **SFC (Method 6):** R_t = 1.305 min.
229		Compound 228, fumaric acid	**LC-MS (ESI) (Method 6)**: R_t = 2.95 min, m/z found 556.3 $[M+H]^+$.
300		Compound 299, fumaric acid	**LC-MS (ESI) (Method 2):** R_t = 2.017 min, m/z found 614.4 $[M+H]^+$. **Chiral HPLC (Method 8):** R_t = 5.212 min.

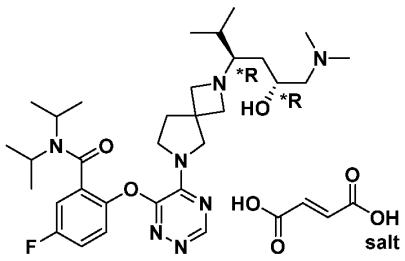
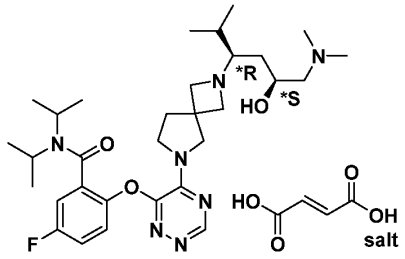
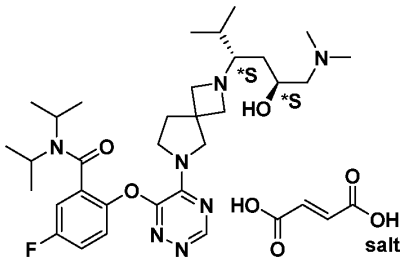
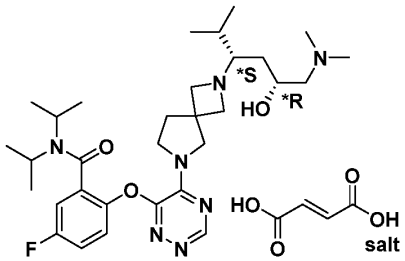
Co. No.	Structure	Starting Materials	Spectra Details
302		Compound 301, fumaric acid	**LC-MS (ESI) (Method 2):** R_t = 2.021 min, m/z found 600.7 $[M+H]^+$.
314		Compound 310, fumaric acid	**LC-MS (ESI) (Method 3):** R_t = 4.900 min, m/z found 586.3 $[M+H]^+$. **SFC (Method 11):** R_t = 4.457 min.
315		Compound 312, fumaric acid	**LC-MS (ESI) (Method 3):** R_t = 4.966 min, m/z found 586.3 $[M+H]^+$. **SFC (Method 11):** R_t = 4.273 min.
323		Compound 319, fumaric acid	**LC-MS (ESI) (Method 2):** R_t = 2.006 min, m/z found 600.3 $[M+H]^+$. **SFC (Method 27):** R_t = 2.598 min.

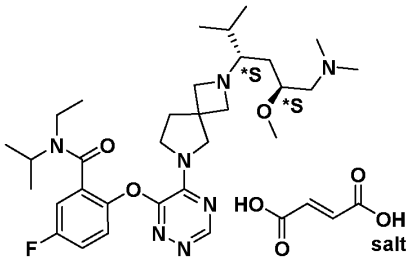
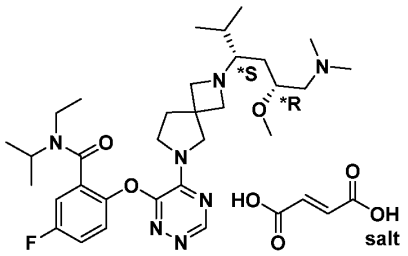
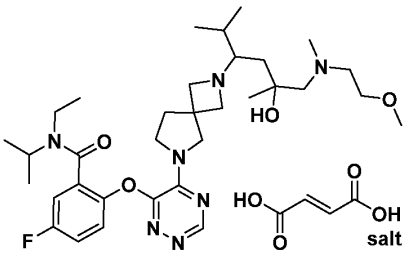
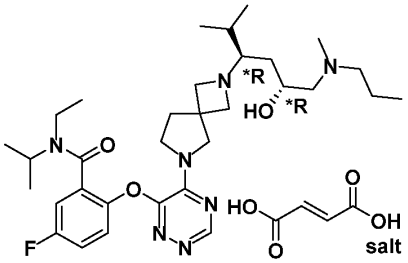
Co. No.	Structure	Starting Materials	Spectra Details
324		Compound 320, fumaric acid	**LC-MS (ESI) (Method 2):** R_t = 2.012 min, m/z found 600.4 $[M+H]^+$. **SFC (Method 27):** R_t = 4.487 min.
325		Compound 321, fumaric acid	**LC-MS (ESI) (Method 2):** R_t = 2.012 min, m/z found 600.3 $[M+H]^+$. **SFC (Method 28):** R_t = 2.196 min.
326		Compound 322, fumaric acid	**LC-MS (ESI) (Method 1):** R_t = 3.045 min, m/z found 600.3 $[M+H]^+$. **SFC (Method 28):** R_t = 2.677 min.
334		Compound 330, fumaric acid	**LC-MS (ESI) (Method 2):** R_t = 2.023 min, m/z found 600.3 $[M+H]^+$. **Chiral HPLC (Method 9):** R_t = 4.014 min.

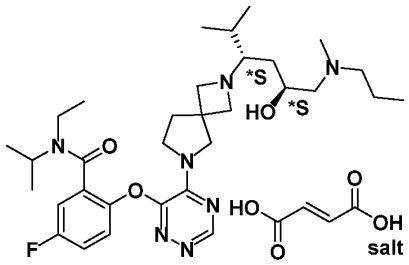
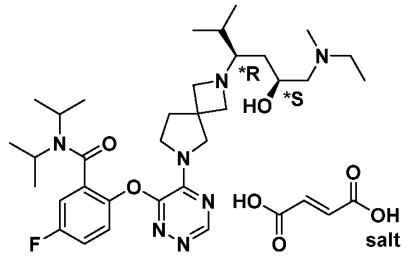
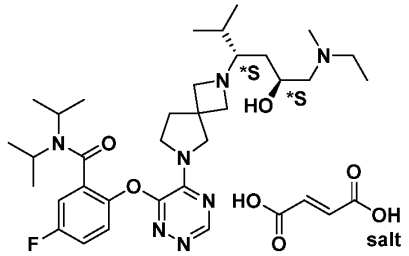
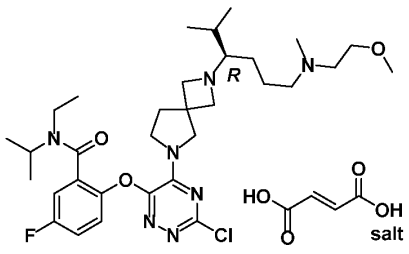
Co. No.	Structure	Starting Materials	Spectra Details
335		Compound 331, fumaric acid	**LC-MS (ESI) (Method 2):** R_t = 2.028 min, m/z found 600.3 $[M+H]^+$. **Chiral HPLC (Method 9):** R_t = 4.265 min.
336		Compound 332, fumaric acid	**LC-MS (ESI) (Method 2):** R_t = 1.967 min, m/z found 600.3 $[M+H]^+$. **SFC (Method 29):** R_t = 4.190 min.
337		Compound 333, fumaric acid	**LC-MS (ESI) (Method 2):** R_t = 1.973 min, m/z found 600.3 $[M+H]^+$. **SFC (Method 29):** R_t = 4.444 min.
342		Compound 340, fumaric acid	**LC-MS (ESI) (Method 1):** R_t = 2.934 min, m/z found 586.5 $[M+H]^+$. **SFC (Method 6):** R_t = 1.326 min.

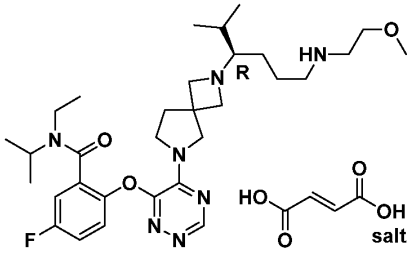
Co. No.	Structure	Starting Materials	Spectra Details
343		Compound 341, fumaric acid	**LC-MS (ESI) (Method 1):** R_t = 2.976 min, m/z found 586.5 $[M+H]^+$. **SFC (Method 6):** R_t = 1.285 min.
346		Compound 344, fumaric acid	**^{1}H NMR (400 MHz, Methanol-d_4):** δ = 8.47 (s, 1H), 7.53-7.16 (m, 3H), 6.68 (s, 4H), 4.49-3.65 (m, 10H), 3.42 (brs, 2H), 3.28-2.99 (m, 5H), 2.88 (s, 3H), 2.34 (brs, 2H), 2.23-2.11 (m, 1H), 1.85-1.63 (m, 2H), 1.40-0.74 (m, 18H). **LC-MS (ESI) (Method 1):** R_t = 2.968 min, m/z found 586.3 $[M+H]^+$. **SFC (Method 8):** R_t = 2.265 min.

Co. No.	Structure	Starting Materials	Spectra Details
352		Compound 350, fumaric acid	**LC-MS (ESI) (Method 1):** R_t = 3.010 min, m/z found 616.3 $[M+H]^+$. **SFC (Method 6):** R_t = 1.235 min.
353		Compound 351, fumaric acid	**LC-MS (ESI) (Method 1):** R_t = 2.967 min, m/z found 616.3 $[M+H]^+$. **SFC (Method 6):** R_t = 1.261 min.
356		Compound 354, fumaric acid	**LC-MS (ESI) (Method 1):** R_t = 2.959 min, m/z found 616.4 $[M+H]^+$. **SFC (Method 28):** R_t = 2.014 min.
357		Compound 355, fumaric acid	**LC-MS (ESI) (Method 1):** R_t = 2.906 min, m/z found 616.3 $[M+H]^+$. **SFC (Method 28):** R_t = 2.973 min.

Co. No.	Structure	Starting Materials	Spectra Details
365		Compound 363, fumaric acid	**LC-MS (ESI) (Method 1):** R_t = 3.150 min, m/z found 586.3 $[M+H]^+$. **SFC (Method 30):** R_t = 2.491 min.
366		Compound 364, fumaric acid	**LC-MS (ESI) (Method 1):** R_t = 3.093 min, m/z found 586.3 $[M+H]^+$. **SFC (Method 30):** R_t = 3.517 min.
369		Compound 367, fumaric acid	**LC-MS (ESI) (Method 1):** R_t = 3.170 min, m/z found 586.3 $[M+H]^+$. **SFC (Method 31):** R_t = 1.863 min.
370		Compound 368, fumaric acid	**LC-MS (ESI) (Method 1):** R_t = 3.137 min, m/z found 586.3 $[M+H]^+$. **SFC (Method 31):** R_t = 2.165 min.

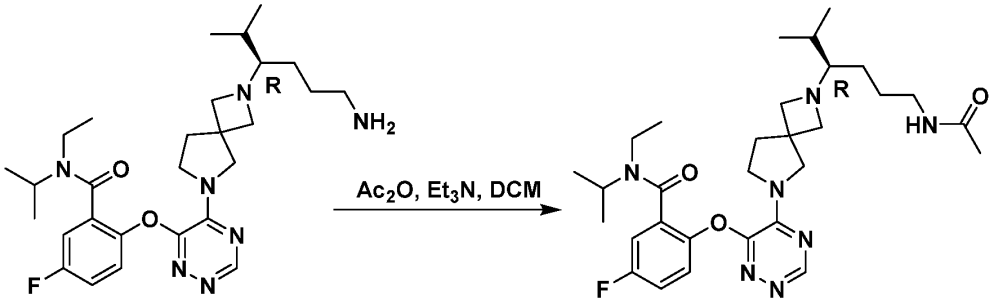
Co. No.	Structure	Starting Materials	Spectra Details
377		Compound 375, fumaric acid	**LC-MS (ESI) (Method 2):** R_t = 1.997 min, m/z found 586.3 $[M+H]^+$. **SFC (Method 11):** R_t = 4.749 min.
378		Compound 376, fumaric acid	**LC-MS (ESI) (Method 3):** R_t = 4.923 min, m/z found 586.3 $[M+H]^+$. **SFC (Method 11):** R_t = 4.663 min.
382		Compound 381, fumaric acid	**LC-MS (ESI) (Method 2):** R_t = 2.019/2.055 min, m/z found 630.5 $[M+H]^+$.
386		Compound 384, fumaric acid	**LC-MS (ESI) (Method 2):** R_t = 2.062 min, m/z found 600.3 $[M+H]^+$. **SFC (Method 27):** R_t = 2.111 min.

Co. No.	Structure	Starting Materials	Spectra Details
387		Compound 385, fumaric acid	**LC-MS (ESI) (Method 2):** R_t = 2.059 min, m/z found 600.3 $[M+H]^+$. **SFC (Method 27):** R_t = 3.466 min.
391		Compound 389, fumaric acid	**LC-MS (ESI) (Method 2):** R_t = 2.159 min, m/z found 600.3 $[M+H]^+$. **Chiral HPLC (Method 9):** R_t = 3.862 min.
392		Compound 390, fumaric acid	**LC-MS (ESI) (Method 2):** R_t = 2.119 min, m/z found 600.3 $[M+H]^+$. **SFC (Method 27):** R_t = 2.386 min.
394		Compound 393, fumaric acid	**LC-MS (ESI) (Method 2):** R_t = 2.442 min, m/z found 634.3 $[M+H]^+$. **SFC (Method 6):** R_t = 1.232 min.

Co. No.	Structure	Starting Materials	Spectra Details
397		Compound 11, fumaric acid	**LC-MS (ESI) (Method 5):** R_t = 1.661 min, m/z found 586.2 $[M+H]^+$.

Compound 6

(*R*)-2-((5-(2-(6-acetamido-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide formate



formate salt

To the solution of (*R*)-2-((5-(2-(6-amino-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide formate (**Compound 1**) (30 mg, 0.057 mmol) and TEA (60 uL, 0.43 mmol) in DCM (1 mL) cooled at 0 °C was added Ac_2O (20 uL, 0.21 mmol), the resulting mixture was stirred at RT under N_2 atmosphere for 0.5 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by preparative HPLC using a Welch Xtimate (column: C18 150x25mm 5um; eluent: ACN/H_2O (0.225% FA) from 30% to 50% (v/v)) to afford the title compound (3.31 mg, 9% yield) as a white solid.

LC-MS (ESI) (Method 5): R_t = 0.633 min, m/z found 570.4 $[M+H]^+$.

SFC (Method 5): R_t = 1.191 min.

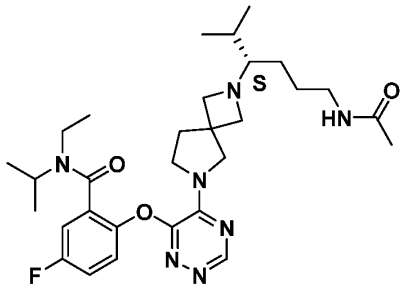
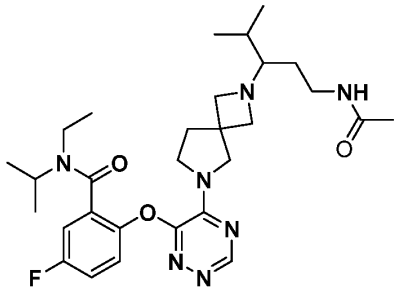
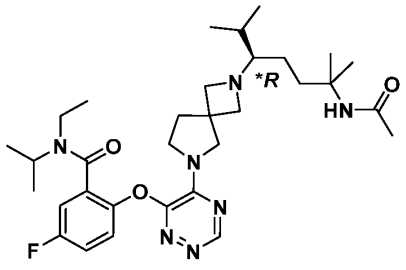
Compound 7, 29, 34

(*S*)-2-((5-(2-(6-acetamido-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

2-((5-(2-(1-acetamido-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

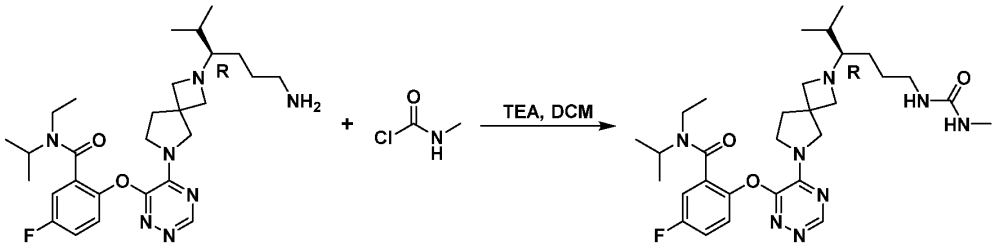
(R*)-2-((5-(2-(6-acetamido-2,6-dimethylheptan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide**

The following Compounds were synthesized by an analogous method described above for Compound 6

Co. No.	Structure	Starting Materials	Conditions	Spectra Details
7		Compound 2	Ac_2O, TEA, DCM	**LC-MS (ESI) (Method 5):** R_t = 0.646 min, m/z found 570.3 $[M+H]^+$. **SFC (Method 5)**: R_t = 1.657 min.
29		Compound 26	Ac_2O, TEA, DCM	LC-MS (ESI) (**Method 1**): R_t = 3.250 min, m/z found 556.4 $[M+H]^+$.
34		Compound 30	AcCl, TEA, DCM	**LC-MS (ESI) (Method 3)**: R_t = 4.573 min, m/z found 598.3 $[M+H]^+$.

Compound 8

(*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(2-methyl-6-(3-methylureido)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide



To the solution of (*R*)-2-((5-(2-(6-amino-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide formate (**Compound 1**) (70 mg, 0.12 mmol) and TEA (0.35 mL, 2.5 mmol) in DCM (10 mL) cooled at 0 °C was added methylcarbamic chloride (18 mg, 0.19 mmo) and the resulting mixture was stirred for 2 h at 0 °C. The reaction mixure was concentrated under reduced pressure and the residue was purified by preparative HPLC over Phenomenex Gemini-NX (column: 150x30mm 5um; eluent: ACN/H_2O (0.04% ammonia+10mM NH_4HCO_3) from 35% to 65%, v/v) to afford the title compound (50 mg, 70% yield) as a white solid.

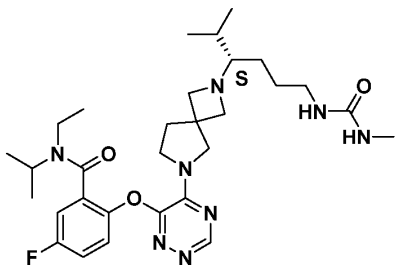
LC-MS (ESI) (method 1): R_t = 3.34 min, m/z found 585.3 $[M+H]^+$.

SFC (Method 6): R_t = 2.222 min.

Compound 9

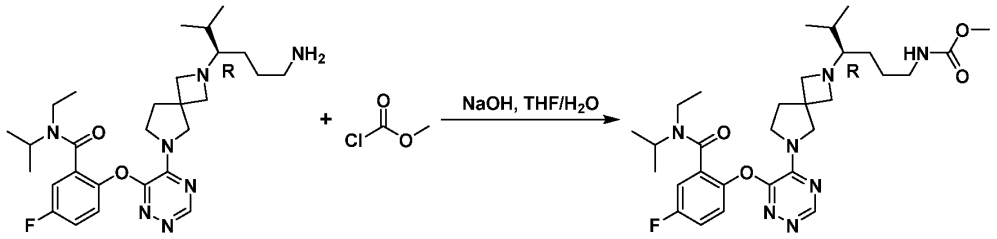
(*S*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(2-methyl-6-(3-methylureido)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide

The following Compound was synthesized by an analogous method described above for Compound 8

Co. No.	Structure	Starting Materials	Spectra Details
9		Compound 2	**LC-MS (ESI) (method 1):** R_t = 3.38 min, m/z found 585.3 $[M+H]^+$. **SFC (Method 6):** R_t = 2.418 min.

Compound 10

methyl (*R*)-(4-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-5-methylhexyl)carbamate



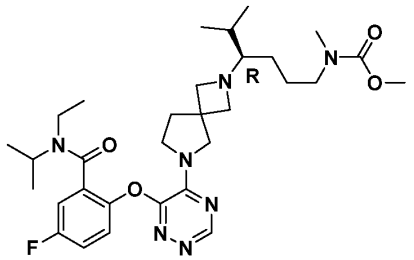
To the mixture of (*R*)-2-((5-(2-(6-amino-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride (**Compound 65**) (0.100 g, crude) in THF/H_2O (2 mL/2 mL) cooled at 0 °C were added 2 M NaOH (0.15 mL, 0.30 mmol) and methyl carbonochloridate (0.030 g, 0.317 mmol, in 0.1 mL DCM). The resulting mixture was stirred at 0 °C for 0.5 h. The mixture was diluted with water (10 mL) and sat. aq. $NaHCO_3$ (15 mL), further extracted with EtOAc (15 mL x 3). The combined organic layers were dried over (Na_2SO_4), filtered and evaporated *in vacuo* to give the crude product, which was further purified by preparative HPLC using Phenomenex Gemini NX (column: C18 75x30mm 3um; eluent: ACN/H_2O (0.05% ammonia+10mM NH_4HCO_3) 35% to 65% (v/v)) to afford the title compound (11.53 mg) as sticky oil.

LC-MS (ESI) (Method 1): R_t = 3.283 min, m/z found 586.3 $[M+H]^+$.

Compound 22

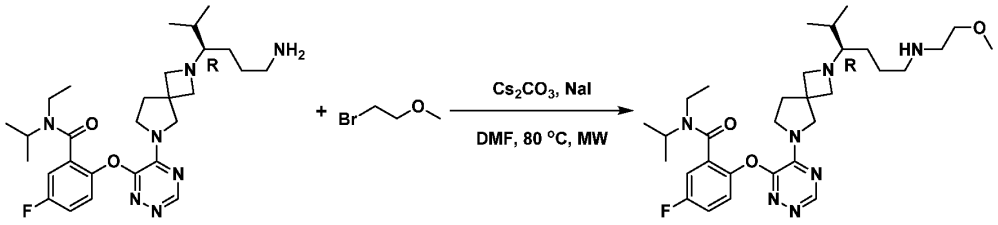
methyl (*R*)-(4-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-5-methylhexyl)(methyl)carbamate

The following Compound was synthesized by an analogous method described above for Compound 10

Co. No.	Structure	Starting Materials	Spectra Details
22		Compound 19	**LC-MS (ESI) (Method 2):** R_t = 2.472 min, m/z found 600.3 $[M+H]^+$.

Compound 11

(*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(6-((2-methoxyethyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide



The mixture of (*R*)-2-((5-(2-(6-amino-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (**Compound 64)** (120 mg, crude), 1-bromo-2-methoxyethane (32 mg, 0.23 mmol), Cs_2CO_3 (222 mg, 0.681 mmol), NaI (102 mg, 0.680 mmol) in DMF (1 mL) was stirred at 80 °C via microwave irradiation for 1 h. After cooling to RT, the mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with H_2O (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product which was further purified by HPLC over a Phenomenex Gemini-NX (column: 150x30 mm 5 μm; eluent: ACN/H_2O (10mM NH_4HCO_3) from 51% to 71% (v/v)) and further purified by SFC over DAICEL CHIRALCEL OD-H (column: 250x30 mm 5 um; eluent: supercritical CO_2 in EtOH (0.1% v/v ammonia) 25/25, v/v) to afford the title compound (5.13 mg, 96% purity) as yellow solid.

LC-MS (ESI) (Method 1): R_t = 2.997 min, m/z found 586.3 $[M+H]^+$.

Compound 28, 90, 93, 287, 149, 226, 257, 228

(*S*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide

(*R*)-2-((5-(2-(6-(bis(2-methoxyethyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide formate

5-fluoro-*N*,*N*-diisopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide formate

(*R*)-2-((5-(2-(6-((2,2-dimethoxyethyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

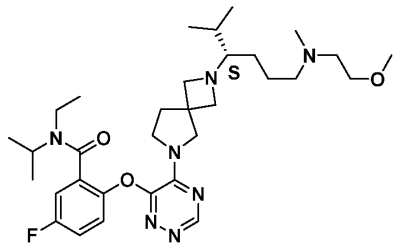
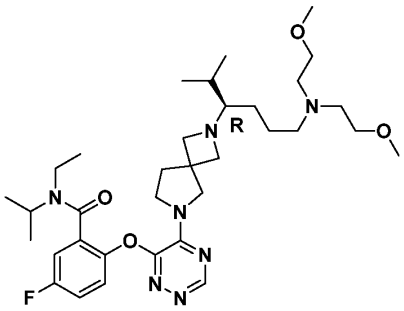
(*R*)-2-((5-(2-(6-((2,2-dimethoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

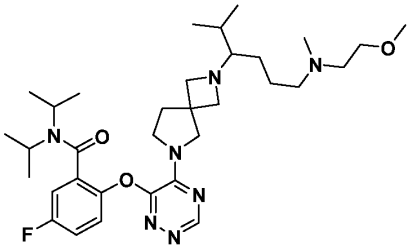
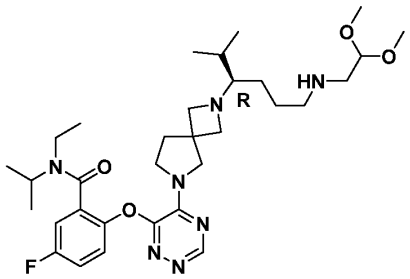
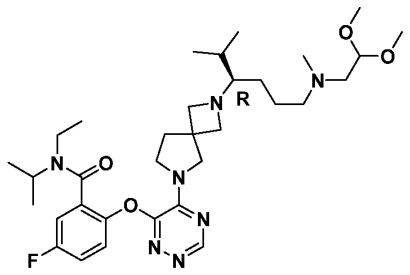
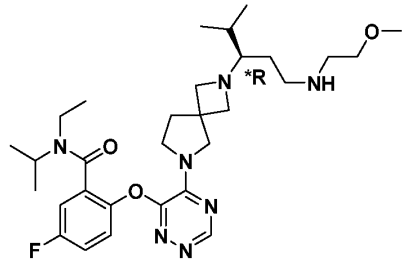
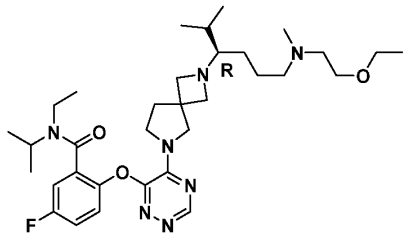
(*R)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(1-((2-methoxyethyl)amino)-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide

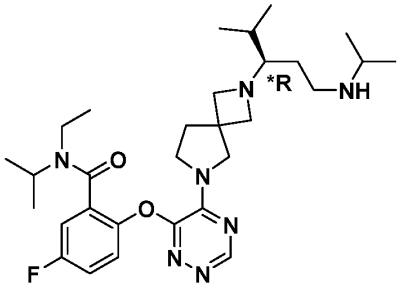
(*R*)-2-((5-(2-(6-((2-ethoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

(*R)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(1-(isopropylamino)-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide

The following Compounds were synthesized by an analogous method described above for Compound 11

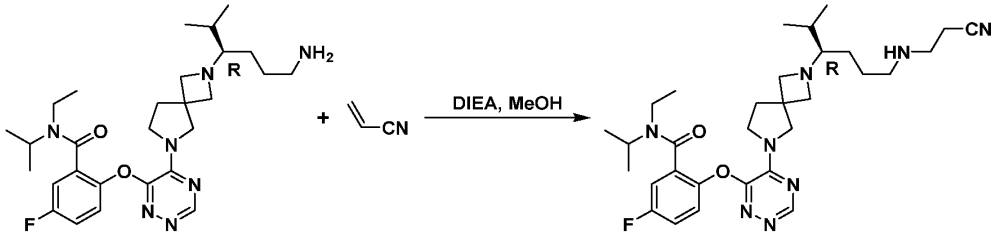
Co. No.	Structure	Starting Materials	Conditions	Spectra Details
28		Compound 20, 1-bromo-2-methoxyethane	K_2CO_3, NaI, DMF, 50 °C	**LC-MS (ESI) (Method 2):** R_t = 2.047 min, m/z found 600.3 $[M+H]^+$. **SFC (Method 11)**: R_t = 5.404 min
90	 formate salt	Compound 1, 1-bromo-2-methoxyethane	Cs_2CO_3, DMF, 80 °C, microwave	**LC-MS (ESI) (Method 2):** R_t = 2.105 min, m/z found 644.4 $[M+H]^+$. **SFC (Method 15):** Rt = 1.105 min.

Co. No.	Structure	Starting Materials	Conditions	Spectra Details
93	 formate salt	Compound 92, 1-bromo-2-methoxyethane	K_2CO_3, NaI, DMF, 50 °C	
287		Compound 1, 2-bromo-1,1-dimethoxy-ethane	K_2CO_3, NaI, DMF, 70 °C	
149		Compound 19, 2-bromo-1,1-dimethoxy-ethane	K_2CO_3, KI, DMF, 80 °C	
226		Compound 218, 1-bromo-2-methoxyethane	DIEA, ACN, 50 °C	
257		Compound 19, 1-bromo-2-ethoxyethane	K_2CO_3, NaI, DMF, 50 °C	

Co. No.	Structure	Starting Materials	Conditions	Spectra Details
228		Compound 218, 2-iodopropane	DIEA, ACN, RT	

Compound 12

(*R*)-2-((5-(2-(6-((2-cyanoethyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide



To a solution of (*R*)-2-((5-(2-(6-amino-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride (**Compound 65)** (260 mg, crude) and DIEA (200 mg, 1.98 mmol) in MeOH (15 mL) was added acrylonitrile (580 mg, 10.9 mmol) at 0 °C. After addition, the reaction mixture was stirred at RT for 18 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by preparative HPLC over Boston Prime (column: C18 150x30mm 5um, Mobile Phase A: water (0.04% ammonia+10mM NH_4HCO_3), Mobile Phase B: ACN, Flow rate: 25 mL/min, gradient condition B/A from 40% to 70%) to afford the title compound (120 mg) as colorless oil.

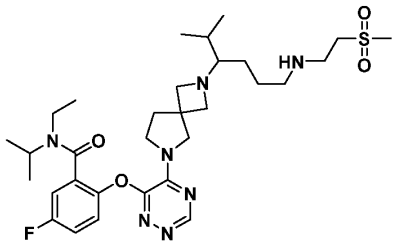
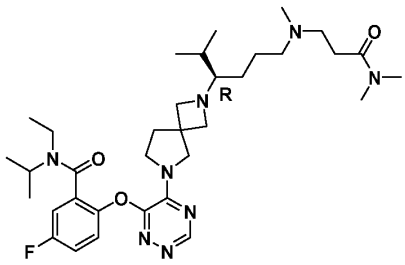
LC-MS (ESI) (Method 1): R_t = 2.938 min, m/z found 581.3 $[M+H]^+$.

Compound 18, 246

***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(2-methyl-6-((2-(methylsulfonyl)ethyl)amino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide**

(*R*)-2-((5-(2-(6-((3-(dimethylamino)-3-oxopropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide formate

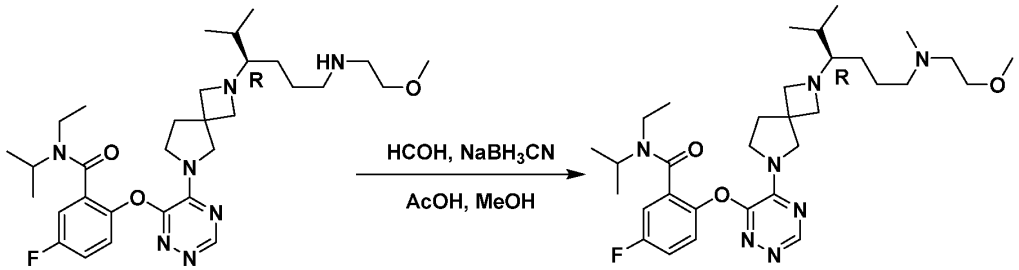
The following Compounds were synthesized by an analogous method described above for Compound 12

Co. No.	Structure	Starting Materials	Conditions	Spectra Details
18		Compound 3, (methylsulfonyl)-ethene	TEA, MeOH, RT	**LC-MS (ESI) (Method 4):** R_t = 2.24 min, m/z found 634.7 $[M+H]^+$
246	 formate salt	Compound 19, *N*,*N*-dimethylacrylamide	TEA, MeOH, reflux	**LC-MS (ESI) (Method 5):** R_t = 1.53 min, m/z found 641.5 $[M+H]^+$.

Compound 27

(*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide

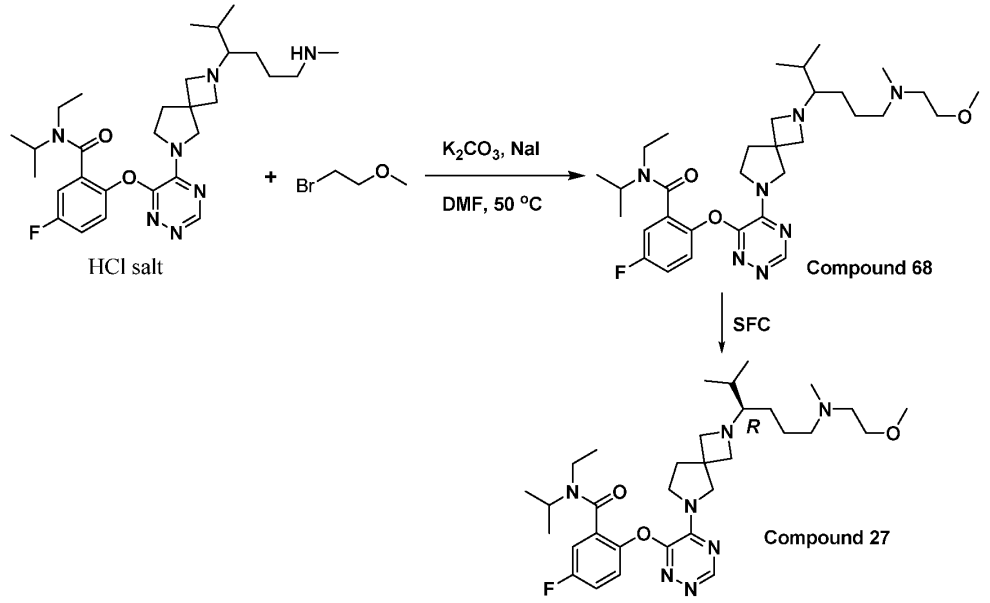
Preparation Method A:



The mixture of (*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(6-((2-methoxyethyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide

(**Compound 11**) (40.0 mg, 0.068 mmol), formaldehyde (55.4 mg, 0.683 mol, 37% in water) and AcOH (8.2 mg, 0.137 mmol) in anhydrous MeOH (2 mL) was stirred at 45 °C for 1 h. Then, $NaBH_3CN$ (8.6 mg, 0.137 mmol) was added to the mixture and the resulting mixture was stirred at 45 °C for another 1 h. After cooling to RT, the reaction mixture was treated with sat. aq. $NaHCO_3$ (40 mL) to adjust the pH value to about 8 and further extracted with DCM (20 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the crude which was purified by preparative HPLC over Boston Prime (column: C18 150x30mm 5um, Mobile Phase A: H_2O (0.04% ammonia+10mM NH_4HCO_3), Mobile Phase B: ACN, Flow rate: 25 mL/min, gradient condition B/A from 50% to 80% (50%B to 80% B)) to afford the title compound (9.62 mg, 99.10% purity, 23.3% yield) as yellow oil.

Preparation Method B:



To the mixture of *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(2-methyl-6-(methylamino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide hydrochloride (**Compound 67**) (480 mg, crude), K_2CO_3 (700 mg, 5.07 mmol) and NaI (400 mg, 2.67 mmol) in DMF (5 mL) was added 1-bromo-2-methoxyethane (230 mg, 1.65 mmol). The resulting mixture was stirred at 50 °C overnight. After cooled to RT, the reaction mixture was quenched with H_2O (30 mL) and extracted with DCM (30 mL x 3). The combined organic layers were washed with brine (30 mL x 3), dried over Na_2SO_4, filtered and concentrated to give a crude residue. The residue was purified by FCC (DCM/MeOH = 10:1) to afford *N*-

ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide (**Compound 68**) (250 mg, 48% yield) as yellow oil.

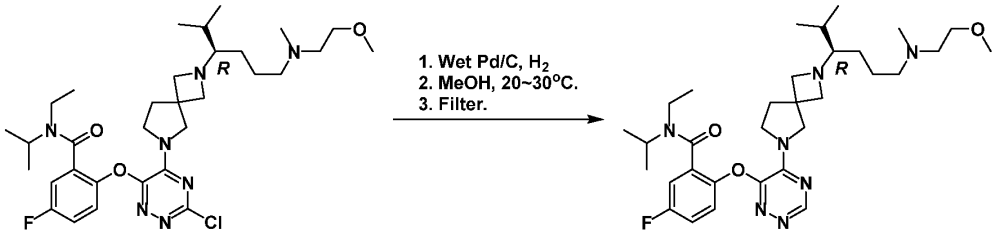
The *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide (**Compound 68**) (960 mg, combined from several batches obtained by Method B) was first separated by SFC using DAICEL CHIRALPAK IG (column: 250x30mm 10um; Mobile phase: A: Supercritical CO_2, B: EtOH (0.1% ammonia), A:B=40:60 at 60 mL/min) and further purified by preparative HPLC using Boston Prime (column: 150x30mm 5um, Mobile Phase A: H_2O (10mM NH_4HCO_3), Mobile Phase B: ACN, Flow rate: 25 mL/min, gradient condition B/A from 55% to 85%) to afford the title compound (270 mg) as colorless oil.

^{1}H NMR (400 MHz, Methanol-d_4): δ = 8.40 (s, 1H), 7.47-7.32 (m, 1H), 7.30-7.10 (m, 2H), 4.24-4.01 (m, 2H), 3.89-3.60 (m, 3H), 3.48 (br s, 3H), 2.63-2.51 (m, 2H), 2.43-2.32 (m, 2H), 2.29-2.07 (m, 6H), 1.86-1.72 (m, 1H), 1.62-1.44 (m, 2H), 1.39-1.02 (m, 10H), 0.99-0.66 (m, 9H). Some protons were hidden by the solvent peak and are not reported.

LCMS (ESI) (Method 2): R_t = 1.965 min, m/z found 600.3 $[M+H]^+$.

SFC (Method 11): R_t = 4.904 min.

Preparation Method C:

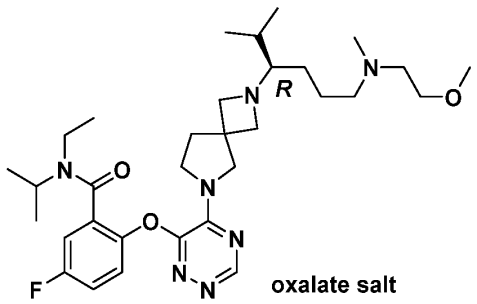


A methanol solution of (*R*)-2-((3-chloro-5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (**Compound 393**) (163.93g of a 60.1 wt % solution in MeOH, 100g corrected of **Compound 393**), palladium on carbon (10 g) and MeOH (316 g) was stirred at 20 to 30°C under a hydrogen atmosphere (0.20 to 0.30 Mpa) for 18 h. The mixture was filtered over diatomite (75 g) and the cake was washed with MeOH (158 g). The filtrate was concentrated under reduced pressure (≤ 40°C) to ~3 vol., then flushed with isopropyl acetate (IPAc, 870 g) concentrating to ~3 vol. The mixture was then diluted with IPAc (696 g) and a 20% Na_2CO_3 aqueous solution was added (500 g). The mixture was stirred for 30 to 60 min. The aqueous layer was removed. The organic layer was washed with water (500 g) then

concentrated under reduced pressure <45°C to ~3 vol. The title intermediate was afforded in approximately 90% assay yield as a 48.1 wt% solution in IPAc.

Compound 70

(*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide oxalate



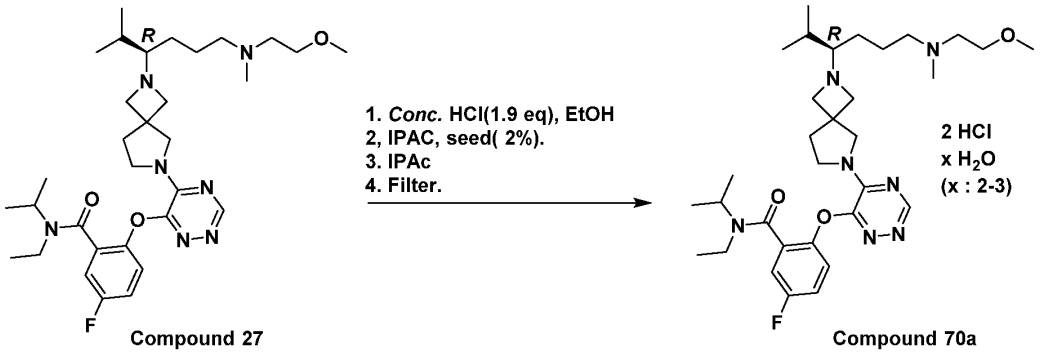
To a solution of (*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide (**Compound 27**) (270 mg, 0.450 mmol) in 20 mL of ACN (20 mL) was added oxalic acid (81.0 mg, 0.900 mmol). After addition, the reaction mixture was stirred at RT for 1 h. Then the reaction mixture was concentrated, the residue was re-dissolved in ACN and deionized water, and lyophilized to afford the title compound (350 mg) as white solid.

^{1}H NMR (400 MHz, Methanol-d_4): δ = 8.48 (s, 1H), 7.52-7.11 (m, 3H), 4.54-3.64 (m, 12H), 3.40-3.34 (m, 5H), 3.23-3.13 (m, 2H), 2.90 (s, 3H), 2.54-2.27 (m, 2H), 2.19-2.03 (m, 1H), 1.97-1.77 (m, 2H), 1.75-1.50 (m, 2H), 1.35-0.65 (m, 17H).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.51 (s, 1H), 7.51-7.29 (m, 3H), 4.29-3.34 (m, 12H), 3.23-2.84 (m, 7H), 2.70 (s, 3H), 2.35-2.09 (m, 2H), 2.05-1.85 (m, 1H), 1.81-1.58 (m, 2H), 1.56-1.33 (m, 2H), 1.18-0.60 (m, 17H).

LCMS (ESI) (Method 2): R_t = 1.969 min, m/z found 600.4 $[M+H]^+$.

