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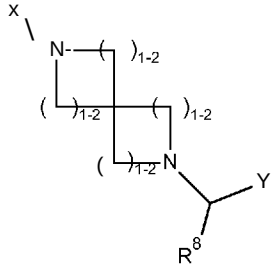

(I)

(57) Abstract: The present invention covers diazaspiroalkylmethyl-indole compounds of general formula (I) in which R^8, X and Y are as defined herein, methods of preparing said compounds, intermediate compounds useful for preparing said compounds, pharmaceutical compositions and combinations comprising said compounds and the use of said compounds for manufacturing pharmaceutical compositions for the treatment or prophylaxis of diseases, in particular of cancer, as a sole agent or in combination with other active ingredients.

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SPIRO CONDENSED AZETIDINE DERIVATIVES AS INHIBITORS OF THE MENIN-MML1 INTERACTION

The present invention covers diazaspiroalkylmethyl-indole compounds of general formula (I) as described and defined herein, methods of preparing said compounds, intermediate compounds useful for preparing said compounds, pharmaceutical compositions and combinations comprising said compounds, and the use of said compounds for manufacturing pharmaceutical compositions for the treatment or prophylaxis of diseases, in particular cancer, as a sole agent or in combination with other active ingredients.

BACKGROUND

The present invention covers diazaspiroalkylmethyl-indole compounds of general formula (I) which inhibit the interaction between menin and MLL-1 .

The mixed lineage leukemia (MLL) protein complex is the oncogenic driver of a subgroup of leukemias characterized by the fusion of MLL proteins, mainly MLL-1 , to different partners at their N- or C-terminal end. Translocation events leading to the fusion of the N-terminal moiety of MLL proteins with one of more than 80 different partners including AF4, AF9 and ENL have frequently been described (R. Marschalek, Arch. Pharm. 2015, 348:221-228). These fusion proteins interact with various nuclear factors and the resulting complexes will bind to promoters to stimulate aberrant gene expression. The oncogenic function of MLL-fused proteins is critically dependent on the interaction with a protein partner named menin (A.T. Thiel et al., Bioessays 2012, 34:771-780). This takes place via the MLL N-terminal region which is conserved in all translocations, and where two menin-binding motifs, MBM1 and MBM2, with high and low affinity respectively, have been identified (J. Grembecka et al., J. Biol. Chem. 2010, 285:40690-40698; A. Shi et al., Blood 2012, 120:4461-4469). They interact with a large central cavity of about 5000 A^3 found in menin (M.J. Murai et al., J. Biol. Chem., 201 1, 286:31742-31748). This interaction is necessary for downstream expression of genes essential for leukemia transformation such as several members of the HOX cluster.

Menin is also involved in breast cancer. It directly binds to the estrogen receptor (ER) in a hormone-dependent way to promote MLL recruitment, stimulate H3K4 methylation and control the expression of estrogen target genes (K.M.A. Dreijerink et al., Cancer Res. 2006, 66:4429-4435; H. Imachi et al., Breast Cancer Res. Treat. 2010, 122:395-407). Silencing of MLL-1 or treatment with a menin inhibitor dramatically reduces proliferation of breast cancer cell lines with a gain-of-function mutation in the p53 tumor suppressor (J. Zhu et al., Nature 2015, 525:206-21 1). This is possibly due to the impact of the p53 mutation on the expression of MLL and of MOZ, which leads to increase of global H3K9 acetylation. In line with these results, high menin expression is linked with poor outcome in ER-positive breast cancer patients (H. Imachi et al., Breast Cancer Res. Treat. 2010, 122:395-407).

Menin is also implicated in prostate cancer and directly interacts with the androgen receptor (AR) N-terminal domain (R. Malik et al., Nat Medicine, 2015, 21:344-352). It is essential for AR signalling and acts as a co-regulator of a number of androgen target genes. Inhibition of menin impairs the AR pathway and reduces the proliferation of prostate cancer models, both in vitro and in vivo, probably due to the disruption of the menin-MLL-1 interaction. Also, high menin expression at the RNA and protein levels is associated with reduced survival in prostate cancer patients (R. Malik et al., Nat. Medicine, 2015, 21:344-352).

Another tumor indication where menin is involved is hepatocellular carcinoma where it is expressed at high levels and regulates the transcription of several genes involved in this disease (B. Xu et al., Proc. Natl. Acad. Sci. USA 2013, 110:17480-17485). Finally, a chemical screen with a cell line model of pediatric glioma harboring a mutation in the H3.3 histone at position K27 identified a menin inhibitor as the compound with the strongest anti-proliferative activity (K. Fumato et al., Science 2014, 346:1529-1533).

Altogether these data indicate menin to be an important coactivator for different transcription factors and enzymes involved in chromatin modulation. Its function is deregulated in a number of tumor types, making it an attractive target for cancer treatment.

First small molecule inhibitors which inhibit the interaction of menin with fused MLL proteins have recently been described. They obviate the oncogenic function of MLL fusion proteins by impairing the expression of a number of downstream target genes involved in the transformation process, and prevent the proliferation and differentiation of leukemias carrying an MLL translocation. Thienopyrimidines were the first menin inhibitors described and their cellular activity was shown in different MLL-fused leukemia models (A. Shi et al., Blood 2012, 120:4461-4469; J. Grembecka et al., Nat. Chem. Biol. 2012, 8:277-284). Subsequently hydroxy- and aminomethylpiperidine inhibitors were described (S. He et al., J. Med. Chem. 2014, 57:1543-1556). They prevent the interaction between menin and MLL-1 and inhibit the growth of different AML cell lines with fused MLL. New thienopyrimidine derivatives containing an aminopiperidine linker were more recently described (D. Borkin et al., Cancer Cell 2015, 27:589-602; D. Borkin et al., J. Med. Chem. 2016, 59:892-913). They show anti-proliferative activity in AML cell lines with fused MLL and in vivo efficacy in xenograft models.

Inhibitors of the interaction between menin and MLL-1 are described in WO 2011/029054, US 2014/0275070, US 2014/0371239, US 2016/9505781, US 2016/9505782, WO 2014/164543, WO 2014/200479, WO 2015/191701, WO 2016/195776 and WO 2016/197027.

WO 1999/065494 relates to conformationally constrained compounds as inhibitors of prenyl-protein transferase.

WO 2005/1 10410 relates to compounds as kinase inhibitors.

EP 1683797 relates to heterocyclic spiro compounds useful for the prevention and/or treatment of disease caused by stress.

WO 2008/033447 relates to azetidine and azetidone derivatives useful in treating pain and disorders of lipid metabolism.

WO 2008/033456 relates to spiro-condensed azetidine derivatives useful in treating pain, diabetes and disorders of lipid metabolism.

However, the state of the art does not describe:

- the diazaspiroalkylmethyl-indole compounds of general formula (I) of the present invention as described and defined herein, *i.e.* compounds having a diazaspiroalkyl core bearing:
  - in its N^1-position, a thieno[2,3-d]pyrimidine-4-yl, a thieno[3,2-d]pyrimidine-4-yl, a pyrrolo[2,1-f][1 ,2,4]triazine-4-yl or a 2H-pyrazolo[3,4-d]pyrimidine-4-yl moiety and
  - in its N^2-position, an indolylmethyl moiety

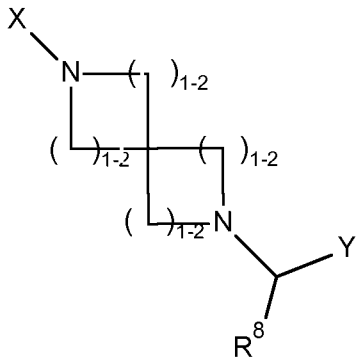
  or stereoisomers, tautomers, N-oxides, hydrates, solvates, salts thereof, or mixtures of same, as described and defined herein, and as hereinafter referred to as "compounds of general formula (I)" or "compounds of the present invention",
- or their pharmacological activity.

It has now been found, and this constitutes the basis of the present invention, that the compounds of the present invention have surprising and advantageous properties.

In particular, the compounds of the present invention have surprisingly been found to effectively inhibit the interaction between menin and MLL-1 for which data are given in biological experimental section and may therefore be used for the treatment or prophylaxis of menin related disorders such as hyperproliferative disorders, conditions and diseases, in particular leukemia, especially acute myeloid leukemia including those harboring an MLL fusion, and breast and prostate cancer, and hepatocellular carcinoma, for example.

DESCRIPTION of the INVENTION

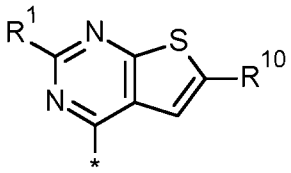
In accordance with a first aspect, the present invention covers compounds of general formula (I):



(I)

in which:

X represents a group selected from: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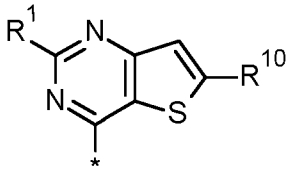
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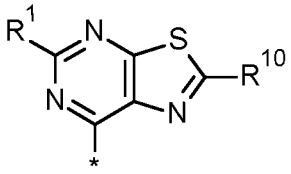
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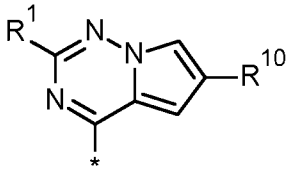
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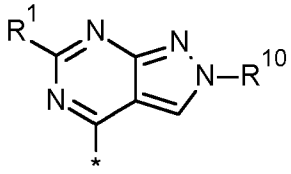
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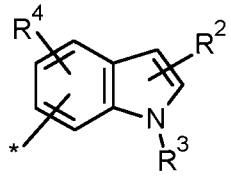
wherein * indicates the point of attachment of said group with the rest of the molecule;

Y represents a group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wherein * indicates the point of attachment of said group with the rest of the molecule;

R^1 represents hydrogen or methyl;

R^2 represents hydrogen, Ci-C_4-hydroxyalkyl, -CN, -$CONH_2$ or -$C0_2R^9$;

R^3 represents hydrogen, Ci-C4-alkyl, Ci-C4-haloalkyl, C2-C4-hydroxyalkyl, -C2-C4-alkylen-NR^6R^7, -$CO2R^9$ or -Ci-C_2-alkylen-R^5;

R^4 represents hydrogen, hydroxy, halogen, methyl or methoxy;

R^5 represents -$CO2R^9$, -$CONR^6R^7$, 4- to 6-membered heterocycloalkyl optionally substituted with -$CO2R^9$, phenyl or 5-membered heteroaryl,
wherein said phenyl group is optionally substituted, one or more times, independently from each other, with hydroxy, halogen, cyano, Ci-C3-alkyl, Ci-C3-haloalkyl, Ci-C3-alkoxy or Ci-C3-haloalkoxy and said 5-membered heteroaryl is optionally substituted with Ci-C4-alkyl;

R^6 and R^7 are the same or different and represent, independently from each other, hydrogen, Ci-C4-alkyl, C_{3-C6}-cycloalkyl, Ci-C4-haloalkyl or
together with the nitrogen atom to which they are attached form a
4- to 6-membered nitrogen containing heterocyclic ring, said ring optionally containing one additional heteroatom selected from O, S, NH, NR^a in which R^a represents a C1-C4-alkyl or Ci-C4-haloalkyl group;

R^8 represents hydrogen or Ci-C4-alkyl;

R^9 represents hydrogen or Ci-C4-alkyl;

R^{10} represents Ci-C4-alkyl, Ci-C4-haloalkyl,-methoxy-Ci-C3-alkyl, methylsulfanylmethyl, methylsulfinylmethyl, methylsulfonylmethyl, S-methylsulfonimidoyl-methyl, -CH2-$CO2R^{11}$ or -CH_2-$CONR^{12}R^{13}$;

R^{11} represents hydrogen or Ci-C4-alkyl;

R^{12}, R^{13} represent, independently from each other, hydrogen, Ci-C4-alkyl, C_{3-C6}-cycloalkyl, Ci-C_4-haloalkyl, C_2-C_3-hydroxyalkyl, tert-butyl-O-C(O)-, -(CO)-Ci-C_3-alkyl, -(S0 $_2$)-Ci-C_3-alkyl, -(S0 $_2$)-phenyl,
wherein said phenyl group is optionally substituted, one or more times, independently from each other, with hydroxy, halogen, cyano, Ci-C3-alkyl, Ci-C3-haloalkyl, Ci-C3-alkoxy or Ci-C3-haloalkoxy, or
together with the nitrogen atom to which they are attached form a
4- to 6-membered nitrogen containing heterocyclic ring, said ring optionally containing one additional heteroatom selected from O, S, NH, NR^a in which R^a represents a C1-C4-alkyl or Ci-C4-haloalkyl group and optionally substituted with an oxo group;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

DEFINITIONS

The term "substituted" means that one or more hydrogen atoms on the designated atom or group are replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded. Combinations of substituents and/or variables are permissible.

The term "optionally substituted" means that the number of substituents can be equal to or different from zero. Unless otherwise indicated, it is possible that optionally substituted groups are substituted with as many optional substituents as can be accommodated by replacing a hydrogen atom with a non-hydrogen substituent on any available carbon or nitrogen atom. Commonly, it is possible for the number of optional substituents, when present, to be 1, 2, 3, 4 or 5, in particular 1, 2 or 3.

As used herein, the term "one or more", *e.g.* in the definition of the substituents of the compounds of general formula (I) of the present invention, means "1, 2, 3, 4 or 5, particularly 1, 2, 3 or 4, more particularly 1, 2 or 3, even more particularly 1 or 2".

The term "ring substituent" means a substituent attached to an aromatic or nonaromatic ring which replaces an available hydrogen atom on the ring.

The term "comprising" when used in the specification includes "consisting of".

If within the present text any item is referred to as "as mentioned herein", it means that it may be mentioned anywhere in the present text.

The terms as mentioned in the present text have the following meanings:

The term "halogen atom" means a fluorine, chlorine or bromine atom, particularly a fluorine or chlorine atom.

The term "Ci-C4-alkyl" means a linear or branched, saturated, monovalent hydrocarbon group having 1, 2, 3 or 4 carbon atoms, *e.g.* a methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl or ie/f-butyl. Particularly, said group has 1, 2 or 3 carbon atoms ("Ci-C3-alkyl"), *e.g.* a methyl, ethyl, propyl or isopropyl group, more particularly 1 or 2 carbon atoms ("Ci-C2-alkyl"), *e.g.* a methyl or ethyl group.

The term "Ci-C4-hydroxyalkyl" means a linear or branched, saturated, monovalent hydrocarbon group having 1, 2, 3 or 4 carbon atoms, *e.g.* a methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl or ie/f-butyl, and in which 1 or 2 hydrogen atoms are replaced with a hydroxy group, *e.g.* a hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1,2-dihydroxyethyl, 3-hydroxy propyl, 2-hydroxypropyl, 1-hydroxypropyl, 1-hydroxypropan-2-yl, 2-hydroxypropan-2-yl, 2,3-dihydroxypropyl, 1,3-dihydroxypropan-2-yl, 3-hydroxy-2-methyl-propyl, 2-hydroxy-2-methyl-propyl, 1-hydroxy-2-methyl-propyl group.

The term "Ci-C4-haloalkyl" means a linear or branched, saturated, monovalent hydrocarbon group in which the term "Ci-C4-alkyl" is as defined *supra,* and in which one or more of the

hydrogen atoms are replaced, identically or differently, with a halogen atom. Particularly, said halogen atom is a fluorine atom. Said Ci-C4-haloalkyl group is, for example, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, 3,3,3-trifluoropropyl or 1,3-difluoropropan-2-yl.

The term "C3-C6 -cycloalkyl" means a saturated, monovalent, mono- or bicyclic hydrocarbon ring which contains 3, 4, 5 or 6 carbon atoms ("C3-C6 -cycloalkyl"). Said C3-C6 -cycloalkyl group is for example, a monocyclic hydrocarbon ring, *e.g.* a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl group.

The term "4- to 6-membered heterocycloalkyl" mean a monocyclic, saturated heterocycle with 4, 5 or 6 ring atoms in total, which contains one or two identical or different ring heteroatoms from the series N, O and S, it being possible for said heterocycloalkyl group to be attached to the rest of the molecule via any one of the carbon atoms or, if present, a nitrogen atom.

Said heterocycloalkyl group, without being limited thereto, can be a 4-membered ring, such as azetidinyl, oxetanyl or thietanyl, for example; or a 5-membered ring, such as tetrahydrofuranyl, 1,3-dioxolanyl, thiolanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, 1,1-dioxidothiolanyl, 1,2-oxazolidinyl, 1,3-oxazolidinyl or 1,3-thiazolidinyl, for example; or a 6-membered ring, such as tetrahydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, dithianyl, thiomorpholinyl, piperazinyl, 1,3-dioxanyl, 1,4-dioxanyl or 1,2-oxazinanyl, for example.

The term "C2-C4-alkylene" means a linear, saturated, bivalent hydrocarbon group having 2, 3 or 4 carbon atoms, *e.g.* an ethylene, propylene or butylene group. Particularly, said group has 2 or 3 carbon atoms ("C2-C3-alkylene"), *e.g.* an ethylene or propylene group, more particularly 2 carbon atoms ("C2-alkylene"), *e.g.* an ethylene group.

The term "5-membered heteroaryl" means a monovalent, monocyclic aromatic ring having 5 ring atoms, which contains at least one ring heteroatom and optionally one, two or three further ring heteroatoms from the series: N, O and/or S, and which is bound via a ring carbon atom or optionally via a ring nitrogen atom (if allowed by valency).

Said 5-membered heteroaryl group can be, such as, for example, thienyl, furanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl or tetrazolyl.

In general, and unless otherwise mentioned, the heteroaryl groups include all possible isomeric forms thereof, *e.g. :* tautomers and positional isomers with respect to the point of linkage to the rest of the molecule. Thus, for some illustrative non-restricting examples, the term thienyl includes thien-2-yl and thien-3-yl.