Preparation of Compound 70a



To a solution of **Compound 27** (207.90 g of a 48 wt% solution in IPAc, 100g of active **compound 27**) in IPAc (360 g) was added EtOH (63 g) at 20 to 25°C. The solution was then treated with conc. HCl (32.9 g) in EtOH (49.5 g) over ~15 min. The mixture was seeded with crystalline **Compound 70a** seed (2 g, 2% seed load) then aged for 18 h. IPAc (870 g) was added slowly over 4 h at between 20 to 25°C and the slurry was stirred for an additional 18 h. After cooling to ~5°C, the product was filtered, washed with IPAc (522 g) and dried under vac at 20-30 °C to afford the weakly crystalline **Compound 70a** as a white solid (91.0% yield, 115.4 g). (Note: A small amount of seed material used in the reaction was obtained via an analogous reaction protocol on small-scale.)

Recrystallisation: A solution of weakly crystalline **Compound 70a** (100 g), EtOH (166 g), purified water (21.5 g) and IPAc (178 g) was stirred at 20 to 30°C for 0.5-2 h to get a clear solution. Extra IPAc (522 g) was added dropwise over 1~2 h, and then the mixture was seeded with crystalline **Compound 70a** seed (2 g, 2% seed load). Then the mixture was aged for 18 ~20 h, IPAc (348 g) was added slowly over 12 h at between 20 to 30°C, and the slurry was stirred for an additional 55~60 h. The product was filtered, washed with IPAc (158 g) and dried *in vacuo* at 20~30°C to afford **Compound 70a** as a white solid (85% yield, 85.0 g, net).

^{1}HNMR (DMSO-*d*$_6$, 400MHz): δ = 11.60 (1H, brs), 10.8 (1H, brs), 8.52 (1H, s), 7.36 (3H, m), 3.97-4.20 (7H, m), 3.64-3.71 (4H, m), 3.47 (7H, m), 3.25 (2H, m), 3.05 (3H, m), 2.73 (3H, s), 2.10-2.45 (1H, m), 1.99 (1H, m), 1.78 (2H, m), 1.55 (2H, m), 0.83-1.12 (12H, m), 0.70 (2H, m).

LCMS (Method 7): R_t = 0.669 min, m/z found 600.5 $[M+H]^+$.

Compound 83, 84, 94, 95, 88, 89, 99, 100, 250, 251, 252, 254, 258, 396, 402

(*R)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)pyridazin-3-yl)oxy)benzamide oxalate

(*S)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)pyridazin-3-yl)oxy)benzamide oxalate

(*R)-5-fluoro-*N*,*N*-diisopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide oxalate

(*S)-5-fluoro-*N*,*N*-diisopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide oxalate

(*R)-5-fluoro-*N*,*N*-diisopropyl-2-((4-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)pyridazin-3-yl)oxy)benzamide oxalate

(*S)-5-fluoro-*N*,*N*-diisopropyl-2-((4-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)pyridazin-3-yl)oxy)benzamide oxalate

(*R)-5-fluoro-*N*,*N*-diisopropyl-2-((5-(2-(6-((2-methoxyethyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide oxalate

(*S)-5-fluoro-*N*,*N*-diisopropyl-2-((5-(2-(6-((2-methoxyethyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide oxalate

***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((*R*)-6-(((*R)-2-methoxypropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide oxalate**

***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((*R*)-6-(((*S)-2-methoxypropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide oxalate**

***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((3*R*)-6-((2-methoxypropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide oxalate**

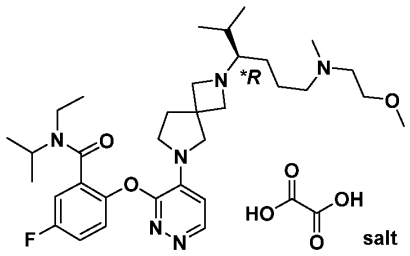
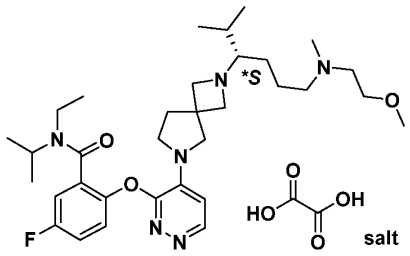
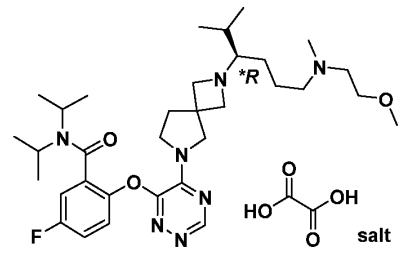
***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((3*S*)-6-((2-methoxypropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide oxalate**

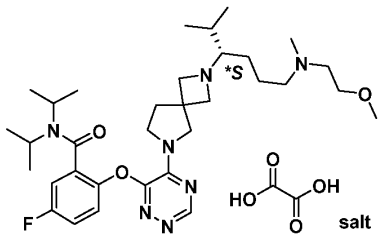
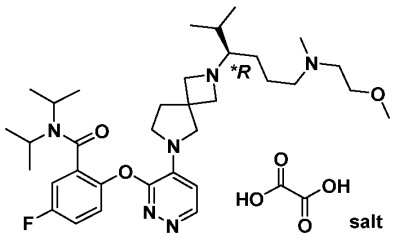
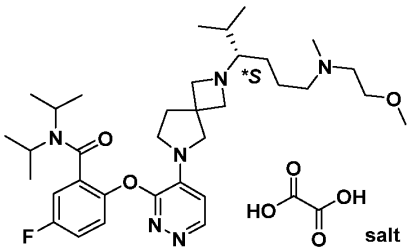
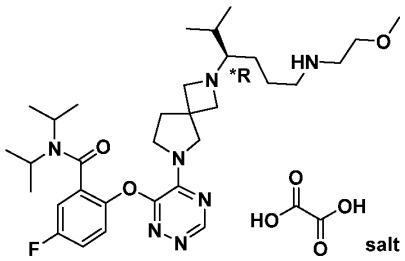
(*R*)-2-((5-(2-(6-((2-ethoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide oxalate

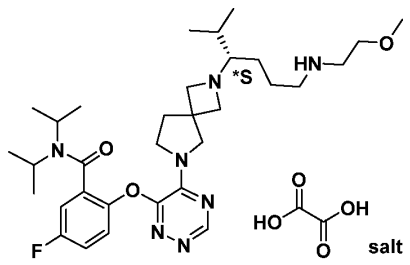
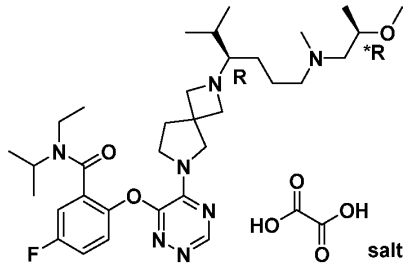
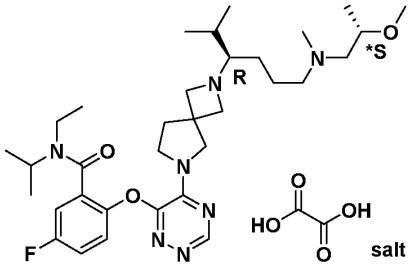
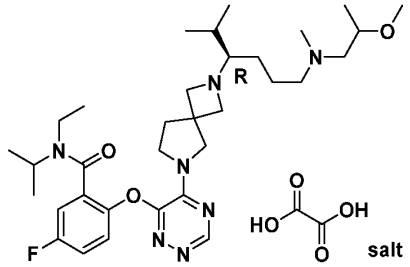
(*R)-2-((5-(2-(6-(dimethylamino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide oxalate

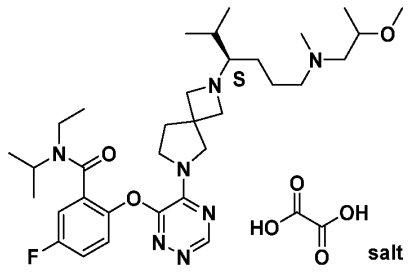
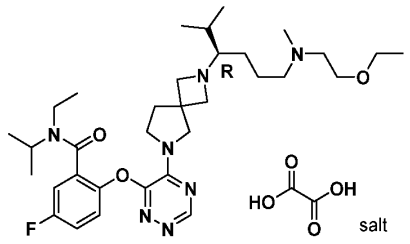
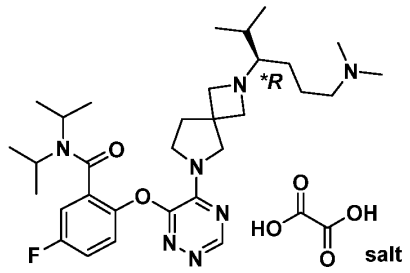
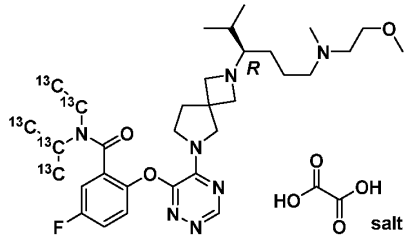
(*R*)-*N*-(ethyl-$^{13}C_2$)-5-fluoro-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(propan-2-yl-$^{13}C_3$)benzamide oxalate

The following Compounds were synthesized by an analogous method described above for Compound 70

Co. No.	Structure	Starting Materials	Spectra Details
83		Compound 107, oxalic acid	**LC-MS (ESI) (Method 3):** R_t = 5.034 min, m/z found 599.3 $[M+H]^+$. **Chiral HPLC (Method 2):** R_t = 8.596 min.
84		Compound 108, oxalic acid	**LC-MS (ESI) (Method 3):** R_t = 4.957 min, m/z found 599.3 $[M+H]^+$. **Chiral HPLC (Method 2):** R_t = 9.726 min.
94		Compound 109, oxalic acid	**LC-MS (ESI) (Method 2):** R_t = 2.431 min, m/z found 614.5 $[M+H]^+$. **Chiral HPLC (Method 3):** R_t = 4.967 min.

Co. No.	Structure	Starting Materials	Spectra Details
95		Compound 110, oxalic acid	**LC-MS (ESI) (Method 2):** R_t = 2.471 min, m/z found 614.5 $[M+H]^+$. **Chiral HPLC (Method 3):** R_t = 5.947 min.
88		Compound 117, oxalic acid	**LC-MS (ESI) (Method 1):** R_t = 2.243 min, m/z found 613.4 $[M+H]^+$. **Chiral HPLC (Method 5):** R_t = 4.873 min.
89		Compound 118, oxalic acid	**LC-MS (ESI) (Method 1):** R_t = 2.271 min, m/z found 613.3 $[M+H]^+$. **Chiral HPLC (Method 5):** R_t = 5.947 min.
99		Compound 115, oxalic acid	**LC-MS (ESI) (Method 2):** R_t = 2.224 min, m/z found 600.3 $[M+H]^+$. **Chiral HPLC (Method 6):** R_t = 3.810 min.

Co. No.	Structure	Starting Materials	Spectra Details
100		Compound 116, oxalic acid	**LC-MS (ESI) (Method 2):** R_t = 2.21 min, m/z found 600.4 $[M+H]^+$. **Chiral HPLC (Method 6):** R_t = 5.322 min.
250		Compound 248, oxalic acid	**LC-MS (ESI) (Method 1):** R_t = 3.107 min, m/z found 614.4 $[M+H]^+$. **SFC (Method 16):** R_t = 4.082 min.
251		Compound 249, oxalic acid	**LC-MS (ESI) (Method 1):** R_t = 3.141 min, m/z found 614.4 $[M+H]^+$. **SFC (Method 16):** R_t = 4.287 min.
252		Compound 247, oxalic acid	**LC-MS (ESI) (Method 1):** R_t = 3.011 min, m/z found 614.4 $[M+H]^+$.

Co. No.	Structure	Starting Materials	Spectra Details
254		Compound 253, oxalic acid	**LC-MS (ESI) (Method 1):** R_t = 3.054 min, m/z found 614.4 $[M+H]^+$.
258		Compound 257, oxalic acid	**LC-MS (ESI) (Method 2):** R_t = 2.047 min, m/z found 614.4 $[M+H]^+$. **SFC (Method 16):** R_t = 4.345 min.
396		Compound 105, oxalic acid	**LC-MS (ESI) (Method 2):** R_t = 2.071 min, m/z found 570.3 $[M+H]^+$. **SFC (Method 4):** R_t = 1.364 min.
402		Compound 401, oxalic acid	**LC-MS (ESI) (Method 5):** R_t = 1.500 min, m/z found 605.3 $[M+H]^+$.

Compound 13, 16, 71, 136, 139, 153, 156, 160, 164, 166, 169, 173, 274, 275, 276, 279, 282, 285, 178, 180, 190, 192, 194, 196, 198, 200, 202, 204, 310, 311, 312, 313, 318, 329, 360, 375, 376, 379, 380, 383, 388, 411

(*R*)-2-((5-(2-(6-((2-cyanoethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

(*R*)-2-((5-(2-(6-((2,2-difluoroethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

(*R*)-*N*-ethyl-2-((5-(2-(6-(ethyl(2-methoxyethyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide

(*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(6-((2-methoxy-2-methylpropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide

(*R*)-*N*-ethyl-5-fluoro-2-((5-(2-(6-((2-hydroxy-2-methylpropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide

***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((*R*)-6-(((*R*)-1-methoxypropan-2-yl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide**

***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((*R*)-6-(((*S*)-1-methoxypropan-2-yl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide**

(*R*)-2-((5-(2-(6-((1,3-dimethoxypropan-2-yl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

***N*-ethyl-5-fluoro-2-((5-(2-((*R*)-6-(((*R*)-1-hydroxy-3-methoxypropan-2-yl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide**

***N*-ethyl-5-fluoro-2-((5-(2-((*R*)-6-(((*S*)-1-hydroxy-3-methoxypropan-2-yl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide**

***N*-ethyl-5-fluoro-2-((5-(2-((3*R*)-6-((3-hydroxy-2-methoxypropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide**

2-((5-(2-((3*R*)-6-((2,3-dimethoxypropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

(R*)-*N*-ethyl-5-fluoro-2-((5-(2-(1-((3-hydroxypropyl)(methyl)amino)-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide**

(R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(1-((3-methoxypropyl)(methyl)amino)-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide**

(R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(1-((2-methoxyethyl)(methyl)amino)-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide**

(R*)-2-((5-(2-(1-((3-amino-3-oxopropyl)(methyl)amino)-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide**

***N*-ethyl-5-fluoro-2-((5-(2-((*R*)-6-(((*R*)-2-hydroxy-3-methoxypropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide**

***N*-ethyl-5-fluoro-2-((5-(2-((*R*)-6-(((*S*)-2-hydroxy-3-methoxypropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide formate**

2-((5-(2-((3*R*)-6-((4-(dimethylamino)-4-oxobutan-2-yl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

2-((5-(2-((3*R*)-6-((3-(dimethylamino)-2-methyl-3-oxopropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((*R*)-2-methyl-6-(methyl((*R*)-4-(methylamino)-4-oxobutan-2-yl)amino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide**

***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((*R*)-2-methyl-6-(methyl((*S*)-4-(methylamino)-4-oxobutan-2-yl)amino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide**

***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((*R*)-2-methyl-6-(methyl((*R*)-2-methyl-3-(methylamino)-3-oxopropyl)amino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide**

_N_-ethyl-5-fluoro-_N_-isopropyl-2-((5-(2-((_R_)-2-methyl-6-(methyl((_S_)-2-methyl-3-(methylamino)-3-oxopropyl)amino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide

2-((5-(2-((*_R_)-6-(((_R_)-4-amino-4-oxobutan-2-yl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-_N_,_N_-diisopropylbenzamide

2-((5-(2-((*_R_)-6-(((_S_)-4-amino-4-oxobutan-2-yl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-_N_,_N_-diisopropylbenzamide

2-((5-(2-((*_R_)-6-(((_R_)-3-amino-2-methyl-3-oxopropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-_N_,_N_-diisopropylbenzamide

2-((5-(2-((*_R_)-6-(((_S_)-3-amino-2-methyl-3-oxopropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-_N_,_N_-diisopropylbenzamide

2-((5-(2-((3*_R_,5*_R_)-6-(dimethylamino)-5-methoxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-_N_-ethyl-5-fluoro-_N_-isopropylbenzamide

_N_-ethyl-2-((5-(2-((3*_R_,5*_R_)-6-(ethyl(methyl)amino)-5-methoxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-_N_-isopropylbenzamide

2-((5-(2-((3*_R_,5*_S_)-6-(dimethylamino)-5-methoxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-_N_-ethyl-5-fluoro-_N_-isopropylbenzamide

_N_-ethyl-2-((5-(2-((3*_R_,5*_S_)-6-(ethyl(methyl)amino)-5-methoxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-_N_-isopropylbenzamide

_N_-ethyl-5-fluoro-2-((5-(2-(5-hydroxy-6-(isopropyl(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-_N_-isopropylbenzamide

2-((5-(2-(6-(diethylamino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-_N_-ethyl-5-fluoro-_N_-isopropylbenzamide

2-((5-(2-(6-(dimethylamino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-_N_,_N_-diisopropylbenzamide

2-((5-(2-((3*_S_,5*_S_)-6-(dimethylamino)-5-methoxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-_N_-ethyl-5-fluoro-_N_-isopropylbenzamide

2-((5-(2-((3*S,5*R)-6-(dimethylamino)-5-methoxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

_N_-ethyl-2-((5-(2-((3*_S_,5*_S_)-6-(ethyl(methyl)amino)-5-methoxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-_N_-isopropylbenzamide

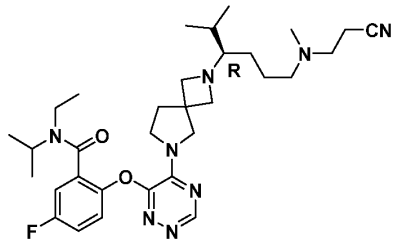
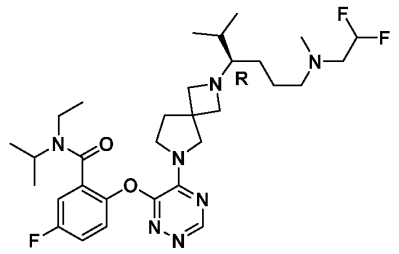
_N_-ethyl-2-((5-(2-((3*_S_,5*_R_)-6-(ethyl(methyl)amino)-5-methoxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-_N_-isopropylbenzamide

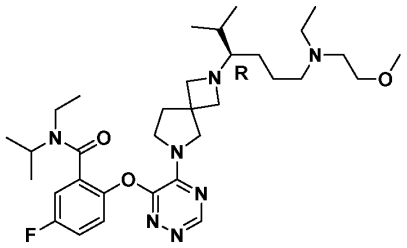
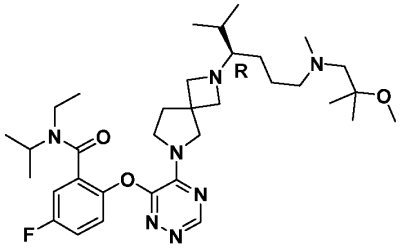
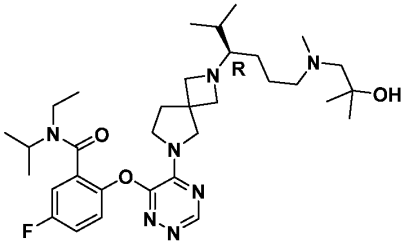
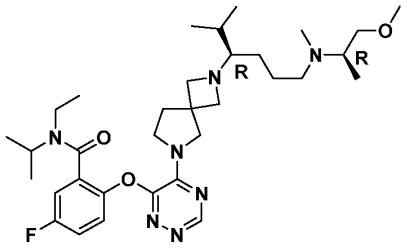
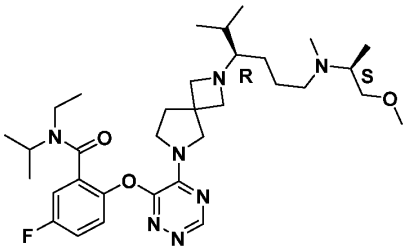
_N_-ethyl-5-fluoro-2-((5-(2-(5-hydroxy-2-methyl-6-(methyl(propyl)amino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-_N_-isopropylbenzamide

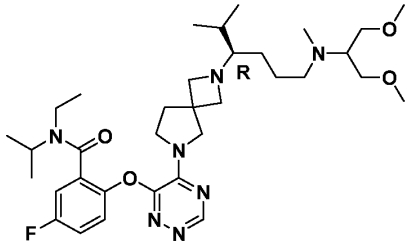
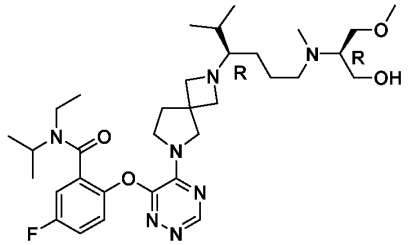
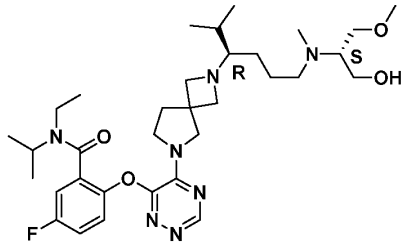
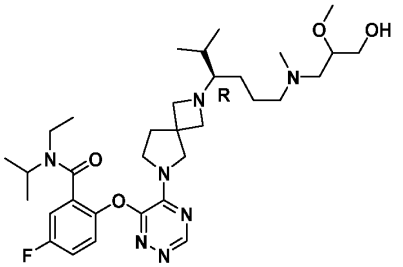
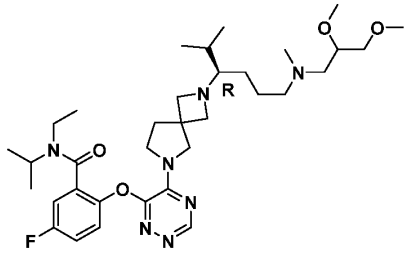
2-((5-(2-(6-(ethyl(methyl)amino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide

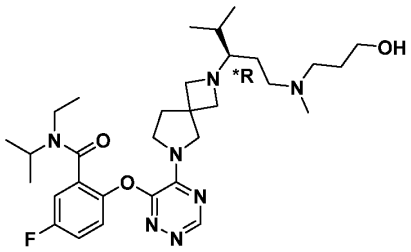
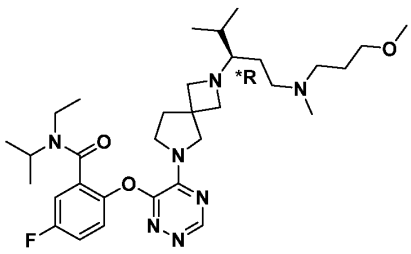
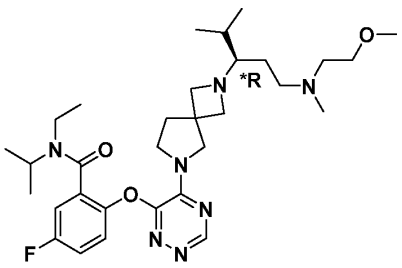
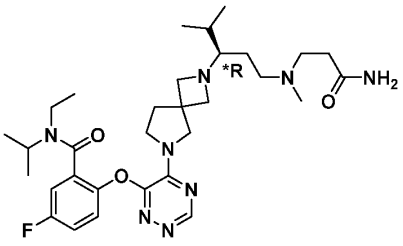
(*R*)-2-((3-chloro-5-(2-(6-(dimethylamino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide formate

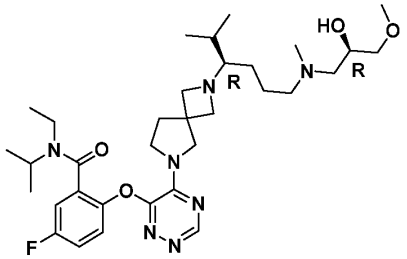
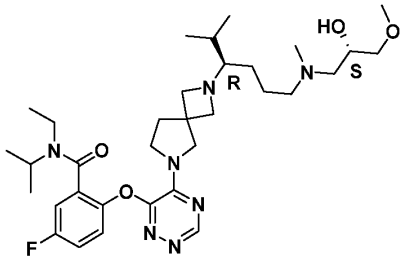
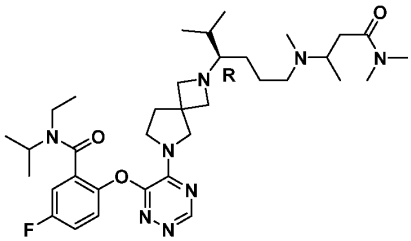
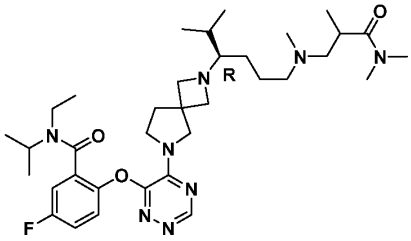
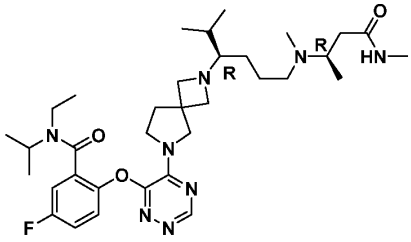
The following Compounds were synthesized by an analogous method described above for Compound 27 by method A

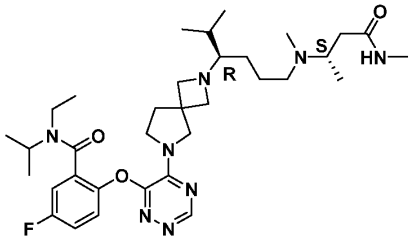
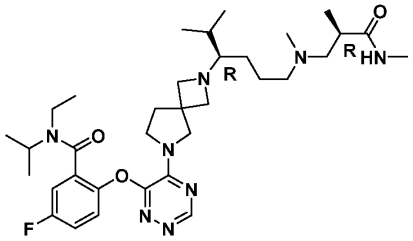
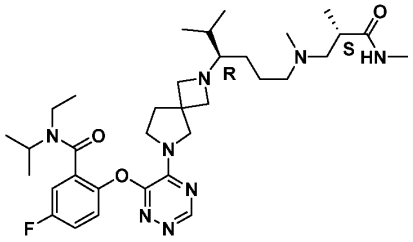
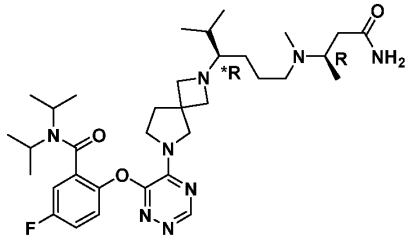
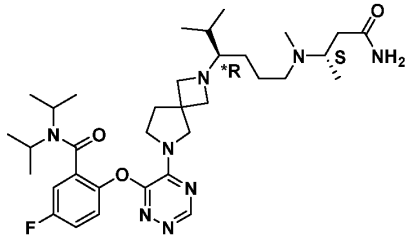
Co. No.	Structure	Starting Material	Spectra Details
13		Compound 12	**LC-MS (ESI) (Method 1):** R_t = 2.897 min, m/z found 595.3 $[M+H]^+$.
16		Compound 15	**LC-MS (ESI) (Method 2):** R_t = 1.893 min, m/z found 606.3 $[M+H]^+$.

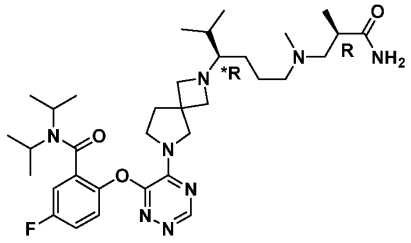
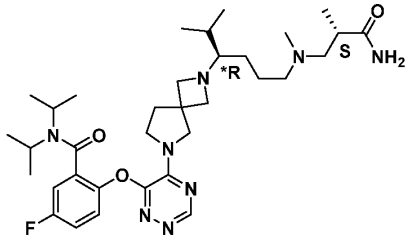
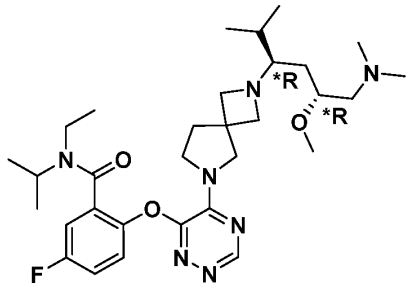
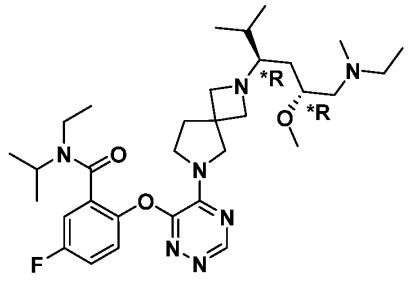
Co. No.	Structure	Starting Material	Spectra Details
71		Compound 11	**LC-MS (ESI) (Method 2):** R_t = 2.002 min, m/z found 614.4 $[M+H]^+$. **SFC (Method 6):** R_t = 1.382 min.
136		Compound 134	
139		Compound 138	
153		Compound 111	
156		Compoun 155	

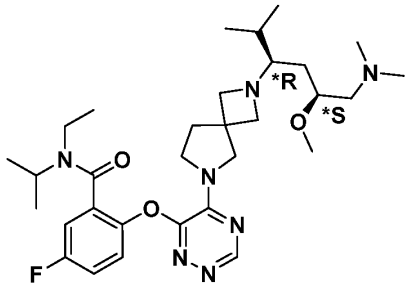
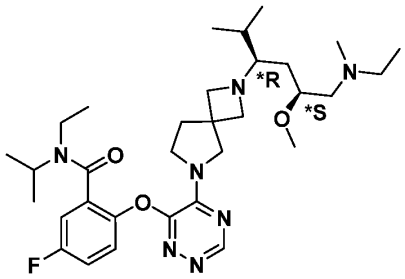
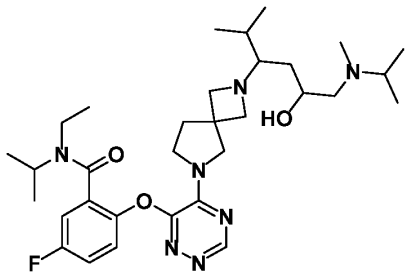
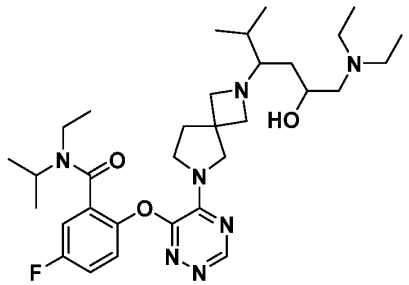
Co. No.	Structure	Starting Material	Spectra Details
160		Compound 158	
164		Compound 162	
166		Compound 163	
169		Compound 168	
173		Compound 171	

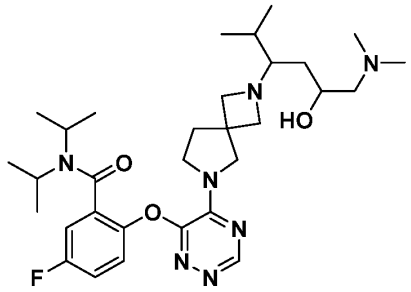
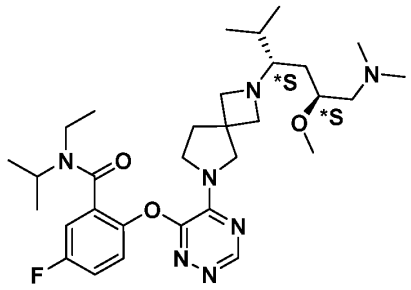
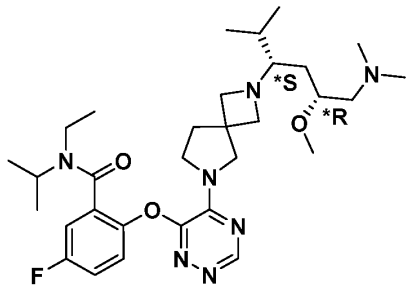
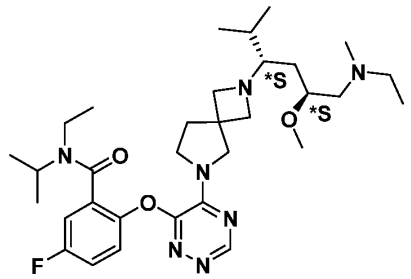
Co. No.	Structure	Starting Material	Spectra Details
274		Compound 273	**LC-MS (ESI) (Method 1):** R_t = 2.969 min, m/z found 586.3 $[M+H]^+$. **SFC (Method 13):** R_t = 2.031 min.
275		Compound 271	**LC-MS (ESI) (Method 2):** R_t = 2.031 min, m/z found 600.3 $[M+H]^+$. **SFC (Method 3):** R_t = 3.479 min.
276		Compound 227	**LC-MS (ESI) (Method 6):** R_t = 2.98 min, m/z found 586.2 $[M+H]^+$.
279		Compound 277	

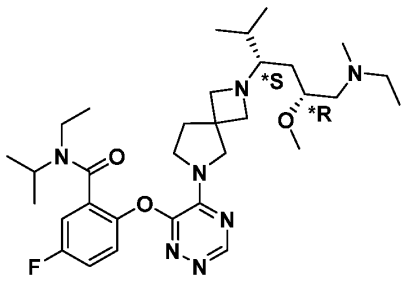
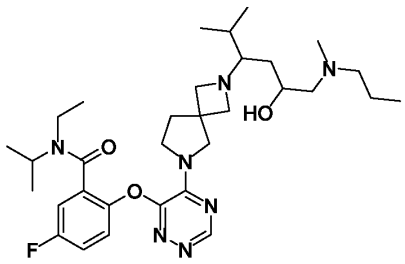
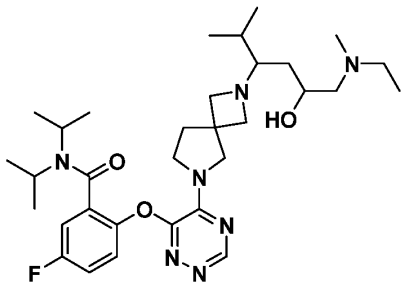
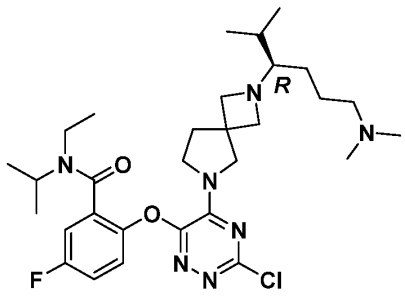
Co. No.	Structure	Starting Material	Spectra Details
282		Compound 281	
285	 formate salt	Compound 284	**LC-MS (ESI) (Method 3):** R_t = 4.980 min, m/z found 630.3 $[M+H]^+$. **SFC (Method 13):** R_t = 1.993 min.
178		Compound 288	
180		Compound 289	
190		Compound 290	

Co. No.	Structure	Starting Material	Spectra Details
192		Compound 291	
194		Compound 292	
196		Compound 293	
198		Compound 294	
200		Compound 295	

Co. No.	Structure	Starting Material	Spectra Details
202		Compound 296	
204		Compound 297	
310		Compound 308	
311		Compound 308	**LC-MS (ESI) (Method 2):** R_t = 2.032 min, m/z found 630.3 $[M+H]^+$. **SFC (Method 24):** R_t = 1.955 min.

Co. No.	Structure	Starting Material	Spectra Details
312		Compound 309	
313		Compound 309	**LC-MS (ESI) (Method 2):** R_t = 2.048 min, m/z found 630.3 $[M+H]^+$. **SFC (Method 24):** R_t = 1.937 min.
318		Compound 317	
329		Compound 328	

Co. No.	Structure	Starting Material	Spectra Details
360		Compound 359	
375		Compound 373	
376		Compound 374	
379		Compound 373	**LC-MS (ESI) (Method 2):** R_t = 2.039 min, m/z found 600.3 $[M+H]^+$. **SFC (Method 24):** R_t = 1.907 min.

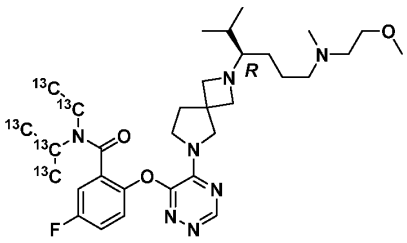
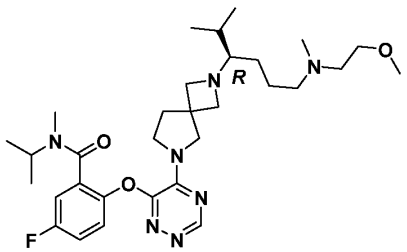
Co. No.	Structure	Starting Material	Spectra Details
380		Compound 374	**LC-MS (ESI) (Method 2):** R_t = 2.047 min, m/z found 600.3 $[M+H]^+$. **SFC (Method 24):** R_t = 1.922 min.
383		Compound 317	
388		Compound 359	
411	 formate salt	Compound 406	**LC-MS (ESI) (Method 2):** R_t = 2.376 min, m/z found 590.3 $[M+H]^+$. **SFC (Method 13):** R_t = 1.823 min.

Compound 401, 415

(*R*)-*N*-(ethyl-$^{13}C_2$)-5-fluoro-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(propan-2-yl-$^{13}C_3$)benzamide

(*R*)-5-fluoro-*N*-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-methylbenzamide

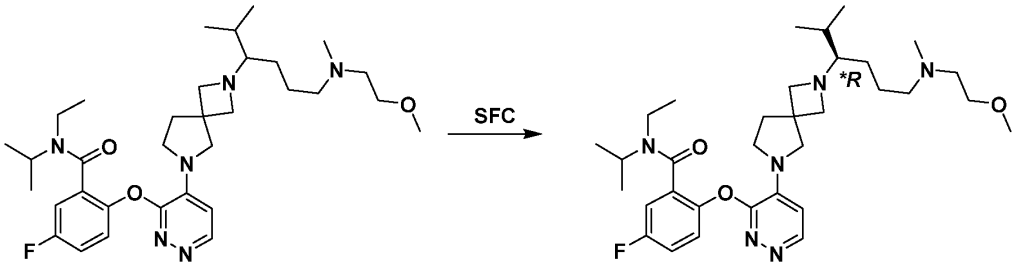
The following compounds were synthesized by an analogous method described above for Compound 27 by method C

Co. No.	Structure	Starting Material	Spectra Details
401		Compound 400	
415		Compound 414	**LC-MS (ESI) (Method 1):** R_t = 2.851 min, m/z found 586.5 $[M+H]^+$. **SFC (Method 13):** R_t = 1.772 min.

Compound 107, 108

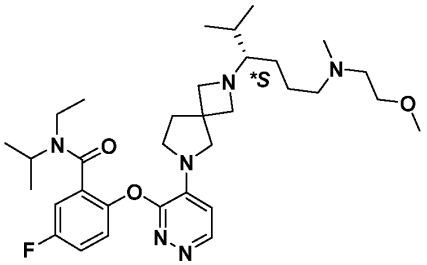
(*R)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)pyridazin-3-yl)oxy)benzamide

(*S)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)pyridazin-3-yl)oxy)benzamide



Compound 82 **Compound 107**

+



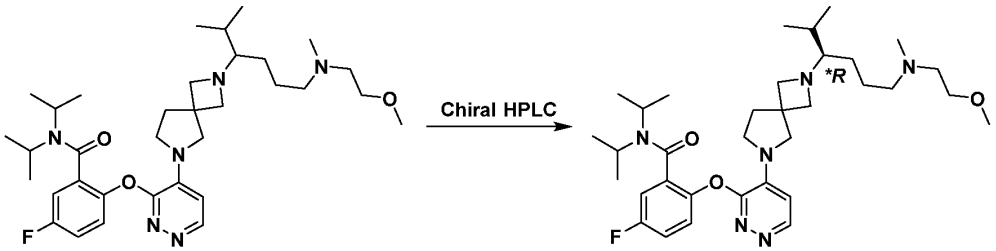
Compound 108

N-ethyl-5-fluoro-*N*-isopropyl-2-((4-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)pyridazin-3-yl)oxy)benzamide (**Compound 82**) (47.0 mg) was purified by SFC over DAICEL CHIRALPAK IE (column: 250x30mm 10um; eluent: 100% MeOH (0.1% ammonia); flowrate: 25 ml/min) to afford the title compounds **Compound 107** (19.0 mg, 40%) and **Compound 108** (21.2 mg, 45%) as white solid.

Compound 117, 118

(*R)-5-fluoro-*N*,*N*-diisopropyl-2-((4-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)pyridazin-3-yl)oxy)benzamide

(*S)-5-fluoro-*N*,*N*-diisopropyl-2-((4-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)pyridazin-3-yl)oxy)benzamide



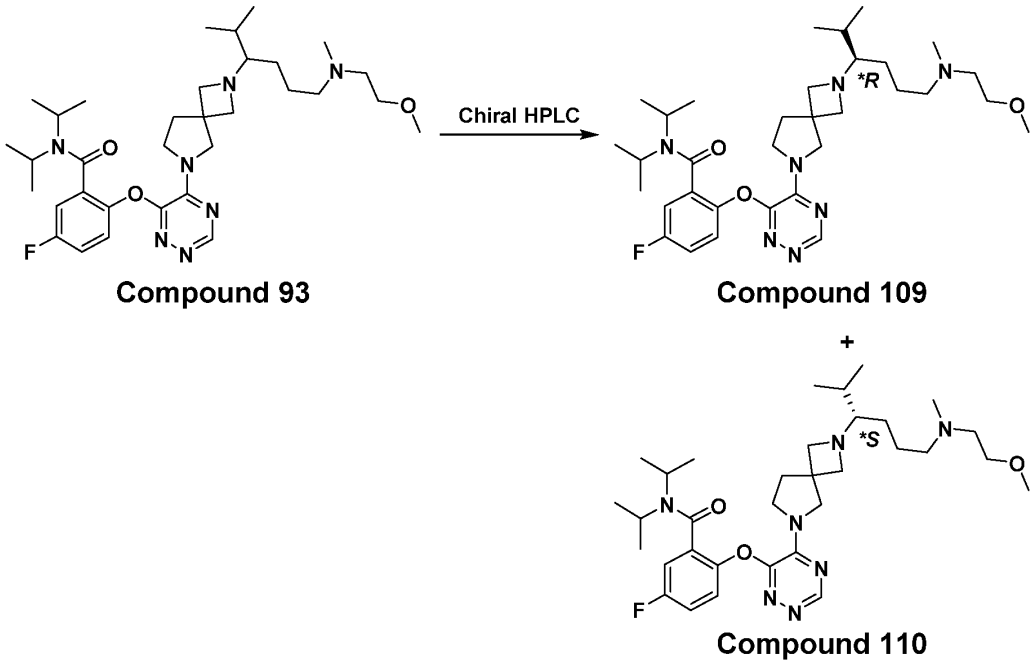
Compound 87 **Compound 117** + **Compound 118**

5-fluoro-*N*,*N*-diisopropyl-2-((4-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)pyridazin-3-yl)oxy)benzamide (**Compound 87**) (300 mg) was purified by chiral HPLC over CHIRALPAK AD-H (column: 5×25 cm, 10 um; Isocratic elution: n-Hexane/EtOH/DEA =90/10/0.1 (v/v/v); Flow rate: 60 mL/min, Temperature: 35 °C) to afford the title compounds **Compound 117** (122.8 mg) and **Compound 118** (137.0 mg) both as white solid.