Particularly, the heteroaryl group is a pyrazolyl group.

The term **"C1-C4",** as used in the present text, *e.g.* in the context of the definition of **"Ci-C4 -alkyl"** or **"Ci-C4** -haloalkyl" means an alkyl group having a finite number of carbon atoms of 1 to 4, *i.e.* 1, 2, 3 or 4 carbon atoms.

Further, as used herein, the term **"C2-C4",** as used in the present text, *e.g.* in the context of the definition of **"C2-C4**-hydroxyalkyl", means a hydroxyalkyl group having a finite number of carbon atoms of 2 to 4, *i.e.* 2, 3 or 4 carbon atoms.

When a range of values is given, said range encompasses each value and sub-range within said range.

For example:

"C1-C4" encompasses **Ci,** C_2, C_3, C_4, **C1-C4, C1-C3, C1-C2, C2-C4, C2-C3** and C_3-C_4;

"C2-C4" encompasses **C2, C3, C4, C2-C4, C2-C3** and **C3-C4,** ;

As used herein, the term "leaving group" means an atom or a group of atoms that is displaced in a chemical reaction as stable species taking with it the bonding electrons. In particular, such a leaving group is selected from the group comprising: halide, in particular fluoride, chloride, bromide or iodide, (methylsulfonyl)oxy, [(trifluoromethyl)sulfonyl]oxy, [(nonafluorobutyl)-sulfonyl]oxy, (phenylsulfonyl)oxy, [(4-methylphenyl)sulfonyl]oxy, [(4-bromophenyl)sulfonyl]oxy, [(4-nitrophenyl)sulfonyl]oxy, [(2-nitrophenyl)sulfonyl]oxy, [(4-isopropylphenyl)sulfonyl]oxy, [(2,4,6-triisopropylphenyl)sulfonyl]oxy, [(2,4,6-trimethylphenyl)sulfonyl]oxy, [(4-ie/f-butyl-phenyl)sulfonyl]oxy and [(4-methoxyphenyl)sulfonyl]oxy.

It is possible for the compounds of general formula (I) to exist as isotopic variants. The invention therefore includes one or more isotopic variant(s) of the compounds of general formula (I), particularly deuterium-containing compounds of general formula (I).

The term "Isotopic variant" of a compound or a reagent is defined as a compound exhibiting an unnatural proportion of one or more of the isotopes that constitute such a compound.

The term "Isotopic variant of the compound of general formula (I)" is defined as a compound of general formula (I) exhibiting an unnatural proportion of one or more of the isotopes that constitute such a compound.

The expression "unnatural proportion" means a proportion of such isotope which is higher than its natural abundance. The natural abundances of isotopes to be applied in this context are described in "Isotopic Compositions of the Elements 1997", Pure Appl. Chem., 70(1), 217-235, 1998.

Examples of such isotopes include stable and radioactive isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine, bromine and iodine, such as ^{2}H (deuterium), ^{3}H (tritium), ^{11}C, ^{13}C, ^{14}C, ^{15}N, $^{17}0$, $^{18}0$, ^{32}P, ^{33}P, ^{33}S, ^{34}S, ^{35}S, ^{36}S, ^{18}F, ^{36}Cl, ^{82}Br, ^{123}I, ^{124}I, ^{125}I, ^{129}I and $^{131}1$, respectively.

With respect to the treatment and/or prophylaxis of the disorders specified herein the isotopic variant(s) of the compounds of general formula (I) preferably contain deuterium ("deuterium-containing compounds of general formula (I)"). Isotopic variants of the compounds of general formula (I) in which one or more radioactive isotopes, such as ^{3}H or ^{14}C, are incorporated are useful e.g. in drug and/or substrate tissue distribution studies. These isotopes are particularly preferred for the ease of their incorporation and detectability. Positron emitting isotopes such as ^{18}F or ^{11}C may be incorporated into a compound of general formula (I). These isotopic variants of the compounds of general formula (I) are useful for in vivo imaging applications. Deuterium-containing and ^{13}C-containing compounds of general formula (I) can be used in mass spectrometry analyses in the context of preclinical or clinical studies.

Isotopic variants of the compounds of general formula (I) can generally be prepared by methods known to a person skilled in the art, such as those described in the schemes and/or examples herein, by substituting a reagent for an isotopic variant of said reagent, preferably for a deuterium-containing reagent. Depending on the desired sites of deuteration, in some cases deuterium from D_2O can be incorporated either directly into the compounds or into reagents that are useful for synthesizing such compounds. Deuterium gas is also a useful reagent for incorporating deuterium into molecules. Catalytic deuteration of olefinic bonds and acetylenic bonds is a rapid route for incorporation of deuterium. Metal catalysts (i.e. Pd, Pt, and Rh) in the presence of deuterium gas can be used to directly exchange deuterium for hydrogen in functional groups containing hydrocarbons. A variety of deuterated reagents and synthetic building blocks are commercially available from companies such as for example C/D/N Isotopes, Quebec, Canada; Cambridge Isotope Laboratories Inc., Andover, MA, USA; and CombiPhos Catalysts, Inc., Princeton, NJ, USA.

The term "deuterium-containing compound of general formula (I)" is defined as a compound of general formula (I), in which one or more hydrogen atom(s) is/are replaced by one or more deuterium atom(s) and in which the abundance of deuterium at each deuterated position of the compound of general formula (I) is higher than the natural abundance of deuterium, which is about 0.015%. Particularly, in a deuterium-containing compound of general formula (I) the abundance of deuterium at each deuterated position of the compound of general formula (I) is higher than 10%, 20%, 30%, 40%, 50%, 60%, 70% or 80%, preferably higher than 90%, 95%, 96% or 97%, even more preferably higher than 98% or 99% at said position(s). It is understood that the abundance of deuterium at each deuterated position is independent of the abundance of deuterium at other deuterated position(s).

The selective incorporation of one or more deuterium atom(s) into a compound of general formula (I) may alter the physicochemical properties (such as for example acidity [C. L. Perrin, et al., J. Am. Chem. Soc, 2007, 129, 4490], basicity [C. L. Perrin et al., J. Am. Chem. Soc, 2005, 127, 9641], lipophilicity [B. Testa et al., Int. J. Pharm., 1984, 19(3), 271]) and/or the

metabolic profile of the molecule and may result in changes in the ratio of parent compound to metabolites or in the amounts of metabolites formed. Such changes may result in certain therapeutic advantages and hence may be preferred in some circumstances. Reduced rates of metabolism and metabolic switching, where the ratio of metabolites is changed, have been reported (A. E. Mutlib et al., Toxicol. Appl. Pharmacol., 2000, 169, 102). These changes in the exposure to parent drug and metabolites can have important consequences with respect to the pharmacodynamics, tolerability and efficacy of a deuterium-containing compound of general formula (I). In some cases deuterium substitution reduces or eliminates the formation of an undesired or toxic metabolite and enhances the formation of a desired metabolite (e.g. Nevirapine: A. M. Sharma et al., Chem. Res. Toxicol., 2013, 26, 410; Efavirenz: A. E. Mutlib et al., Toxicol. Appl. Pharmacol., 2000, 169, 102). In other cases the major effect of deuteration is to reduce the rate of systemic clearance. As a result, the biological half-life of the compound is increased. The potential clinical benefits would include the ability to maintain similar systemic exposure with decreased peak levels and increased trough levels. This could result in lower side effects and enhanced efficacy, depending on the particular compound's pharmacokinetic/ pharmacodynamic relationship. ML-337 (C. J. Wenthur et al., J. Med. Chem., 2013, 56, 5208) and Odanacatib (K. Kassahun et al., WO2012/1 12363) are examples for this deuterium effect. Still other cases have been reported in which reduced rates of metabolism result in an increase in exposure of the drug without changing the rate of systemic clearance (e.g. Rofecoxib: F. Schneider et al., Arzneim. Forsch. / Drug. Res., 2006, 56, 295; Telaprevir: F. Maltais et al., J. Med. Chem., 2009, 52, 7993). Deuterated drugs showing this effect may have reduced dosing requirements (e.g. lower number of doses or lower dosage to achieve the desired effect) and/or may produce lower metabolite loads.

A compound of general formula (I) may have multiple potential sites of attack for metabolism. To optimize the above-described effects on physicochemical properties and metabolic profile, deuterium-containing compounds of general formula (I) having a certain pattern of one or more deuterium-hydrogen exchange(s) can be selected. Particularly, the deuterium atom(s) of deuterium-containing compound(s) of general formula (I) is/are attached to a carbon atom and/or is/are located at those positions of the compound of general formula (I), which are sites of attack for metabolizing enzymes such as e.g. cytochrome P450.

Where the plural form of the word compounds, salts, polymorphs, hydrates, solvates and the like, is used herein, this is taken to mean also a single compound, salt, polymorph, isomer, hydrate, solvate or the like.