Compound 109, 110

(R*)-5-fluoro-*N*,*N*-diisopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide**

(S*)-5-fluoro-*N*,*N*-diisopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide**

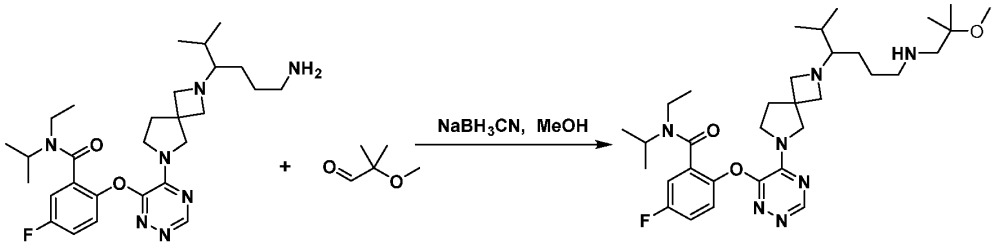


Compound 93 Compound 109 + Compound 110

5-fluoro-*N*,*N*-diisopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide (**Compound 93**) (110 mg) was first separated by preparative chiral HPLC over DAICEL CHIRALPAK AD (column: 5×25 cm 10 um; Mobile phase: A: n-Hexane, B: Ethanol/DEA=10/0.1(v/v), A:B=90:10 at 60 mL/min; Column Temp: 38 °C) and further purified by preparative HPLC using Phenomenex Gemini NX (column: 75x30 mm 3um; Mobile Phase A: water (0.05% NH_3H_2O+10mM NH_4HCO_3), B: ACN, gradient from 50% B to 80% B; Flow rate: 25 mL/min) to afford the title compounds **Compound 109** (27 mg) and **Compound 110** (27 mg).

Compound 69

***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(6-((2-methoxy-2-methylpropyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide**



$NaBH_3CN$ (42 mg, 0.666 mmol) was added to a mixture of 2-((5-(2-(6-amino-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-

isopropylbenzamide (**Compound 3**) (200 mg, 0.333 mmol) and 2-methoxy-2-methylpropanal (72 mg, 0.333 mmol) in MeOH (5 mL) and the reaction mixture was stirred at RT overnight. The reaction mixture was diluted with DCM and basified with 10% aq. K_2CO_3 solution. The organic layer was decanted, filtered through Chromabond® and evaporated to dryness. The residue was purified twice by chromatography over silica gel (iregular SiOH, 24g; mobile phase: gradient from 0.3% NH4OH, 3% MeOH, 97% DCM to 1% NH4OH, 10% MeOH, 90% DCM). The pure fractions were collected and evaporated to dryness to afford the title compound (68 mg, 33% yield).

LC-MS (ESI) (Method 4): R_t = 2.39 min, m/z found 614.8 $[M+H]^+$.

Compound 14, 17, 255, 82, 87

(*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(2-methyl-6-((3,3,3-trifluoropropyl)amino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide

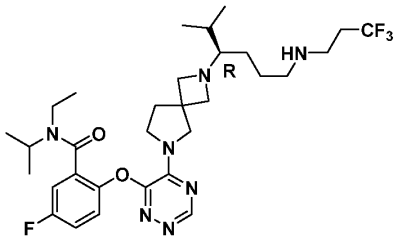
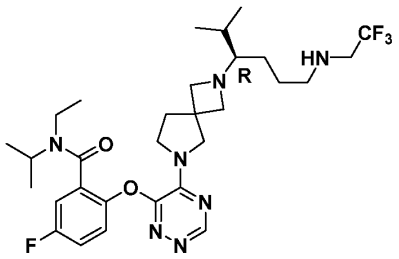
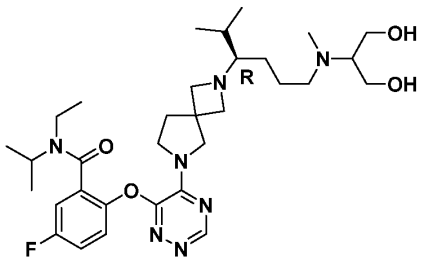
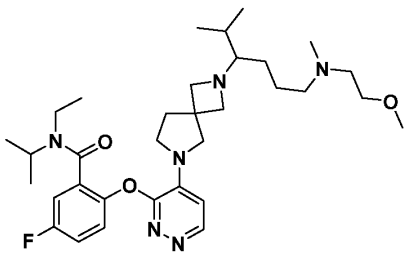
(*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(2-methyl-6-((2,2,2-trifluoroethyl)amino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide

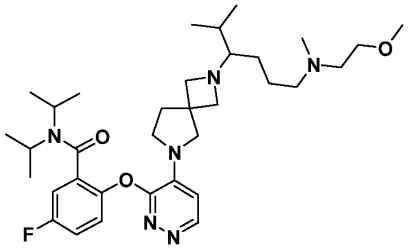
(*R*)-2-((5-(2-(6-((1,3-dihydroxypropan-2-yl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

***N*-ethyl-5-fluoro-*N*-isopropyl-2-((4-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)pyridazin-3-yl)oxy)benzamide**

5-fluoro-*N*,*N*-diisopropyl-2-((4-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)pyridazin-3-yl)oxy)benzamide

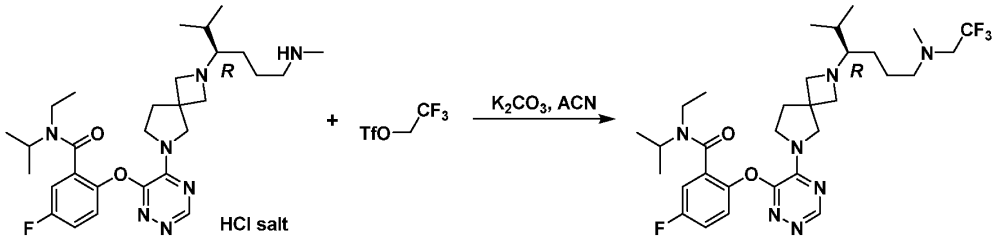
The following Compounds were synthesized by an analogous method described above for Compound 69

Ex. No.	Structure	Starting Materials	Conditions	Spectra Details
14		Compound 64, 3,3,3-trifluoro-propanal	$ZnCl_2$, $NaBH_3CN$, MeOH, RT	**LC-MS (ESI) (Method 2)**: R_t = 2.145 min, m/z found 624.3 $[M+H]^+$.
17		Compound 64, 2,2,2-trifluoro-acetal-dehyde	$ZnCl_2$, $NaBH_3CN$, MeOH, 80 °C	**LC-MS (ESI) (Method 2):** R_t = 2.085 min, m/z found 610.3 $[M+H]^+$.
255		Compound 19, 1,3-dihydroxy-propan-2-one	$ZnCl_2$, $NaBH_3CN$, MeOH, 45 °C	
82		Compound 80, 1,1,2-trimethoxy-ethane, HCl	$NaBH_3CN$, AcOH, EtOH	

Ex. No.	Structure	Starting Materials	Conditions	Spectra Details
87		Compound 86, 1,1,2-trimethoxyethane, HCl	$NaBH_3CN$, AcOH, EtOH	

Compound 21

(*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(2-methyl-6-(methyl(2,2,2-trifluoroethyl)amino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide



The mixture of (*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(2-methyl-6-(methylamino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide hydrochloride (**Compound 19**) (50 mg, 0.086 mmol), 2,2,2-trifluoroethyl trifluoromethanesulfonate (60.2 mg, 0.259 mmol) and K_2CO_3 (112 mg, 0.865 mmol) in ACN (1 mL) was stirred at RT for 16 h. The reaction mixture was filtered and the filtrate was purified by preparative HPLC over Phenomenex Gemini-NX (column: 80x40mm 3um, Mobile Phase A: water (0.05% ammonia + 10mM NH_4HCO_3), Mobile Phase B: ACN, Flow rate: 25 mL/min, gradient condition B/A from 52% B to 82%) to afford the title compound (12.06 mg, 97% purity, 22% yield) as brown oil.

LC-MS (ESI) (Method 2): R_t = 2.345 min, m/z found 624.3 $[M+H]^+$.

Compound 15, 23, 247, 253

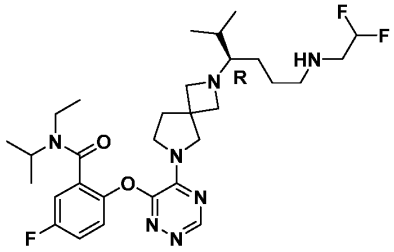
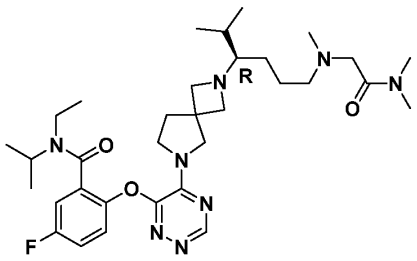
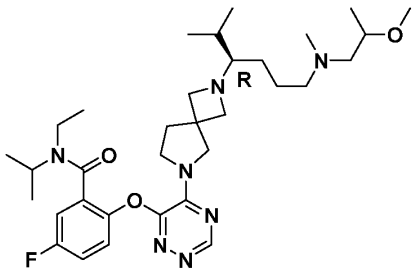
(*R*)-2-((5-(2-(6-((2,2-difluoroethyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

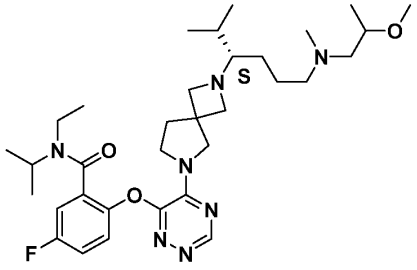
(*R*)-2-((5-(2-(6-((2-(dimethylamino)-2-oxoethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

5 *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((3*R*)-6-((2-methoxypropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide

***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((3*S*)-6-((2-methoxypropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide**

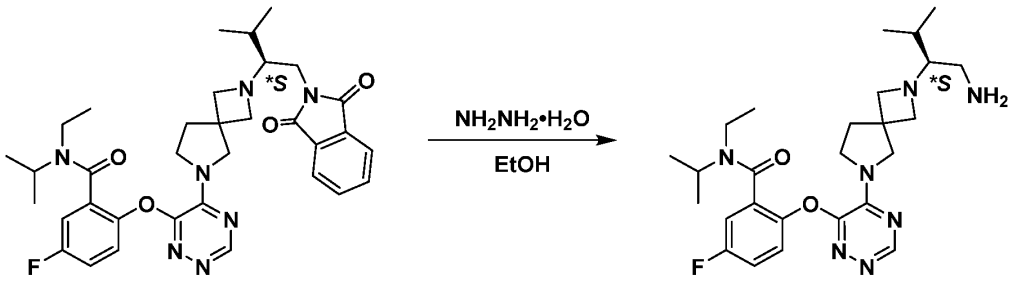
10 The following Compounds were synthesized by an analogous method described above for Compound 21

Co. No.	Structure	Starting Materials	Conditions	Spectra Details
15		Compound 65, 2,2-difluoroethyl trifluoro-methane-sulfonate	DIEA, DMF, 40 °C	**LC-MS (ESI) (Method 2):** R_t = 3.025 min, m/z found 592.3 $[M+H]^+$.
23		Compound 19, 2-chloro-*N*,*N*-dimethyl-acetamide	K_2CO_3, MeOH	**LC-MS (ESI) (Method 1):** R_t = 2.875 min, m/z found 627.3 $[M+H]^+$.
247		Compound 19, intermediate 139	Cs_2CO_3, NaI, DMF	

Co. No.	Structure	Starting Materials	Conditions	Spectra Details
253		Compound 20, intermediate 139	Cs_2CO_3, NaI, DMF	

Compound 24

(*S)-2-((5-(2-(1-amino-3-methylbutan-2-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide



To a solution of (*S)-2-((5-(2-(1-(1,3-dioxoisoindolin-2-yl)-3-methylbutan-2-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (**intermediate 18**) (0.05 g, 0.079 mmol) in EtOH (2 mL) was added hydrazinium hydroxide (0.127 g, 3.97 mmol). The resulting mixture was stirred at 25 °C for 8 h. The reaction was concentrated under reduced pressure and the residue was purified by preparative HPLC over Boston Prime (column: C18 150x30mm 5um, Mobile Phase A: water (0.04% ammonia+10mM NH_4HCO_3), Mobile Phase B: ACN, Flow rate: 30 mL/min, gradient condition B/A from 25% to 55%) to afford the title compound (5.74 mg, 99.5% purity, 14.4% yield) as a white solid.

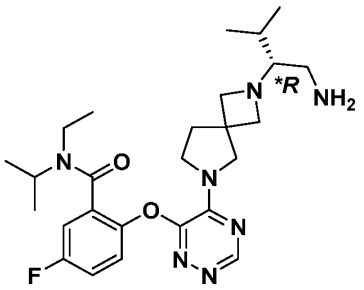
LC-MS (ESI) (Method 1): R_t = 2.94 min, m/z found 500.4 $[M+H]^+$.

SFC (Method 7): R_t = 5.183 min.

Compound 25

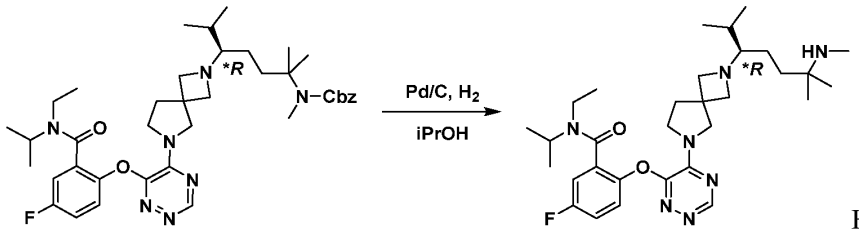
(*R)-2-((5-(2-(1-amino-3-methylbutan-2-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

The following Compound was synthesized by an analogous method described above for Compound 24

Co. No.	Structure	Starting Materials	Spectra Details
25		intermediate 17	**LC-MS (ESI) (Method 1):** R_t = 2.91 min, m/z found 500.4 $[M+H]^+$. **SFC (Method 7)**: R_t = 3.879 min.

Compound 35

(R*)-2-((5-(2-(2,6-dimethyl-6-(methylamino)heptan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride**



HCl salt

To the mixture of benzyl (**R*)-(5-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-2,6-dimethylheptan-2-yl)(methyl)carbamate (**intermediate 40**) (210 mg, 0.298 mmol) and HCl (18 μL, 0.22 mmol) in *i*-PrOH (5 mL) was added Pd/C (20 mg, 10%) under Ar. The resulting mixture was stirred at 25 °C for 12 h under H_2 (15 PSI) atmosphere. The mixture was filtered and the filtrate was concentrated under reduced pressure to give a crude product, which was further purified by preparative HPLC over Phenomenex Gemini-NX (column: 150x30mm 5um, Mobile Phase A: H_2O (0.05% HCl), Mobile Phase B: ACN, Flow rate: 35 mL/min, gradient condition B/A from 3% to 29%) to afford the title compound (170 mg, 98% purity, 92% yield) as a white solid.

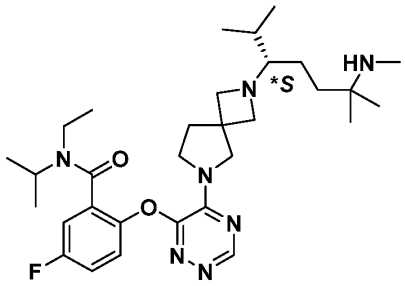
LC-MS (ESI) (Method 2): R_t = 2.040 min, m/z found 570.3 $[M+H]^+$.

SFC (Method 8): R_t = 2.145 min.

Compound 36

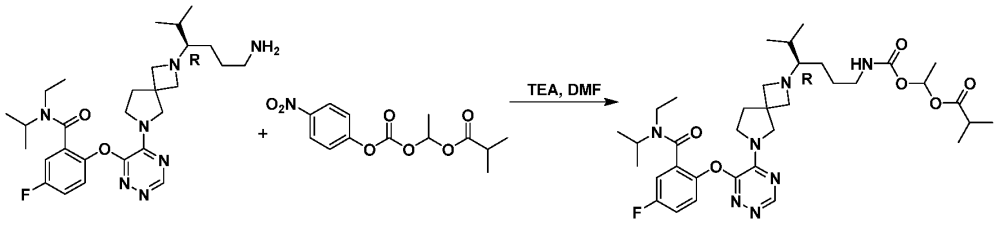
(*S)-2-((5-(2-(2,6-dimethyl-6-(methylamino)heptan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride

The following Compound was synthesized by an analogous method described above for Compound 35

Co. No.	Structure	Starting Materials	Spectra Details
36	 HCl salt	intermediate 41	**LC-MS (ESI) (Method 2):** R_t = 1.970 min, m/z found 570.3 $[M+H]^+$. **SFC (Method 8)**: R_t = 2.347 min.

Compound 39

1-((((*R*)-4-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-5-methylhexyl)carbamoyl)oxy)ethyl isobutyrate



The mixture of (*R*)-2-((5-(2-(6-amino-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (**Compound 64**) (150 mg, crude), 1-(((4-nitrophenoxy)carbonyl)oxy)ethyl isobutyrate (102 mg, 0.343 mmol) and TEA (144 mg, 1.42 mmol) in anhydrous DMF (5 mL) was stirred at 25 °C for 2 h. The mixture was concentrated under reduced pressure to give the crude product which was further purified by preparative HPLC over Boston Prime (column: C18 150x30mm 5um, Mobile Phase A: H_2O (0.04% ammonia+10mM NH_4HCO_3), Mobile Phase B: ACN, Flow rate: 25 mL/min, gradient condition B/A from 55% to 85%) to afford the title compound (82.20 mg) as a yellow solid.

LC-MS (ESI) (Method 1): R_t = 3.901 min, m/z found 686.3 $[M+H]^+$.

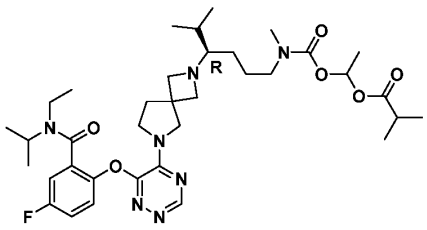
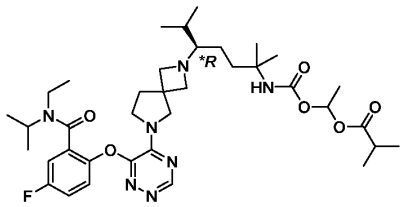
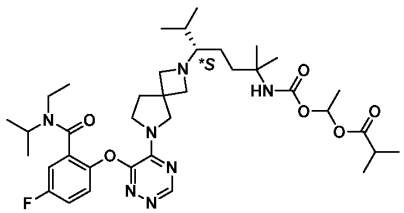
Compound 40, 41, 42

1-((((*R*)-4-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-5-methylhexyl)(methyl)carbamoyl)oxy)ethyl isobutyrate

1-((((R*)-5-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-2,6-dimethylheptan-2-yl)carbamoyl)oxy)ethyl isobutyrate formate**

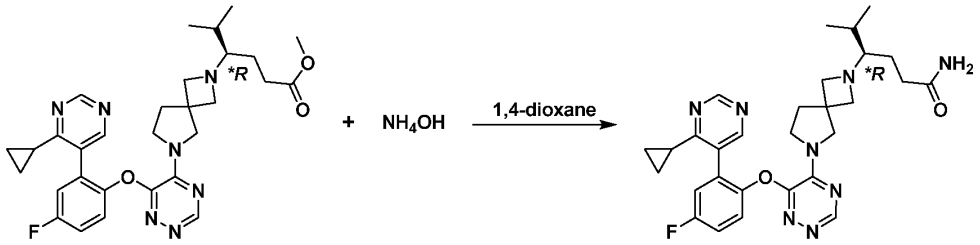
1-((((S*)-5-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-2,6-dimethylheptan-2-yl)carbamoyl)oxy)ethyl isobutyrate**

The following Compounds were synthesized by an analogous method described above for Compound 39

Co. No.	Structure	Starting Materials	Spectra Details
40		Compound 19	**LC-MS (ESI) (method 2):** R_t = 2.990 min, m/z found 700.3 $[M+H]^+$.
41	 formate salt	Compound 30	**LC-MS (ESI) (method 3)** R_t = 5.523 min, m/z found 714.3 $[M+H]^+$.
42		Compound 31	**LC-MS (ESI) (Method 3)**: R_t = 5.516 min, *m/z* found 714.4 $[M+H]^+$.

Compound 43

(R*)-4-(6-(6-(2-(4-cyclopropylpyrimidin-5-yl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-5-methylhexanamide**



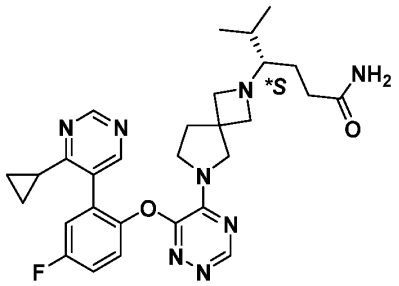
To the mixture of methyl (*R)-4-(6-(6-(2-(4-cyclopropylpyrimidin-5-yl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-5-methylhexanoate (**intermediate 48**) (110 mg, 0.178 mmol) in NH_4OH (10 mL) and 1,4-dioxane (5 mL) was added NH_4Cl (95 mg, 1.78 mmol). The resulting mixture was stirred at 40 °C for 16 h. After cooling to RT, the reaction mixture was concentrated *in vacuo* and the residue was purified by preparative HPLC using a Boston Prime (column: C18 150x30mm 5um; eluent: ACN/H_2O (0.04% ammonia+10mM NH_4HCO_3) from 30% to 60% (v/v)) to afford the title compound (34 mg, 34%) as a white solid.

LC-MS (ESI) (Method 1): R_t = 3.287 min, m/z found 547.2 $[M+H]^+$.

SFC (Method 9): R_t = 6.275 min.

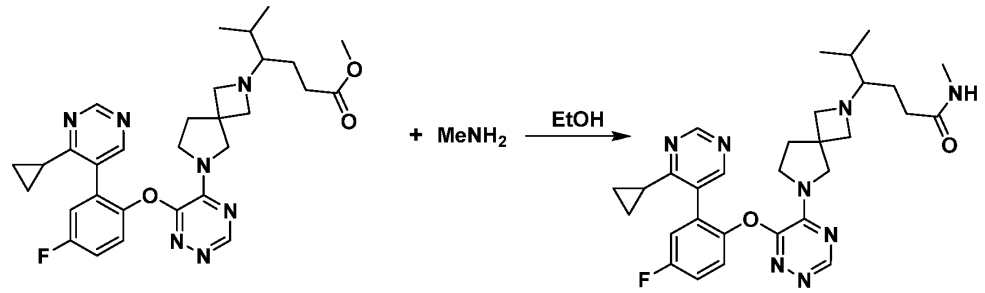
Compound 44

The following Compound was synthesized by an analogous method described above for Compound 43

Co. No.	Structure	Starting Materials	Spectra Details
44		intermediate 49	**LC-MS (ESI) (Method 1):** R_t = 3.292 min, m/z found 547.2 $[M+H]^+$. **SFC (Method 9)**: R_t = 7.506 min.

Compound 50

4-(6-(6-(2-(4-cyclopropylpyrimidin-5-yl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-*N*,5-dimethylhexanamide

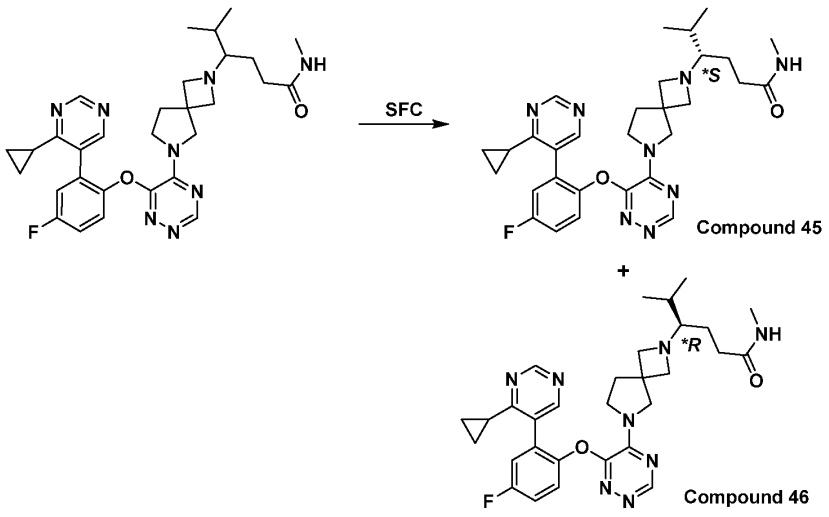


Methanamine hydrochloride (600 mg, 8.89 mmol) was added to a solution consisting of methyl 4-(6-(6-(2-(4-cyclopropylpyrimidin-5-yl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-5-methylhexanoate (**intermediate 47**) (500 mg, 0.890 mmol) in $MeNH_2$/EtOH (33%, 20 mL). The reaction mixture was stirred at 80 °C for 5 h. After cooling to RT, the reaction mixture was concentrated under reduced pressure to afford the crude product which was further purified by FCC (DCM/MeOH = 10:1) to afford the title compound (100 mg, 18% yield) as a yellow solid.

Compound 45 and 46

(*S)-4-(6-(6-(2-(4-cyclopropylpyrimidin-5-yl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-*N*,5-dimethylhexanamide

(*R)-4-(6-(6-(2-(4-cyclopropylpyrimidin-5-yl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-*N*,5-dimethylhexanamide



4-(6-(6-(2-(4-cyclopropylpyrimidin-5-yl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-*N*,5-dimethylhexanamide (**Compound 50**) (250 mg, 0.446 mmol) was purified by SFC over DAICEL CHIRALPAK AS (250x30 mm 10 um) (eluent: supercritical CO_2 in EtOH (0.1% v/v ammonia) 20/20, v/v) to afford the title compounds

Compound 45 (81.10 mg, 98% purity, 32% yield) and **Compound 46** (72.53 mg, 98% purity, 28% yield) both as white solid.

Compound 45

LC-MS (ESI) (Method 1): R_t = 3.323 min, m/z found 561.2 $[M+H]^+$.

SFC (Method 10): R_t = 3.880 min.

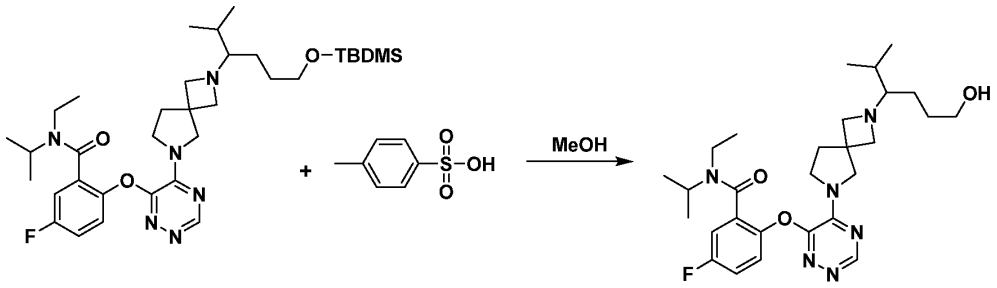
Compound 46

LC-MS (ESI) (Method 1): R_t = 3.353 min, m/z found 561.2 $[M+H]^+$.

SFC (Method 10): R_t = 3.707 min.

Compound 49

***N*-ethyl-5-fluoro-2-((5-(2-(6-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide**

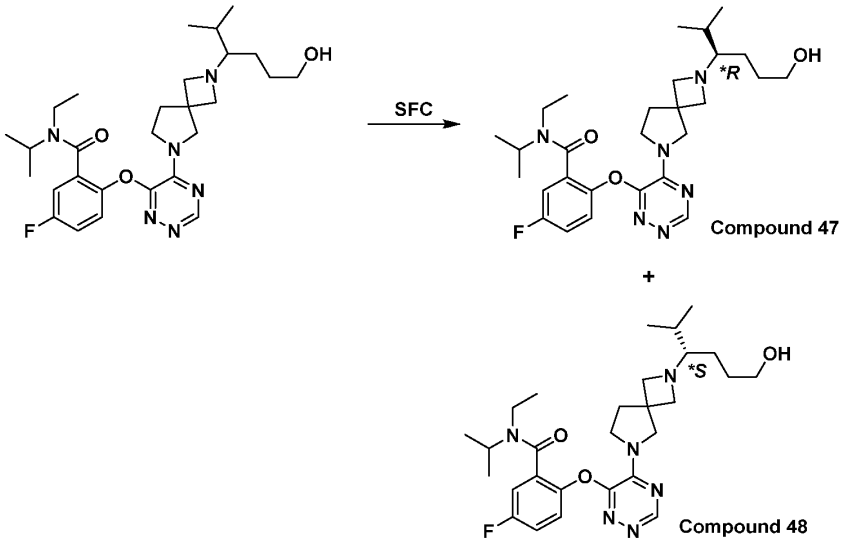


To the solution of 2-((5-(2-(6-((*tert*-butyldimethylsilyl)oxy)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (**intermediate 55**) (217 mg, 0.338 mmol) in MeOH (2 mL) was added 4-methylbenzenesulfonic acid (203 mg, 1.18 mmol). The reaction mixture was stirred at RT overnight. The mixture was concentrated under reduced pressure to give the crude product which was further purified by preparative HPLC using a Phenomenex Gemini NX-C18 (column: 75x30mm 3μm; eluent: ACN/H_2O (0.04% ammonia+10mM NH_4HCO_3) from 35% to 60% (v/v)) to afford the title compound (45 mg, 25% yield) as a white solid.

Compound 47 and 48

(R*)-*N*-ethyl-5-fluoro-2-((5-(2-(6-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide**

(S*)-*N*-ethyl-5-fluoro-2-((5-(2-(6-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide**



N-ethyl-5-fluoro-2-((5-(2-(6-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide (**Compound 49**) (45.0 mg, 0.0850 mmol) was further purified by SFC over DAICEL CHIRALPAK IG (250x30mm 10um) (eluent: 40% to 40% (v/v) supercritical CO_2 in EtOH with 0.1% ammonia) to afford the title compounds **Compound 47** (17.38 mg, 39% yield) and **Compound 48** (15.79 mg, 35% yield) both as a white solid.

Compound 47

LCMS (ESI) (Method 1): R_t = 3.240 min, m/z found 529.2 $[M+H]^+$.

SFC (Method 11): R_t = 4.778 min

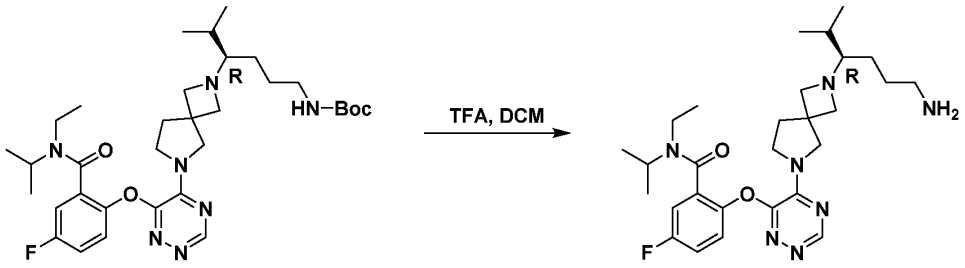
Compound 48

LCMS (ESI) (Method 1): R_t = 3.212 min, m/z found 529.3 $[M+H]^+$.

SFC (Method 11): R_t= 5.161min.

Compound 64

(*R*)-2-((5-(2-(6-amino-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

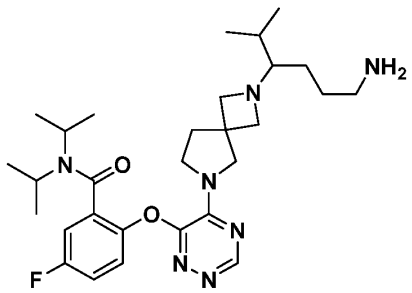


To the solution of *tert*-butyl (*R*)-(4-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-5-methylhexyl)carbamate (**Compound 62**) (550 mg, 0.876 mmol) in DCM (4 mL) was slowly added TFA (4 mL), and the resulting mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted in DCM (40 mL) and the pH value was adjusted to around 12 by aq. NaOH (2 M, 16 mL) solution. The aqueous layer was extracted with DCM (10 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford the title compound (460 mg, crude) as yellow solid, which was used directly in next step without further purification.

Compound 97

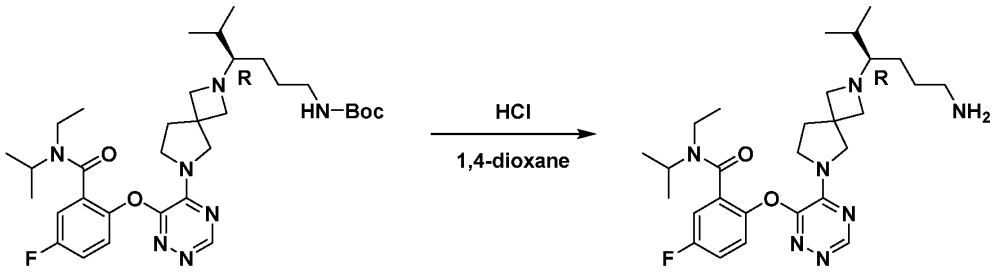
2-((5-(2-(6-amino-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide

The following compound was synthesized by an analogous method as described above for Compound 64

Co. No.	Structure	Starting Material
97		Compound 96

Compound 65

(*R*)-2-((5-(2-(6-amino-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride

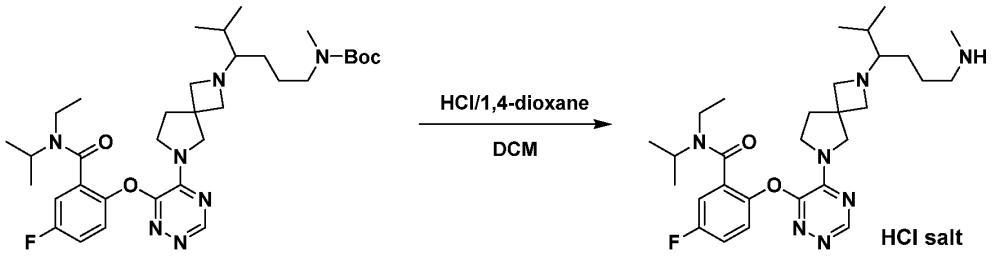


HCl salt

To the solution of *tert*-butyl (*R*)-(4-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-5-methylhexyl)carbamate (**Compound 62**) (250 mg, 0.398 mmol) in 1,4-dioxane (5 mL) was added a solution of 4M HCl in dioxane (10 mL, 40 mmol), the resulting mixture was stirred at RT for 16 h. The reaction mixture was concentrated *in vacuo* to afford the title compound (220 mg, crude, HCl salt) as yellow oil, which was used directly in next step without further purification.

Compound 67

***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(2-methyl-6-(methylamino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide hydrochloride**



To a solution of *tert*-butyl (4-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-5-methylhexyl)(methyl)carbamate (**Compound 60**) (1 g, 1.56 mmol) in DCM (10 mL) was added 4M HCl in dioxane (5 mL, 20 mmol), the resulting mixture was stirred at RT for 1 h. The reaction mixture was concentrated *in vacuo* to afford the title compound (960 mg, crude, HCl salt) which was used directly in next step without further purification.

Compound 66, 73, 92

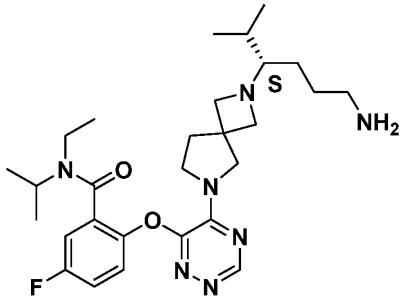
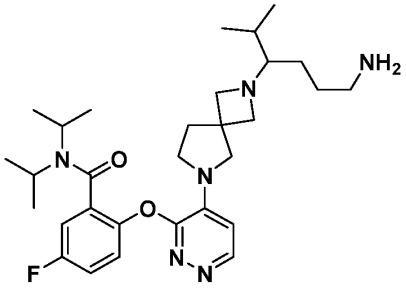
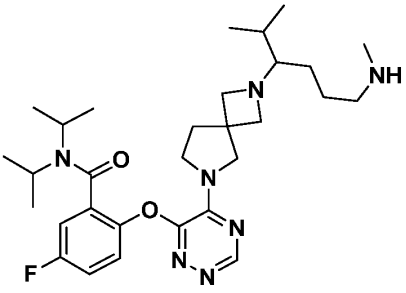
(*S*)-2-((5-(2-(6-amino-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide hydrochloride

2-((4-(2-(6-amino-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)pyridazin-3-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide hydrochloride

5-fluoro-*N*,*N*-diisopropyl-2-((5-(2-(2-methyl-6-(methylamino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide hydrochloride

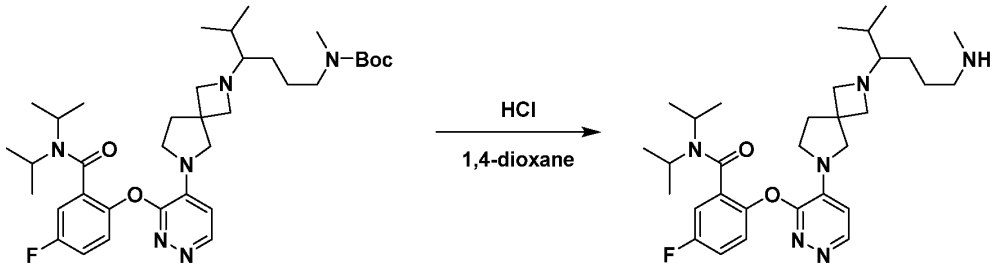
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The following compounds were synthesized by an analogous method as described above for Compound 65 and Compound 67

Co. No.	Structure	Starting Material
66	 HCl salt	Compound 63
73	 HCl salt	Compound 72
92	 HCl salt	Compound 91

Compound 86

5-fluoro-*N*,*N*-diisopropyl-2-((4-(2-(2-methyl-6-(methylamino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)pyridazin-3-yl)oxy)benzamide



To the solution of *tert*-butyl (4-(6-(3-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)pyridazin-4-yl)-2,6-diazaspiro[3.4]octan-2-yl)-5-methylhexyl)(methyl)carbamate (**Compound 85**) (1.0 g, 1.5 mmol) in 1,4-dioxane (10 mL) cooled at 0 °C was added a solution of 4M HCl in 1,4-dioxane (5 mL, 20 mmol) in portions. The resulting mixture was slowly warmed to 25 °C and stirred for 2 h. The reaction mixture was concentrated under reduced pressure to give a residue, which was re-dissolved in DCM (30 mL). Then, 1 M NaOH (20 mL) was added to adjust the pH value to about 12. The resulting mixture was further extracted with DCM (30 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford the title compound (1.26 g, crude) as a yellow solid, which was used directly in next step without further purification.

Compound 58, 59, 213, 234, 235, 260, 303, 79, 85, 91, 72, 96, 206, 316, 327, 338, 339, 348, 349, 358, 381, 399, 403

***tert*-butyl (5-(6-(6-(2-(4-cyclopropylpyrimidin-5-yl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-2,6-dimethylheptan-2-yl)carbamate**

***tert*-butyl (5-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-2,6-dimethylheptan-2-yl)carbamate**

***N*-ethyl-5-fluoro-2-((5-(2-(1-hydroxy-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide**

***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((5**R*)-6-((2-methoxyethyl)(methyl)amino)-2,5-dimethylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide**

***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((5**S*)-6-((2-methoxyethyl)(methyl)amino)-2,5-dimethylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide**

***N*-ethyl-5-fluoro-2-((5-(2-(6-hydroxy-2,4-dimethylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide**

tert-butyl (4-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-2-methoxy-5-methylhexyl)(methyl)carbamate

tert-butyl (4-(6-(3-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)pyridazin-4-yl)-2,6-diazaspiro[3.4]octan-2-yl)-5-methylhexyl)(methyl)carbamate

tert-butyl (4-(6-(3-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)pyridazin-4-yl)-2,6-diazaspiro[3.4]octan-2-yl)-5-methylhexyl)(methyl)carbamate

tert-butyl (4-(6-(6-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-5-methylhexyl)(methyl)carbamate

tert-butyl (4-(6-(3-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)pyridazin-4-yl)-2,6-diazaspiro[3.4]octan-2-yl)-5-methylhexyl)carbamate

tert-butyl (4-(6-(6-(2-(diisopropylcarbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-5-methylhexyl)carbamate

tert-butyl (5-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-6-methylheptyl)carbamate

tert-butyl (4-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-2-hydroxy-5-methylhexyl)(methyl)carbamate

tert-butyl ethyl(4-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-2-hydroxy-5-methylhexyl)carbamate

N-ethyl-2-((5-(2-((5*S*)-6-(ethyl(methyl)amino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide

N-ethyl-2-((5-(2-((5*R*)-6-(ethyl(methyl)amino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide

N-ethyl-5-fluoro-2-((5-(2-((5*S*)-5-hydroxy-6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide

N-ethyl-5-fluoro-2-((5-(2-((5*R*)-5-hydroxy-6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide

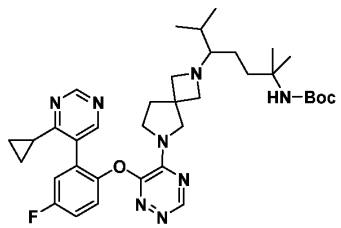
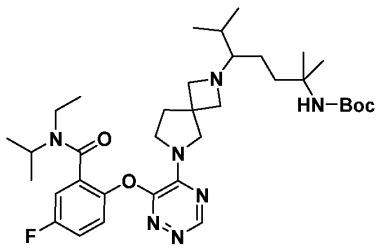
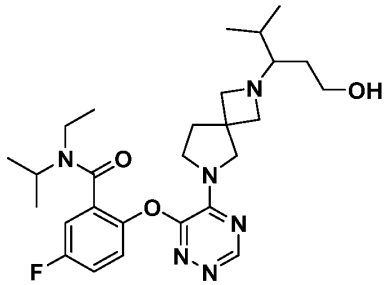
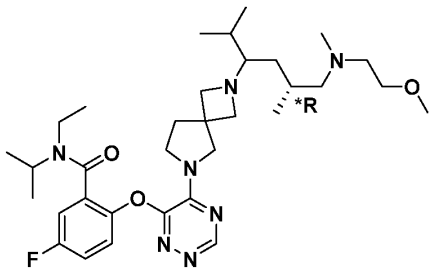
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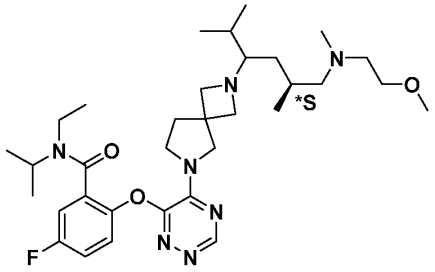
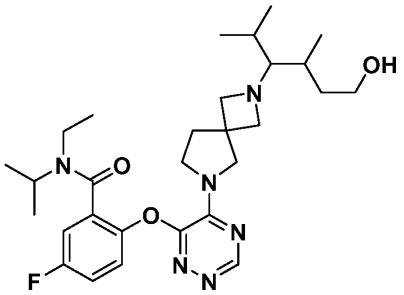
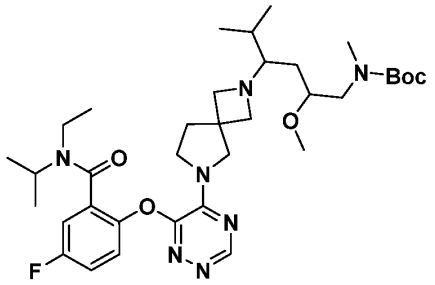
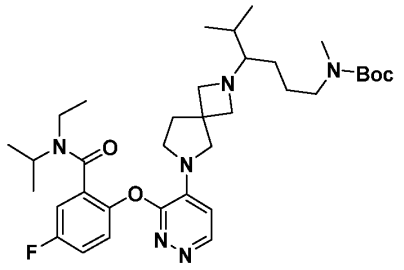
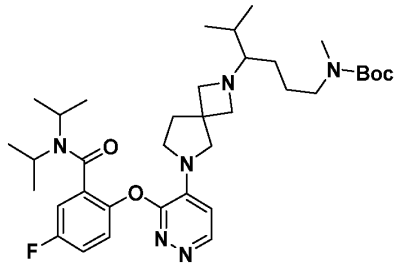
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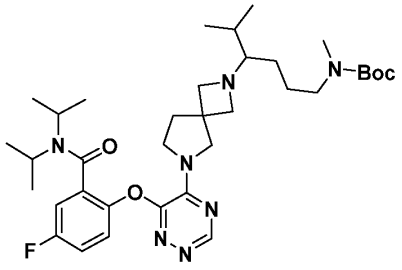
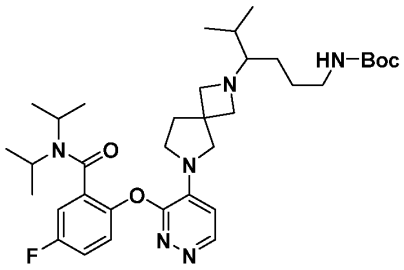
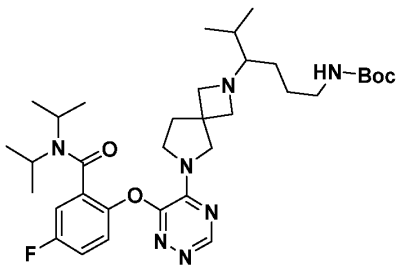
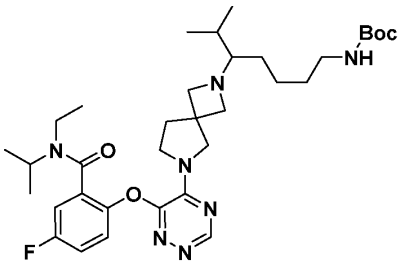
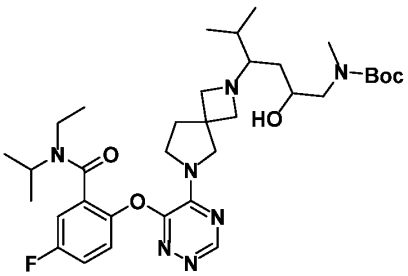
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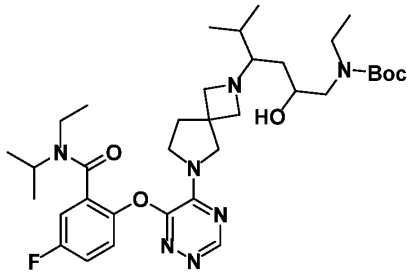
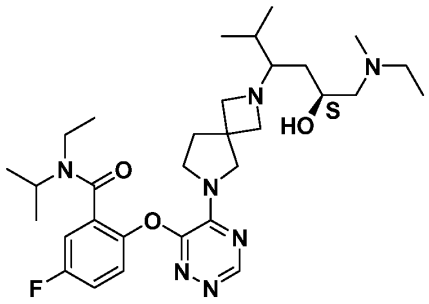
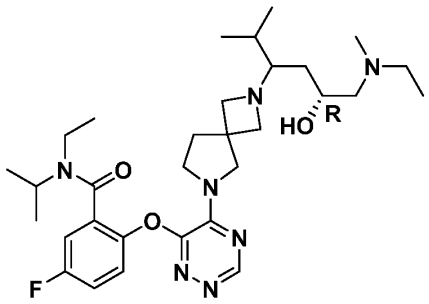
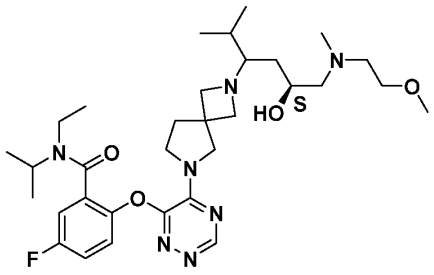
***tert*-butyl (4-(6-(3-chloro-6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-5-methylhexyl)carbamate**

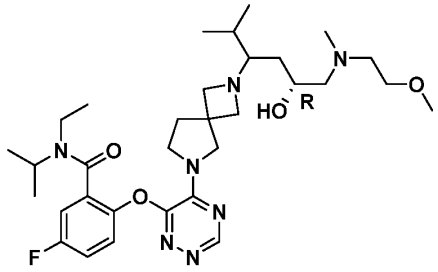
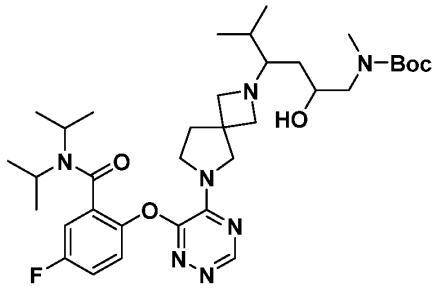
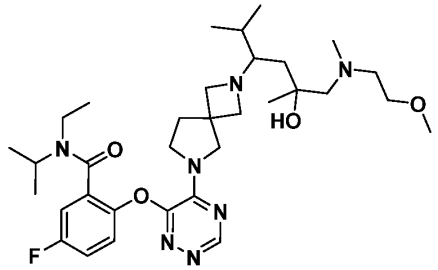
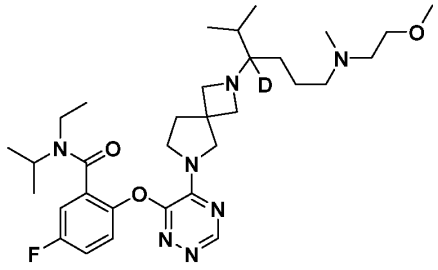
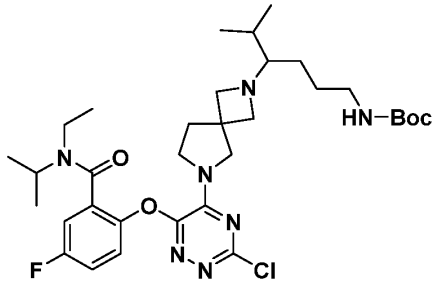
The following compounds were synthesized by an analogous method as described for Compound 60 and Compound 61

Co. No.	Structure	Starting Material	Conditions
58		intermediate 59, intermediate 30	$ZnCl_2$, $NaBH_3CN$, MeOH, 65 °C
59		intermediate 3, intermediate 30	$ZnCl_2$, $NaBH_3CN$, MeOH, 65 °C
213		intermediate 3, intermediate 116	AcOH, $NaBH_3CN$, MeOH, RT
234		intermediate 3, intermediate 135	$ZnCl_2$, $NaBH_3CN$, MeOH, 60 °C

Co. No.	Structure	Starting Material	Conditions
235		intermediate 3, intermediate 136	$ZnCl_2$, $NaBH_3CN$, MeOH, 60 °C
260		intermediate 3, intermediate 141	$Ti(OiPr)_4$, $NaBH_3CN$, MeOH, 80 °C
303		intermediate 244, intermediate 166	NaOAc, $NaBH_3CN$, MeOH, RT
79		intermediate 9, intermediate 75	$ZnCl_2$, $NaBH_3CN$, MeOH, 80 °C
85		intermediate 9, intermediate 71	AcOH, $NaBH_3CN$, MeOH, 70 °C

Co. No.	Structure	Starting Material	Conditions
91		intermediate 9, intermediate 85	$ZnCl_2$, $NaBH_3CN$, MeOH, 80 °C
72		intermediate 1, intermediate 71	AcOH, $NaBH_3CN$, MeOH, 80 °C
96		intermediate 1, intermediate 85	$ZnCl_2$, $NaBH_3CN$, MeOH, 80 °C
206		intermediate 110, intermediate 3	$ZnCl_2$, $NaBH_3CN$, MeOH, 65 °C
316		intermediate 165, intermediate 244	NaOAc, $NaBH_3CN$, MeOH, 26 °C

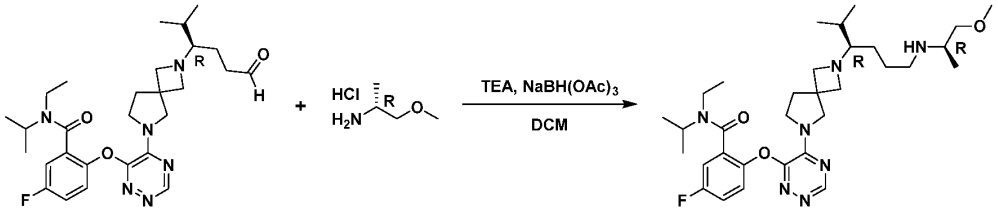
Co. No.	Structure	Starting Material	Conditions
327		intermediate 174, intermediate 244	NaOAc, $NaBH_3CN$, MeOH, RT
338		intermediate 195, intermediate 244	NaOAc, $NaBH_3CN$, MeOH, RT
339		intermediate 196, intermediate 244	NaOAc, $NaBH_3CN$, MeOH, RT
348		intermediate 209, intermediate 244	TEA, $NaBH_3CN$, DCM, 30 °C

Co. No.	Structure	Starting Material	Conditions
349		intermediate 210, intermediate 244	TEA, $NaBH(OAc)_3$, DCM, 35 °C
358		intermediate 165, intermediate 243	NaOAc, $NaBH_3CN$, MeOH, RT
381		intermediate 221, intermediate 244	NaOAc, $NaBH_3CN$, MeOH, 60 °C
399		intermediate 162, intermediate 3	$NaBD_3CN$, CD_3OD, RT
403		intermediate 1, intermediate 238	NaOAc, $NaBH_3CN$, MeOH, 45 °C

For Co. No. 399: LC-MS (ESI) (Method 8): Rt = 1.21 min, m/z found 601.6 $[M+H]^+$

Compound 111

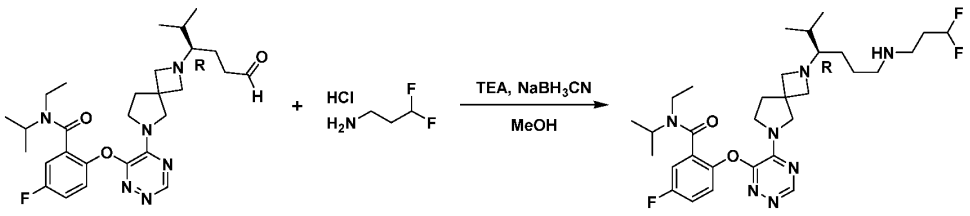
***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((*R*)-6-(((*R*)-1-methoxypropan-2-yl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide**



The mixture of (*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(2-methyl-6-oxohexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide (**intermediate 97**) (150 mg, 0.285 mmol) and (*R*)-1-methoxypropan-2-amine hydrochloride (71.5 mg, 0.569 mmol) and TEA (288 mg, 2.85 mmol) in DCM (2 mL) was stirred at 25 °C for 2 h. Then $NaBH(OAc)_3$ (181 mg, 0.854 mmol) was added to above mixture and the reaction was further stirred at 25 °C for additional 8 h. The mixture was quenched with H_2O (20 mL) and extracted with DCM (30 mL*3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford a crude product, which was purified by preparative HPLC (column: Boston Green ODS 150x30mm 5um; Mobile Phase: A: H_2O (0.05% ammonia)), B: ACN, flow rate: 30 mL/min, gradient condition: from 45% B to 85% B) to afford the title compound **Compound 111** (63 mg, 98.5% purity, 36.3% yield) as a colorless sticky oil.

Compound 113

(*R*)-2-((5-(2-(6-((3,3-difluoropropyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide



The mixture of (*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(2-methyl-6-oxohexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide (**intermediate 97**) (160 mg, 0.304 mmol), 3,3-difluoropropan-1-amine hydrochloride (160 mg, 1.22 mmol) and TEA (128 mg, 1.27 mmol) in MeOH (5 ml) was first stirred at RT for 10 min. Then AcOH (39 mg, 0.649 mmol) and $NaBH_3CN$ (77 mg, 1.26 mmol) were added and the resulting mixture was stirred at RT for additional 16 h. The mixture was concentrated under reduced pressure to remove MeOH. The resulting residue was diluted with H_2O (30 mL) and extracted with DCM (20 mL x 3). The combined organic layers were washed with brine (10 mL x 2), dried over Na_2SO_4, filtered and concentrated to afford a crude product, which was purified by preparative HPLC (column: Boston Prime C18 150x30mm 5μm; Mobile phase: A: water (0.05% ammonia), B: ACN; gradient condition: 46% B to 76% B (v/v)) to afford the title compound **Compound 113** (32 mg, 17% yield) as a white solid.

Compound 115, 116, 119, 124, 129, 134, 138, 141, 143, 144, 147, 151, 155, 158, 162, 163, 168, 171, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 232, 244, 263, 264, 281, 284, 299

(*R)-5-fluoro-*N*,*N*-diisopropyl-2-((5-(2-(6-((2-methoxyethyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide

(*S)-5-fluoro-*N*,*N*-diisopropyl-2-((5-(2-(6-((2-methoxyethyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide

***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(6-(isopropyl(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide**

***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(2-methyl-6-(methyl(propyl)amino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide**

***N*-ethyl-2-((5-(2-(6-(ethyl(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide**

(*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(6-((2-methoxy-2-methylpropyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide

(*R*)-*N*-ethyl-5-fluoro-2-((5-(2-(6-((2-hydroxy-2-methylpropyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide

(*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(6-((3-methoxypropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide

(*R)-2-((5-(2-(6-((3-(dimethylamino)-3-oxopropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide

(*S)-2-((5-(2-(6-((3-(dimethylamino)-3-oxopropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide

(*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(2-methyl-6-(methyl(2-(*N*-methylacetamido)ethyl)amino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide

(*R*)-2-((5-(2-(6-((4-(dimethylamino)-4-oxobutyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((*R*)-6-(((*S*)-1-methoxypropan-2-yl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide**

(*R*)-2-((5-(2-(6-((1,3-dimethoxypropan-2-yl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

***N*-ethyl-5-fluoro-2-((5-(2-((*R*)-6-(((*R*)-1-hydroxy-3-methoxypropan-2-yl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide**

***N*-ethyl-5-fluoro-2-((5-(2-((*R*)-6-(((*S*)-1-hydroxy-3-methoxypropan-2-yl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide**

***N*-ethyl-5-fluoro-2-((5-(2-((3*R*)-6-((3-hydroxy-2-methoxypropyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide**

2-((5-(2-((3*R*)-6-((2,3-dimethoxypropyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

2-((5-(2-((3*R*)-6-((4-(dimethylamino)-4-oxobutan-2-yl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

2-((5-(2-((3*R*)-6-((3-(dimethylamino)-2-methyl-3-oxopropyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((*R*)-2-methyl-6-(((*R*)-4-(methylamino)-4-oxobutan-2-yl)amino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide**

***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((*R*)-2-methyl-6-(((*S*)-4-(methylamino)-4-oxobutan-2-yl)amino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide**

***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((*R*)-2-methyl-6-(((*R*)-2-methyl-3-(methylamino)-3-oxopropyl)amino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide**

***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((*R*)-2-methyl-6-(((*S*)-2-methyl-3-(methylamino)-3-oxopropyl)amino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide**

2-((5-(2-((R*)-6-(((*R*)-4-amino-4-oxobutan-2-yl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide**

2-((5-(2-((R*)-6-(((*S*)-4-amino-4-oxobutan-2-yl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide**

2-((5-(2-((R*)-6-(((*R*)-3-amino-2-methyl-3-oxopropyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide**

2-((5-(2-((R*)-6-(((*S*)-3-amino-2-methyl-3-oxopropyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide**

(*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(6-((2-methoxyethyl-1,1-d_2)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide

(*R*)-2-((5-(2-(6-((2-acetamidoethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2,4-dimethylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide (mixture of *R*,*S* and *S*,*R*; or mixture of *R*,*R* and *S*,*S*)**

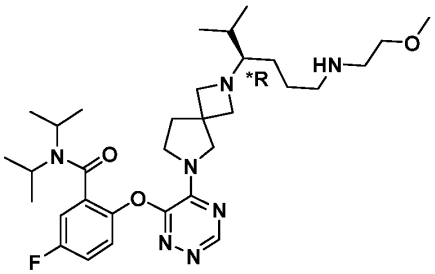
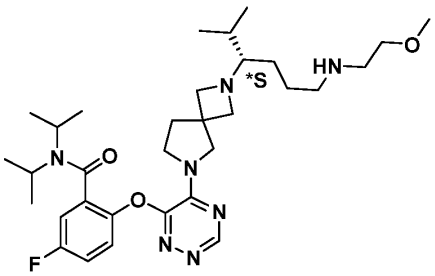
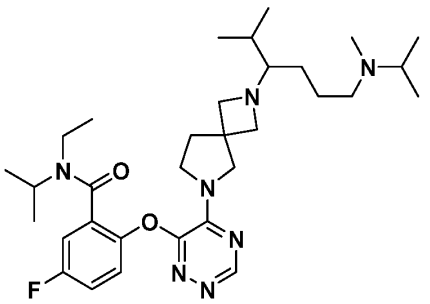
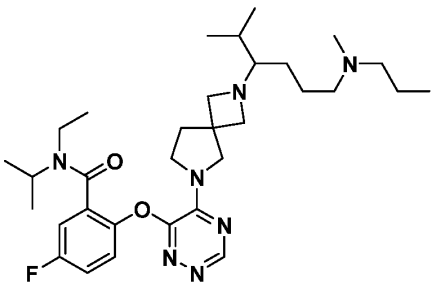
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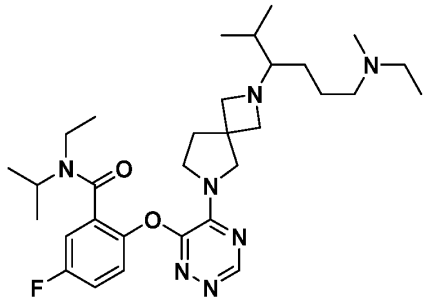
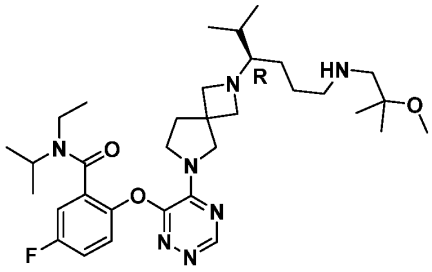
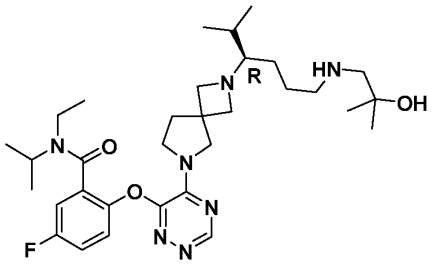
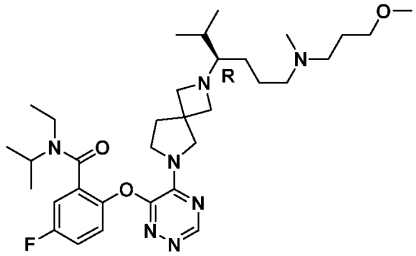
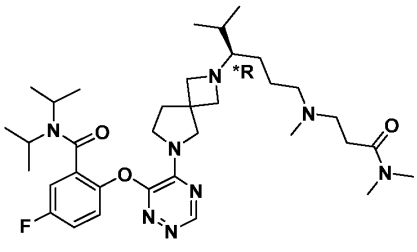
***N*-ethyl-5-fluoro-2-((5-(2-((*R*)-6-(((*R*)-2-hydroxy-3-methoxypropyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide formate**

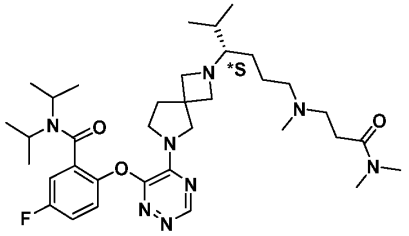
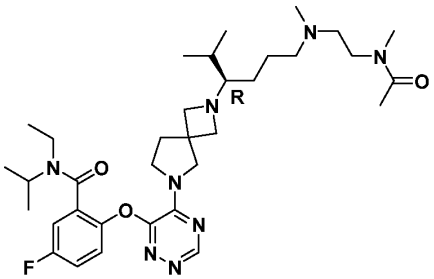
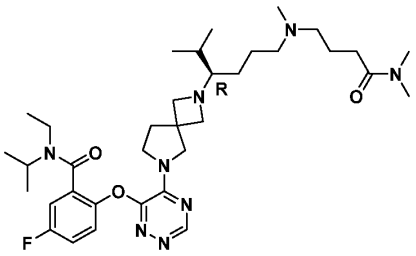
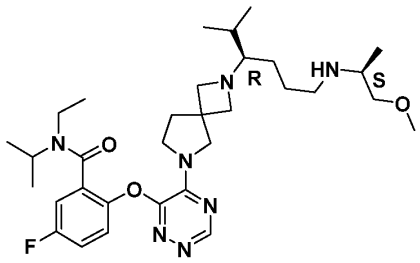
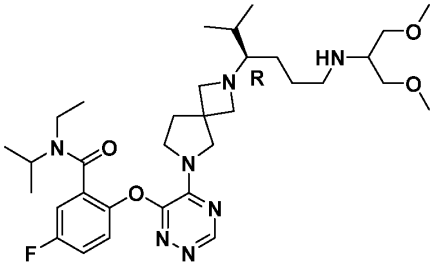
***N*-ethyl-5-fluoro-2-((5-(2-((*R*)-6-(((*S*)-2-hydroxy-3-methoxypropyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide formate**

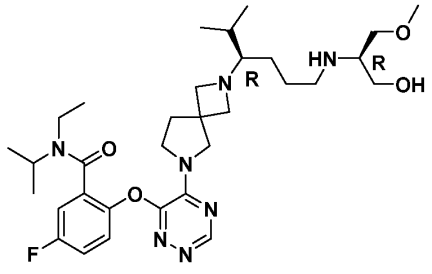
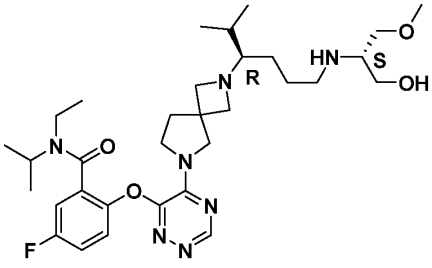
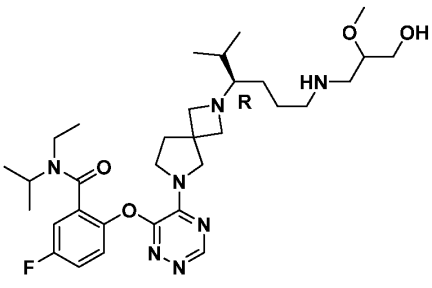
***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((3*R*)-6-((2-methoxyethyl)(methyl)amino)-2-methylheptan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide**

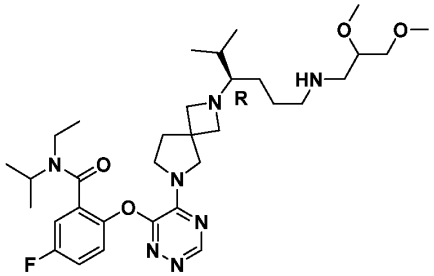
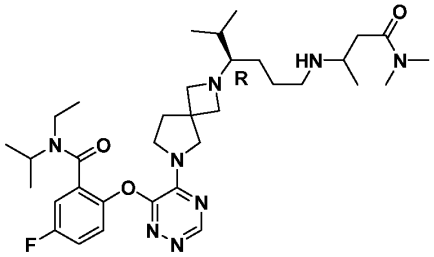
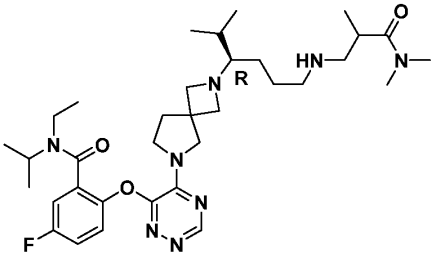
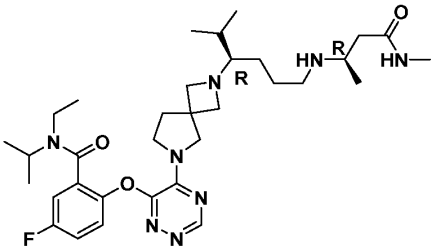
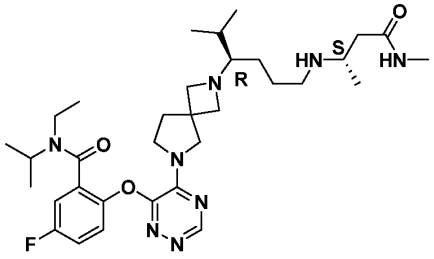
The following compounds were synthesized by an analogous method as described above for Compound 111 and 113

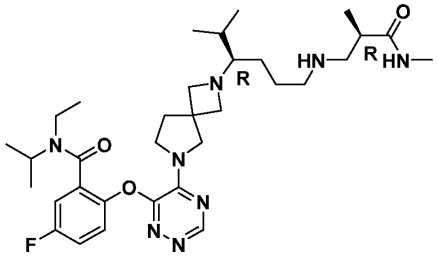
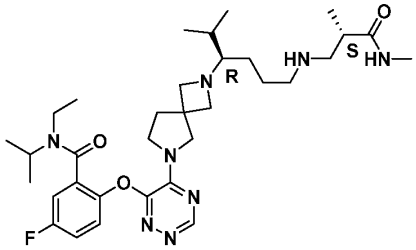
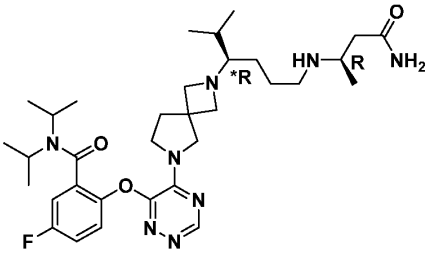
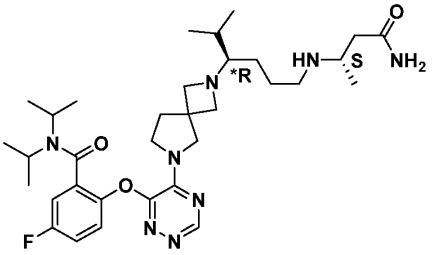
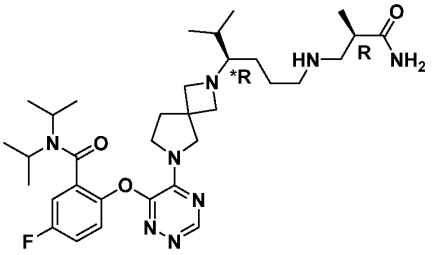
Co. No.	Structure	Starting Material	Conditions	Spectra Details
115		intermediate 101, 2-methoxyethan-1-amine	NaOAc, $NaBH_3CN$, MeOH, 60 °C	
116		intermediate 102, 2-methoxyethan-1-amine	NaOAc, $NaBH_3CN$, MeOH, 60 °C	
119		intermediate 103, *N*-methylpropan-2-amine	$NaBH(OAc)_3$, TEA, DCM, 25 °C	
124		intermediate 103, *N*-methylpropan-1-amine	$NaBH(OAc)_3$, DCM, 25 °C	

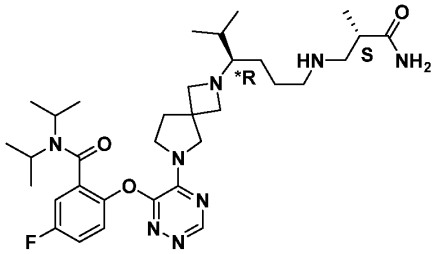
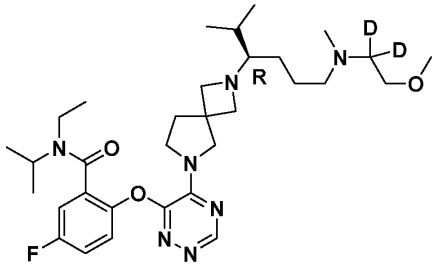
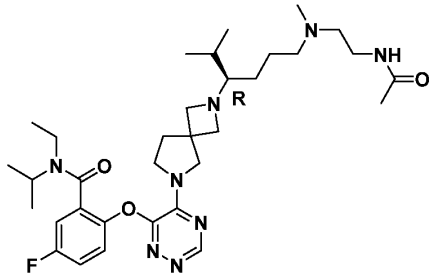
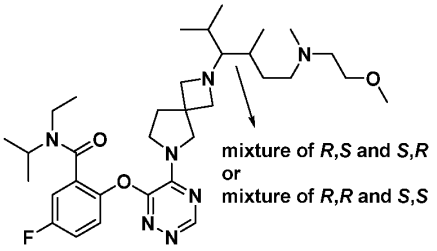
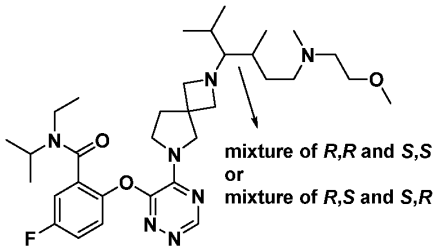
Co. No.	Structure	Starting Material	Conditions	Spectra Details
129		intermediate 103, *N*-methylethanamine	$NaBH(OAc)_3$, DCM, 25 °C	
134		intermediate 97, 2-methoxy-2-methylpropan-1-amine	NaOAc, $NaBH_3CN$, MeOH, 45 °C	
138		intermediate 97, 1-amino-2-methylpropan-2-ol	$NaBH_3CN$, AcOH, MeOH, 45 °C	
141		intermediate 97, 3-methoxy-*N*-methylpropan-1-amine	NaOAc, $NaBH_3CN$, MeOH, RT	
143		intermediate 101, *N*,*N*-dimethyl-3-(methylamino)propanamide	$NaBH(OAc)_3$, TEA, DCM, 25 °C	

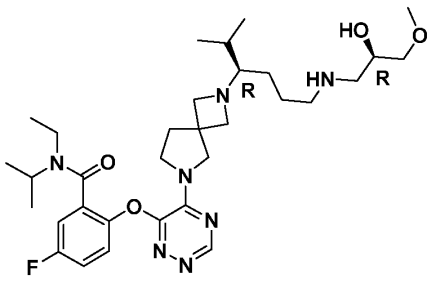
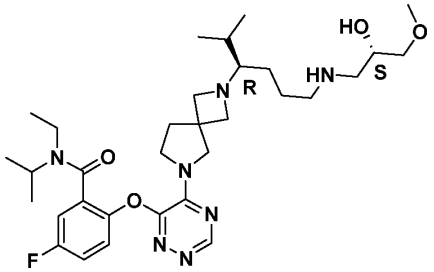
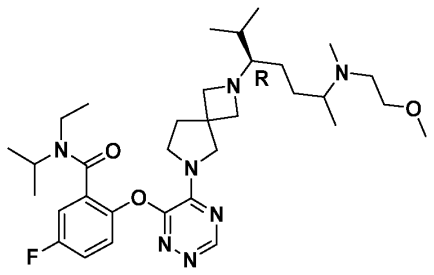
Co. No.	Structure	Starting Material	Conditions	Spectra Details
144		intermediate 102, *N*,*N*-dimethyl-3-(methylamino)propanamide	$NaBH(OAc)_3$, TEA, DCM, 25 °C	
147		intermediate 97, *N*-methyl-*N*-(2-(methylamino)ethyl)acetamide	$NaBH(OAc)_3$, TEA, DCM, 45 °C	
151		intermediate 97, *N*,*N*-dimethyl-4-(methylamino)butanamide	NaOAc, $NaBH_3CN$, MeOH, RT	
155		intermediate 97, (*S*)-1-methoxypropan-2-amine	$NaBH(OAc)_3$, DCM, 25 °C	
158		intermediate 97, 1,3-dimethoxypropan-2-amine	$NaBH_3CN$, TEA, DCM, RT	

Co. No.	Structure	Starting Material	Conditions	Spectra Details
162		intermediate 97, (*R*)-2-amino-3-methoxypropan-1-ol	$NaBH_3CN$, AcOH, MeOH, 50 °C	**LC-MS (ESI) (Method 1):** R_t = 2.912 min, m/z found 616.3 $[M+H]^+$. **SFC (Method 3):** R_t = 4.465 min.
163		intermediate 97, (*S*)-2-amino-3-methoxypropan-1-ol	$NaBH_3CN$, AcOH, MeOH, 40 °C	**LC-MS (ESI) (Method 3):** R_t = 4.462 min, m/z found 616.4 $[M+H]^+$. **SFC (Method 3):** R_t = 4.812 min.
168		intermediate 97, 3-amino-2-methoxypropan-1-ol	$NaBH_3CN$, AcOH, MeOH, 60 °C	**LC-MS (ESI) (Method 3):** R_t = 4.791 min, m/z found 616.5 $[M+H]^+$.

Co. No.	Structure	Starting Material	Conditions	Spectra Details
171		intermediate 97, 2,3-dimethoxypropan-1-amine	$NaBH_3CN$, AcOH, MeOH, 25 °C	
288		intermediate 97, 3-amino-*N*,*N*-dimethylbutanamide	NaOAc, $NaBH_3CN$, MeOH, 20 °C	
289		intermediate 97, 3-amino-*N*,*N*,2-trimethylpropanamide	NaOAc, $NaBH_3CN$, MeOH, 20 °C	
290		intermediate 97, (*R*)-3-amino-*N*-methylbutanamide	NaOAc, $NaBH_3CN$, MeOH, 20 °C	
291		intermediate 97, (*S*)-3-amino-*N*-methylbutanamide	NaOAc, $NaBH_3CN$, MeOH, 20 °C	

Co. No.	Structure	Starting Material	Conditions	Spectra Details
292		intermediate 97, (*R*)-3-amino-*N*,2-dimethylpropanamide	NaOAc, $NaBH_3CN$, MeOH, 20 °C	
293		intermediate 97, (*S*)-3-amino-*N*,2-dimethylpropanamide	NaOAc, $NaBH_3CN$, MeOH, 20 °C	
294		intermediate 101, (*R*)-3-aminobutanamide	NaOAc, $NaBH_3CN$, MeOH, 20 °C	
295		intermediate 101, (*S*)-3-aminobutanamide	NaOAc, $NaBH_3CN$, MeOH, 20 °C	
296		intermediate 101, (*R*)-3-amino-2-methylpropanamide	NaOAc, $NaBH_3CN$, MeOH, 20 °C	

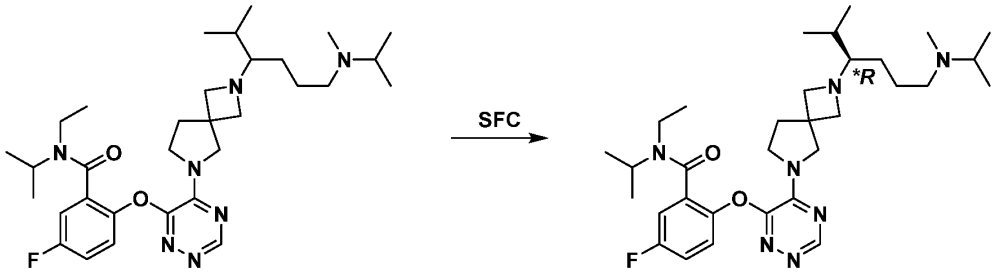
Co. No.	Structure	Starting Material	Conditions	Spectra Details
297		intermediate 101, (*S*)-3-amino-2-methylpropanamide	NaOAc, $NaBH_3CN$, MeOH, 20 °C	
232		intermediate 97, intermediate 127	$NaBH_3CN$, MeOH, 25 °C	
244		intermediate 97, *N*-(2-(methylamino)ethyl)acetamide	$NaBH_3CN$, TEA, MeOH, RT	
263		intermediate 145, 2-methoxy-*N*-methylethan-1-amine	$NaBH_3CN$, MeOH, 40 °C	
264		intermediate 146, 2-methoxy-*N*-methylethan-1-amine	$NaBH_3CN$, MeOH, 40 °C	

Co. No.	Structure	Starting Material	Conditions	Spectra Details
281	 formate salt	intermediate 97, (*R*)-1-amino-3-methoxypropan-2-ol	$NaBH_3CN$, $ZnCl_2$, MeOH, 25 °C	**LC-MS (ESI) (Method 1):** R_t = 3.016 min, m/z found 616.3 $[M+H]^+$. **SFC (Method 13)**: R_t = 2.306 min.
284	 formate salt	intermediate 97, (*S*)-1-amino-3-methoxypropan-2-ol	$NaBH_3CN$, $ZnCl_2$, MeOH, 25 °C	**LC-MS (ESI) (Method 1):** R_t = 3.048 min, m/z found 616.3 $[M+H]^+$. **SFC (Method 13)**: R_t = 2.333 min.
299		intermediate 158, 2-methoxy-*N*-methylethan-1-amine	NaOAc, $NaBH_3CN$, MeOH, RT	

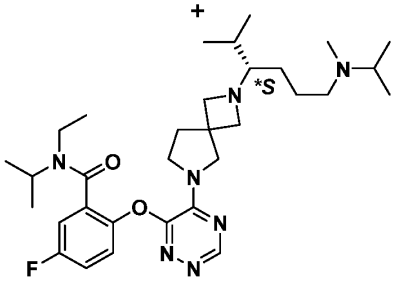
Compound 120 and 121

(*R)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(6-(isopropyl(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide

(*S)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(6-(isopropyl(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide



Compound 119 **Compound 120**



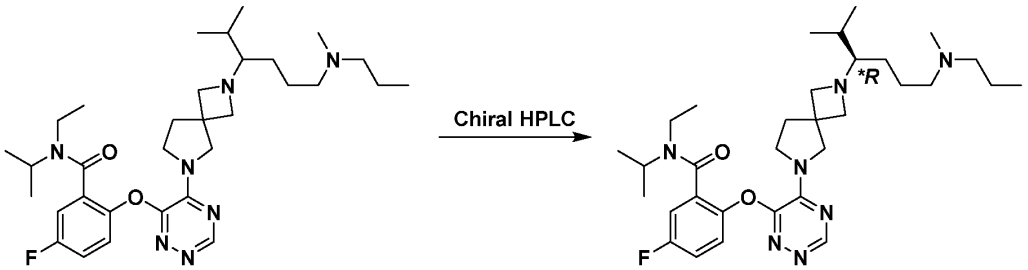
Compound 121

N-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(6-(isopropyl(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide (**Compound 119**) (100 mg) was separated by SFC over DAICEL CHIRALPAK IG (column: 250x30mm 10um; Mobile phase: A: Supercritical CO_2, B: MeOH (0.1% ammonia), A:B = 55:45 at 70 mL/min; Column Temp: 38 °C; Nozzle Pressure: 100 Bar; Nozzle Temp: 60 °C; Evaporator Temp: 20 °C; Trimmer Temp: 25 °C; Wavelength: 220nm) to afford the title compounds (**Compound 120**) (22.1 mg) and (**Compound 121**) (32.5 mg) both as light yellow solid.