By "stable compound' or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The compounds of the present invention optionally contain one or more asymmetric centres, depending upon the location and nature of the various substituents desired. It is possible that one or more asymmetric carbon atoms are present in the (R) or (S) configuration, which can result in racemic mixtures in the case of a single asymmetric centre, and in diastereomeric mixtures in the case of multiple asymmetric centres. In certain instances, it is possible that asymmetry also be present due to restricted rotation about a given bond, for example, the central bond adjoining two substituted aromatic rings of the specified compounds.

Preferred compounds are those which produce the more desirable biological activity. Separated, pure or partially purified isomers and stereoisomers or racemic or diastereomeric mixtures of the compounds of the present invention are also included within the scope of the present invention. The purification and the separation of such materials can be accomplished by standard techniques known in the art.

Preferred isomers are those which produce the more desirable biological activity. These separated, pure or partially purified isomers or racemic mixtures of the compounds of this invention are also included within the scope of the present invention. The purification and the separation of such materials can be accomplished by standard techniques known in the art.

The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example, by the formation of diastereoisomeric salts using an optically active acid or base or formation of covalent diastereomers. Examples of appropriate acids are tartaric, diacetyltartaric, ditoluoyltartaric and camphorsulfonic acid. Mixtures of diastereoisomers can be separated into their individual diastereomers on the basis of their physical and/or chemical differences by methods known in the art, for example, by chromatography or fractional crystallisation. The optically active bases or acids are then liberated from the separated diastereomeric salts. A different process for separation of optical isomers involves the use of chiral chromatography (e.g., HPLC columns using a chiral phase), with or without conventional derivatisation, optimally chosen to maximise the separation of the enantiomers. Suitable HPLC columns using a chiral phase are commercially available, such as those manufactured by Daicel, e.g., Chiracel OD and Chiracel OJ, for example, among many others, which are all routinely selectable. Enzymatic separations, with or without derivatisation, are also useful. The optically active compounds of the present invention can likewise be obtained by chiral syntheses utilizing optically active starting materials.

In order to distinguish different types of isomers from each other reference is made to IUPAC Rules Section E (Pure Appl Chem 45, 11-30, 1976).

The present invention includes all possible stereoisomers of the compounds of the present invention as single stereoisomers, or as any mixture of said stereoisomers, e.g. (R)- or (S)-isomers, in any ratio. Isolation of a single stereoisomer, e.g. a single enantiomer or a single

diastereomer, of a compound of the present invention is achieved by any suitable state of the art method, such as chromatography, especially chiral chromatography, for example.

Further, the compounds of the present invention can exist as N-oxides, which are defined in that at least one nitrogen of the compounds of the present invention is oxidised. The present invention includes all such possible N-oxides.

The present invention also covers useful forms of the compounds of the present invention, such as metabolites, hydrates, solvates, prodrugs, salts, in particular pharmaceutically acceptable salts, and/or co-precipitates.

The compounds of the present invention can exist as a hydrate, or as a solvate, wherein the compounds of the present invention contain polar solvents, in particular water, methanol or ethanol for example, as structural element of the crystal lattice of the compounds. It is possible for the amount of polar solvents, in particular water, to exist in a stoichiometric or non-stoichiometric ratio. In the case of stoichiometric solvates, *e.g.* a hydrate, hemi-, (semi-), mono-, sesqui-, di-, tri-, tetra-, penta- *etc.* solvates or hydrates, respectively, are possible. The present invention includes all such hydrates or solvates.

Further, it is possible for the compounds of the present invention to exist in free form, *e.g.* as a free base, or as a free acid, or as a zwitterion, or to exist in the form of a salt. Said salt may be any salt, either an organic or inorganic addition salt, particularly any pharmaceutically acceptable organic or inorganic addition salt, which is customarily used in pharmacy, or which is used, for example, for isolating or purifying the compounds of the present invention.

The term "pharmaceutically acceptable salt" refers to an inorganic or organic acid addition salt of a compound of the present invention. For example, see S. M. Berge, *et al.* "Pharmaceutical Salts," J. Pharm. Sci. 1977, 66, 1-19.

A suitable pharmaceutically acceptable salt of the compounds of the present invention may be, for example, an acid-addition salt of a compound of the present invention bearing a nitrogen atom, in a chain or in a ring, for example, which is sufficiently basic, such as an acid-addition salt with an inorganic acid, or "mineral acid", such as hydrochloric, hydrobromic, hydroiodic, sulfuric, sulfamic, bisulfuric, phosphoric, or nitric acid, for example, or with an organic acid, such as formic, acetic, acetoacetic, pyruvic, trifluoroacetic, propionic, butyric, hexanoic, heptanoic, undecanoic, lauric, benzoic, salicylic, 2-(4-hydroxybenzoyl)-benzoic, camphoric, cinnamic, cyclopentanepropionic, digluconic, 3-hydroxy-2-naphthoic, nicotinic, pamoic, pectinic, 3-phenylpropionic, pivalic, 2-hydroxyethanesulfonic, itaconic, trifluoromethanesulfonic, dodecylsulfuric, ethanesulfonic, benzenesulfonic, para-toluenesulfonic, methanesulfonic, 2-naphthalenesulfonic, naphthalinedisulfonic, camphorsulfonic acid, citric, tartaric, stearic, lactic, oxalic, malonic, succinic, malic, adipic, alginic, maleic, fumaric,

D-gluconic, mandelic, ascorbic, glucoheptanoic, glycerophosphoric, aspartic, sulfosalicylic, or thiocyanic acid, for example.

Further, another suitably pharmaceutically acceptable salt of a compound of the present invention which is sufficiently acidic, is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium, magnesium or strontium salt, or an aluminium or a zinc salt, or an ammonium salt derived from ammonia or from an organic primary, secondary or tertiary amine having 1 to 20 carbon atoms, such as ethylamine, diethylamine, triethylamine, ethyldiisopropylamine, monoethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, dimethylaminoethanol, diethylaminoethanol, tris(hydroxymethyl)aminomethane, procaine, dibenzylamine, /V-methylmorpholine, arginine, lysine, 1,2-ethylenediamine, /V-methylpiperidine, /V-methyl-glucamine, /V,/V-dimethyl-glucamine, /V-ethyl-glucamine, 1,6-hexanediamine, glucosamine, sarcosine, serinol, 2-amino-1 ,3-propanediol, 3-amino-1 ,2-propanediol, 4-amino-1 ,2,3-butanetriol, or a salt with a quarternary ammonium ion having 1 to 20 carbon atoms, such as tetramethylammonium, tetraethylammonium, tetra(n-propyl)ammonium, tetra(/>butyl)ammonium, /V-benzyl-/V,/V,/V-trimethylammonium, choline or benzalkonium.

Those skilled in the art will further recognise that it is possible for acid addition salts of the claimed compounds to be prepared by reaction of the compounds with the appropriate inorganic or organic acid via any of a number of known methods. Alternatively, alkali and alkaline earth metal salts of acidic compounds of the present invention are prepared by reacting the compounds of the present invention with the appropriate base via a variety of known methods.

The present invention includes all possible salts of the compounds of the present invention as single salts, or as any mixture of said salts, in any ratio.

In the present text, in particular in the Experimental Section, for the synthesis of intermediates and of examples of the present invention, when a compound is mentioned as a salt form with the corresponding base or acid, the exact stoichiometric composition of said salt form, as obtained by the respective preparation and/or purification process, is, in most cases, unknown.

Unless specified otherwise, suffixes to chemical names or structural formulae relating to salts, such as "hydrochloride", "trifluoroacetate", "sodium salt", or "x HCl", "x CF3COOH", "x Na^+", for example, mean a salt form, the stoichiometry of which salt form not being specified.

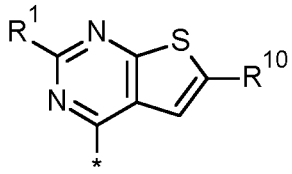
This applies analogously to cases in which synthesis intermediates or example compounds or salts thereof have been obtained, by the preparation and/or purification processes described, as solvates, such as hydrates, with (if defined) unknown stoichiometric composition.

Furthermore, the present invention includes all possible crystalline forms, or polymorphs, of the compounds of the present invention, either as single polymorph, or as a mixture of more than one polymorph, in any ratio.

Moreover, the present invention also includes prodrugs of the compounds according to the invention. The term "prodrugs" here designates compounds which themselves can be biologically active or inactive, but are converted (for example metabolically or hydrolytically) into compounds according to the invention during their residence time in the body.

In accordance with a second embodiment of the first aspect, the present invention covers compounds of general formula (I), *supra,* in which:

X represents a group selected from: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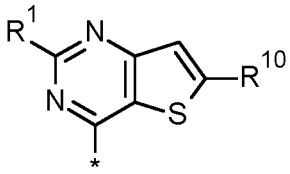
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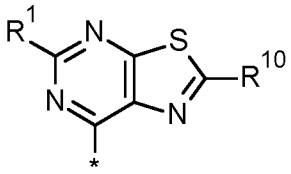
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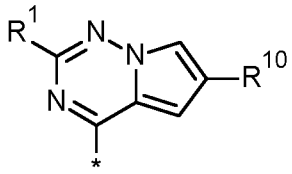
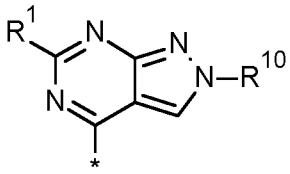
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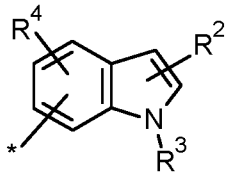
wherein * indicates the point of attachment of said group with the rest of the molecule;

Y represents a group


,

wherein * indicates the point of attachment of said group with the rest of the molecule;

R^1 represents hydrogen or methyl;

R^2 represents hydrogen, Ci-C3-hydroxyalkyl, -CN, -$CONH_2$ or -CC>2R^9;

R^3 represents hydrogen, methyl, Ci-C3-haloalkyl, C2-C3-hydroxyalkyl, -CH2-CH2-NR $^6R^7$, -C0 $_2R^9$ or
-Ci-C_2-alkylen-R ^{5};

R^4 represents hydrogen, methyl or methoxy;

R^5 represents -CO2R^9, -CONH2, phenyl, pyrazolyl, methylpyrazolyl or 4- to 6-membered heterocycloalkyl;

R^6 and R^7 are the same or different and represent, independently from each other, hydrogen, Ci-C4-alkyl or

together with the nitrogen atom to which they are attached form a 4- to 6-membered nitrogen containing heterocyclic ring, said ring optionally containing one additional heteroatom selected from O, S, NH, NR^a in which R^a represents a C1-C4-alkyl or Ci-C4-haloalkyl group;

R^8 represents hydrogen or methyl;

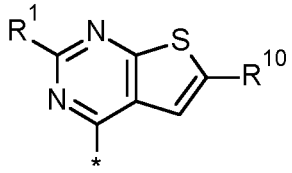
R^9 represents hydrogen or methyl;

R^{10} represents ethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2,2-difluoropropyl, methoxyethyl, methylsulfanylmethyl, methylsulfinylmethyl, methylsulfonylmethyl, 5-methylsulfonimidoyl-methyl, -CH2-CO2CH3 or -CH_2-$CONH_2$;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In accordance with a third embodiment of the first aspect, the present invention covers compounds of general formula (I), *supra,* in which:

X represents a group selected from: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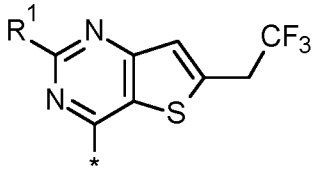
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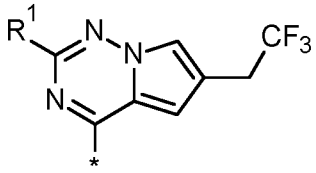
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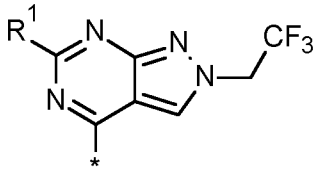
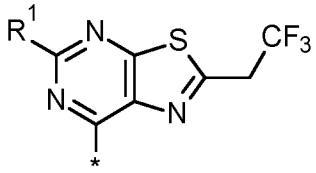
or
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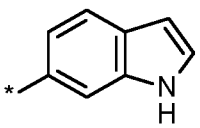
wherein * indicates the point of attachment of said group with the rest of the molecule;

Y represents a group selected from: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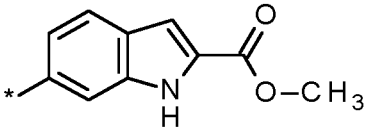
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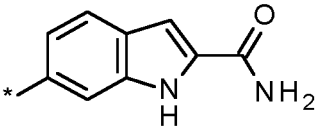
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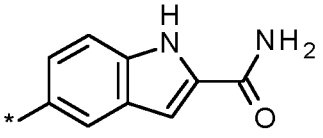
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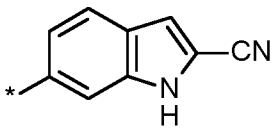
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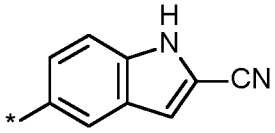
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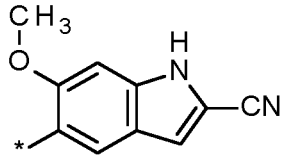
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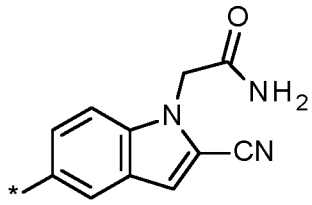
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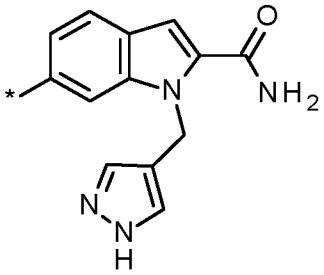
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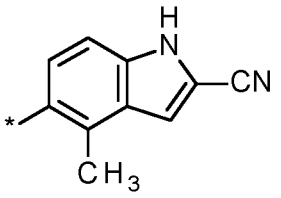
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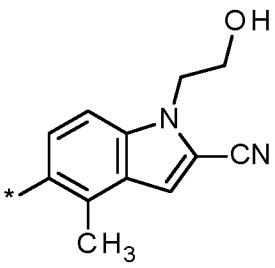
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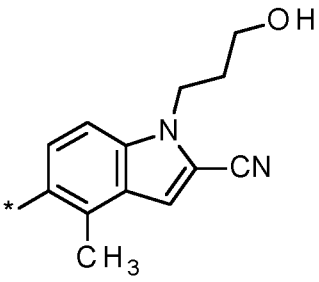
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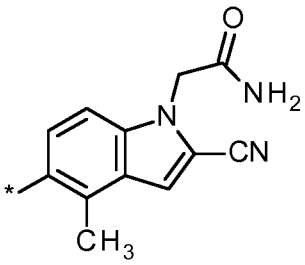
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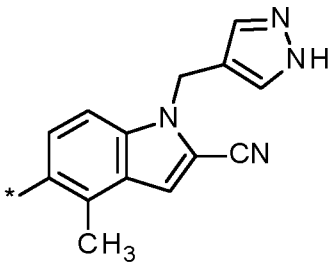
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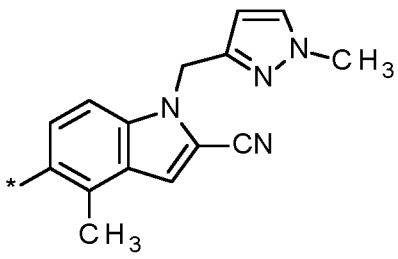
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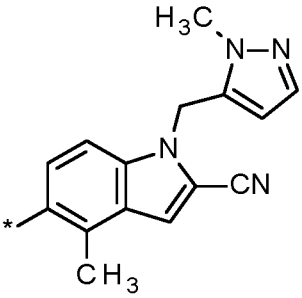
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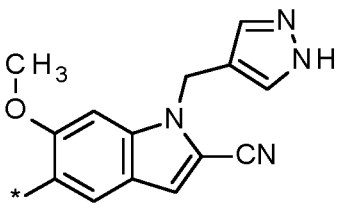
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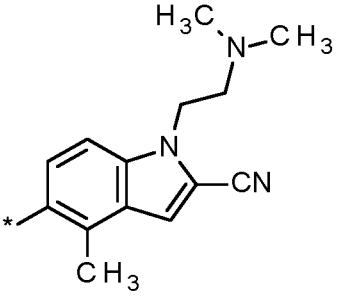
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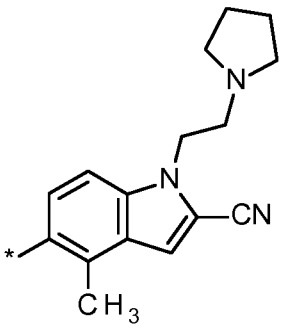
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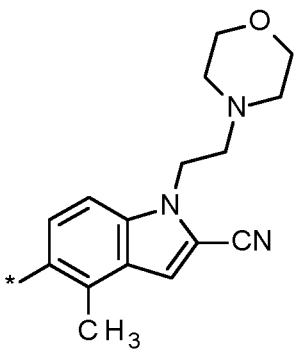
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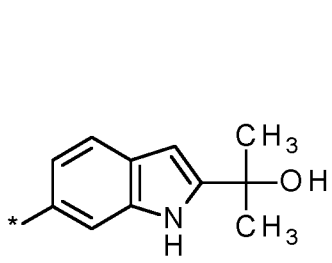
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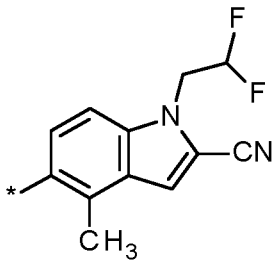
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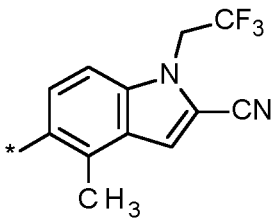
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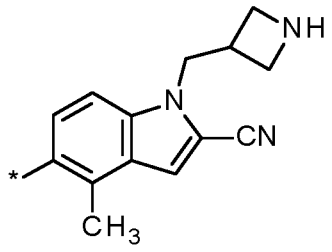
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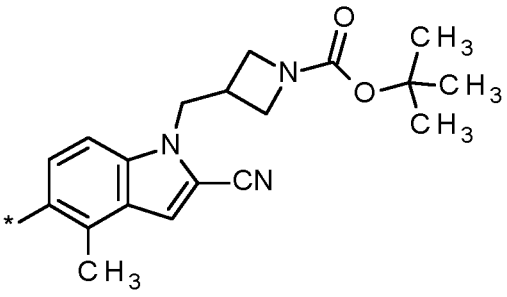
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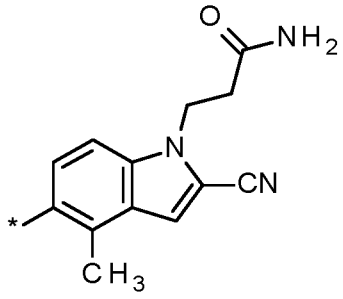
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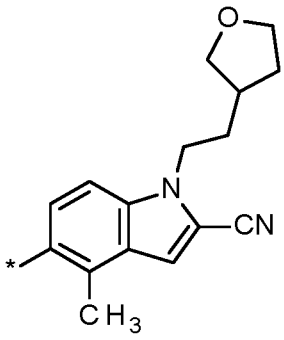
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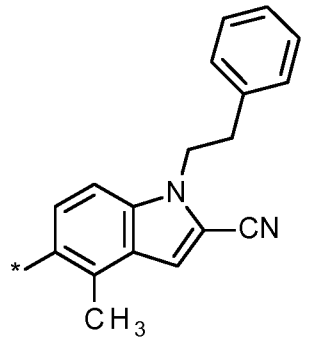
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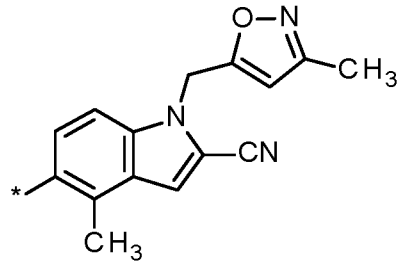
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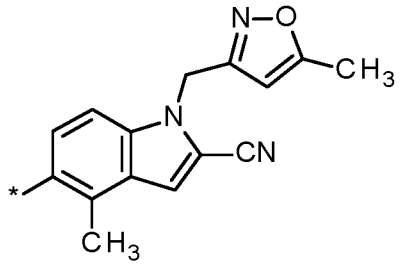
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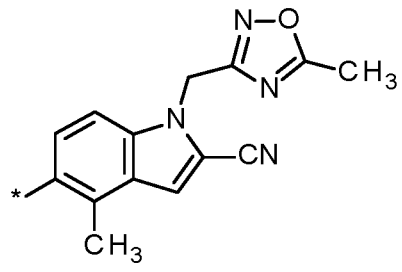
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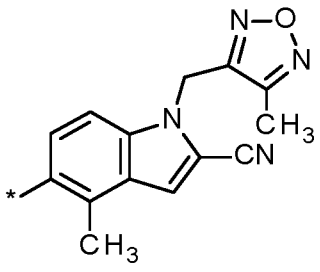