Compound 125 and 126

(*R)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(2-methyl-6-(methyl(propyl)amino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide

(*S)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(2-methyl-6-(methyl(propyl)amino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide



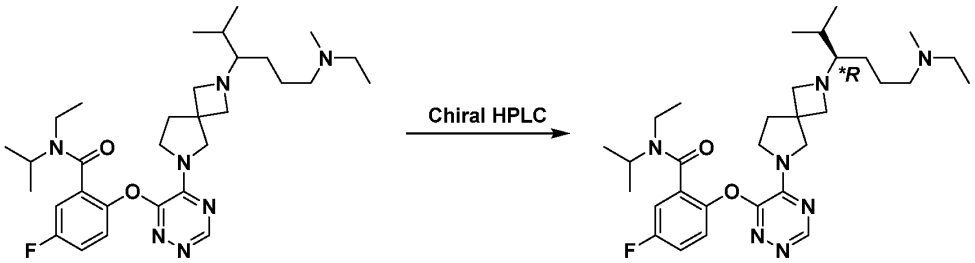
Compound 124 **Compound 125** + **Compound 126**

N-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(2-methyl-6-(methyl(propyl)amino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide (**Compound 124**) (150 mg) was separated by chiral HPLC over Daicel ChiralPak IG (column: 250x30mm 10um; Mobile Phase A: Hexane; Mobile Phase B: EtOH; Flow rate: 20 mL/min; gradient condition from 20% B to 100% B) to afford the title compounds (**Compound 125**) (38.0 mg) and (**Compound 126**) (27.2 mg) both as light yellow solid.

Compound 130 and 131

(R*)-*N*-ethyl-2-((5-(2-(6-(ethyl(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide**

(S*)-*N*-ethyl-2-((5-(2-(6-(ethyl(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide**



Compound 129 **Compound 130**

+

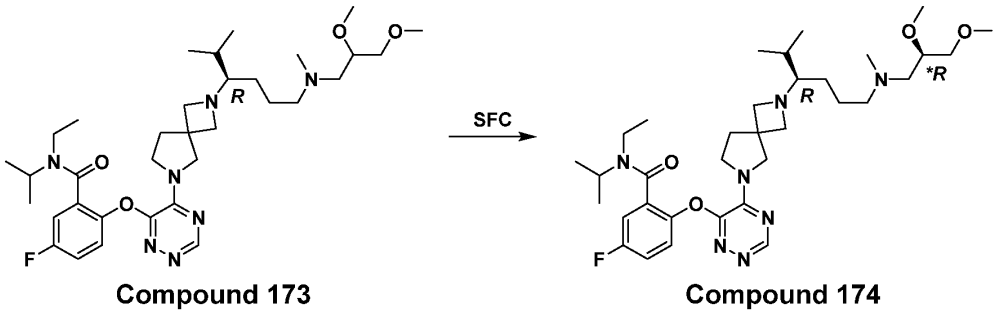
Compound 131

N-ethyl-2-((5-(2-(6-(ethyl(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (**Compound 129**) (300 mg) was separated by chiral HPLC over Daicel ChiralPak IG (column: 250x30mm 10um; Mobile Phase A: Hexane; Mobile Phase B: EtOH; Flow rate: 20 mL/min; gradient condition from 20% B to 100% B) to afford the title compounds (**Compound 130**) (68.4 mg) and (**Compound 131**) (54.8 mg) both as light yellow solid.

Compound 174 and 175

2-((5-(2-((*R*)-6-(((R*)-2,3-dimethoxypropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide**

2-((5-(2-((*R*)-6-(((S*)-2,3-dimethoxypropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide**



Compound 173 Compound 174

+

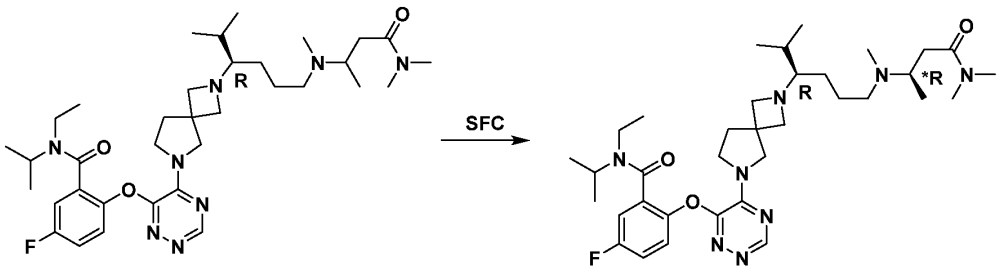
Compound 175

2-((5-(2-((3*R*)-6-((2,3-dimethoxypropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (**Compound 173**) (60 mg) was purified by SFC over DAICEL CHIRALPAK AD (column: 250x30mm 10um; Mobile phase: A: Supercritical CO_2, B: IPA (0.1% ammonia), A: B=70%:30% isocratic (v/v) at 70 mL/min) to afford the title compounds (**Compound 174**) (10 mg) and (**Compound 175**) (10 mg) both as colorless sticky oil.

Compound 182 and 183

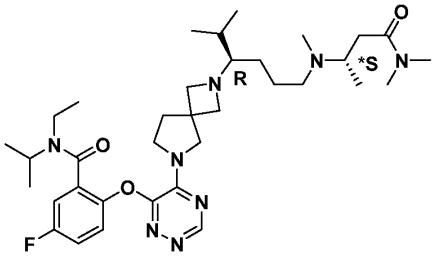
2-((5-(2-((*R*)-6-(((*R)-4-(dimethylamino)-4-oxobutan-2-yl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

2-((5-(2-((*R*)-6-(((*S)-4-(dimethylamino)-4-oxobutan-2-yl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide



Compound 179 **Compound 182**

+



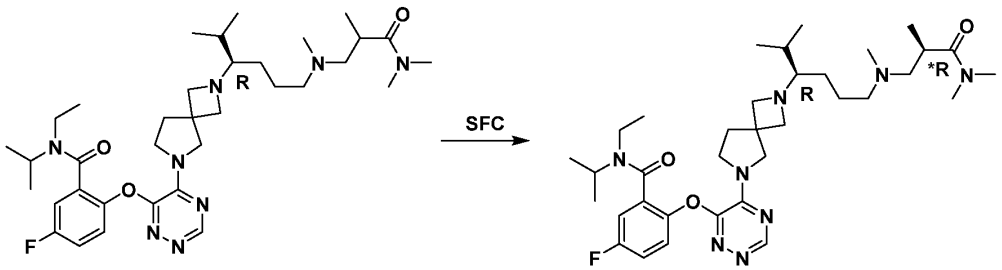
Compound 183

2-((5-(2-((3*R*)-6-((4-(dimethylamino)-4-oxobutan-2-yl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide fumarate (**Compound 179**) (58.0 mg) was separated by SFC over DAICEL CHIRALPAK IG (column: 250x30mm 10um; Mobile phase: A: Supercritical CO_2, B: EtOH (0.1% ammonia), A:B = 45:55 at 80 mL/min; Column Temp: 38 °C; Nozzle Pressure: 100 Bar; Nozzle Temp: 60 °C; Evaporator Temp: 20 °C; Trimmer Temp: 25 °C; Wavelength: 220 nm) to afford the title compounds (**Compound 182**) (12.0 mg) and (**Compound 183**) (16.0 mg) both as colorless sticky oil.

Compound 186 and 187

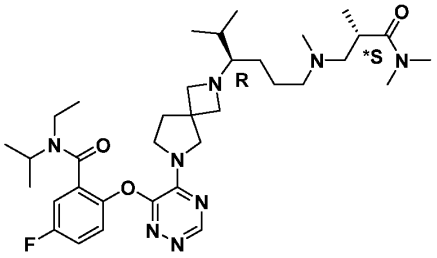
2-((5-(2-((*R*)-6-(((R*)-3-(dimethylamino)-2-methyl-3-oxopropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide**

2-((5-(2-((*R*)-6-(((S*)-3-(dimethylamino)-2-methyl-3-oxopropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide**



Compound 180 **Compound 186**

+



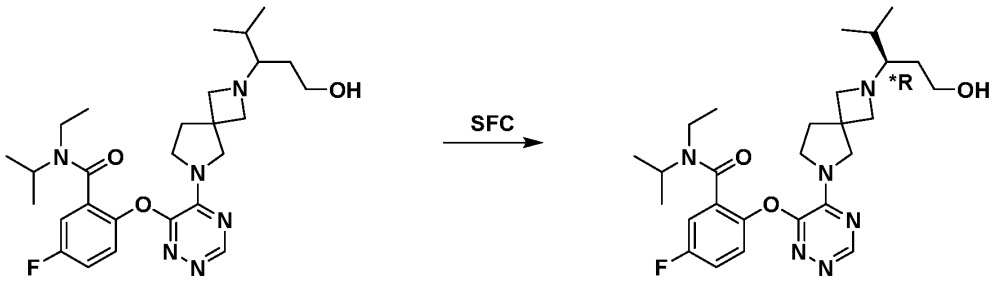
Compound 187

2-((5-(2-((3*R*)-6-((3-(dimethylamino)-2-methyl-3-oxopropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (**Compound 180**) (42.0 mg) was separated by SFC over DAICEL CHIRALPAK AD-H (column: 250x30mm 5um; Mobile phase: A: Supercritical CO_2, B: IPA (0.1% ammonia), A:B =70:30 at 60 mL/min; Column Temp: 38 °C; Nozzle Pressure: 100Bar; Nozzle Temp: 60 °C; Evaporator Temp: 20 °C; Trimmer Temp: 25 °C; Wavelength: 220nm) to afford the title compounds (**Compound 186**) (20.0 mg) and (**Compound 187**) (20.0 mg) both as light yellow sticky oil.

Compound 214 and 215

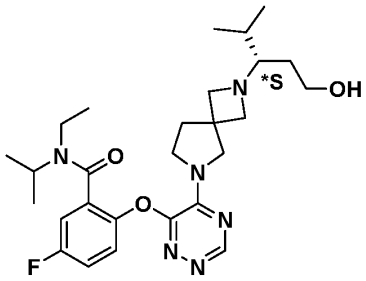
(*R)-*N*-ethyl-5-fluoro-2-((5-(2-(1-hydroxy-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide

(*S)-*N*-ethyl-5-fluoro-2-((5-(2-(1-hydroxy-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide



Compound 213 **Compound 214**

+



Compound 215

N-ethyl-5-fluoro-2-((5-(2-(1-hydroxy-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide (**Compound 213**) (300 mg, crude) was first purified by preparative HPLC over Phenomenex Gemini-NX (column: C18 75x30 mm 3um; eluent: ACN/H_2O (0.05% ammonia+10mM NH_4HCO_3) from 30% to 60%, v/v) to afford a pure product (100 mg). This pure product was further purified by SFC over DAICEL CHIRALPAK IG (column: 250x30 mm 10 μm; Mobile phase: A: supercritical CO_2, B: MeOH (containing 0.1% ammonia), A:B = 45%:55% isocratic elution) to afford the title compounds (**Compound 214**) (38.8 mg) and (**Compound 215**) (40.7 mg) both as white solid.

Compound 214

LC-MS (ESI) (Method 1): R_t = 3.000 min, m/z found 515.2 $[M+H]^+$.

SFC (Method 22): R_t = 4.406 min.

Compound 215

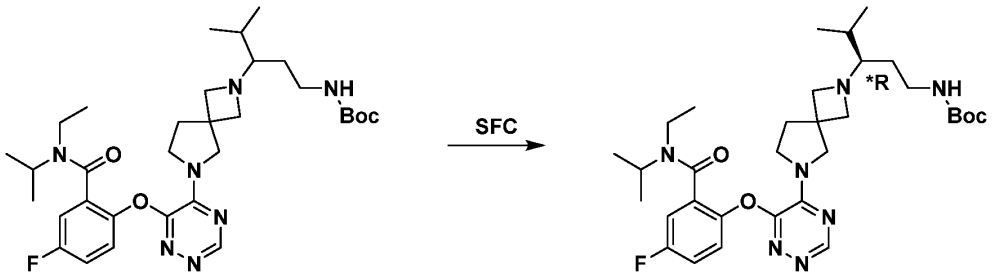
LC-MS (ESI) (Method 1): R_t = 3.145 min, m/z found 515.2 $[M+H]^+$.

SFC (Method 22): R_t = 4.925 min.

Compound 216 and 217

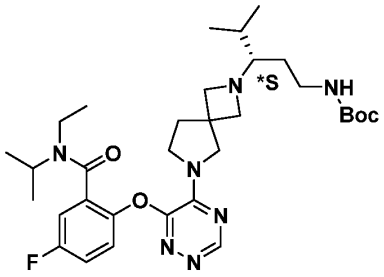
***tert*-butyl (**R*)-(3-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-4-methylpentyl)carbamate**

***tert*-butyl (**S*)-(3-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-4-methylpentyl)carbamate**



Compound 51 **Compound 216**

+

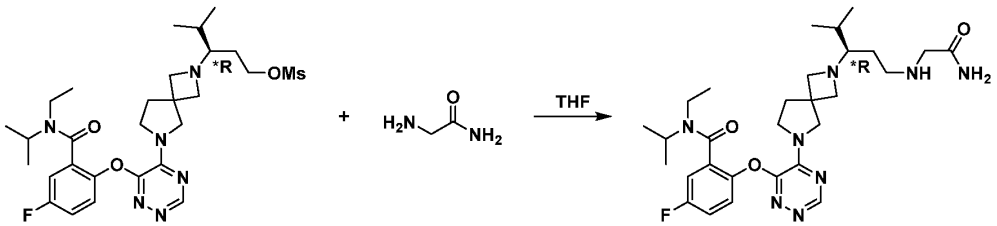


Compound 217

Tert-butyl (3-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-4-methylpentyl)carbamate (**Compound 51**) (1.00 g) was purified by SFC over DAICEL CHIRALPAK IG (column: 250x30mm 10um; Mobile phase: A: Supercritical CO_2, B: MeOH (0.1% ammonia), A:B = 60:40 (v/v)) to afford the title compounds (**Compound 216**) (400 mg) and (**Compound 217**) (450 mg) both as white solid.

Compound 230

(R*)-2-((5-(2-(1-((2-amino-2-oxoethyl)amino)-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide**



The solution of (**R*)-3-(6-(6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-4-methylpentyl methanesulfonate (**intermediate 124**)

(160 mg, crude) in THF (2 mL) was added to a solution 2-aminoacetamide (150 mg, 2.03 mmol) in THF (5 mL). The resulting mixture was stirred at RT for 2 h. The reaction mixture was filtered and washed with THF (20 mL). The filtrate was concentrated *in vacuo* to afford the crude product, which was purified by preparative HPLC over a Xtimate (column: C18 150x40mm 5um; eluent: ACN/H_2O (0.05% ammonia) from 25% to 55%, v/v) to afford the title compound (22.1 mg) as a white solid.

LC-MS (ESI) (Method 1): R_t = 2.849 min, m/z found 571.2 $[M+H]^+$.

SFC (Method 6): R_t = 1.598 min.

Compound 267, 269, 271, 272, 273, 277

(*R)-*N*-ethyl-5-fluoro-2-((5-(2-(1-((2-hydroxyethyl)amino)-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide

(*R)-*N*-ethyl-5-fluoro-2-((5-(2-(1-((2-hydroxyethyl)(methyl)amino)-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide

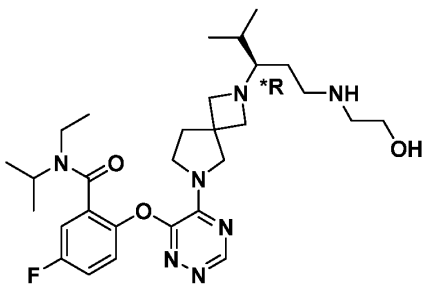
(*R)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(1-((3-methoxypropyl)amino)-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide

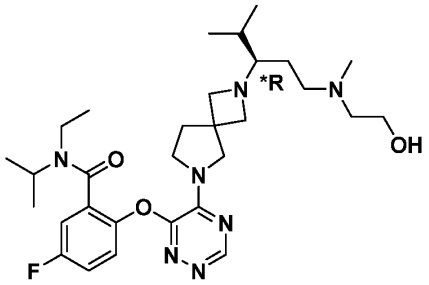
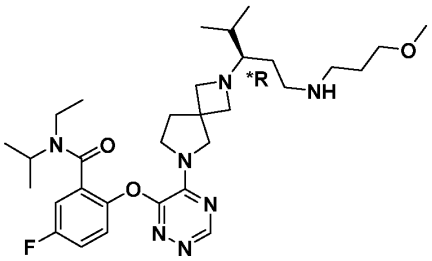
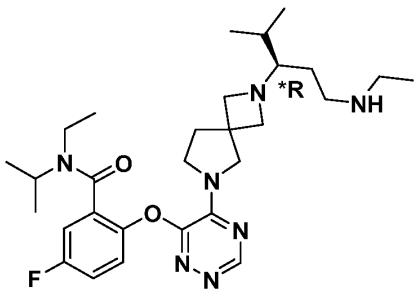
(*R)-*N*-ethyl-2-((5-(2-(1-(ethylamino)-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide formate

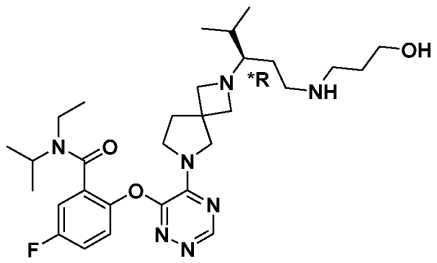
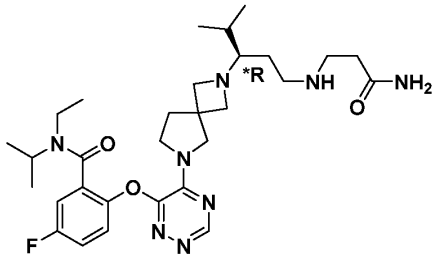
(*R)-*N*-ethyl-5-fluoro-2-((5-(2-(1-((3-hydroxypropyl)amino)-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide

(*R)-2-((5-(2-(1-((3-amino-3-oxopropyl)amino)-4-methylpentan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

The following compounds were synthesized by an analogous method as described above for Compound 230

Co. No.	Structure	Starting Material	Conditions	Spectra Details
267		intermediate 124, 2-aminoethan-1-ol	ACN, 60 °C	

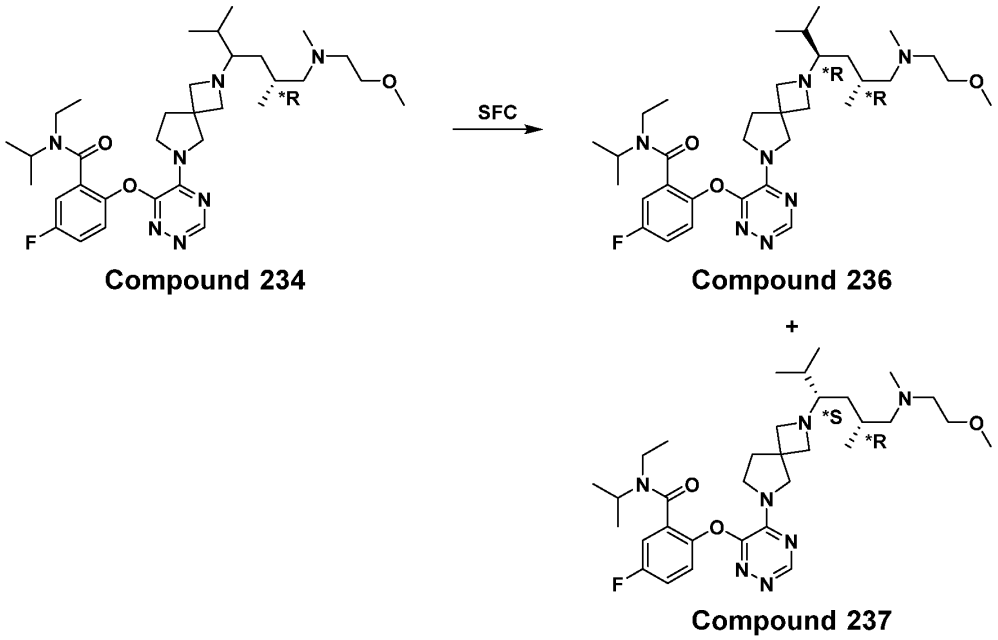
Co. No.	Structure	Starting Material	Conditions	Spectra Details
269		intermediate 124, 2-(methyl-amino)ethan-1-ol	ACN, 60 °C	
271		intermediate 124, 3-methoxy-propan-1-amine	THF, RT	**LC-MS (ESI) (Method 2):** R_t = 1.995 min, m/z found 586.3 $[M+H]^+$. **SFC (Method 13):** R_t = 2.152 min.
272	 formate salt	intermediate 124, ethanamine	THF, RT	**LC-MS (ESI) (Method 2):** R_t = 1.892 min, m/z found 542.3 $[M+H]^+$. **SFC (Method 14):** R_t = 2.753 min.

Co. No.	Structure	Starting Material	Conditions	Spectra Details
273		intermediate 124, 3-aminopropan-1-ol	THF, RT	**LC-MS (ESI) (Method 1):** R_t = 2.894 min, m/z found 572.4 $[M+H]^+$. **SFC (Method 6):** R_t = 1.421 min.
277		intermediate 124, 3-aminopropanamide	THF, 60 °C	

Compound 236 and 237

***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((3**R*,5**R*)-6-((2-methoxyethyl)(methyl)amino)-2,5-dimethylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide**

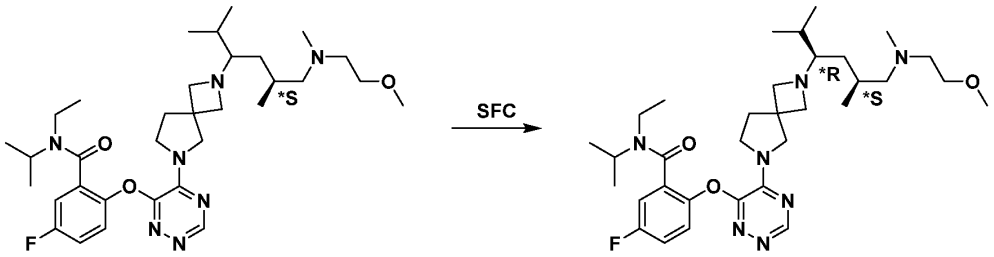
***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((3**S*,5**R*)-6-((2-methoxyethyl)(methyl)amino)-2,5-dimethylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide**



N-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((5**R*)-6-((2-methoxyethyl)(methyl)amino)-2,5-dimethylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide (**Compound 234**) (89.0 mg) was purified by SFC over DAICEL CHIRALPAK AD (column: 250x30 mm 10um; Mobile phase: A: Supercritical CO_2, B: IPA (0.1% ammonia), A:B = 80:20 at 60 mL/min) to afford the title compounds (**Compound 236**) (31.0 mg, 34% yield) and (**Compound 237**) (24.7 mg, 27% yield) both as yellow sticky solid.

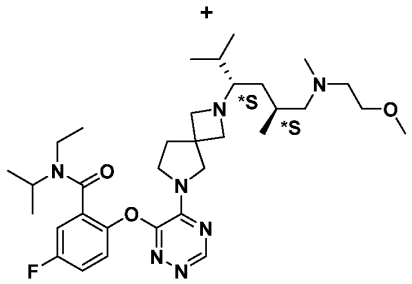
Compound 238 and 239

***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((3*R,5*S)-6-((2-methoxyethyl)(methyl)amino)-2,5-dimethylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide**
***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((3*S,5*S)-6-((2-methoxyethyl)(methyl)amino)-2,5-dimethylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide**



Compound 235 **Compound 238**

+



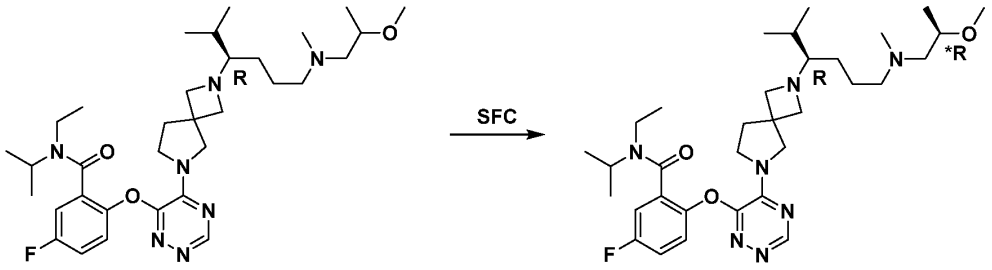
Compound 239

N-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((5*S*)-6-((2-methoxyethyl)(methyl)amino)-2,5-dimethylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide (**Compound 235**) (51 mg) was purified by SFC over DAICEL CHIRALCEL OD-H (column: 250x30mm 5um; Mobile phase: A: Supercritical CO_2, B: EtOH (0.1% ammonia), A:B = 85:15 at 60 mL/min) to afford the title compounds (**Compound 238**) (17.9 mg, 35%) and (**Compound 239**) (14.3 mg, 28%) both as white solid.

Compound 248 and 249

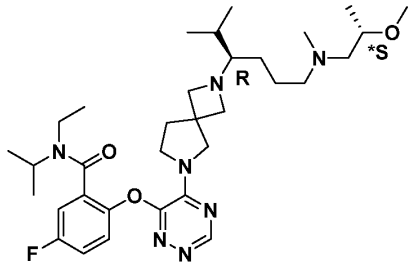
_N_-ethyl-5-fluoro-_N_-isopropyl-2-((5-(2-((_R_)-6-(((*_R_)-2-methoxypropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide

_N_-ethyl-5-fluoro-_N_-isopropyl-2-((5-(2-((_R_)-6-(((*_S_)-2-methoxypropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide



Compound 247 **Compound 248**

+



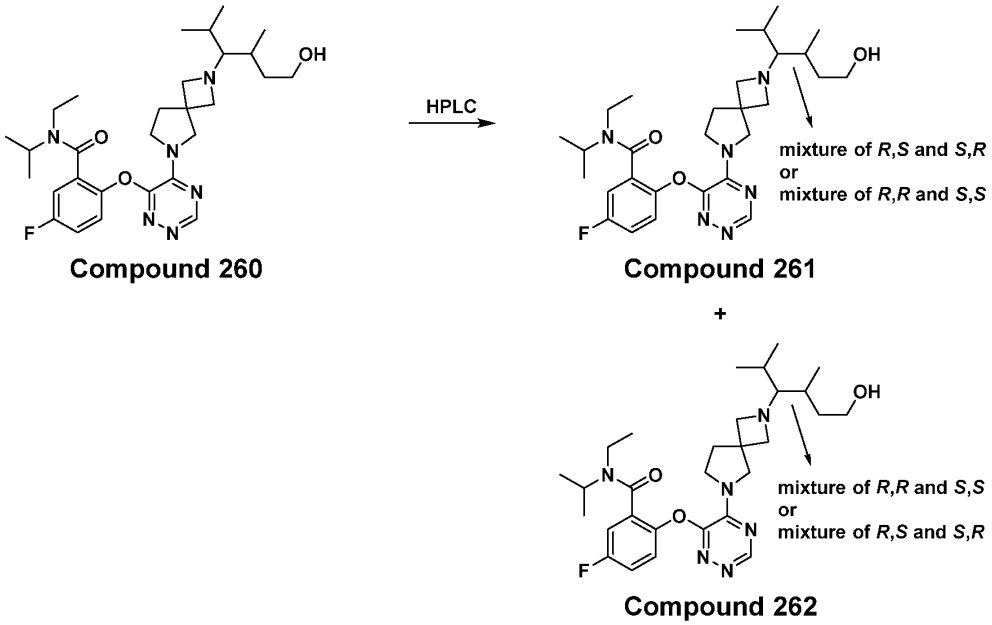
Compound 249

N-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-((3*R*)-6-((2-methoxypropyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide (**Compound 247**) (70 mg) was purified by SFC over DAICEL CHIRALPAK AD-H (column: 250x30mm 5μm; Mobile phase: A: supercritical CO_2, B: IPA (0.1% ammonia), A:B = 75%:25% at 60 mL/min) to afford the title compounds (**Compound 248**) (10 mg) and (**Compound 249**) (30 mg) both as light yellow sticky oil.

Compound 261 and 262

_N_-ethyl-5-fluoro-2-((5-(2-(6-hydroxy-2,4-dimethylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-_N_-isopropylbenzamide (mixture of _R_,_S_ and _S_,_R_; or mixture of _R_,_R_ and _S_,_S_)

_N_-ethyl-5-fluoro-2-((5-(2-(6-hydroxy-2,4-dimethylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-_N_-isopropylbenzamide (mixture of _R_,_R_ and _S_,_S_; or mixture of _R_,_S_ and _S_,_R_)



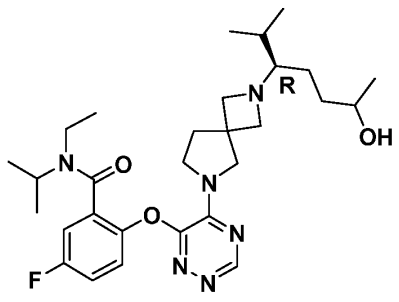
Compound 260 **Compound 261** + **Compound 262**

N-ethyl-5-fluoro-2-((5-(2-(6-hydroxy-2,4-dimethylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide (**Compound 260**) (5.0 g, crude) was purified by HPLC (column: Xtimate C18 150x40 mm 5 μm; Mobile Phase: A: H_2O (0.05% ammonia), B: ACN, Flow rate: 60 mL/min, gradient: from 40% B to 60% B) to afford the title compounds (**Compound 261**) (220 mg) and (**Compound 262**) (300 mg) both as white solid.

Compound 298

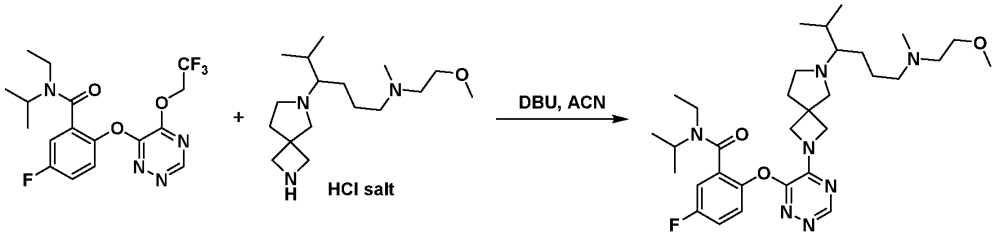
_N_-ethyl-5-fluoro-2-((5-(2-((3*R*)-6-hydroxy-2-methylheptan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-_N_-isopropylbenzamide

The following compound was synthesized by an analogous method described above for intermediate 53

Co. No.	Structure	Starting Materials
298		intermediate 97, methylmagnesium bromide

Compound 301

***N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(6-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-2-yl)-1,2,4-triazin-6-yl)oxy)benzamide**



To a solution of *N*-(2-methoxyethyl)-*N*,5-dimethyl-4-(2,6-diazaspiro[3.4]octan-6-yl)hexan-1-amine hydrochloride (**intermediate 164**) (2.10 g, crude) and DBU (1.80 g, 11.8 mmol) in ACN (40 mL) was added *N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2,2,2-trifluoroethoxy)-1,2,4-triazin-6-yl)oxy)benzamide (**intermediate 159**) (600 mg, 88% purity, 1.31 mmol) under N_2 atmosphere. The resulting mixture was stirred at 26 °C for 16 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by preparative HPLC over Phenomenex Gemini-NX (column: 80×40 mm 3 μm, Mobile Phase: A: H_2O (0.05% ammonia), B: ACN, Flow rate: 30 mL/min, gradient condition: from 29% B to 99% B) to afford the title compound (130 mg) as colorless oil.

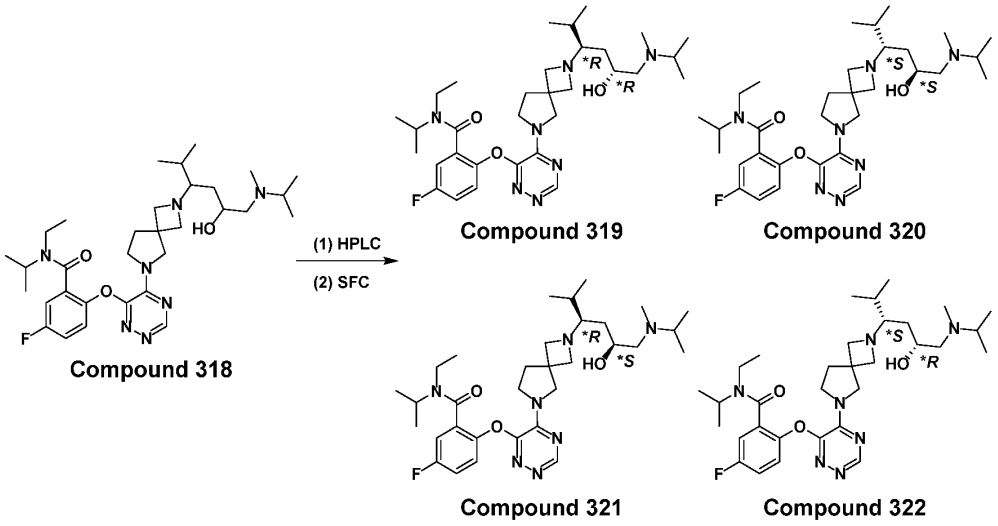
Compound 319, 320, 321 and 322

***N*-ethyl-5-fluoro-2-((5-(2-((3*R,5*R)-5-hydroxy-6-(isopropyl(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide**

***N*-ethyl-5-fluoro-2-((5-(2-((3*S,5*S)-5-hydroxy-6-(isopropyl(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide**

***N*-ethyl-5-fluoro-2-((5-(2-((3*R,5*S)-5-hydroxy-6-(isopropyl(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide**

***N*-ethyl-5-fluoro-2-((5-(2-((3*S,5*R)-5-hydroxy-6-(isopropyl(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide**



N-ethyl-5-fluoro-2-((5-(2-(5-hydroxy-6-(isopropyl(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide (**Compund 318**) (235 mg, 91.5% purity) was first separated by preparative HPLC over Welch Xtimate (column: 150×25 mm 5 μm, Mobile Phase A: H_2O (0.2% FA), Mobile Phase B: ACN, Flow rate: 25 mL/min, gradient condition: from 2% B to 32%) to afford a mixture of (**Compound 319** and **Compound 320**) (95 mg, 88% purity by LCMS) and a mixture of (**Compound 321** and **Compound 322**) (97 mg, 81% purity by LCMS).

The mixture of (**Compound 319** and **Compound 320**) (95 mg, 88% purity by LCMS) and the mixture of (**Compound 321** and **Compound 322**) (97 mg, 81% purity by LCMS) were further separately purified by preparative HPLC over Welch Xtimate (column: C18 100×40 mm 3 μm, Mobile Phase A: H_2O (0.075% TFA), Mobile Phase B: ACN, Flow rate: 30 mL/min, gradient condition: from 10% B to 40% B) to afford a mixture of (**Compound 319** and **Compound 320**) (73 mg, 98.9% purity by LCMS) and a mixture of (**Compound 321** and **Compound 322**) (70 mg, 100% purity by LCMS) both as TFA salts.

The mixture of (**Compound 319** and **Compound 320**) (70 mg, 98.9% purity by LCMS, asTFA salt) was further separated by SFC over DAICEL CHIRALPAK IG (column: 250×30 mm, 10 um); Mobile phase: A: Supercritical CO_2, B: MeOH (0.1% ammonia), A:B = 40:60 at 80 mL/min) to affford **Compound 319** (15.5 mg) and **Compound 320** (16.2 mg) both as colorless sticky oil.

The mixture of (**Compound 321** and **Compound 322**) (65 mg, 100% purity by LCMS, as TFA salt) was further separated by SFC over DAICEL CHIRALPAK IG (column: 250×30 mm, 10 um; Mobile phase: A: Supercritical CO_2, B: MeOH (0.1% ammonia), A:B = 65:35 at

80 mL/min) to afford **Compound 322** (24 mg) and another fraction (22 mg) which was further separated by SFC over DAICEL CHIRALPAK AD (column: 250×30mm, 10um; Mobile phase: A: Supercritical CO_2, B: EtOH (0.1% ammonia), A:B = 75:25 at 60 mL/min) to afford **Compound 321** (16 mg).

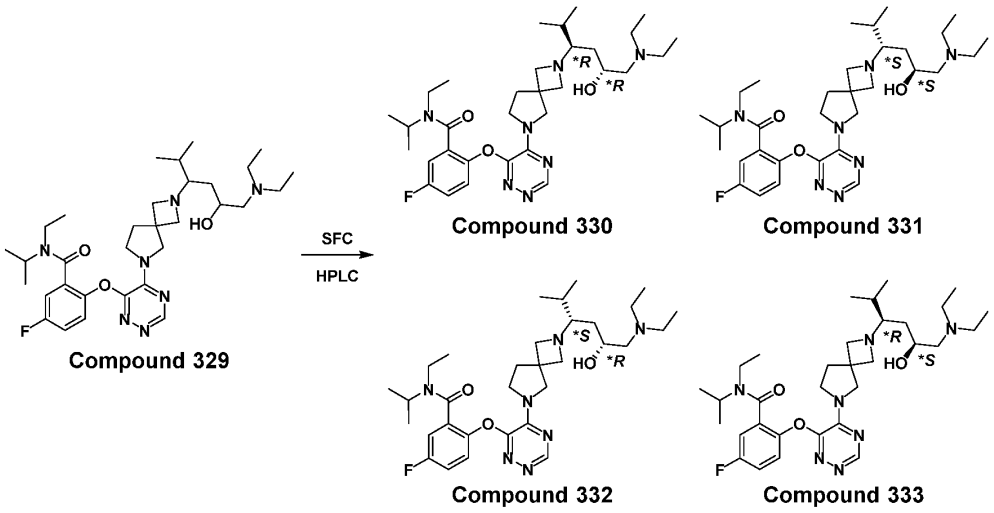
Compound 330, 331, 332, 333

2-((5-(2-((3*R,5*R)-6-(diethylamino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

2-((5-(2-((3*S,5*S)-6-(diethylamino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

2-((5-(2-((3*S,5*R)-6-(diethylamino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

2-((5-(2-((3*R,5*S)-6-(diethylamino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide



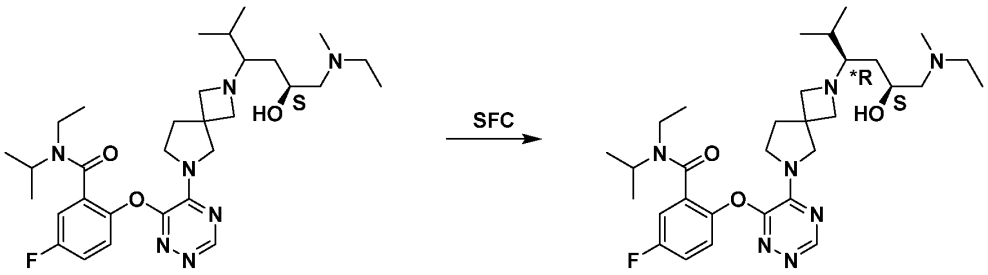
2-((5-(2-(6-(diethylamino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (**Compound 329**) (450 mg) was first separated by SFC over Daicel chiralpak AD (column: 250×30 mm, 10 μm, Mobile phase: A: Supercritical CO_2, B: EtOH (0.1% ammonia), A:B = 80:20 at 60 mL/min) to afford

a mixture of (**Compound 330** and **Compound 331**) (200 mg), **Compound 332** (70 mg, 100% purity by LCMS) and **Compound 333** (170 mg, 88.9% purity by LCMS).
The **Compound 333** (170 mg, 88.9% purity by LCMS) was further purified by preparative HPLC over Phenomenex Gemini-NX (column: 75×30 mm, 3 um, Mobiel phase: A: H_2O (0.05% ammonia + 10 mM NH_4HCO_3), B: ACN, gradient condition: from 33% B to 63%, Flow rate: 25 mL/min) to afford **Compound 333** (69 mg, 97.5% purity by LCMS).
The mixture of (**Compound 330** and **Compound 331**) (200 mg) was further separated by chiral HPLC over DAICEL CHIRALPAK IG (column: 250×30 mm, 10 μm, Mobile phase: A: Heptane, B: EtOH (0.1% ammonia), gradient from 30% B to 50%, Flow rate: 25 mL/min) to afford **Compound 330** (60 mg, 75% purity by LCMS) and **Compound 331** (60 mg, 92% purity by LCMS).
The **Compound 330** (60 mg, 75% purity by LCMS) and **Compound 331** (60 mg, 92% purity by LCMS) were further separately purified by preparative HPLC over Welch Xtimate (column: 150×25 mm, 5 μm; Mobile phase: A: H_2O (0.2% FA), B: ACN, Flow rate: 25 mL/min, gradient condition: from 2% B to 32% B) and basified with ammonia to afford **Compound 330** (29 mg, 100% purity by LCMS) and **Compound 331** (23 mg, 100% purity by LCMS).

Compound 340 and 341

***N*-ethyl-2-((5-(2-((3**R*,5*S*)-6-(ethyl(methyl)amino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide**

***N*-ethyl-2-((5-(2-((3**S*,5*S*)-6-(ethyl(methyl)amino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide**



Compound 338 **Compound 340**

+

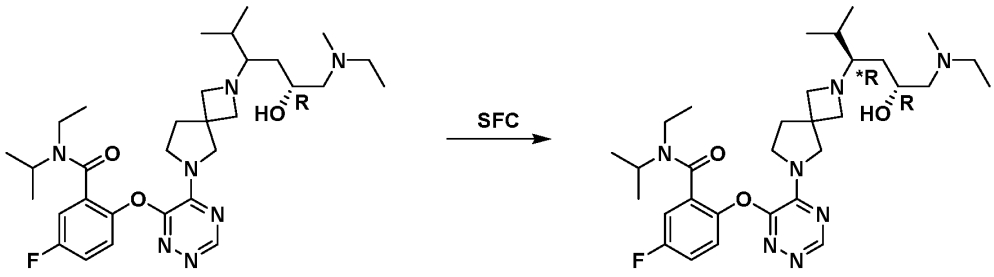
Compound 341

N-ethyl-2-((5-(2-((5*S*)-6-(ethyl(methyl)amino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (**Compound 338**) (160 mg) was separated by SFC over DAICEL CHIRALPAK IG (column: 250×30 mm, 10 μm; Mobile phase: A: Supercritical CO_2, B: IPA (0.1% ammonia), A: B = 55:45 at 80 mL/min) to afford the title compounds (**Compound 340**) (30 mg) and (**Compound 341**) (66 mg) both as colorless oil.

Compound 344 and 345

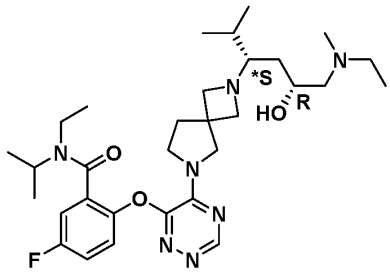
_N_-ethyl-2-((5-(2-((3*_R_,5_R_)-6-(ethyl(methyl)amino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-_N_-isopropylbenzamide

_N_-ethyl-2-((5-(2-((3*_S_,5_R_)-6-(ethyl(methyl)amino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-_N_-isopropylbenzamide



Compound 339 Compound 344

+

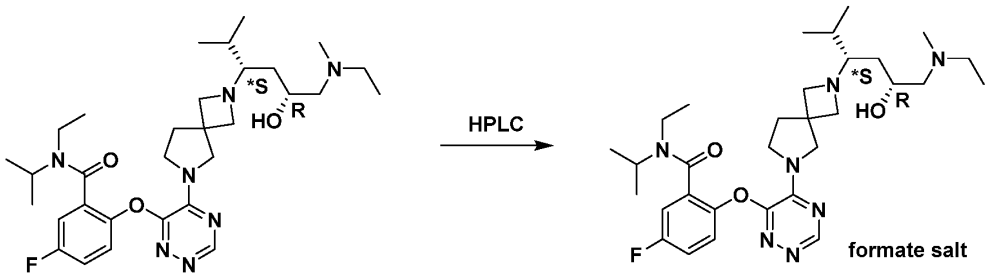


Compound 345

N-ethyl-2-((5-(2-((5*R*)-6-(ethyl(methyl)amino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (**Compound 339**) (200 mg) was separated by SFC over DAICEL CHIRALPAK IG (column: 250×30 mm, 10 μm; Mobile phase: A: Supercritical CO_2, B: EtOH (0.1% ammonia), A:B = 45:55 at 80 mL/min) to afford **Compound 344** (100 mg, 98.4% purity by LCMS) and **Compound 345** (70 mg, 76% purity by LCMS) both as colorless sticky solid.

Compound 347

_N_-ethyl-2-((5-(2-((3*_S_,5_R_)-6-(ethyl(methyl)amino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-_N_-isopropylbenzamide formate



Compound 345 Compound 347

N-ethyl-2-((5-(2-((3*S*,5*R*)-6-(ethyl(methyl)amino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropylbenzamide (**Compound 345**) (70 mg, 76% purity by LCMS) was further purified by preparative HPLC over Phenomenex Gemini-NX (column: 150×30 mm, 5 um; Mobile Phase A: H_2O (0.225% FA), Mobile Phase B: ACN, Flow rate: 35 mL/min, gradient condition: from 15% B to 45% B) to afford the title compound (40.0 mg, 99.6% purity by LCMS) as a white solid.

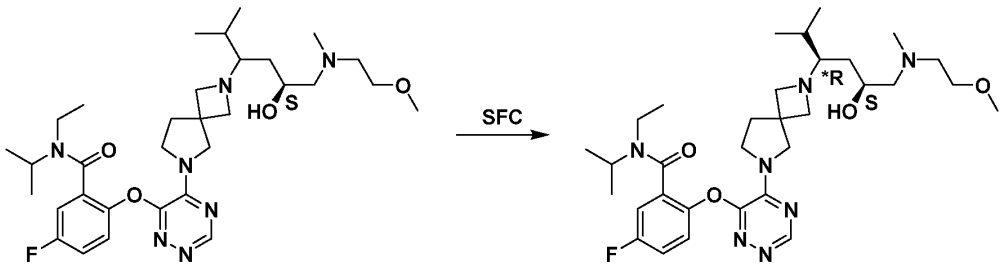
LC-MS (ESI) (Method 1): R_t = 2.891 min, m/z found 586.4 $[M+H]^+$.

SFC (Method 8): R_t = 2.652 min.

Compound 350 and 351

_N_-ethyl-5-fluoro-2-((5-(2-((3*_R_,5_S_)-5-hydroxy-6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-_N_-isopropylbenzamide

_N_-ethyl-5-fluoro-2-((5-(2-((3*_S_,5_S_)-5-hydroxy-6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-_N_-isopropylbenzamide



Compound 348 **Compound 350** + **Compound 351**

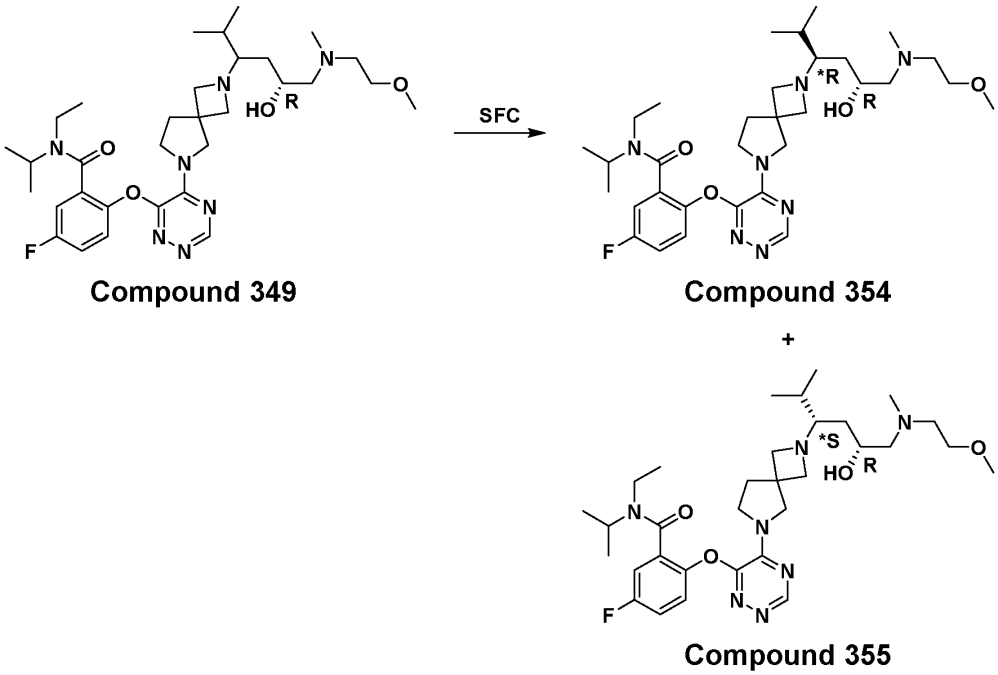
N-ethyl-5-fluoro-2-((5-(2-((5*S*)-5-hydroxy-6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide (**Compound 348**) (60 mg) was separated by SFC over DAICEL

CHIRALPAK IG (column: 250×30 mm, 10 um; Mobile phase: A: Supercritical CO_2, B: EtOH (0.1% ammonia), A:B = 55:45 at 80 mL/min) to afford the title compounds (**Compound 350**) (22 mg) and (**Compound 351**) (27.7 mg).

Compound 354 and 355

***N*-ethyl-5-fluoro-2-((5-(2-((3**R*,5*R*)-5-hydroxy-6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide**

***N*-ethyl-5-fluoro-2-((5-(2-((3**S*,5*R*)-5-hydroxy-6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide**

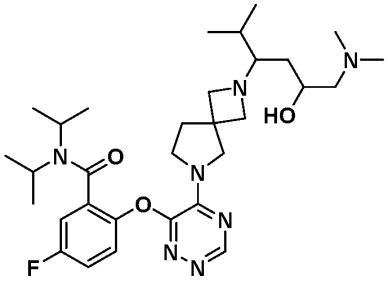


N-ethyl-5-fluoro-2-((5-(2-((5*R*)-5-hydroxy-6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide (**Compound 349**) (200 mg) was separated by SFC over DAICEL CHIRALPAK IG (column: 250×30 mm, 10 um; Mobile phase: A: Supercritical CO_2, B: EtOH (0.1% ammonia), A:B = 50:50 at 80 mL/min) to afford the title compounds (**Compound 354**) (100 mg) and (**Compound 355**) (70 mg) both as colorless sticky solid.

Compound 361 and 362

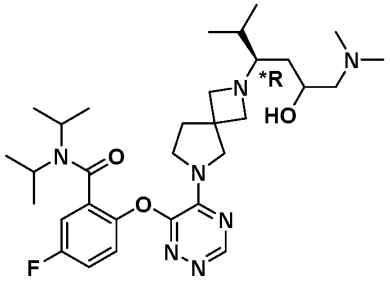
2-((5-(2-((3R*)-6-(dimethylamino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide**

2-((5-(2-((3S*)-6-(dimethylamino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide**



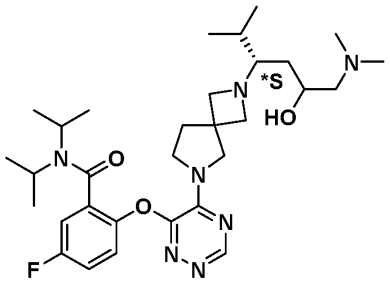
Compound 360

SFC



Compound 361

+



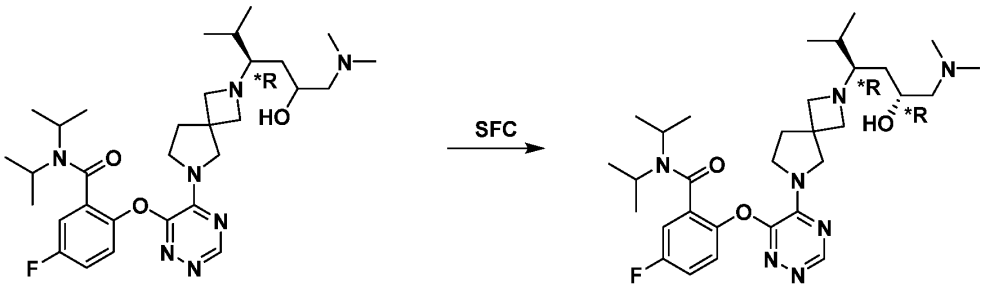
Compound 362

2-((5-(2-(6-(dimethylamino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide (**Compound 360**) (250 mg) was separated by SFC over DAICEL CHIRALPAK IG (column: 250×30 mm, 10 um; Mobile phase: A: Supercritical CO_2, B: IPA (0.1% ammonia), A:B = 40:40 at 80 mL/min) to afford the title compounds (**Compound 361**) (105 mg) and (**Compound 362**) (120 mg) both as white solid.

Compound 363 and 364

2-((5-(2-((3R*,5**R*)-6-(dimethylamino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide**

2-((5-(2-((3R*,5**S*)-6-(dimethylamino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide**



Compound 361

Compound 363

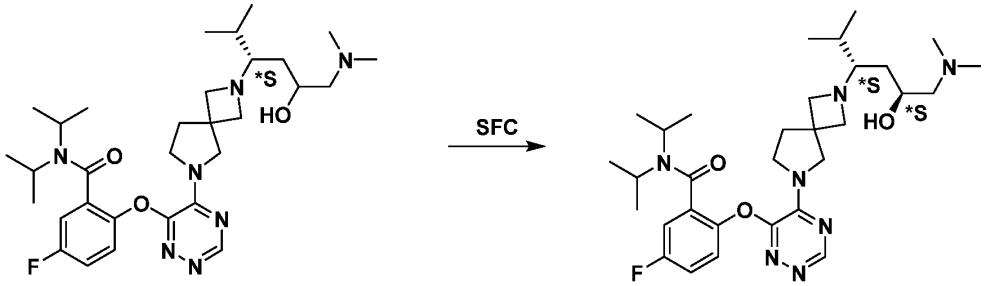
+

Compound 364

2-((5-(2-((3*R)-6-(dimethylamino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide (**Compound 361**) (105 mg) was separated by SFC over Phenomenex-Cellulose-2 (column: 250x30 mm,10 um; Mobile phase: A: Supercritical CO_2, B: 0.1%NH_3H_2O EtOH (0.1% ammonia), A:B = 65:35 at 80 mL/min) to afford the title compounds (**Compound 363**) (45 mg) and (**Compound 364**) (35 mg) both as colorless sticky solid.

Compound 367 and 368

2-((5-(2-((3*S*,5*S*)-6-(dimethylamino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide
2-((5-(2-((3*S*,5*R*)-6-(dimethylamino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide



Compound 362

Compound 367

+

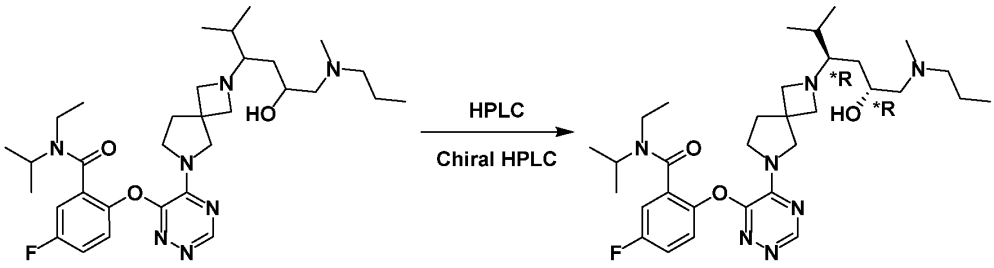
Compound 368

2-((5-(2-((3*S*)-6-(dimethylamino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide (**Compuond 362**) (120 mg) was separated by SFC over DAICEL CHIRALPAK AS (column: 250×30 mm,10um; Mobile phase: A: Supercritical CO_2, B: EtOH (0.1% ammonia), A:B = 75:25 at 60 mL/min) to afford the title compounds (**Compound 367**) (48 mg) and (**Compound 368**) (34 mg) both as colorless oil.

Compound 384 and 385

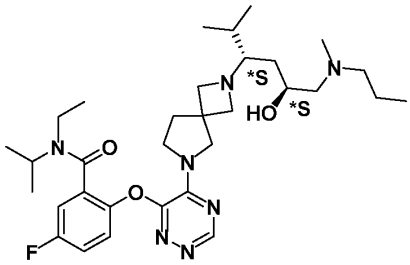
***N*-ethyl-5-fluoro-2-((5-(2-((3*R*,5*R*)-5-hydroxy-2-methyl-6-(methyl(propyl)amino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide**

***N*-ethyl-5-fluoro-2-((5-(2-((3*S*,5*S*)-5-hydroxy-2-methyl-6-(methyl(propyl)amino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide**



Compound 383 Compound 384

+



Compound 385

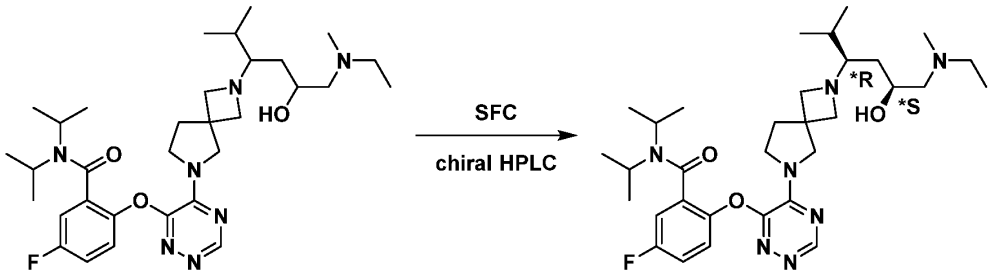
N-ethyl-5-fluoro-2-((5-(2-(5-hydroxy-2-methyl-6-(methyl(propyl)amino)hexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide (**Compound 383**) (432 mg) was purified by preparative HPLC over Welch Xtimate (column: C18 100×40 mm 3 μm, Mobile Phase A: H_2O (0.075%TFA), Mobile Phase B: ACN, Flow rate: 30 mL/min, gradient condition: from 10% B to 40% B) to afford a mixture of **Compound 384** and **Compound 385** (166 mg, as TFA salt).

The mixture of **Compound 384** and **Compound 385** (166 mg, TFA salt) was further separated by chiral HPLC over Daicel ChiralPak IG (column: 250×30 mm, 10 μm; Mobile phase: A: Heptane, B: EtOH (0.1% ammonia), Flow rate: 25mL/min, gradient condition: from 20% B to 50% B) to afford the title compounds (**Compound 384**) (30.7 mg) and (**Compound 385**) (14.4 mg) both as colorless sticky oil.

Compound 389 and 390

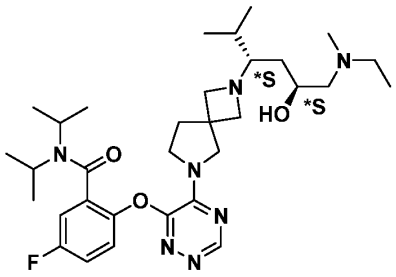
2-((5-(2-((3R*,5**S*)-6-(ethyl(methyl)amino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide**

2-((5-(2-((3*S,5*S)-6-(ethyl(methyl)amino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide



Compound 388 **Compound 389**

+



Compound 390

2-((5-(2-(6-(ethyl(methyl)amino)-5-hydroxy-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*,*N*-diisopropylbenzamide (**Compound 388**) (190 mg) was first separated by SFC over Daicel chiralpak IG (column: 250×30 mm, 10 μm; Mobile phase: A: Supercritical CO_2, B: EtOH (0.1% ammonia), A:B = 60:40; Flow rate: 80 mL/min) to afford **Compound 390** (45 mg) and a mixture of 3 diastereoisomers. (120 mg).

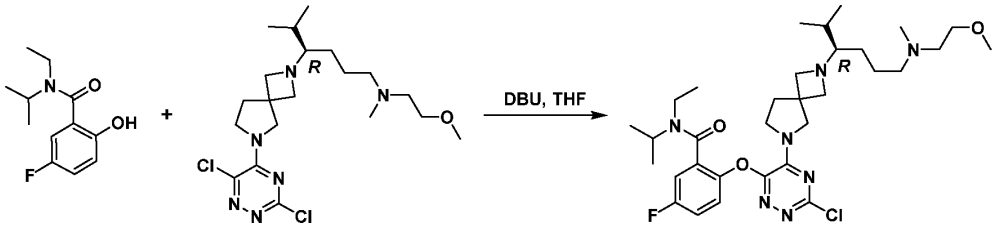
The mixture of 3 diastereoisomers (120 mg) was further separated by chiral HPLC over Daicel Daicel chiralpak IG (column: 250×30 mm, 10 μm), Mobile phase: A: Heptane, B: EtOH (0.1% ammonia), A:B = from 70:30 to 50:50, Flow rate: 25 mL/min) to afford **Compound 389** (22.0 mg, 86.6% purity by LCMS).

The **Compound 389** (22.0 mg, 86.6% purity by LCMS) was further purified by preparative HPLC over Welch Xtimate (column: C18 150×25 mm 5 μm, Mobile phase: A: H_2O (0.2% FA), B: ACN, gradient condition: from 2% B to 32%, Flow rate: 25 mL/min) and basified with ammonia to afford **Compound 389** (15.0 mg, 100% purity by LCMS).

Compound 393

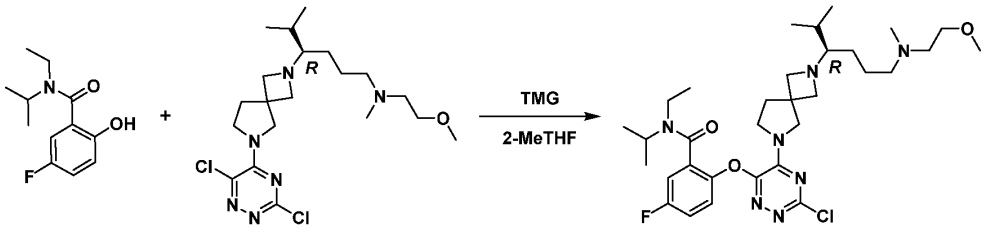
(*R*)-2-((3-chloro-5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide

Preparation Method A:



The mixture of *N*-ethyl-5-fluoro-2-hydroxy-*N*-isopropylbenzamide (**intermediate 28**) (1.10 g, 4.88 mmol), (*R*)-4-(6-(3,6-dichloro-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-*N*-(2-methoxyethyl)-*N*,5-dimethylhexan-1-amine (**intermediate 225**) (1.70 g, 3.82 mmol) and DBU (750 mg, 4.93 mmol) in anhydrous THF (15 mL) was stirred at 40 °C for 8 h. After cooled to RT, the mixture was concentrated under reduced pressure, the resulting residue was diluted with DCM (60 mL) and washed with H_2O (20 mL × 3). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product which was purified FCC (MeOH/DCM = 0% to 10%) to afford a yellow oil (1.40 g), which was further separated by SFC over DAICEL CHIRALPAK AD (column: 250×50 mm,10 um; Mobile phase: A: Supercritical CO_2, B: EtOH (0.1% ammonia), A:B = 50:50 at 70 mL/min; Column Temp: 38 °C; Nozzle Pressure: 100Bar; Nozzle Temp: 60 °C; Evaporator Temp: 20 °C; Trimmer Temp: 25 °C; Wavelength: 220nm) to afford the title compound (1.0 g).

Preparation Method B:



To a 2-MeTHF solution of (*R*)-4-(6-(3,6-dichloro-1,2,4-triazin-5-yl)-2,6-diazospiro[3.4]octan-2-yl)-*N*-(2-methoxyethyl)-*N*,5-dimethylhexan-1-amine (**intermediate 225**) (676g of a 14.8 wt% solution in 2-MeTHF, 100g corrected of **intermediate 225**) and *N*-ethyl-5-fluoro-2-hydroxy-*N*-isopropylbenzamide (**intermediate 28**) (50.6 g) in 2-MeTHF (40 g) at 20 to 30°C was added tetramethylguanidine (31 g) and the mixture was stirred for 40 to 48 h. A 7% $NaHCO_3$ aqueous solution (500g) was added and the mixture was stirred for 30 to 60 min. The aqueous layer was removed and the organic layer was washed with twice with 4% NaOH aqueous solution (2 x 500 g) and once with 10% Na_2SO_4 aqueous solution (500 g). The

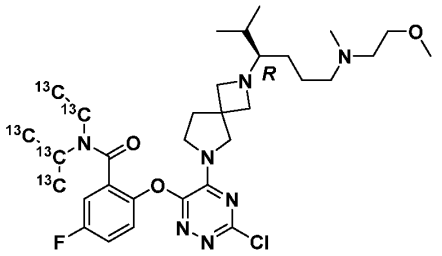
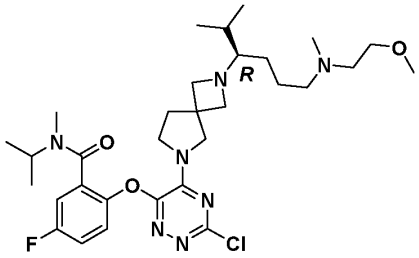
organic layer was concentrated under reduced pressure (<40°C) to 2.2~3.0 vol. and flushed three times with MeOH (1 × 790g and 2 × 395g) until both 2-MeTHF and water content were both ≤1.0% to afford the desired compound in 86% assay yield as a 60.1 wt% solution in methanol.

Compound 400, 414

(*R*)-2-((3-chloro-5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-(ethyl-$^{13}C_2$)-5-fluoro-*N*-(propan-2-yl-$^{13}C_3$)benzamide

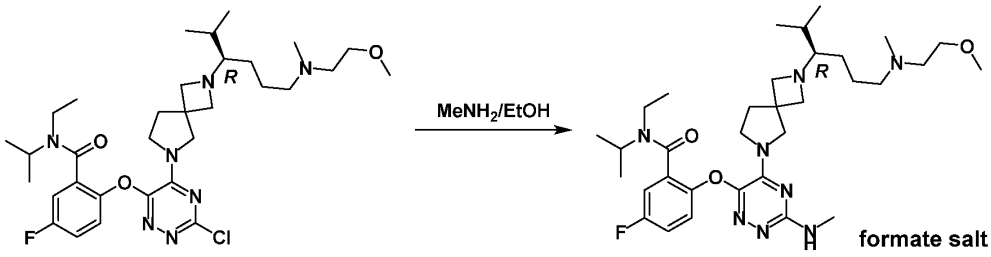
(*R*)-2-((3-chloro-5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-5-fluoro-*N*-isopropyl-*N*-methylbenzamide

The following compounds were synthesized by an analogous method described above for compound 393 by method A

Co. No.	Structure	Starting Materials
400		intermediate 237, intermediate 225
414		intermediate 247, intermediate 225

Compound 395

(*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-3-(methylamino)-1,2,4-triazin-6-yl)oxy)benzamide formate



The mixture of (*R*)-2-((3-chloro-5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide **(Compound 393)** (100 mg, 0.158 mmol) and methanamine (1 mL, 33% in EtOH) was stirred at 90 °C for 1 h. After cooled to RT, the mixture was concentrated under reduced pressure to give the crude product which was purified by preparative HPLC (Column: Welch Xtimate C18 150×25 mm 5 um, Mobile Phase A: H_2O (0.2% FA), Mobile Phase B: ACN, Flow rate: 25 mL/min, gradient condition: from 5% B to 35%) to afford the title compound (49.8 mg, 43.6% yield) as sticky solid.

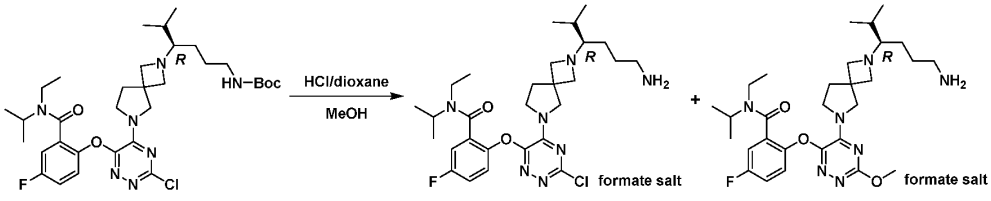
LC-MS (ESI) (Method 2): R_t = 1.997 min, m/z found 629.4 $[M+H]^+$.

SFC (Method 6): R_t = 1.228 min.

Compound 406 and 407

(*R*)-2-((5-(2-(6-amino-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-3-chloro-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide formate

(*R*)-2-((5-(2-(6-amino-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-3-methoxy-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide formate



Compound 404 **Compound 406** **Compound 407**

To a solution of *tert*-butyl (*R*)-(4-(6-(3-chloro-6-(2-(ethyl(isopropyl)carbamoyl)-4-fluorophenoxy)-1,2,4-triazin-5-yl)-2,6-diazaspiro[3.4]octan-2-yl)-5-methylhexyl)carbamate **(Compound 404)** (1.10 g, 1.66 mmol) in MeOH (15.0 mL) was added HCl/dioxane (15.0 mL, 60.0 mmol, 4M) and the resulting mixture was stirred at 20 °C for 12 h. The reaction mixture was concentrated under reduced pressure to give a residue which was purified by

preparative HPLC over Welch Xtimate (column: C18 150×25 mm, 5um, Mobile Phase A: H_2O (0.2%FA), Mobile Phase B: ACN, Flow rate: 25 mL/min, gradient condition from 3% B to 33% B) to afford the title compounds (**Compound 406**) (360 mg) and (**Compound 407**) (160 mg) both as sticky oil.

(**Compound 406**) (60 mg) was further purified by preparative HPLC over Boston Green ODS (column: 150×30 mm, 5 um; Mobile Phase A: H_2O (0.225%FA), Mobile Phase B: ACN, Flow rate: 35 mL/min, gradient condition from 5% B to 35% B) to afford the title compound (**Compound 406**) (40 mg).

Compound 406

LC-MS (ESI) (Method 1): R_t = 3.400 min, m/z found 562.3 $[M+H]^+$.

SFC (Method 32): R_t = 2.093 min.

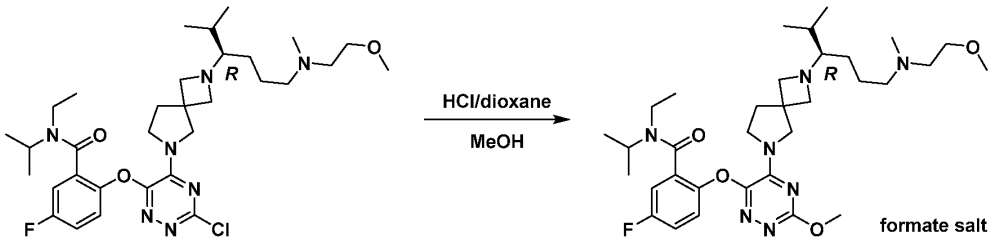
Compound 407

LC-MS (ESI) (Method 1): R_t = 2.028 min, m/z found 558.3 $[M+H]^+$.

SFC (Method 6): R_t = 1.42 min.

Compound 416

(*R*)-*N*-ethyl-5-fluoro-*N*-isopropyl-2-((3-methoxy-5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide formate



Compound 393 **Compound 416**

To the solution of *(R)*-2-((3-chloro-5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (**Compound 393**) (100 mg, 0.158 mmol) in anhydrous MeOH (2 mL) was added HCl (1.6 mL, 6.40 mmol, 4 M in dioxane). The resulting mixture was stirred at 25 °C for 60 h. The mixture was concentrated under reduced pressure to give the crude product which was purified by preparative HPLC (Column: Boston Green ODS 150×30 mm 5 um, Mobile Phase A: H_2O (0.225% FA), Mobile Phase B: ACN, Flow rate: 35 mL/min,

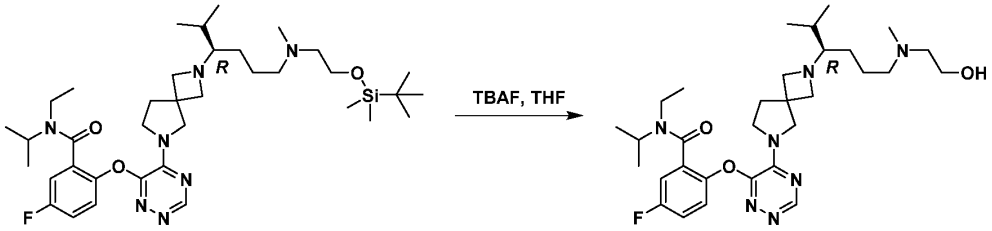
gradient condition from 12% B to 42% B) to afford the title compound (70.6 mg, 65.2% yield) as yellow sticky solid.

LC-MS (ESI) (Method 2): Rt = 2.096 min, m/z found 630.4 $[M+H]^+$.

SFC (Method 33): Rt = 2.587 min.

Compound 286

(*R*)-*N*-ethyl-5-fluoro-2-((5-(2-(6-((2-hydroxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-isopropylbenzamide



TBAF (79 µL; 0.079 mmol) was added dropwise to a solution of (*R*)-2-((5-(2-(6-((2-((*tert*-butyldimethylsilyl)oxy)ethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)-*N*-ethyl-5-fluoro-*N*-isopropylbenzamide (**intermediate 245**) (46 mg, 0.066 mmol) in THF (2 mL) at RT. The reaction mixture was stirred at RT for 20 h, then poured out into ice water and EtOAc was added. The mixture was basified with a 10% aqueous solution of K_2CO_3 and the organic layer was separated, washed with brine, dried over $MgSO_4$ and filtered. The solvent was evaporated to dryness to give a crude (45 mg) which was purified by silica gel chromatography (Stationary phase: irregular bare silica 4g, Mobile phase: 0.7% NH_4OH, 93% DCM, 7% MeOH). The fractions containing the product were mixed and concentrated. The resulting product was freeze-dried with ACN/H_2O 20/80 to give the title compound (30mg, 78% yield).

LC-MS (ESI) (Method 4): R_t = 3.048 min, m/z found 586.6 $[M+H]^+$; 644.6 $[M+CH3COO]^-$

ANALYTICAL METHODS

The analytical information in the Compounds above or in the Tables below, was generated by using the analytical methods described below.

NMR-Methods

Some NMR experiments were carried out using a Bruker Avance III 400 spectrometer at ambient temperature (298.6 K), using internal deuterium lock and equipped with BBO 400MHz S1 5 mm probe head with z gradients and operating at 400 MHz for the proton and

100MHz for carbon. Chemical shifts (δ) are reported in parts per million (ppm). J values are expressed in Hz.

Some NMR experiments were carried out using a Varian 400-MR spectrometer at ambient temperature (298.6 K), using internal deuterium lock and equipped with Varian 400 4NUC PFG probe head with z gradients and operating at 400 MHz for the proton and 100MHz for carbon. Chemical shifts (δ) are reported in parts per million (ppm). J values are expressed in Hz.

Some NMR experiments were carried out using a Varian 400-VNMRS spectrometer at ambient temperature (298.6 K), using internal deuterium lock and equipped with Varian 400 ASW PFG probe head with z gradients and operating at 400 MHz for the proton and 100MHz for carbon. Chemical shifts (δ) are reported in parts per million (ppm). J values are expressed in Hz.

Some NMR experiments were carried out using a Bruker AVANCE III HD 300 spectrometer at ambient temperature (298.6 K), using internal deuterium lock and equipped with PA BBO 300S1 BBF-H-D-05 Z 5 mm probe head with z gradients and operating at 300 MHz for the proton and 75 MHz for carbon. Chemical shifts (d) are reported in parts per million (ppm). J values are expressed in Hz.

LCMS (Liquid chromatography/Mass spectrometry)

General procedure

The High Performance Liquid Chromatography (HPLC) measurement was performed using a LC pump, a diode-array (DAD) or a UV detector and a column as specified in the respective methods. If necessary, additional detectors were included (see table of methods below).

Flow from the column was brought to the Mass Spectrometer (MS) which was configured with an atmospheric pressure ion source. It is within the knowledge of the skilled person to set the tune parameters (e.g. scanning range, dwell time…) in order to obtain ions allowing the identification of the compound's nominal monoisotopic molecular weight (MW). Data acquisition was performed with appropriate software.

Compounds are described by their experimental retention times (R_t) and ions. If not specified differently in the table of data, the reported molecular ion corresponds to the $[M+H]^+$ (protonated molecule) and/or $[M-H]^-$ (deprotonated molecule). In case the compound was not directly ionizable the type of adduct is specified (i.e. $[M+NH_4]^+$, $[M+HCOO]^-$, etc…). For molecules with multiple isotopic patterns (Br, Cl..), the reported value is the one obtained for the lowest isotope mass. All results were obtained with experimental uncertainties that are commonly associated with the method used.

Hereinafter, "SQD" means Single Quadrupole Detector, "RT" room temperature, "BEH" bridged ethylsiloxane/silica hybrid, "HSS" High Strength Silica, "DAD" Diode Array Detector.

Table 1a. LCMS Method Codes (Flow expressed in mL/min; column temperature (T) in °C; Run time in minutes).

Method code	Instrument	Column	Mobile phase	Gradient	Flow ---- Column T	Run time
1	Agilent	Waters XBridge C18 (2.0x50 mm, 5 uM)	mobile phase A: H_2O with 0.04 % TFA; mobile phase B: ACN with 0.02 % TFA	100%A was held for 1 min, A gradient from 100% A to 40% A is applied in 4 min, and 40%A down to 15%A in 2.5 min. And then return to 100%A in 2 min and held for 0.5 min. The post time is 0.5 min.	0.8 ---- 50	10
2	Agilent	Waters XBridge C18 (2.0x50 mm, 5 um)	mobile phase A: H_2O with 0.04 % TFA; mobile phase B: ACN with 0.02 % TFA	First, 90% A was held for 0.8 min. Then a gradient was applied to 20% A and 80% B in 3.7 min and held for 3 min. And then return to 90% A in 2 min and held for 0.5 min. The post time is 0.5 min.	0.8 ---- 50	10
3	Agilent	Waters XBridge Shield RP18 (2.1x50 mm, 5 um)	mobile phase A: H_2O with 0.05% ammonia; mobile phase B: ACN	First, 100% A was held for 1 min. Then a gradient was applied to 40% A and 60 % B in 4 min and then to 5% A and 95% B in 2.5 min. Finally return to 100% A in 2 min and held for 0.5 min. Post Time is 0.5 min.	0.8 ---- 40	10

Method code	Instrument	Column	Mobile phase	Gradient	Flow ---- Column T	Run time
4	Waters: Acquity UPLC® - DAD and Quattro Micro™	Waters BEH C18 (2.1x100 mm, 1.7 uM)	mobile phase A: 95% CH_3COONH_4 7mM / 5% ACN mobile phase B: ACN	84.2% A for 0.49min, to 10.5% A in 2.18min, held for 1.94min, back to 84.2% A in 0.73min, held for 0.73min.	0.343 ---- 40	6.2
5	Agilent 1260/6120	Waters Sunfire C18 (2.0x30 mm, 2.5 uM)	mobile phase A: H_2O with 0.1 % FA; mobile phase B: ACN	gradient from 5% B to 95% B is applied in 2.5 min, and held for 1.0 min. The post time is 0.8 min.	1 ---- 40	3.5
6	Agilent 1260/6120	Waters Sunfire C18 (2.0x30 mm, 2.5 uM)	mobile phase A: H_2O with 0.1 % FA; mobile phase B: ACN	5% B was held for 1 min, gradient from 5% B to 30% B is applied in 2 min, and 30% B to 95% B in 0.5 min, and held for 1.0 min. The post time is 0.8 min.	1 ---- 40	4.5
7	Agilent LC 1260 with MS6120	XBridge C18, 4.6 ×150 mm, 3.5 µm	Mobile phase A 0.05% TFA in H_2O Mobile phase B 0.05 % TFA in ACN	Time (min) A% B% Initial 95 5 11.0 65 35 13.0 5 95 15.0 5 95 16.0 95 5 20.0 95 5	1.5 ---- 45	20
8	Waters: Acquity® H-Class - DAD and SQD2™	Waters BEH® C18 (1.7µm, 2.1x50mm)	A: CH_3COONH_4 7mM 95% / CH_3CN 5%, B: CH_3CN	From 95% A/5% B to 5% A in 1min, held for 1.6min, back to 95% A/5% B in 0.2min, held for 0.5min.	0.5 ---- 40	3.5

Analytical SFC

General procedure for SFC methods

The SFC measurement was performed using an Analytical Supercritical fluid chromatography (SFC) system composed by a binary pump for delivering carbon dioxide (CO_2) and modifier, an autosampler, a column oven, a diode array detector equipped with a high-pressure flow cell standing up to 400 bars. If configured with a Mass Spectrometer (MS) the flow from the column was brought to the (MS). It is within the knowledge of the skilled person to set the tune parameters (e.g. scanning range, dwell time…) in order to obtain ions allowing the identification of the compound's nominal monoisotopic molecular weight (MW). Data acquisition was performed with appropriate software.

Table 2a. Analytical SFC Methods (Flow expressed in mL/min; column temperature (T) in °C; Run time in minutes, Backpressure (BPR) in bars or pound-force per square inch (psi). "ACN" means acetonitrile; "MeOH" means methanol; "EtOH" means ethanol; "DEA" means diethylamine. All other abbreviations used in the table below are as defined before)

Method code	column	mobile phase	gradient	Flow	Run time
				Col T	BPR
1	Waters UPCC with PDA (Chiralpak IG-3 100×4.6 mm I.D., 3 um)	A: Supercritical CO_2 B: MeOH (0.05% DEA)	40% of MeOH (0.05% DEA) in CO_2	3.2	10
				35	1500 psi
2	Waters UPCC with PDA (Chiralpak IG-3 100×4.6 mm I.D., 3 um)	A: Supercritical CO_2 B: IPA (0.05% DEA)	from 5% to 40% of B in 4 min and hold 40% for 2.5 min, then 5% of B for 1.5 min	2.8	8
				35	1500 psi
3	Agilent 1260 with DAD (ChiralPak AD-3 150×4.6 mm I.D., 3 um)	A: Supercritical CO_2 B: EtOH (0.05% DEA)	from 5% to 40% of B in 5.5 min and hold 40% for 3 min, then 5% of B for 1.5 min	2.5	10
				40	100 bar

Method code	column	mobile phase	gradient	Flow	Run time
				Col T	BPR
4	Waters UPCC with PDA (Chiralpak AD-3 50×4.6 mm I.D., 3 um)	A: Supercritical CO_2 B: IPA (0.05% DEA)	from 5% to 40% of B in 2 min and hold 40% for 1.2 min, then 5% of B for 0.8 min	4	4
				35	1500 psi
5	Waters UPCC with PDA (Chiralpak IG-3 100×4.6 mm I.D., 3 um)	A: Supercritical CO_2 B: MeOH (0.05% DEA)	40% of MeOH (0.05% DEA) in CO_2	3.2	3
				35	1500 psi
6	Waters UPCC with PDA (Chiralpak AD-3 50×4.6 mm I.D., 3 um)	A: Supercritical CO_2 B: EtOH (0.05% DEA)	from 5% to 40% of B in 2 min and hold 40% for 1.2 min, then 5% of B for 0.8 min	4	4
				35	1500 psi
7	Waters UPCC with PDA (Chiralpak IG-3 100×4.6 mm I.D., 3 um)	A: Supercritical CO_2 B: MeOH (0.05% DEA)	25% of MeOH (0.05% DEA) in CO_2	3.5	9
				35	1500 psi
8	Waters UPCC with PDA (Chiralpak IG-3 50×4.6 mm I.D., 3 um)	A: Supercritical CO_2 B: EtOH (0.05% DEA)	from 5% to 40% of B in 2 min and hold 40% for 1.2 min, then 5% of B for 0.8 min	4	4
				35	1500 psi
9	Waters UPCC with PDA (Cellulose 2 150×4.6 mm I.D., 5um)	A: Supercritical CO_2 B: EtOH (0.05% DEA)	50% B hold for 10 min	2.5	11
				35	1500 psi
10	Agilent 1260 with DAD (ChiralPak AS-3 150×4.6 mm I.D., 3 um)	A: Supercritical CO_2 B: EtOH (0.05% DEA)	from 5% to 40% of B in 5.5min, then 5% of B for 1.5 min	2.5	7
				40	100 bar

Method code	column	mobile phase	gradient	Flow	Run time
				Col T	BPR
11	Waters UPCC with PDA (Chiralpak IG-3 100×4.6 mm I.D., 3 um)	A: Supercritical CO_2 B: EtOH (0.05% DEA)	from 5% to 40% of B in 4 min and hold 40% for 2.5 min, then 5% of B for 1.5 min	2.8	8
				35	1500 psi.
12	Agilent 1260 with DAD (ChiralPak IG-3 100×4.6 mm I.D., 3 um)	A: Supercritical CO_2 B: MeOH (0.1% Ethanolamine)	Isocratic: 40% B	3	3
				40	100 bar
13	Waters UPCC with PDA (Chiralpak AS-3 100×4.6 mm I.D., 3 um)	A: Supercritical CO_2 B: EtOH (0.05% DEA)	from 5% to 40% of B in 4 min and hold 40% for 2.5 min, then 5% of B for 1.5 min	2.8	8
				35	1500 psi
14	Waters UPCC with PDA (Chiralcel OD-3 100×4.6 mm I.D., 3 um)	A: Supercritical CO_2 B: EtOH (0.05% DEA)	from 5% to 40% of B in 4 min and hold 40% for 2.5 min, then 5% of B for 1.5min	2.8	8
				35	1500 psi
15	Waters UPCC with PDA (Chiralcel OD-3 50×4.6 mm I.D., 3 um)	A: Supercritical CO_2 B: EtOH (0.05% DEA)	from 5% to 40% of B in 2 min and hold 40% for 1.2 min, then 5% of B for 0.8 min	4	4
				35	1500 psi
16	Waters UPCC with PDA (Chiralpak AD-3 150×4.6 mm I.D., 3 um)	A: Supercritical CO_2 B: IPA (0.05% DEA)	from 5% to 40% of B in 5 min and from 40% to 5% of B in 0.5min, hold 5% of B for 1.5 min	2.5	7
				35	1500 psi
17	Waters UPCC with PDA (Cellulose-4 100×4.6 mm I.D., 3 um)	A: Supercritical CO_2 B: EtOH (0.05% DEA)	Isocratic: 40% B	28	6
				35	1500 psi

Method code	column	mobile phase	gradient	Flow	Run time
				Col T	BPR
18	Waters UPCC with PDA (Chiralpak IG-3 50×4.6 mm I.D., 3 um)	A: Supercritical CO_2 B: MeOH (0.05% DEA)	from 5% to 40% of B in 2 min and hold 40% for 1.2 min, then 5% of B for 0.8 min	1	10
				35	1500 psi
19	Agilent 1260 with DAD (ChiralPak IG-3 100×4.6 mm I.D., 3 um)	A: Supercritical CO_2 B: IPA (0.05% DEA)	Isocratic: 40% B	2.5	7
				40	1500 psi
20	Agilent 1260 with DAD (ChiralPak AD-3 150×4.6 mm I.D., 3 um)	A: Supercritical CO_2 B: EtOH (0.05% DEA)	Isocratic: 40% B	2.5	5
				40	1500 psi
21	Waters UPCC with PDA (Chiralpak AD-3 150×4.6 mm I.D., 3 um)	A: Supercritical CO_2 B: IPA (0.05% DEA)	from 5% to 40% of B in 5 min and hold 40% for 2.5 min, then 5% of B for 2.5 min	2.5	10
				35	1500 psi
22	Waters UPCC with PDA (Chiralpak IG-3 100×4.6 mm I.D., 3 um)	A: Supercritical CO_2 B: MeOH (0.05% DEA)	from 5% to 40% of B in 4 min and hold 40% for 2.5 min, then hold 5% of B for 1.5 min	2.8	8
				35	1500 psi
23	Agilent 1260 with DAD (ChiralPak AD-3 150×4.6 mm I.D., 3 um)	A: Supercritical CO_2 B: IPA (0.05% DEA)	from 5% to 40% of B in 5.5min and hold 40% for 3 min, then 5% of B for 1.5 min	2.5	10
				40	100 bar

Method code	column	mobile phase	gradient	Flow	Run time
				Col T	BPR
24	Waters UPCC with PDA (Chiralcel OJ-3 150×4.6 mm I.D., 3 um)	A: Supercritical CO_2 B: EtOH (0.05% DEA)	from 5% to 40% of B in 5min and from 40% to 5% of B in 0.5min, hold 5% of B for 1.5 min	2.5	7
				35	1500 psi
25	Waters UPCC with PDA (Chiralpak AS-3 100×4.6 mm I.D., 3 um)	A: Supercritical CO_2 B: EtOH (0.05% DEA)	from 5% to 40% of B in 2 min and hold 40% for 2.5 min, then 5% of B for 1.5 min	2.8	6
				35	1500 psi
26	Waters UPCC with PDA (Chiralpak AD-3 150×4.6 mm I.D., 3 um)	A: Supercritical CO_2 B: EtOH (0.05% DEA)	from 5% to 40% of B in 5 min and hold 40% for 2.5 min, then 5% of B for 2.5 min	2.5	10
				35	1500 psi
27	Waters UPCC with PDA (Chiralpak IG-3 100×4.6 mm I.D., 3um)	A: Supercritical CO_2 B: EtOH (0.05% DEA)	Isocratic: 40% B	3.2	9
				35	1500 psi
28	Agilent 1260 with DAD (ChiralPak IG-3 100×4.6 mm I.D., 3 um)	A: Supercritical CO_2 B:MeOH (0.05% DEA)	Isocratic: 40% B	2.5	6
				40	100 bar
29	Waters UPCC with PDA (Chiralpak AD-3 150×4.6 mm I.D., 3 um)	A: Supercritical CO_2 B: EtOH (0.05% DEA)	from 5% to 40% of B in 5 min and from 40% to 5% of B in 0.5min, hold 5% of B for 1.5 min	2.5	7
				35	1500 psi

Method code	column	mobile phase	gradient	Flow	Run time
				Col T	BPR
30	Waters UPCC with PDA (Cellulose-2 100×4.6 mm I.D., 3 um)	A: Supercritical CO_2 B: EtOH (0.05% DEA)	Isocratic: 40% B	2.8	5
				35	1500 psi
31	Agilent 1260 with DAD (ChiralPak IG-3 100×4.6 mm I.D., 3 um)	A: Supercritical CO_2 B: EtOH (0.05% DEA)	Isocratic: 40% B	2.5	6
				40	100 bar
32	Waters UPCC with PDA Chiralcel OJ-3 100×4.6 mm I.D., 3 um	A: Supercritical CO_2 B: EtOH (0.05% DEA)	from 5% to 40% of B in 4 min and hold 40% for 2.5 min, then 5% of B for 1.5 min	2.8	8
				35	1500 psi
33	Waters UPCC with PDA Chiralcel OD-3 100×4.6 mm I.D., 3 um	A: Supercritical CO_2 B: EtOH (0.05% DEA)	from 5% to 40% of B in 4 min and hold 40% for 0.5 min, then 5% of B for 1.5 min	2.8	6
				35	1500 psi

Analytical chiral HPLC

General method

The Chiral HPLC measurement was performed using a Chiral High Performance Liquid Chromatography (Chiral HPLC) system composed by a LC pump, a diode-array (DAD) or a UV detector and a chiral column as specified in the respective methods. Data acquisition was performed with appropriate software.

Table 2b. Analytical chiral HPLC Methods (Flow expressed in mL/min; column temperature (T) in °C; Run time in minutes, Backpressure (BPR) in bars or pound-force per square inch (psi). “ACN” means acetonitrile; “MeOH” means methanol; “EtOH” means ethanol; “DEA”

means diethylamine. All other abbreviations used in the table below are as defined before)

Method code	column	mobile phase	gradient	Flow	Run time
				Col T	BPR
1	Shimadzu LC-20AB with PDA (Lux Cellulose 2 150×4.6 mm I.D., 3 um)	A: Hexane (0.1% DEA) B:EtOH (0.1% DEA)	Isocratic: A:B = 70:30	1	15
				35	1500 psi
2	Agilent 1260 with DAD (IE-3 150×4.6 mm I.D., 3 um)	MeOH (0.05% DEA)	hold 100% of MeOH (0.05% DEA) for 20 min	1	20
				25	100 bar
3	Shimadzu LC-20AT (CHIRALPAK AD-3 150×4.6 mm I.D., 5 um)	A: Hexane B: EtOH	Isocratic: A:B = 90:10	1	11
				35	1500 psi
4	Shimadzu LC-20AB with PDA (Chiralpak IG-3 50×4.6 mm I.D., 3 um)	A: Hexane (0.1% DEA) B: IPA	Isocratic: A:B = 80:20	1	15
				35	1500 psi
5	Shimadzu LC-20AT CP-HPLC-09 (CHIRALPAK AD-H 150×4.6 mm I.D., 5 um)	A: Hexane (0.1% DEA) B: EtOH (0.1% DEA)	Isocratic: A:B = 90 : 10	1	15
				35	1500 psi

Method code	column	mobile phase	gradient	Flow	Run time
				Col T	BPR
6	Shimadzu LC-20AB with PDA (Chiralpak IG-3 50×4.6 mm I.D., 3 um)	A: Hexane (0.1% DEA) B: EtOH (0.1% DEA)	Isocratic: A:B = 70:30	1	10
				35	1500 psi
7	Shimadzu LC-20AB with PDA (Chiralpak IG-3 50×4.6 mm I.D., 3 um)	A: Hexane (0.1% DEA) B: EtOH (0.1% DEA)	Isocratic: A:B = 80 : 20	1	10
				35	1500 psi
8	Shimadzu LC-20AD with PDA (Chirapak IE 100×4.6 mm I.D., 3 um)	A: Hexane (0.1% DEA) B: EtOH (0.1% DEA)	Isocratic: A:B = 40:60	1	15
				35	1500 psi
9	Shimadzu LC-20AD with PDA (Chirapak ID 100×4.6 mm I.D., 3 um)	A: Hexane (0.1%DEA) B: EtOH (0.1% DEA)	Isocratic: A:B = 60:40	1	10
				35	1500 psi

PHARMACOLOGICAL PART

1) Menin/MLL homogenous time-resolved fluorescence (HTRF) assay

To an untreated, white 384-well microtiter plate was added 40 nL 200X test compound in DMSO and 4 µL 2X terbium chelate-labeled menin (vide infra for preparation) in assay buffer (40 mM Tris·HCl, pH 7.5, 50 mM NaCl, 1 mM DTT (dithiothreitol) and 0.05% Pluronic F-127). After incubation of test compound and terbium chelate-labeled menin for 30 min at ambient temperature, 4 µL 2X FITC-MBM1 peptide (FITC-β-alanine-SARWRFPARPGT-NH_2) ("FITC" means fluorescein isothiocyanate) in assay buffer was added, the microtiter plate centrifuged at 1000 rpm for 1 min and the assay mixtures incubated for 15 min at ambient temperature. The relative amount of menin·FITC-MBM1 complex present in an

assay mixture is determined by measuring the homogenous time-resolved fluorescence (HTRF) of the terbium/FITC donor /acceptor fluorphore pair using an EnVision microplate reader (ex. 337 nm/terbium em. 490 nm/FITC em. 520 nm) at ambient temperature. The degree of fluorescence resonance energy transfer (the HTRF value) is expressed as the ratio of the fluorescence emission intensities of the FITC and terbium fluorophores (F^{em} 520 nm/F^{em} 490 nm). The final concentrations of reagents in the binding assay are 200 pM terbium chelate-labeled menin, 75 nM FITC-MBM1 peptide and 0.5% DMSO in assay buffer. Dose-response titrations of test compounds are conducted using an 11 point, four-fold serial dilution scheme, starting typically at 10 µM.

Compound potencies were determined by first calculating % inhibition at each compound concentration according to equation 1:

$$\% \text{ inhibition} = ((HC - LC) - (HTRF^{compound} - LC)) / (HC - LC)) * 100 \quad (Eqn\ 1)$$

Where LC and HC are the HTRF values of the assay in the presence or absence of a saturating concentration of a compound that competes with FITC-MBM1 for binding to menin, and $HTRF^{compound}$ is the measured HTRF value in the presence of the test compound. HC and LC HTRF values represent an average of at least 10 replicates per plate. For each test compound, % inhibition values were plotted *vs.* the logarithm of the test compound concentration, and the IC_{50} value derived from fitting these data to equation 2:

$$\% \text{ inhibition} = \text{Bottom} + (\text{Top-Bottom})/(1+10\text{^}((\log IC_{50}-\log[\text{cmpd}])*h)) \quad (Eqn\ 2)$$

Where Bottom and Top are the lower and upper asymptotes of the dose-response curve, respectively, IC_{50} is the concentration of compound that yields 50% inhibition of signal and h is the Hill coefficient.

Preparation of Terbium cryptate labeling of Menin: Menin (a.a 1-610-6xhis tag, 2.3 mg/mL in 20mM Hepes (2-[4-(2-Hydroxyethyl)-1-piperazinyl]ethane sulfonic acid), 80 mM NaCl, 5mM DTT (Dithiothreitol), pH 7.5) was labeled with terbium cryptate as follows. 200 µg of Menin was buffer exchanged into 1x Hepes buffer. 6.67 µM Menin was incubated with 8-fold molar excess NHS (N-hydroxysuccinimide)-terbium cryptate for 40 minutes at room temperature. Half of the labeled protein was purified away from free label by running the reaction over a NAP5 column with elution buffer (0.1M Hepes, pH 7 + 0.1% BSA (bovine serum albumin)). The other half was eluted with 0.1M phosphate buffered saline (PBS), pH7. 400 µl of eluent was collected for each, aliquoted and frozen at -80°C. The final concentration of terbium-labeled Menin protein was 115 µg/mL in Hepes buffer and 85 µg/mL in PBS buffer, respectively.

MENIN Protein Sequence (SEQ ID NO: 1):

MGLKAAQKTLFPLRSIDDVVRLFAAELGREEPDLVLLSLVLGFVEHFLAVNRVIPTNVPELT
FQPSPAPDPPGGLTYFPVADLSIIAALYARFTAQIRGAVDLSLYPREGGVSSRELVKKVSDV
IWNSLSRSYFKDRAHIQSLFSFITGTKLDSSGVAFAVVGACQALGLRDVHLALSEDHAWVVF
GPNGEQTAEVTWHGKGNEDRRGQTVNAGVAERSWLYLKGSYMRCDRKMEVAFMVCAINPSID
LHTDSLELLQLQQKLLWLLYDLGHLERYPMALGNLADLEELEPTPGRPDPLTLYHKGIASAK
TYYRDEHIYPYMYLAGYHCRNRNVREALQAWADTATVIQDYNYCREDEEIYKEFFEVANDVI
PNLLKEAASLLEAGEERPGEQSQGTQSQGSALQDPECFAHLLRFYDGICKWEEGSPTPVLHV
GWATFLVQSLGRFEGQVRQKVRIVSREAEAAEAEEPWGEEAREGRRRGPRRESKPEEPPPPK
KPALDKGLGTGQGAVSGPPRKPPGTVAGTARGPEGGSTAQVPAPAASPPPEGPVLTFQSEKM
KGMKELLVATKINSSAIKLQLTAQSQVQMKKQKVSTPSDYTLSFLKRQRKGLHHHHHH

2a) Proliferation assay

The anti-proliferative effect of menin/MLL protein/protein interaction inhibitor test compounds was assessed in human leukemia cell lines. The cell line MOLM14 harbors a MLL translocation and expresses the MLL fusion protein MLL-AF9, respectively, as well as the wildtype protein from the second allele. OCI-AML3 cells that carry the NPM1c gene mutation were also tested. MLL rearranged cell lines (e.g. MOLM14) and NPM1c mutated cell lines exhibit stem cell-like HOXA/MEIS1 gene expression signatures. KO-52 was used as a control cell line containing two *MLL (KMT2A)* wildtype alleles in order to exclude compounds that display general cytotoxic effects.

MOLM14 cells were cultured in RPMI-1640 (Sigma Aldrich) supplemented with 10% heat-inactivated fetal bovine serum (HyClone), 2 mM L-glutamine (Sigma Aldrich) and 50µg/ml gentamycin (Gibco). KO-52 and OCI-AML3 cell lines were propagated in alpha-MEM (Sigma Aldrich) supplemented with 20% heat-inactivated fetal bovine serum (HyClone), 2 mM L-glutamine (Sigma Aldrich) and 50µg/ml gentamycin (Gibco). Cells were kept at 0.3 – 2.5 million cells per ml during culturing and passage numbers did not exceed 20.

In order to assess the anti-proliferative effects, 200 MOLM14 cells, 200 OCI-AML3 cells or 300 KO-52 cells were seeded in 200µl media per well in 96-well round bottom, ultra-low attachment plates (Costar, catalogue number 7007). Cell seeding numbers were chosen based on growth curves to ensure linear growth throughout the experiment. Test compounds were added at different concentrations and the DMSO content was normalized to 0.3%. Cells were incubated for 8 days at 37°C and 5% CO_2. Spheroid like growth was measured in real-time by live-cell imaging (IncuCyteZOOM, Essenbio, 4x objective) acquiring images at day 8. Confluence (%) as a measure of spheroid size was determined using an integrated analysis tool.

In order to determine the effect of the test compounds over time, the confluence in each well as a measure of spheroid size, was calculated. Confluence of the highest dose of a reference compound was used as baseline for the LC (Low control) and the confluence of DMSO treated cells was used as 0% cytotoxicity (High Control, HC).

Absolute IC_{50} values were calculated as percent change in confluence as follows:

LC = Low Control: cells treated with e.g. 1 μM of the cytotoxic agent staurosporin, or e.g. cells treated with a high concentration of an alternative reference compound

HC = High Control: Mean confluence (%) (DMSO treated cells)

% Effect = 100 - (100*(Sample-LC)/(HC-LC))

GraphPad Prism (version 7.00) was used to calculate the IC_{50}. Dose-response equation was used for the plot of % Effect vs Log10 compound concentration with a variable slope and fixing the maximum to 100% and the minimum to 0%.

2b) MEIS1 mRNA expression assay

MEIS1 mRNA expression upon treatment of compound was examined by Quantigene Singleplex assay (Thermo Fisher Scientific). This technology allows for direct quantification of mRNA targets using probes hybridizing to defined target sequences of interest and the signal is detected using a Multimode plate reader Envision (PerkinElmer). The MOLM14 cell line was used for this experiment. Cells were plated in 96-well plates at 3,750 cells/well in the presence of increasing concentrations of compounds. After incubation of 48 hours with compounds, cells were lysed in lysis buffer and incubated for 45 minutes at 55°C. Cell lysates were mixed with human MEIS1 specific capture probe or human RPL28 (Ribosomal Protein L28) specific probe as a normalization control, as well as blocking probes. Cell lysates were then transferred to the custom assay hybridization plate (Thermo Fisher Scientific) and incubated for 18 to 22 hours at 55°C. Subsequently, plates were washed to remove unbound materials followed by sequential addition of preamplifiers, amplifiers, and label probe. Signals (= gene counts) were measured with a Multimode plate reader Envision. IC_{50}s were calculated by dose-response modelling using appropriate software. For all non-housekeeper genes response equal counts corrected for background and relative expression. For each sample, each test gene signal (background subtracted) was divided by the normalization gene signal (RPL28: background subtracted). Fold changes were calculated by dividing the normalized values for the treated samples by the normalized values for the DMSO treated sample. Fold changes of each target gene were used for the calculation of IC_{50}s.

Table 3. Biological data – HTRF assay, proliferation assay, and MEIS1 mRNA expression assay

Compound Number	HTRF-30min incubation IC_{50} (nM)	MEIS1 IC_{50} (μM)	spheroid assay_OneTime MOLM14 IC_{50} (μM)	OCI-AML3 IC_{50} (μM)	spheroid assay_OneTime KO-52 IC_{50} (μM)
1	0.13	0.075	0.23	0.17	>15
2	3.31	>2.5	2.22		>15
3	0.10	0.095	0.042	0.31	>15
4	0.095	0.02	0.03	0.39	>15
5	2.26	~0.99	0.84		>15
6	0.61	0.36	0.48	1.86	>15
7	86.20	>2.5	>3.75		>15
8	0.43	~0.65	1.02	2.15	>15
9	44.66		>3.75		>15
10	0.18	0.41	0.34	1.68	>15
11	0.11	0.018	0.021	0.21	8.38
12	0.12	0.039	0.036	0.63	8.24
13	0.40	0.077	0.061	0.21	>15
14	0.05	0.0085	0.01	0.069	3.10
15	0.25	0.071	0.10	0.46	3.70
16	1.85	~0.67	0.37		10.51
17	0.61	0.24	0.30	1.44	6.79
18	0.30	0.15	0.12	0.66	>15
19	0.11	0.033	0.058	0.16	>15
20	4.19	>1	>0.94		>15
21	10.41	>1	>0.94		>15
22	1.79	~0.76	0.36		12.82
23	0.22	0.15	0.17	0.81	13.82
24	0.97	~0.84	0.69	2.68	>15
25	10.52	~1.2	>3.75		>15
26	0.28	0.49	0.27	1.34	>15
27	0.09	0.02	0.021	0.091	6.85

Compound Number	HTRF-30min incubation IC_{50} (nM)	MEIS1 IC_{50} (μM)	spheroid assay_OneTime MOLM14 IC_{50} (μM)	OCI-AML3 IC_{50} (μM)	spheroid assay_OneTime KO-52 IC_{50} (μM)
28	2.75	>1	0.60	1.36	>15
29	2.42	~2.25	0.97		>15
30	0.067	0.099	0.13	0.47	>15
31	2.28	>1	>0.94		>15
32	0.10	0.088	0.058	0.28	12.9
33	2.84	>1	>0.94		>15
34	0.87	>1	3.84	3.44	>15
35	0.15	0.12	0.20	0.49	>15
36	2.60	>1	>0.94		>15
37	0.12	0.039	0.04	0.43	>15
38	1.16	~1.1	0.52		>15
39	0.26	0.044	0.027	0.14	>15
40	0.40	0.019	0.019	0.074	9.54
41	0.36	0.024	0.011	0.17	>15
42	15.00				
43	0.55	~0.24	0.29	1.20	>15
44	46.62	>2.5	>3.75		>15
45	0.37	0.21	0.22	1.25	>15
46	59.70	>2.5	>3.75		>15
47	0.31	0.14	0.22	0.6	10.84
48	70.39	>1	>0.94		>15
69	0.099	0.016	0.02	0.087	7.18
70	0.098	0.017	0.017	0.12	7.75
70a	0.18	0.017	0.011	0.08	
71		0.38	0.56	1.47	12.81
74	0.51	0.26	0.14	1.29	10.57
75	0.21	0.14	0.053	0.41	>15
76	2.56		0.34	2.39	
77	0.51	0.12	0.10	1.32	13.66

Compound Number	HTRF-30min incubation IC_{50} (nM)	MEIS1 IC_{50} (μM)	spheroid assay_OneTime MOLM14 IC_{50} (μM)	OCI-AML3 IC_{50} (μM)	spheroid assay_OneTime KO-52 IC_{50} (μM)
78	3.69	>1	>0.94	12.18	>15
83	0.14	0.092	0.17	0.42	6.24
84	5.90	>1	>0.94	7.17	>15
88	0.083	0.13	0.12	0.81	14
89	3.79				
90	0.16		0.04	0.19	1
94	0.12	0.0082	0.01	0.096	4.75
95	4.98	~0.62	0.39	1.62	>15
99	0.20	0.026	0.0085	0.082	11.5
100	2.05				
102	0.11	0.033	0.016	0.11	>15
103	2.43	0.42	0.29	1.36	>15
104	0.074	0.015	0.0067	0.15	10.74
112	0.049	0.009	0.0098	0.081	>15
114	0.05	0.022	0.014	0.042	1.69
122	0.065	0.034	0.021	0.15	>15
123	3.98	>1	>0.94	3.55	>15
127	0.089	0.044	0.026	0.14	11.27
128	1.64	~0.68	0.63	1.99	11.39
132	0.11	0.015	0.033	0.19	10.41
133	2.13	>1	>0.94	3.50	>15
135	0.057	0.016	0.013	0.23	9.69
137	0.18	0.025	0.045	0.16	7.29
140	0.093	0.028	0.11	0.33	5.75
142	0.071	0.051	0.012	0.22	>15
145	0.07	0.021	0.014	0.11	>15
146	0.081	0.44	0.32	1.79	>15
148	0.35	0.06	0.041	0.34	>15
150	0.26	0.013	0.014	0.16	8.70

Compound Number	HTRF-30min incubation IC_{50} (nM)	MEIS1 IC_{50} (μM)	spheroid assay_OneTime MOLM14 IC_{50} (μM)	OCI-AML3 IC_{50} (μM)	spheroid assay_OneTime KO-52 IC_{50} (μM)
152	0.19	0.087	0.037	0.35	>15
154	0.051	0.027	0.022	0.067	>15
157	0.12	0.022	0.021	0.083	13.80
159	0.10	~0.017	0.01	0.012	6.30
161	0.23	0.041	0.016	0.055	>15
162	0.096	~0.019	0.013	0.026	>15
163	0.089	0.02	0.018	0.12	>15
165	0.06	0.023	0.03	0.099	>15
167	0.16	0.018	0.017	0.065	>15
168	0.10	0.074	0.049	0.37	>15
170	0.10	0.037	0.025	0.041	>15
172	0.13	0.013	0.023	0.038	13.4
176	0.13	0.017	0.038	0.12	>15
177	0.062	0.0073	0.024	0.064	>15
179	0.13	0.027	0.033	0.059	>15
181	0.079	0.017	0.023	0.044	14.02
184	~0.36	0.11	0.23	0.19	3.00
185	0.20	0.044	0.079	0.061	1.7
188	0.43	0.034	0.055	0.34	>15
189	0.22	0.019	0.03	0.19	>15
191	0.28	0.22	0.28	0.56	>15
193	~0.26	0.12	0.17	0.29	>15
195	~0.4	0.056	0.07	0.058	>15
197	0.30	0.036	0.045	0.036	>15
199	0.13	~0.26	0.46	1.91	>15
201	0.13	0.052	0.04	0.065	>15
203	0.30	0.042	0.038	0.075	>15
205	0.21	0.035	0.029	0.043	>15
209	0.27	0.13	0.27	0.24	>15

Compound Number	HTRF-30min incubation IC_{50} (nM)	MEIS1 IC_{50} (μM)	spheroid assay_OneTime MOLM14 IC_{50} (μM)	OCI-AML3 IC_{50} (μM)	spheroid assay_OneTime KO-52 IC_{50} (μM)
210	5.57	>1	>0.94	4.63	
211	0.35	0.11	0.15	0.097	>15
212	9.45				
214	0.49	0.14	0.12	0.38	>15
215	88.84	>1	1.49	9.24	
219	0.27	~0.23	0.13	0.43	>15
223	0.40	0.20	0.18	0.99	>15
225	8.31	>1	>0.94	7.09	
227	0.15	0.076	0.046	0.13	>15
229	0.37	0.36	0.32	0.87	>15
230	~0.88	~0.94	>0.94	1.16	>15
231	1.77	~0.56	0.79	1.80	
233	0.058	0.019	0.026	0.15	5.03
240	12.31				
241	1.36	0.28	0.18	1.12	
242	0.26	0.23	0.17	1.07	>15
243	7.39				
245	0.26	0.14	0.073	0.43	>15
246	0.063	0.18	0.06	0.38	>15
250	0.18	0.091	0.22	0.41	7.05
251	0.18	0.019	0.052	0.13	3.90
252	0.065	0.053	0.032	0.64	7.26
254	4.16		0.59	4.69	>15
256	0.15	0.13	0.084	0.36	>15
258	0.33	0.026	0.027	0.74	5.44
259	0.16	0.065	0.046	0.25	>15
265	0.29		0.028	0.061	
266	0.92	0.039	0.029	0.049	>15
268	0.29	0.34	0.20	0.53	>15

Compound Number	HTRF-30min incubation IC_{50} (nM)	MEIS1 IC_{50} (μM)	spheroid assay_OneTime MOLM14 IC_{50} (μM)	OCI-AML3 IC_{50} (μM)	spheroid assay_OneTime KO-52 IC_{50} (μM)
270	0.54	0.22	0.14	0.48	>15
271	0.27	0.1	0.065	0.16	>15
272	0.58	0.17	0.13	0.44	>15
273	0.21	~0.39	0.39	0.83	>15
274	0.38	0.23	0.20	0.64	>15
275	0.66	0.1	0.078	0.33	>15
276	0.50	0.39	0.24	1.61	>15
278	0.068	>1	>0.94	3.21	>15
280	0.20	1.07	0.69	0.92	>15
281	0.24	0.038	0.048	0.09	>15
283	0.054	0.01	0.014	0.046	>15
284	~0.36	0.05	0.023	0.073	>15
285	1.02	0.27	0.16	0.13	>15
286		0.096	0.076	0.29	22.94
300	0.066	0.029	0.036	0.071	>15
302	0.26	0.16	0.097	0.77	
311	1.01	~0.63	0.51	2.88	>15
313	1.99	~0.26			
314	1.53	0.16	0.30		
315	0.51	~0.33	0.29	1.09	>15
323	0.49	0.062	0.11	0.17	13.39
324	18.4				
325	~0.16	0.015	0.016	0.19	>15
326	18.51				
334	0.079	0.011	0.012	0.13	>15
335	5.49				
336	0.21	0.061	0.07	0.87	>15
337	4.57	>1			
342	0.17	0.078	0.01	0.025	0.023

Compound Number	HTRF-30min incubation IC_{50} (nM)	MEIS1 IC_{50} (μM)	spheroid assay_OneTime MOLM14 IC_{50} (μM)	OCI-AML3 IC_{50} (μM)	spheroid assay_OneTime KO-52 IC_{50} (μM)
343	~3.93	0.53			
346	0.058	0.033	0.036	0.13	>15
347	12.02	>1	>0.94	4.98	
352	0.077	0.13	0.018	0.15	>15
353	4.19				
356	0.053	~0.0082	0.007	0.046	>15
357	7.77				
365	0.097	0.01	0.011	0.037	>15
366	0.088	0.02	0.017	0.076	>15
369	1.82	~0.36	0.42		
370	5.42				
377	15.41				
378	27.28				
379	14.21				
380	40.55				
382	0.41	0.15	0.14	0.40	11.82
386	~0.59	0.061	0.16	0.81	9.6
387	9.52				
391	0.90	0.16	0.49	2.10	>15
392	10.34				
394	0.23	0.049	0.11	0.33	>15
395	0.20	0.14	0.056	0.28	
396	0.08	0.017	0.023	0.14	8.51
397	0.08	0.018	0.015	0.027	>15
398	0.24	0.043	0.064	0.22	>15
402	0.067	0.018	0.007	0.04	
406	0.033	0.13	0.22	0.49	
407	0.086	0.38			
409	0.12	~0.44	0.64	1.85	

Compound Number	HTRF-30min incubation IC_{50} (nM)	MEIS1 IC_{50} (μM)	spheroid assay_OneTime MOLM14 IC_{50} (μM)	OCI-AML3 IC_{50} (μM)	spheroid assay_OneTime KO-52 IC_{50} (μM)
410	0.12	0.12	0.16	0.38	
411	0.33	0.11	0.21	0.68	
413	0.051	~0.59	0.72	1.49	
415	0.084				
416	~0.035	0.049			

3) Mouse PK (In vivo T1/2 and oral bioavailability)

In vivo pharmacokinetics (PK) were assessed in fasted male CD-1 mice (age 6-8 weeks) following a single intravenous (IV, 0.5 or 1.0 mg/kg administered at 2.5 ml/kg) or oral (PO, 5 mg/kg administered at 10 ml solution/kg) dose of test article formulated in a 20% (w:vol) HP-β-CD solution or in Pyrogen free water.

Plasma and/or whole blood samples were collected from the dorsal metatarsal vein at desired timepoints via serial capillary microsampling (approx. 0.03 mL) using EDTA as an anticoagulant. Concentrations of compound in the plasma and blood samples were analyzed using a qualified LC-MS/MS method. In silico analysis of main pharmacokinetic parameters was performed using WinNonlin (PhoenixTM, version 6.1) or similar software. (Results see Table 4)

4) Metabolic stability in human/mouse liver microsomes

Experimental Procedure

The objective of this study is to measure *in vitro* metabolic stability of test compound(s) in human and mouse liver microsomes and provide quantitative information on the rate of metabolic turnover (i.e. determination of the apparent intrinsic clearance of test).

Test items were prepared at a stock concentration of 10 mM in DMSO. For determination of metabolic turnover, a final working solution was prepared by adding 2 μL of 10 mM DMSO stock solution for test compound or positive control compounds to 198 μL of acetonitrile (100 μM final concentration).

Incubations were performed as follows: First, liver microsomes were thawed on ice and a master solution containing liver microsomes in 100 mM PBS (phosphate-buffered saline) at pH 7.4 is prepared. Next, the liver microsomes solution was added to the incubation plates and 10

mM NADPH (Nicotinamide-adenine dinucleotide phosphate) was added (MW: 833.4 g/mol; Roche Diagnostics GmbH, Germany. Dissolved in phosphate buffer (100 mmol/L, pH 7.4)). The mixture was mixed for 10 seconds and pre-warmed in the incubation plate at 37°C for 10 minutes. The metabolic reaction was initiated with the addition of 5 µL of the 100 µM working solution for test compound or positive control compounds to incubation plate (final test item concentration = 1 µM). The reaction final mixture should contain 1 mM NADPH, 0.5 mg/mL microsomes protein and 1 µM test compound or positive control compound in 100 mM PBS at pH 7.4. The percentage of organic solvent in incubation mixture is 1% with DMSO ≤ 0.02%.

The reaction was quenched by transferring 50 µL of the incubated mixture at selected time points into the quenching plate containing 200 µL of cold methanol. After sampling of all the timepoints the quenching plate was centrifuged at 4000 rpm for 40 minutes to precipitate protein. A total of 90 µL of the supernatant was transferred to an analysis plate and ultra-pure H_2O water is added into each well for LC/MS/MS analysis. All incubations and analysis were performed in duplicate.

Data analysis

All calculations were carried out using Microsoft Excel. The slope value, k, was determined by linear regression of the natural logarithm of the remaining percentage of the parent drug vs. incubation time curve.

The *in vitro* half-life (*in vitro* $t_{1/2}$) was determined from the slope value:

$$\textit{in vitro}\ t_{1/2} = -(0.693 / k)$$

Conversion of the *in vitro* $t_{1/2}$ (in min) into the *in vitro* intrinsic clearance (*in vitro* CL_{int}, in µL/min/mg proteins) was done using the following equation:

$$in\ vitro\ Cl_{int} = \left(\frac{0.693}{t_{\frac{1}{2}}}\right) * \left(\frac{volume\ of\ incubation\ (\mu L)}{amount\ of\ proteins\ (mg)}\right)$$

Results see Table 4

Table 4: Mouse PK and metabolic stability ("NA" means not analyzed)

Example number	Formulating agent	In vivo T1/2 (IV) (h)	Bio-availability (PO) (%)	Human LM Clint (μl/min/mg)	Mouse LM Clint (μl/min/mg)
27	HP-β-CD	6.7	17	19	<7.5
70	Pyrogen free water	9.0	34	19	<7.5
346	HP-β-CD	5.2	5.1	11	<7.5
102	HP-β-CD	11	9.7	NA	NA
396		NA	NA	22	<7.5
104	HP-β-CD	8.7	6.1	19	<7.5
114	HP-β-CD	9.5	8.7	26	15
1	HP-β-CD	15	<1	<7.5	21
112	HP-β-CD	6.2	4.0	17	<7.5
245	HP-β-CD	7.0	<1	18	<7.5
37	HP-β-CD	>12	<1	<7.5	<7.5
6	HP-β-CD	NA	NA	35	28
45	HP-β-CD	NA	NA	43	110
13	HP-β-CD	NA	NA	75	44
47	HP-β-CD	NA	NA	38	47
83	HP-β-CD	NA	NA	539	>1000
161	HP-β-CD	NA	NA	70	55
214	HP-β-CD	NA	NA	44	80
99	HP-β-CD	NA	NA	27	13
397	HP-β-CD	NA	NA	14	<7.5
11	HP-β-CD	NA	NA	14	<7.5

5) Protocol for pharmacodynamics (PD) activity in subcutaneous (sc or SC) xenografts of MOLM-14 or OCI-AML3 cells

Test Agents and Controls

Compound 70 was formulated in 20% hydroxypropyl-beta-cyclodextrin (HP-β-CD) and prepared to reach a total volume of 0.2 mL (10 mL/kg) per dose for a 20 g animal. Doses were adjusted by individual body weight each day. Working stocks of Compound 70 were prepared once per week for each study and stored at room temperature. Compound 70 was administered orally (PO), daily.

Assay

The in vivo pharmacodynamics (PD) activity of compounds was evaluated in subcutaneous (SC) xenografts of MOLM14 cells or OCI-AML3. Nude NMRI mice (Crl:NMRI-Foxn1nu/-) harboring MOLM14 or OCI-AML3 tumors were treated with 3 daily doses of vehicle or compounds. Plasma samples were collected at 23 hours after day 2 dose, 0.5 hours post final

dose, and 16 hours post final dose and tumor samples were collected 16 hours post final dose. To examine the effects of compounds on the expression of multiple Menin-MLL target genes (e.g. MEIS1, MEF2C, FLT3) QuantiGene Plex technology (Thermo Fisher Scientific) was used. Frozen tumors were homogenized and transferred to individual lysing matrix tubes in lysis buffer and incubated for 30 minutes at 55°C. Cell lysates were mixed with target-specific capture probes, Luminex beads, and blocking probes, transferred to the custom assay hybridization plate (Thermo Fisher Scientific) and incubated for 18 to 22 hours at 54°C. Subsequently, plates were transferred to a magnetic separation plate and washed to remove unbound materials from beads followed by sequential hybridization of preamplifiers, amplifiers, and label probe and subsequent streptavidin phycoerythrin binding. Signals from the beads were measured with a Luminex FlexMap three-dimensional instrument. For all non-housekeeper genes response equal counts corrected for background and relative expression. For each sample, each test gene signal (background subtracted) was divided by the normalization gene signal (RPL19, RPL28, ATP6V1A: background subtracted). Fold changes were calculated by dividing the normalized values for the treated samples by the normalized values for the DMSO treated sample.

Table 5: Expression level (% relative to vehicle) of selected genes from MOLM14 SC model (mean values and standard deviations).

Compound 70 (mg/kg)	MEIS1	FLT3	MEF2C
0	101.30 ± 15.06	104.80 ± 10.07	103.50 ± 11.02
3	83.49 ± 25.48	78.67 ± 20.74	85.50 ± 22.77
10	62.84 ± 4.06	74.91 ± 8.97	68.04 ± 14.43
30	23.16 ± 2.75	52.61 ± 4.51	27.83 ± 2.17
50	14.40 ± 3.39	36.14 ± 3.50	18.75 ± 2.38
100	10.97 ± 3.21	35.82 ± 1.10	14.18 ± 1.56

Table 6: Expression level (% relative to vehicle) of selected genes from OCI-AML3 SC model (mean values and standard deviations).

Compound 70 (mg/kg)	MEIS1
0	100.30 ± 8.53
3	87.90 ± 39.75
10	48.81 ± 15.30
30	32.66 ± 3.71
50	23.83 ± 1.34
100	16.76 ± 1.92

6) Efficacy study in MOLM-14 subcutaneous model

Test Agents and Controls

Compound 70 was formulated in 20% hydroxypropyl-beta-cyclodextrin (HP-β-CD) and prepared to reach a total volume of 0.2 mL (10 mL/kg) per dose for a 20 g animal. Doses were adjusted by individual body weight each day. Working stocks of Compound 70 were prepared once per week for each study and stored at 25°C.

Animals

Female NMRI Nude mice (MOLM-14 SC) were used when they were approximately 6 to 8 weeks of age and weighed approximately 25 g. All animals could acclimate and recover from any shipping-related stress for a minimum of 7 days prior to experimental use. Autoclaved water and irradiated food were provided ad libitum, and the animals were maintained on a 12hour light and dark cycle. Cages, bedding, and water bottles were autoclaved before use and changed weekly.

Tissue Culture and Cell Injection Reagents

DPBS (Dulbecco's phosphate-buffered saline)
Heat-inactivated fetal bovine serum
RPMI 1640 medium
L-glutamine
Gentamycin
T175 Culture Flask
Roller Bottle

Tumor Model and Cell Culture Method

Human AML cells MOLM-14 were cultured at 37°C, 5% CO_2 in the indicated complete culture media (RPMI 1640 + 10% HI-FBS + 2mM L-glutamine + 50ug/ml Gentamycin). Cells were harvested while in logarithmic growth and resuspended in cold (4°C) Roswell Park Memorial Institute (RPMI) 1640 in serum-free medium.

Each mouse received 5×10^6 MOLM-14 cells in 50% Matrigel in the right flank, in a total volume of 0.2 mL using a 1cc syringe and a 27-gauge needle.

Study Designs

Compound 70 was administered orally (PO), daily.

Day 0 is the day of tumor cell implantation and study initiation

Mice bearing SC MOLM-14 tumors were randomized on Day 16 post-tumor implantation and assigned to treatment groups according to tumor volume (mean of ~130 mm^3; n=10/group). Treatment with vehicle or Compound 70 (at 30 and 100 mg/kg) was initiated on the same day, with daily oral dosing for 21 days. Plasma was collected at 1, 2, 4, 8, and 23 hours after the last dose (n=4-5/group/time point) for PK (pharmacokinetics) analysis.

Animal Monitoring

SC tumor volume were measured for each animal 2 to 3 times per week or more throughout the study.

Calculations

Tumor volume was calculated using the formula:

Tumor volume (mm^3) = ($D\times d^2/2$); where 'D' represents the larger diameter and 'd' the smaller diameter of the tumor as determined by caliper measurements. Tumor volume data was graphed as the mean tumor volume ± SEM.

The % ΔTGI was defined as the difference between mean tumor burden of the treatment and control groups, calculated as % $\Delta TGI = ([(TV_cTVc_0)(TV_tTV_{t0})]/(TV_cTVc_0))\times100$ where 'TV_c' is the mean tumor burden of a given control group, 'TVc_0' is the mean initial tumor burden of a given control group, 'TV_t' is the mean tumor burden of the treatment group, and 'TV_{t0}' is the mean initial tumor burden of the treatment group. % TGI was defined as the difference between Mean tumor volumes of the treated and control groups, calculated as:

% $TGI = ((TV_cTV_t)/TV_c)\times100$ where 'TV_c' is the mean tumor volume of the control group and 'TV_t' is the mean tumor volume of the treatment group. As defined by National Cancer Institute criteria, ≥60% TGI is considered biologically significant.

The % Tumor Regression (TR), quantified to reflect the treatment-related reduction of tumor volume as compared to baseline independent of the control group, was calculated as %TR= (1-mean ($TV_ti/TV_{t0}i$)) x 100 where 'TV_ti' is the tumor burden of individual animals in a treatment group, and '$TV_{t0}i$' is the initial tumor burden of the animal.

Data Analysis

Tumor volume were graphed using Prism software (GraphPad version 7 or 8). Statistical significance for most studies was evaluated for Compound 70 -treated groups compared with HPβCD vehicle-treated controls on the last day of the study when 2/3 or more mice remained in each group. Differences between groups were considered significant when $p \leq 0.05$.

Statistical significance for animal tumor volume was calculated using the linear mixed-effects (LME) analysis in R software version 3.4.2 (using Janssen's internally developed Shiny application version 4.0), with treatment and time as fixed effects and animal as random effect. Logaritmic transformation was performed if individual longitudinal response trajectories were not linear.

The information derived from this model was used to make pairwise treatment comparisons of tumor volumes to that of the control group or between all the treatment groups.

Results in Fig. 1.

7) Cardio-electrophysiological effects of the testing compounds in synchronously beating human pluripotent stem cell-derived cardiomyocytes (hSC-CMs) using a Ca^{2+}-fluorescence assay (CTCM human)

Protocol

Compounds were tested in the 96-well plates

Compounds were tested at 0.1 μM, 0.2 μM, 0.5 μM, 1 μM, 2.5 μM and 5 μM (n = 4 per dose) on Cor.4U ®-Cardiomyocytes or on iCell® Cardiomyocytes2

Alternatively, compounds were tested at 0.1 μM, 0.3 μM; 1 μM, 3 μM,10 μM and 30 μM (n = 4 per dose) mostly on iCell® Cardiomyocytes2

Positive and Negative controls

Dofetilide	at 3 nM
Isoproterenol	at 100 nM
Nimodipine	at 100-300 nM
Cetirizine	at 3 μM

Vehicle control:

Dimethylsulfoxide (DMSO). The solutions of the compound in DMSO or its solvent (final concentration of 0.1% DMSO; n = 8)

Preparation of Test Article and Controls

Tested compounds were dissolved in DMSO at 1000-fold the intended concentrations. A compound "mother-plate" was made, containing the test compounds and positive and negative controls at 1000-fold the final concentrations. At the experiment day, these stock solutions were diluted with Tyrode (Sigma), supplemented with 10 mM HEPES (Gibco), to 2-fold the intended concentration (in round bottom compound plates). Final DMSO concentration in test solutions and vehicle control was 0.1%.

Cells

hSC-CMs (Cor.4U® Cardiomyocytes) were obtained from CDI (Ncardia, Germany). Cells are pre-plated and seeded in fibronectin-coated 96-well plates at a density suited to form a monolayer and maintained in culture in a stage incubator (37°C, 5% CO_2), according to the instructions of the cell provider.

Second line hSC derived cardiomyocyte called iCell® Cardiomyocytes2 were purchased from FUJIFILM Cellular Dynamics (USA). The experiments with test drugs are carried out 5 to 7 days after plating the cells onto the plate to have a living, beating monolayer of hiPSC-derived cardiomyocytes. The beating monolayer in 96-well-plates are normally taken from 2 Vials of frozen iCell® Cardiomyocytes*2* (≈5 million cells/vial), which will be plated onto three 96-well plates (≈50K/well).

Before start of experiment

At least one hour before the start of the experiments the normal cell medium was replaced with Tyrode solution with Calcium dye (see below).

Cal 520 dye (AAT Bioquest) was dissolved in 11 ml of Tyrode supplemented with 10 mM HEPES and warmed up to 37 C before adding to the cells.

35 µl cell culture medium was removed from each well and replaced with 35 µl of pre-warmed Cal 520 dye solution and cell plate was incubated for 45 min at 37 °C / 5% CO_2. Cells were incubated for 5 min at 37 °C.

Experiment

Spontaneous electrical activity is recorded, using Cal520™ (AAT Bioquest) calcium fluorescence-dye signaling. This dye integrates the total intracellular calcium activity over the whole well. A bottle of Cal520 dye (50µg, MW: 1103/mol) is dissolved with 50 µl DMSO as a stock solution of 0.9 mM. 50 µL of the stock solution of the dye was added to 10 ml Tryodes solution to have dye concentration of 4.5 µM. Subsequently, 35 µl of this dye solution was added into each well, to have a final dye concentration of 1.58 µM. The current dye protocol on this CTCM human assay was established recently (Ivan Kopljar et al, Journal of

Pharmacological and toxicological methods 2018. 91: 80-86; Lu et al., Tox Sci 2019. 170 (2): 345-356).

Fluorescent signals (Ca^{2+} transient morphology) were measured using the Functional Drug Screen System (FDSS/μCell; Hamamatsu, Japan) and the recordings were subsequently analyzed off-line, using appropriate software e.g. Notocord.

The cell plate was loaded into the FDSS/μCell for a test run: Ca^{2+} transients were measured for 4 minutes to check for synchronous beating of the cardiomyocytes in each well. All 96 wells were measured simultaneously (sampling interval: 0.06 s, short exposure time: 10 ms; excitation wavelength 480 nm; emission wavelength 540 nm; FDSS/μCell warmed to 37°C). When all showed synchronous beating, the 96-well plate was measured repeatedly for 3 times (to verify synchronous beating in all 96-well at baseline, wells that did not meet the preset criteria were excluded from the study and not treated with compound):

T = 0: control period (-5 to -1 min) + compound addition, followed for 3 min.

T = 30: measured from 29 to 34 min after compound addition

During the compound addition step, 100 μl of the respective double-concentrated test solutions was pipetted into each well simultaneously.

Data were analyzed off-line using appropriate software e.g. Notocord-Hem (version 4.3).

The following parameters of the Ca^{2+} transient morphology were measured:

- beat rate (BR)
- amplitude of the Ca^{2+} transient (Amp),
- CTD_{90}: Ca^{2+} transient duration at 90% (time to 90% of the initial base value).

The presence of various *'arrhythmia-like'* activities were also noted during the experimental periods. These included:

- '*early afterdepolarization-like'* (EAD-*like*) events (defined as "an extra small peak of the transient waveform following the initial peak of the transient"),
- *'ventricular tachycardia-like'* (VT-*like*) events (defined as a very fast beating rate) or
- '*ventricular fibrillation-like'* (VF-*like*) events (defined as "small amplitude, fast-rate Ca^{2+} waveforms with irregularities and non-measurable transient potentials)
- *'cessation of beating'* of the cells (no Ca^{2+} transients observed).

If compound-induced changes on the calcium transient signal could not be analyzed by the software, then these signals were identified as BQL (below quality analyses level).

Data Analysis

Data, measured from the FDSS-μCell, were copied for off-line analysis and were analyzed and uploaded in SPEC-II (our operational management system) for further analysis. The values of

the variables before and after administration of the compound were collected and transferred into an Excel workbook.

All values (actual units and percentage changes from the baseline values) are expressed as median (minimum and maximum). Changes versus the corresponding baseline values (in actual units) observed in the compound group were compared with those in the solvent control group using the Wilcoxon-Mann-Whitney Test. Two-tailed tests with Bonferroni correction for multiplicity adjustment were conducted. Since there are 10 treatment groups each compared to the solvent group, alpha level of 0.05/10 (0.005) was considered to reflect a statistically significant difference from the solvent group. All statistical analysis was performed using appropriate software e.g. R software version 3.5.2.

Quality Control of the hiPSC-CMs in the plate:

Plates were rejected if they did not meet following criteria:

- Stable regular beating
- Amplitude > 500 relative units
- Beat rate between 25 and 80 beats per minute
- CTD_{90} between 300 and 800 ms

In the present study, the hiPSC-CMs in the plates met the above criteria.

These parameters combined with incidence of arrhythmia or cessation of beating were used to calculate the potential hazard level using a weighted scoring method (based on Kopljar et al., Stem Cell Reports 2018. 11, 1365-1377). This hazard score is calculated per concentration by adding weighted points based on the Tolerance Intervals (TI) on the changes of CTD_{90}, the beat rate and amplitude (ΔΔ%) and incidence of beating stop and early afterdepolarization (EAD). Consequently, for each concentration one of four different hazard levels will be generated. This will be done after 30-min of incubated with compound. The hazard levels are:

No hazard: within the vehicle effect levels or small non-relevant changes.
Low hazard: relevant effect but potentially low risk for cardiac liabilities.
High hazard: relative high risk for cardiac liabilities.
Very high hazard: very high risk due to arrhythmic like events (EAD's).

The '*Hazard Score*' results provide an identification for potential acute cardiac drug-induced effects at free drug equivalent (*as no plasma proteins are added to the wells*). Evaluation of hazard identification is conducted using a 'scoring reference book' called *CTCM_Scoring_version 1* (Kopljar et al., Stem Cell Reports 2018. 11: 1365-1377), and levels are indicated according to the following color scheme:

Color	Hazard identification legend
Green	No concern
Yellow	Low concern
Red	High concern
Black	Very high concern due to arrhythmic events

Ranking of a testing compound according to hazard score severity on the Ca^{2+} transient assay measured in HiPSc-CMs as listed above in different colors and in the associated table.

RESULTS

Using iCell® Cardiomyocytes2 as cell line

Positive and negative controls:

The positive and negative controls all had expected pharmacological effects in this assay

Compounds:

Compound	Color @ 0.1μM	Color @ 0.2μM	Color @ 0.5μM	Color @ 1μM	Color @ 2.5μM	Color @ 5μM
70	Green	Green	Green	Green	Green	Green
246	Green	Green	Green	Green	Green	Green

Compound	Color @ 0.1μM	Color @ 0.3μM	Color @ 1μM	Color @ 3μM	Color @ 10μM	Color @ 30μM
70a	Green	Green	Green	Green	Green	yellow
398	Green	Green	Green	Green	Green	Green
11	Green	Green	Green	Green	Green	Green
286	Green	Green	Green	Green	Green	Green

For compound 70a: with an efficacious dose in mouse xenograft models of 30 mpk (mg/kg), CTCM human concentration vs free Cmax would be estimated as followed

Margin CTCM human 10 μM vs free Cmax >16 (mouse, human)
Margin CTCM human 30 μM vs free Cmax >45 (mouse, human)

Using Cor.4U ®-Cardiomyocytes as cell line

Compounds	Color @ 0.1μM	Color @ 0.2μM	Color @ 0.5μM	Color @ 1μM	Color @ 2.5μM	Color @ 5μM
37	Green	Green	Green	Green	Green	Green
19	Green	Green	Green	Green	Green	Green

8) Effect on the membrane potassium current I_{Kr} in hERG transfected cell lines

Protocol 1:

List of abbreviations

Abbreviations	
CHO	Chinese hamster ovary cell line
DMSO	Dimethylsulfoxide
hERG	human *ether-à-go-go*-related gene
I_{Kr}	rapidly activating delayed-rectifier K^+ current

Methods

Experiments were performed using CHO cells stably expressing the hERG potassium channel. Cells were grown at 37°C and 5% CO_2 in culture flasks in Ham's F12 Medium supplemented with 10% heat-inactivated fetal calf serum, hygromycin B (100 μg/ml) and geneticin (100 μg/ml). For use in the automated patch-clamp system QPatch (Sophion) cells were harvested to obtain cell suspension of single cells.

Solutions: The bath solution contained (in mM) 145 NaCl, 4 KCl, 10 glucose, 10 HEPES ((4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid), 2 $CaCl_2$ and 1 $MgCl_2$ (pH 7.4 with NaOH). The pipette solution contained (in mM) 120 KCl, 10 EGTA (Ethylene glycol-*bis*(2-aminoethylether)-*N*,*N*,*N*',*N*'-tetraacetic acid), 10 HEPES, 5.374 $CaCl_2$ and 1.75 $MgCl_2$ (pH 7.2 with KOH).

Patch-clamp experiments were performed in the voltage-clamp mode and whole-cell currents were recorded with an automated patch-clamp assay utilizing the QPatch system (Sophion). Current signals were amplified and digitized, stored and analyzed by using the QPatch assay software.

The holding potential was -80 mV. The hERG current (K^+-selective outward current) was determined as the maximal tail current at -40 mV after a 2 second depolarization to +60 mV. Pulse cycling rate was 15 s. A short pulse (90 ms) to -40 mV served as a baseline step to calculate the tail current amplitude. After establishing whole-cell configuration and a stability period, the solvent control (0.3% DMSO) was applied for 5 minutes followed by the test substance by four increasing concentrations of 3×10^{-7} M, 3×10^{-6} M, 10^{-5} M and 3×10^{-5} M. Each concentration of the test substance was applied twice. The effect of each concentration was determined after 5 min as an average current of 3 sequential voltage pulses. To determine the extent of block the residual current was compared with vehicle pre-treatment. Concentration/response relations were calculated by non-linear least-squares fits to the individual data points. The half-maximal inhibiting concentration (IC50) was calculated by the fitting routine.

Protocol 2:

Cells

The compound, vehicle control and positive control were tested on hERG-transfected HEK293 cells. A human embryonic kidney cell line (HEK293) with a stable transfection of hERG (Zhou Z et al. Biophysical Journal 1998. 74, 230-241; McDonald T.V.et al, Nature 1997. 388, 289-292) was used (University of Wisconsin, Madison, USA). The cells were kept in culture in MEM (Minimum Essential Medium, Gibco) which was supplemented with (amounts indicated added to 500 ml MEM): 5 ml L-Glutamine-Penicillin-Streptomycin (Sigma), 50 ml Fetal Bovine serum (Bio-Whittaker), 5 ml Non-essential Amino Acids 100x (Gibco), 5 ml sodium pyruvate 100 mM (Gibco) and 4 ml geneticin 50 mg/ml (Gibco) using T175 flasks. The cells were incubated at 37°C in 5% CO_2 atmosphere (in air).

Cell Harvesting for assay

Cells were harvested as described below using accumax™ (Sigma) as the dissociating reagent. Cells were then resuspended in a mixture of 33% DMEM/F12 (Dulbecco's Modified Eagle Medium/Nutrient Mixture F-12 - Sigma) media/67% extracellular physiological solution.

The flasks were washed twice carefully with ~5-10 ml phosphate buffered saline (PBS) (Gibco™) containing 2mM EDTA (Ethylenediaminetetraacetic acid) (Sigma). The cells were dissociated using ~3 ml of accumax™ (cell detachment solution) and incubated for ~5 to 10 min. at 37°C. Cold external physiological solution (2-5 ml) was added and the flasks are incubated at ~4 °C for 5-10 min. Then, the cell suspension in each flask was gently dissociated with a 5ml pipette. The cell suspension was transferred to a low

binding petri-dish (~10 mm diameter). Each flask was washed with ~ additional 5 ml cold external physiological solution and this solution was also added to the petri-dish. The petri-dish was then incubated for another 5 to 10 minutes at ~4 °C. After another gentle dissociation of the cell suspension in the petri dish, the cells were transferred to a reservoir kept on an orbital shaker at 200 rpm at 16°C. Before experiments were performed, the cells recovered for ~20 min.

Compounds

A 10 mM solution of the compound was used and plated in a 384 well plate. Aliquots of the stock solutions are diluted with the recording solution (see section 3) using automated liquid handling (Biomek FXP; final DMSO concentration: 0.03 to 0.3 %). A standard range of screening concentrations was used ranging from 1 µM to 30 µM.

A positive control (E-4031) was included within each run to evaluate the sensitivity of the assay.

External and intracellular solutions used in the experiments

In the table below the composition of the intracellular and external buffer solutions is shown in [mM] ("NMDG" means N-methyl-D-glucamine)

Intracellular Solution		Extracellular Physiological Solution / Chip Fill Solution		Seal Enhancer Solution		Recording Solution	
KCl	10	NaCl	140	NMDG	60	NMDG	60
KF	110	KCl	4	NaCl	80	NaCl	80
NaCl	10	Glucose	5	KCl	4	KCl	4
HEPES	10	HEPES	10	$CaCl_2$	10	$CaCl_2$	2
EGTA	10	$CaCl_2$	2	$MgCl_2$	1	$MgCl_2$	1
		$MgCl_2$	1	Glucose	5	Glucose	5
				HEPES	10	HEPES	10
pH 7.2 (KOH)		pH 7.4 (NaOH)		pH 7.4 (HCL)		pH 7.4 (HCL)	

Study design

The whole cell patch clamp technique on transfected cells allows the study of ion-channels with no - or limited interference from other ion-channels. The effects of the compounds on the hERG current were studied with an automated planar patch clamp system, SyncroPatch 384PE (Obergrussberger et al, Journal of Laboratory Automation 2016. *21 (6),* 779-793). All cells were recorded in the whole cell mode of the patch clamp

technique. The module is incorporated in a liquid handling pipetting robot system, Biomek FXP, for application of cells and compounds, vehicle control and positive control.

The different concentrations of the compounds were applied in two cumulatively increasing concentrations for the compunds (1 μM and 10 μM, and 3 μM and 30 μM, respectively). The hERG current was determined as the maximal tail current at -30 mV and percent inhibition upon compound or vehicle and positive control addition was reported.

After cells are caught onto the individual holes of the recording chips using the chip fill solution, the seal is increased with the seal enhancer solution (increased [Ca^{2+}]; then the cells were washed twice with recording solution before using a pressure protocol to go into the whole cell mode.

After the whole cell mode was achieved, test pulses were given for ~10 minutes to quantify the hERG current in control conditions. During this control period vehicle control solution (recording solution containing 0.03% DMSO) was added three times into the individual wells. While continuing the pulse protocol, cumulatively increasing concentrations of the vehicle control, compound or positive control was added. The effect of the vehicle, compound and positive control was measured after 5 minutes of drug application. Two concentrations of the compound were tested per cell.

The use of the internal and recording solutions will result in ~10 mV liquid junction potential and the command voltage step will take this into account.

Electrophysiological measurements: The membrane current of the cells was measured at distinct membrane potentials with the patch clamp technique by means of an automated patch clamp system. The holding potential is -70 mV. The hERG current (K^+-selective outward current) was determined as the maximal tail current at -30 mV after a 2 second depolarization to +70 mV (refs. 1, 4). Pulse cycling rate was 15 s.

Data analysis

The leak corrected hERG current (K^+-selective outward current) was determined as the maximal tail current at -30 mV after a 2-second of depolarization to +70 mV measured between 2336.3 ms and 3083.6 ms. The median of three current amplitudes was taken at the end of the control period and at the end of each addition of compound, vehicle and positive control to calculate the percent inhibition.

QC parameters were set in the SyncroPatch 384PE PatchControl384 software to automatically exclude wells from the analysis if values fall outside the range. The QC criteria are dependent on the type of recording plate (chip). Typically, a 4xChip (medium size hole) was used to record from hERG-transfected HEK293 cells. QC criteria 4-6

were set before the first addition of the compound; QC criteria 4 and 5 were also set at the end of each compound addition.

QC Criteria and acceptable ranges:

1. Board Check: -500pA - 500pA
2. Contact seal resistance: -100kOhm - 10MOhm
3. Junction potential offset: 0 - 100mV
4. Rseal ≥ 100 MOhm
5. Rseries: between 1 - 25 MOhm
6. hERG tail current ≥ 0.2 nA before compound addition

Each compound was replicated on the same plate in at least 5 wells. Percent inhibition of at least 2-3 replicates per concentration will be reported as median.

Results:

Protocol 1

Compound Number	hERG- IC_{50} (μM)
17	4.1
40	5.0
83	6.0
41	6.3
39	7.6
45	12.6
14	20.0
22	20.9
13	25.7
94	30.9
1	>30.2

Compound Number	hERG- IC_{50} (μM)
4	>30.2
37	>30.2
30	>30.2
19	>30.2
12	>30.2
18	>30.2
11	>30.2
34	>30.2
49	>30.2
47	>30.2
35	>30.2
27	>30.2
32	>30.2
23	>30.2
10	>30.2
71	>30.2
258	>30.2
75	>30.2
252	>30.2
396	>30.2

Protocol 2:

Example Number	hERG IC_{50} μM
148	12.3
11	>30.2
246	>30.2
99	>30.2
132	>30.2
233	>30.2
104	>30.2
242	>30.2
146	>30.2
112	>30.2
114	>30.2
245	>30.2
223	>30.2
227	>30.2

9) Efficacy study in disseminated OCI-AML3 model

Test Agents and Controls

Compound 70 was formulated in 20% hydroxypropyl-beta-cyclodextrin (HP-β-CD) and prepared to reach a total volume of 0.2 mL (10 mL/kg) per dose for a 20 g animal. Doses were adjusted by individual body weight each day. Working stocks of Compound 70 were prepared once per week for each study and stored at 25°C.

Animals

Female SCID beige mice (CB17.Cg-PrkdcscidLystbg-J/Crl/-) were used when they were approximately 6 to 8 weeks of age and weighed approximately 25 g. All animals could acclimate and recover from any shipping-related stress for a minimum of 7 days prior to

experimental use. Autoclaved water and irradiated food were provided ad libitum, and the animals were maintained on a 12hour light and dark cycle. Cages, bedding, and water bottles were autoclaved before use and changed weekly.

Tissue Culture and Cell Injection Reagents
DPBS (Dulbecco's phosphate-buffered saline)
Heat-inactivated fetal bovine serum
MEM Alpha medium
L-glutamine
Gentamycin
T175 Culture Flask
Roller Bottle

Tumor Model and Cell Culture Method

Human AML cell line OCI-AML3 was cultured at 37°C, 5% CO_2 in the indicated complete culture media (MEM Alpha + 20% HI-FBS (Heat-Inactivated Fetal Bovine Serum) + 2mM L-glutamine + 50ug/ml Gentamycin). Cells were harvested while in logarithmic growth and resuspended in cold (4°C) MEM ((Minimum Essential Medium) Alpha in serum-free medium. For the disseminated OCI-AML3 model, each mouse received $5x10^5$ cells via IV injection in a total volume of 0.2 mL using a 26-gauge needle.

Study Designs

Compound 70 was administered orally (PO), daily.

Day 0 is the day of tumor cell implantation and study initiation

In the efficacy study, mice bearing IV OCI-AML3 xenograft tumors were randomly assigned to treatment groups 3 days post-tumor cell engraftment. Treatment with vehicle or Compound 70 (at 30, 50,100 mg/kg) was initiated on the same day, with daily dosing for 28 days.

Animal Monitoring

Animals were monitored daily for clinical signs related to either compound toxicity or tumor burden (i.e., hind limb paralysis, lethargy, etc.).

Calculations

For survival assessment, results were plotted as the percentage survival against days post tumor implant. Negative clinical signs and/or ≥20% body weight loss was used as a surrogate endpoint for death. Median survival was determined utilizing Kaplan-Meier survival analysis. The

percent increased life span (ILS) was calculated as: ((median survival day of treated group - median survival day of control group) / median survival day of control group) × 100. Animals failing to reach the surrogate endpoint due to adverse clinical signs (such as ulcerated tumors, body weight loss, etc.) or death unrelated to treatment were censored for the survival assessment. As defined by NCI criteria, ≥25% ILS is considered biologically significant. (Johnson JI et al. Br J Cancer. 2001. 84(10), 1424-1431).

Data Analysis

Survival and body weight data were graphically represented utilizing Prism (Version 7). Statistical significance for body weights was evaluated as described above. Statistical significance was evaluated for Kaplan-Meier survival plots comparing therapeutic treatment group *vs.* appropriate vehicle-treated control using log-rank (Mantel-Cox) test in R software version 3.4.2. Differences between groups were considered significant when the p value was ≤0.05.

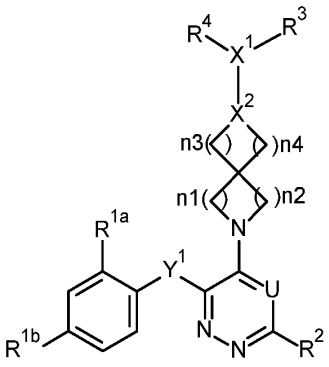
Survival

The Kaplan-Meier survival curve is shown in below figure. Mice bearing established OCI-AML3 tumors were orally dosed daily with Compound 70 at 30, 50, 100 mg/kg in 20% HP-β-CD formulation for a total of 28 days (n=9-10/group). For Compound 70 treated groups, the median days of survival were reached at the following days for 30mg/kg at day 75.5, for 50mg/kg at day 58.5 and for 100mg/kg at day 75 this compared to a median survival of 38.5 days for the vehicle-treated control group. Compound 70 treatment resulted in statistically significant increased lifespan of OCI-AML3 tumor-bearing mice by 96.1%, 51.9% and 94.8% (at the 30, 50 and 100 mg/kg dose levels) as compared to that of control mice, ($p \leq 0.001$). This was a biologically significant ILS as per NCI criteria threshold of ≥25% ILS (Johnson JI et al. Br J Cancer. 2001. 84(10), 1424-1431).

Results in Fig. 2.

CLAIMS

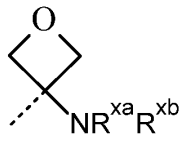
1. A compound of Formula (I)



(I)

,

or a tautomer or a stereoisomeric form thereof, wherein

R^{1a} represents -C(=O)-$NR^{xa}R^{xb}$; Het; or  ;

Het represents a 5- or 6-membered monocyclic aromatic ring containing one, two or three nitrogen atoms and optionally a carbonyl moiety;
wherein said 5- or 6-membered monocyclic aromatic ring is optionally substituted with one or two substituents selected from the group consisting of C_{3-6}cycloalkyl and C_{1-4}alkyl;

R^{xa} and R^{xb} are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl and C_{3-6}cycloalkyl;

R^{1b} represents F or Cl;

Y^1 represents -$CR^{5a}R^{5b}$-, -O- or -NR^{5c}-;

R^2 is selected from the group consisting of hydrogen, halo, C_{1-4}alkyl, -O-C_{1-4}alkyl, and -$NR^{7a}R^{7b}$;

U represents N or CH;

n1, n2, n3 and n4 are each independently selected from 1 and 2;

X^1 represents CH, and X^2 represents N;

R^4 represents isopropyl;

R^{5a}, R^{5b}, R^{5c}, R^{7a}, and R^{7b}, are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl and C_{3-6}cycloalkyl;

R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$, -C_{1-6}alkyl-C(=O)-$NR^{9a}R^{9b}$, -C_{1-6}alkyl-OH, or -C_{1-6}alkyl-NR^{11}-C(=O)-O-C_{1-4}alkyl-O-C(=O)-C_{1-4}alkyl;
wherein each of the C_{1-4}alkyl or C_{1-6}alkyl moieties in the R^3 definitions independently of each other may be substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo, -OH, and -O-C_{1-4}alkyl;

R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; -C(=O)-C_{1-4}alkyl; -C(=O)-O-C_{1-4}alkyl; -C(=O)-$NR^{12a}R^{12b}$; and C_{1-6}alkyl substituted with one, two or three substituents each independently selected from the group consisting of -OH, cyano, halo, -S(=O)$_2$-C_{1-4}alkyl, -O-C_{1-4}alkyl, -C(=O)-$NR^{10a}R^{10b}$, and -NR^{10c}-C(=O)-C_{1-4}alkyl;

R^{9a}, R^{9b}, R^{10a}, R^{10b}, R^{10c}, R^{11}, R^{12a}, and R^{12b} are each independently selected from the group consisting of hydrogen and C_{1-6}alkyl;

or a pharmaceutically acceptable salt or a solvate thereof.

2. The compound according to claim 1, wherein

R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$, -C_{1-6}alkyl-C(=O)-$NR^{9a}R^{9b}$, -C_{1-6}alkyl-OH, or -C_{1-6}alkyl-NR^{11}-C(=O)-O-C_{1-4}alkyl-O-C(=O)-C_{1-4}alkyl;
wherein each of the C_{1-4}alkyl or C_{1-6}alkyl moieties in the R^3 definitions independently of each other may be substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo or -O-C_{1-4}alkyl;

R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; -C(=O)-C_{1-4}alkyl; -C(=O)-O-C_{1-4}alkyl; -C(=O)-$NR^{12a}R^{12b}$; and C_{1-6}alkyl substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo, -S(=O)$_2$-C_{1-4}alkyl, -O-C_{1-4}alkyl, and -C(=O)-$NR^{10a}R^{10b}$;

R^{9a}, R^{9b}, R^{10a}, R^{10b}, R^{11}, R^{12a}, and R^{12b} are each independently selected from the group consisting of hydrogen and C_{1-6}alkyl.

3. The compound according to claim 2, wherein

R^{1a} represents -C(=O)-$NR^{xa}R^{xb}$; or Het;

Het represents a 6-membered monocyclic aromatic ring containing two nitrogen atoms; wherein said 6-membered monocyclic aromatic ring is optionally substituted with one C_{3-6}cycloalkyl;
R^{xa} and R^{xb} represent C_{1-4}alkyl;

R^{1b} represents F;

Y^1 represents -O-;

R^2 is hydrogen;

U represents N;

R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$, -C_{1-6}alkyl-C(=O)-$NR^{9a}R^{9b}$, -C_{1-6}alkyl-OH, or -C_{1-6}alkyl-NR^{11}-C(=O)-O-C_{1-4}alkyl-O-C(=O)-C_{1-4}alkyl;

R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; -C(=O)-C_{1-4}alkyl; -C(=O)-O-C_{1-4}alkyl; -C(=O)-$NR^{12a}R^{12b}$; and C_{1-6}alkyl substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo, -$S(=O)_2$-C_{1-4}alkyl, and -O-C_{1-4}alkyl.

4. The compound according to claim 2, wherein

R^{1a} represents -C(=O)-$NR^{xa}R^{xb}$;

R^{xa} and R^{xb} represent C_{1-4}alkyl;

R^{1b} represents F;

Y^1 represents -O-;

R^2 is hydrogen;

U represents N;

R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$, -C_{1-6}alkyl-C(=O)-$NR^{9a}R^{9b}$, or -C_{1-6}alkyl-OH;
R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; -C(=O)-C_{1-4}alkyl; -C(=O)-O-C_{1-4}alkyl; -C(=O)-$NR^{12a}R^{12b}$; and C_{1-6}alkyl substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo, -$S(=O)_2$-C_{1-4}alkyl, and -O-C_{1-4}alkyl.

5. The compound according to claim 1, wherein

R^{1a} represents -C(=O)-$NR^{xa}R^{xb}$ or Het;

Het represents a 6-membered monocyclic aromatic ring containing two nitrogen atoms; wherein said 6-membered monocyclic aromatic ring is substituted with one C_{3-6}cycloalkyl;

R^{xa} and R^{xb} represent C_{1-4}alkyl;

R^{1b} represents F;

Y^1 represents -O-;

R^2 represents hydrogen;

U represents N or CH;

n1, n2, n3 and n4 are each independently selected from 1 and 2;

X^1 represents CH, and X^2 represents N;

R^4 represents isopropyl;

R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$, -C_{1-6}alkyl-C(=O)-$NR^{9a}R^{9b}$, -C_{1-6}alkyl-OH, or -C_{1-6}alkyl-NR^{11}-C(=O)-O-C_{1-4}alkyl-O-C(=O)-C_{1-4}alkyl;
wherein each of the C_{1-4}alkyl or C_{1-6}alkyl moieties in the R^3 definitions independently of each other may be substituted with one, two or three substituents each independently selected from the group consisting of -OH and -O-C_{1-4}alkyl;

R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; -C(=O)-C_{1-4}alkyl; -C(=O)-O-C_{1-4}alkyl; -C(=O)-$NR^{12a}R^{12b}$; and C_{1-6}alkyl substituted with one, two or three substituents each independently selected from the group consisting of -OH, cyano, halo, -S(=O)$_2$-C_{1-4}alkyl, -O-C_{1-4}alkyl, -C(=O)-$NR^{10a}R^{10b}$, and -NR^{10c}-C(=O)-C_{1-4}alkyl;

R^{9a}, R^{9b}, R^{10a}, R^{10b}, R^{10c}, R^{11}, R^{12a}, and R^{12b} are each independently selected from the group consisting of hydrogen and C_{1-6}alkyl.

6. The compound according to claim 1, wherein

R^{1a} represents -C(=O)-$NR^{xa}R^{xb}$ or Het;

Het represents a 6-membered monocyclic aromatic ring containing two nitrogen atoms; wherein said 6-membered monocyclic aromatic ring is substituted with one C_{3-6}cycloalkyl;

R^{xa} and R^{xb} represent C_{1-4}alkyl;

R^{1b} represents F;

Y^1 represents -O-;

R^2 represents hydrogen;

U represents N or CH;

n1, n2, n3 and n4 are each independently selected from 1 and 2;

X^1 represents CH, and X^2 represents N;

R^4 represents isopropyl;

R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$;
wherein the C_{1-6}alkyl moiety in the R^3 definition may be substituted with one, two or three substituents each independently selected from the group consisting of -OH and -O-C_{1-4}alkyl;

R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; and C_{1-6}alkyl substituted with one, two or three substituents each independently selected from the group consisting of -OH, cyano, halo, -$S(=O)_2$-C_{1-4}alkyl, -O-C_{1-4}alkyl, -$C(=O)$-$NR^{10a}R^{10b}$, and -NR^{10c}-$C(=O)$-C_{1-4}alkyl;

R^{10a}, R^{10b}, and R^{10c} are each independently selected from the group consisting of hydrogen and C_{1-6}alkyl.

7. The compound according to claim 1, wherein

R^{1a} represents -$C(=O)$-$NR^{xa}R^{xb}$;

R^{xa} and R^{xb} represent C_{1-4}alkyl;

R^{1b} represents F;

Y^1 represents -O-;

R^2 represents hydrogen;

U represents N;

n1, n2, n3 and n4 are each independently selected from 1 and 2;

X^1 represents CH, and X^2 represents N;

R^4 represents isopropyl;

R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$;

R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; and C_{1-6}alkyl substituted with one, two or three substituents each independently selected from the group consisting of -OH, cyano, halo, -$S(=O)_2$-C_{1-4}alkyl, -O-C_{1-4}alkyl, and -$C(=O)$-$NR^{10a}R^{10b}$;

R^{10a} and R^{10b} are each independently selected from the group consisting of hydrogen and C_{1-6}alkyl.

8. The compound according to claim 1, wherein
Y^1 represents -O-.

9. The compound according to claim 1, wherein
R^{1b} represents F.

10. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 9 and a pharmaceutically acceptable carrier or diluent.

11. A process for preparing a pharmaceutical composition as defined in claim 10 comprising mixing a pharmaceutically acceptable carrier with a therapeutically effective amount of a compound according to any one of claims 1 to 9.

12. A compound as claimed in any one of claims 1 to 9 or a pharmaceutical composition as claimed in claim 10 for use as a medicament.

13. A compound as claimed in any one of claims 1 to 9 or a pharmaceutical composition as claimed in claim 10 for use in the prevention or treatment of cancer.

14. A compound as claimed in any one of claims 1 to 9 or a pharmaceutical composition as claimed in claim 10 for use in the prevention or treatment of leukemia, myelodysplastic syndrome (MDS), and myeloproliferative neoplasms (MPN).

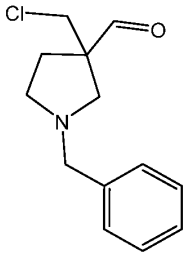
15. The compound or a pharmaceutical composition for use according to claim 14 in the prevention or treatment of leukemia wherein the leukemia is (NPM1)-mutated leukemia.

16. The compound or a pharmaceutical composition for use according to claim 13, wherein cancer is selected from leukemias, lymphomas, myelomas or solid tumor cancers such as prostate cancer, lung cancer, breast cancer, pancreatic cancer, colon cancer, liver cancer, melanoma and glioblastoma.

17. The compound or a pharmaceutical composition for use according to claim 14, in the prevention or treatment of leukemia wherein the leukemia is selected from acute leukemias, chronic leukemias, myeloid leukemias, myelogeneous leukemias, lymphoblastic leukemias, lymphocytic leukemias, Acute myelogeneous leukemias (AML), Chronic myelogenous leukemias (CML), Acute lymphoblastic leukemias (ALL), Chronic lymphocytic leukemias (CLL), T cell prolymphocytic leukemias (T-PLL), Large granular lymphocytic leukemia, Hairy cell leukemia (HCL), MLL-rearranged leukemias, MLL-PTD leukemias, MLL amplified leukemias, MLL-positive leukemias, and leukemias exhibiting *HOX/MEIS1* gene expression signatures.

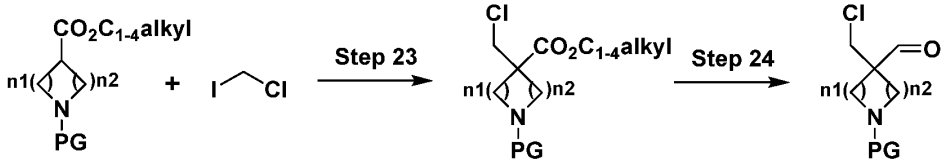
18. A method of treating or preventing a disorder selected from cancer, comprising administering to a subject in need thereof, a therapeutically effective amount of a compound as claimed in any one of claims 1 to 9 or a pharmaceutical composition as claimed in claim 10.

19. An intermediate with the structure



or a tautomer or a stereoisomeric form thereof ;
or a pharmaceutically acceptable addition salt or a solvate thereof.

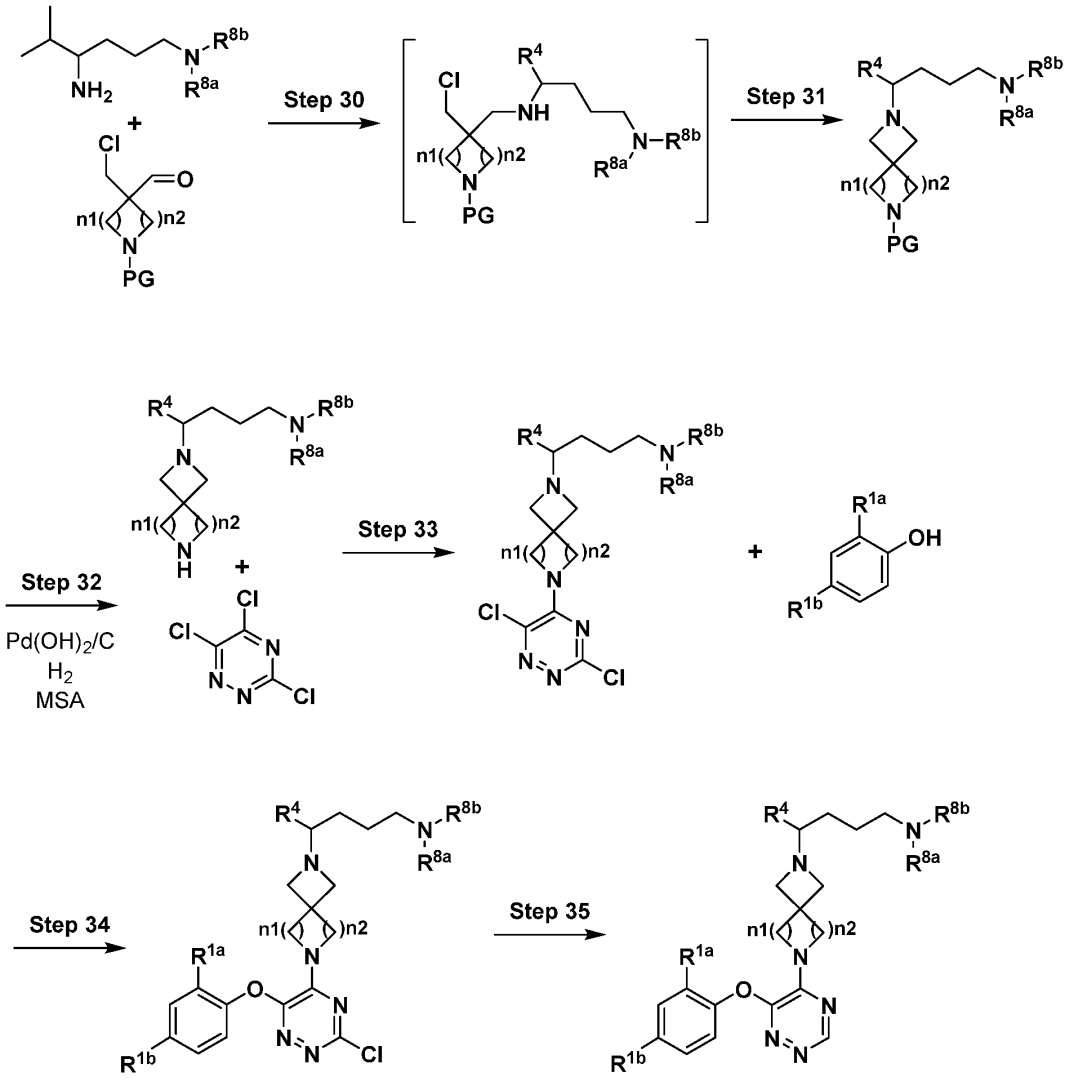
20. A process for the preparation of an intermediate comprising the following steps:



wherein PG is a suitable protecting group such as benzyl;
wherein n1 and n2 are as defined for formula (I);

Step 23: at a suitable temperature such as for example from -78 °C to -25 °C, in the presence of suitable bases such as for example DIEA and n-BuLi, in a suitable solvent such as for example THF;
Step 24: at a suitable temperature such as for example between -55°C and -65 °C, in the presence of suitable reducing agent such as for example DIBAL-H, in a suitable solvent such as for example toluene, conducted in a suitable flow chemistry system.

21. A process for the preparation of an intermediate comprising the following steps:



PG is a suitable protecting group such as benzyl;

other variables are as defined for formula (I);

Step 30: at a suitable temperature such as for example from 5 °C to 30 °C, in the presence of a suitable base such as for example TEA, in the presence of suitable reducing agent such as for example $NaBH(OAc)_3$, in a suitable solvent such as for example toluene;

Step 31: at a suitable temperature such as for example from 50 °C to 55 °C, in the presence of a suitable base such as for example K_2HPO_4, in a suitable solvent such as for example H_2O;

Step 32: at a suitable temperature such as for example from -5 °C to 45 °C, under a hydrogen atmosphere within a suitable pressure range such as for example from 0.27 to 0.40 MPa, in the presence of palladium hydroxide on carbon, in the presence of MSA in a suitable solvent such as EtOH;

Step 33: at a suitable temperature such as for example from -50 °C to -40 °C, in the presence of suitable base such as for example TEA, in a suitable solvent such as 2-methyltetrahydrofuran;

Step 34: at a suitable temperature such as for example from 20 °C to 30 °C, in the presence of suitable base such as for example TMG, in a suitable solvent such as 2-methyltetrahydrofuran;
Step 35: at a suitable temperature such as for example from 20 °C to 30 °C, under a hydrogen atmosphere within a suitable pressure range such as for example from 0.20 to 0.30 Mpa, in the presence of a suitable catalyst such as for example palladium on carbon, in a suitable solvent such as MeOH.