or
,

wherein: * indicates the point of attachment of said group with the rest of the molecule;

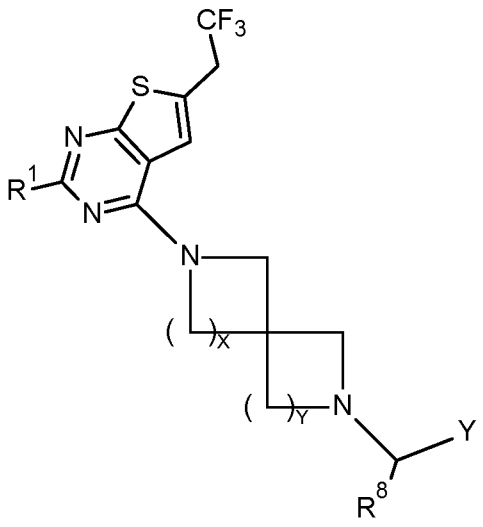
R^1 represents hydrogen or methyl;

R^8 represents hydrogen;

R^{10} represents ethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2,2-difluoropropyl, methoxyethyl, methylsulfanylmethyl, methylsulfinylmethyl, methylsulfonylmethyl, S-methylsulfonimidoyl-methyl, -CH2-CO2CH3 or $-CH_2-CONH_2$;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

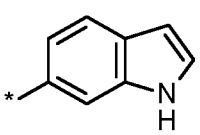
In accordance with a fourth embodiment of the first aspect, the present invention covers compounds of general formula (Ia),



(Ia)

in which:

Y represents a group selected from: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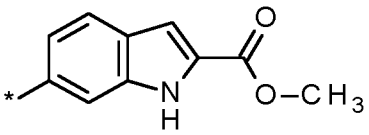
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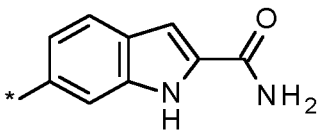
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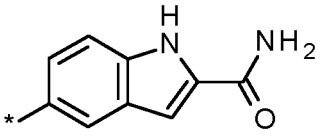
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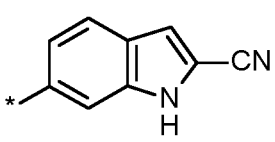
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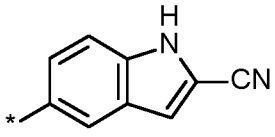
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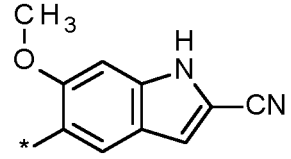
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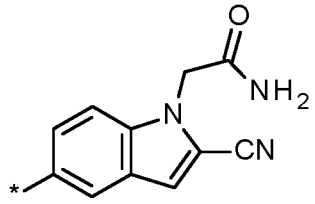
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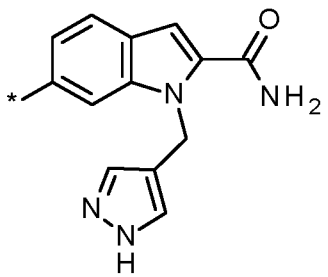
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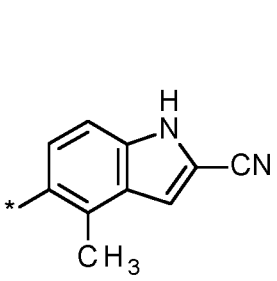
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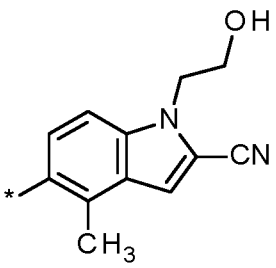
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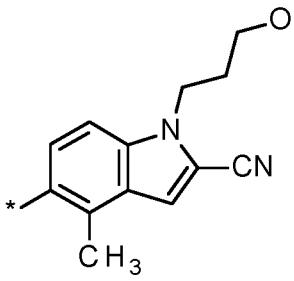
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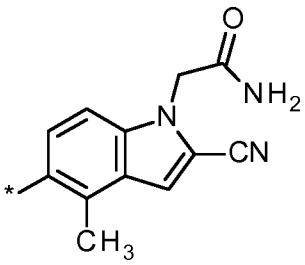
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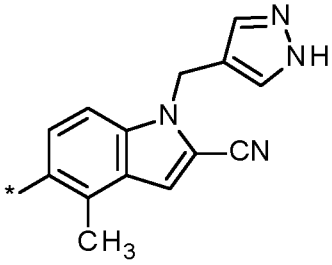
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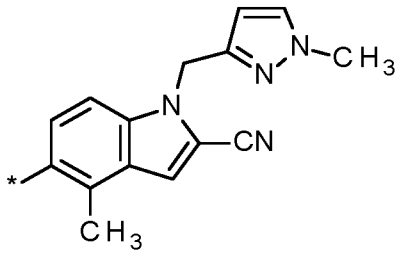
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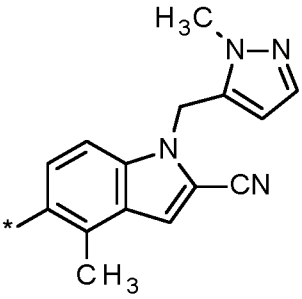
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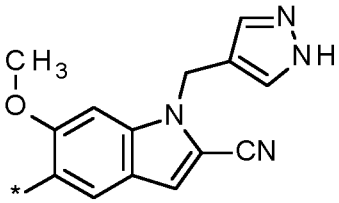
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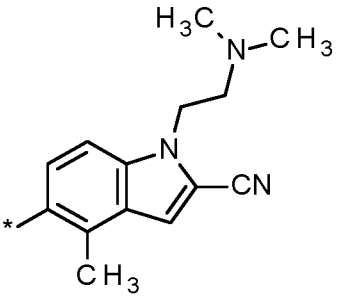
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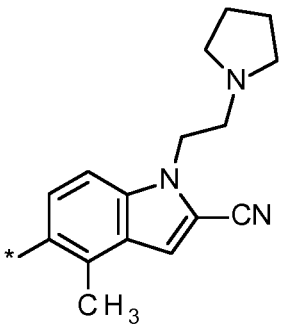
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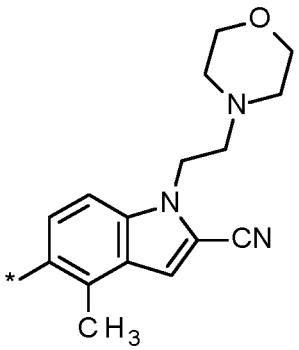
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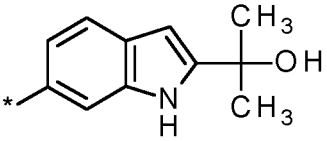
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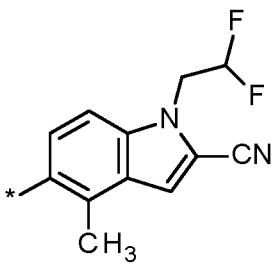
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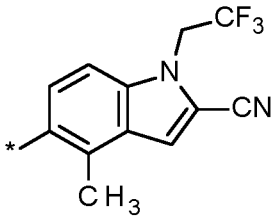
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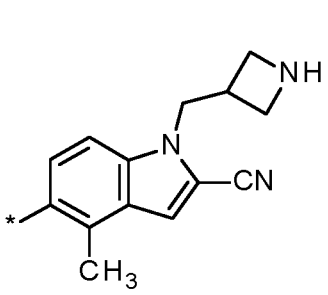
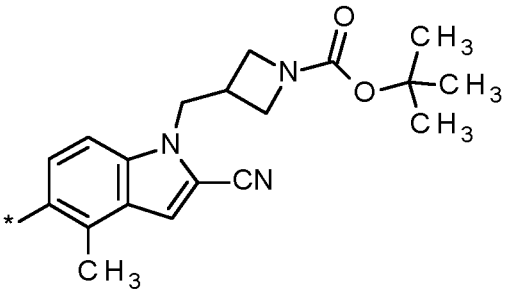
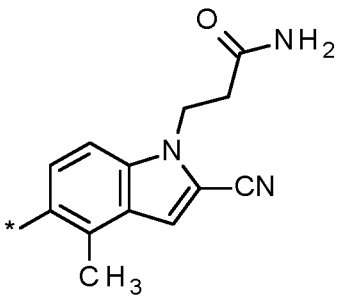
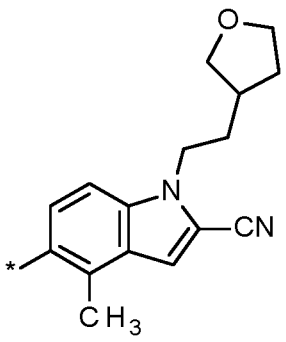
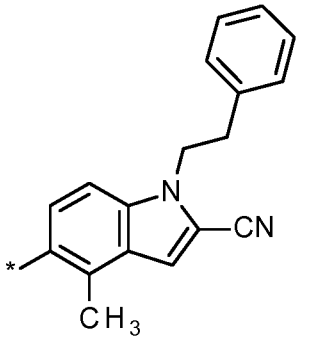
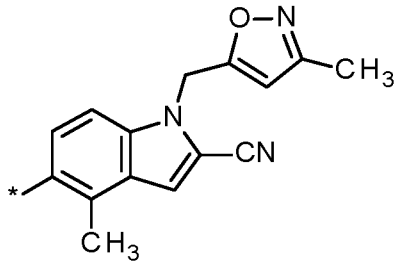
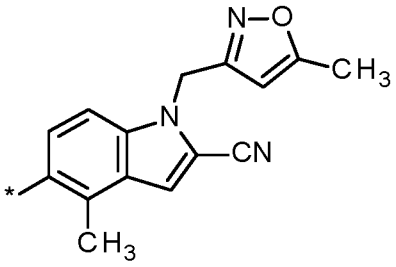
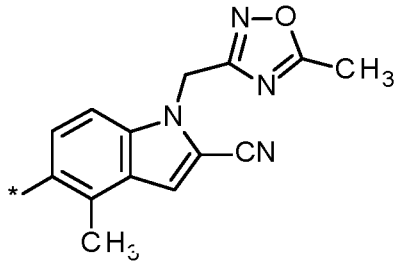
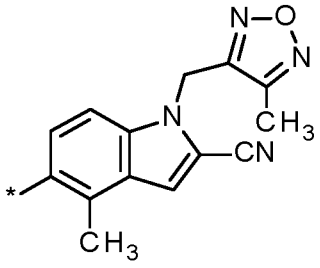










or ,

wherein: * indicates the point of attachment of said group with the rest of the molecule;

R^1 represents hydrogen or methyl;

R^8 represents hydrogen or methyl;

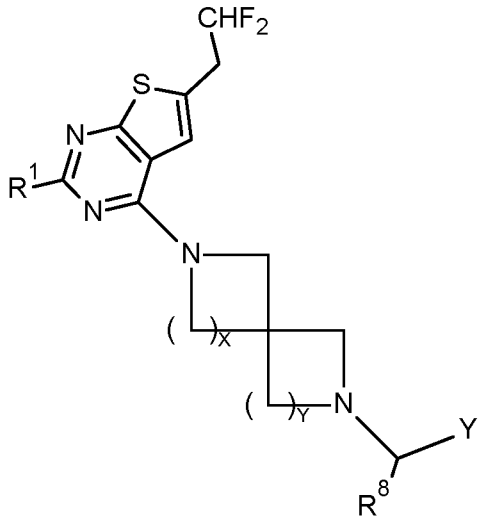
x represents 1 or 2;

y represents 1 or 2,

wherein at least one of x and y represent 2;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

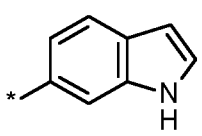
In accordance with a fifth embodiment of the first aspect, the present invention covers compounds of general formula (Id),



(Id)

in which:

Y represents a group selected from: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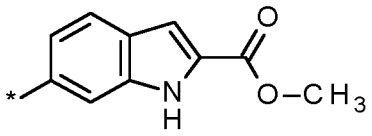
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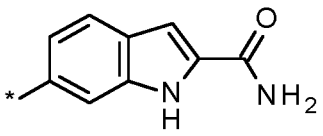
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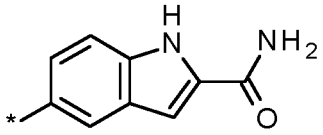
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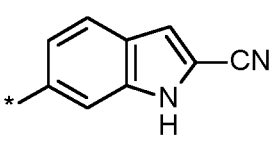
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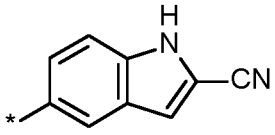
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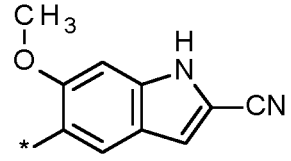
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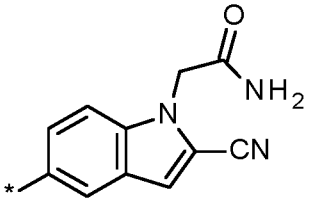
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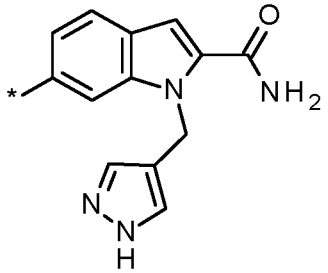
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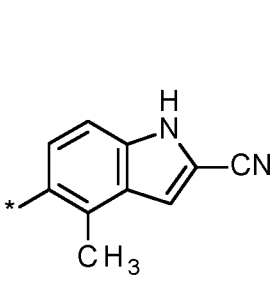
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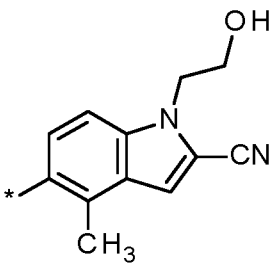
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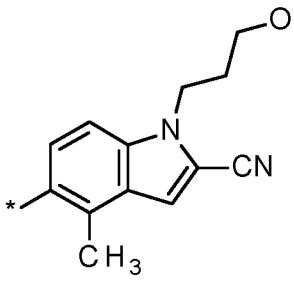
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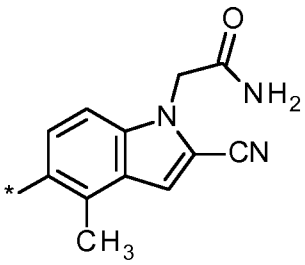
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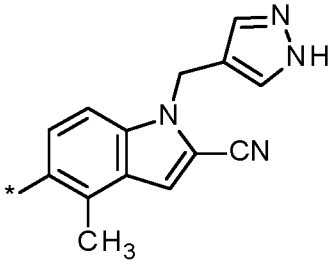
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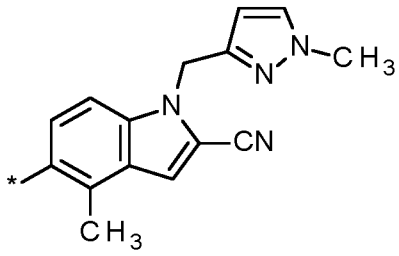
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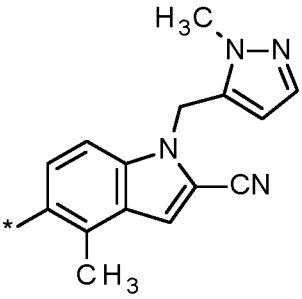
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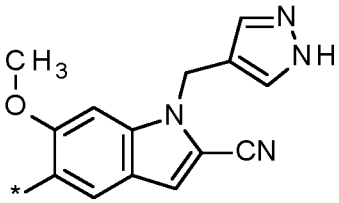
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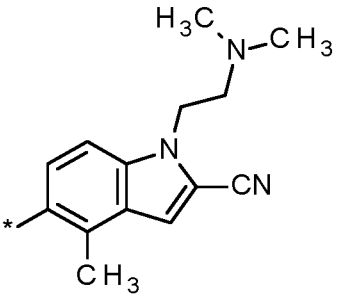
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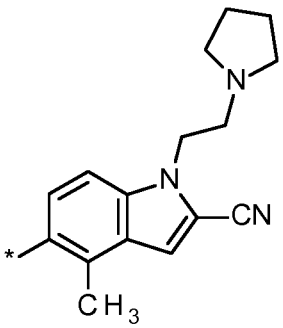
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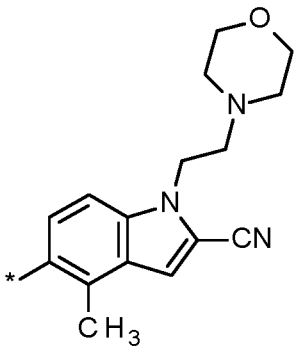
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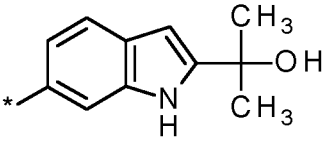
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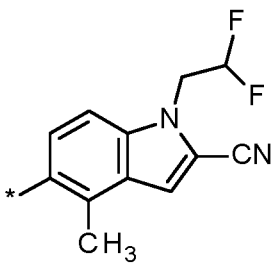
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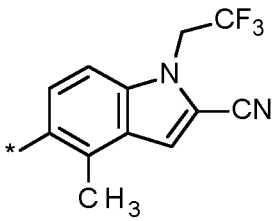
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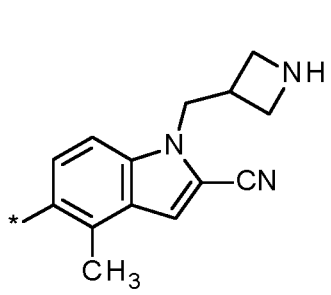
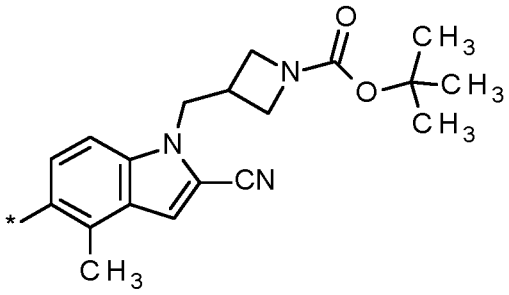
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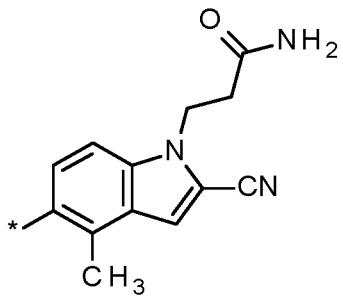
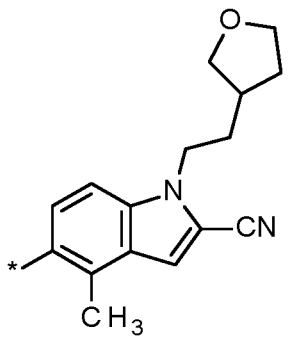
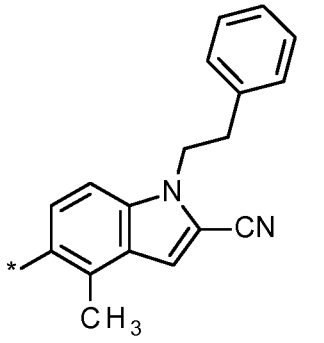
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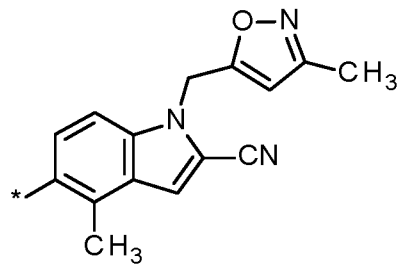
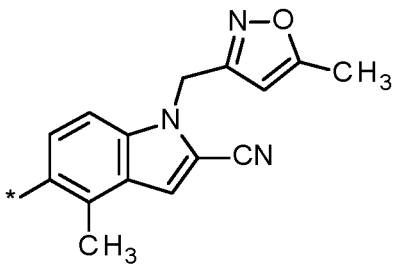
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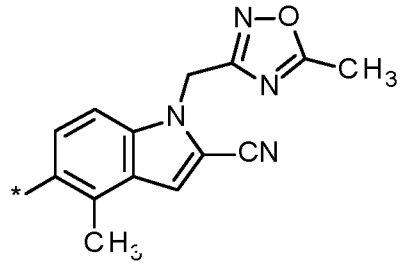
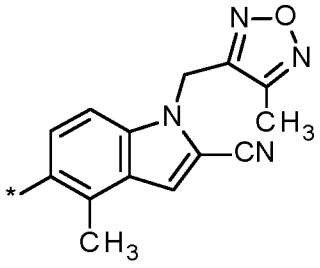


or
,

wherein: * indicates the point of attachment of said group with the rest of the molecule;

R^1 represents hydrogen or methyl;

R^8 represents hydrogen or methyl;

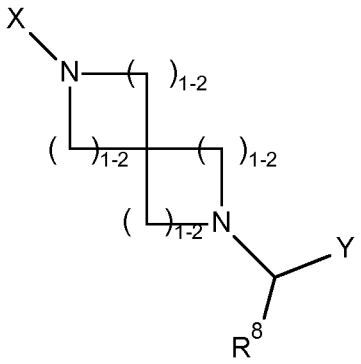
x represents 1 or 2;

y represents 1 or 2,

wherein at least one of x and y represent 2;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

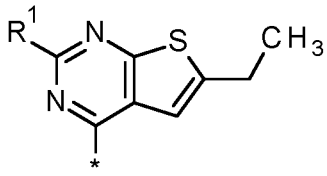
In accordance with a second aspect, the present invention covers compounds of general formula (I):



(I)

in which:

X represents a group selected from: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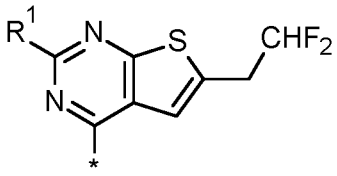
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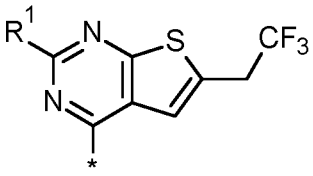
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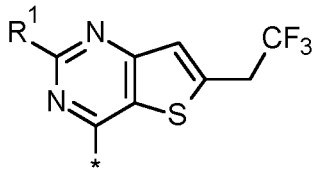
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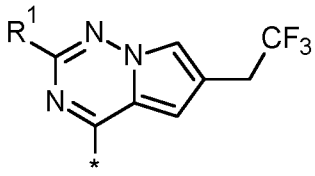
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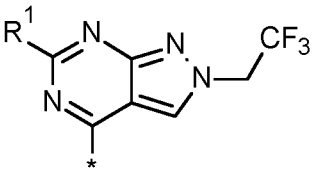
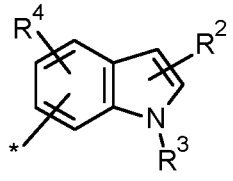

,

wherein * indicates the point of attachment of said group with the rest of the molecule;

Y represents a group


,

wherein * indicates the point of attachment of said group with the rest of the molecule;

R^1 represents hydrogen or methyl;

R^2 represents hydrogen, -CN, $-CONH_2$ or $-C0_2R^9$;

R^3 represents hydrogen, Ci-C_4-alkyl, C_2-C_4-hydroxyalkyl, -C_2-C_4-alkylen-N R^6R^7, -CO2R^9 or -Ci-C_2-alkylen-R^5;

R^4 represents hydrogen, hydroxy, halogen, methyl or methoxy;

R^5 represents -C0$_2R^9$, -CON R^6R^7 or 5-membered heteroaryl, wherein said 5-membered heteroaryl is optionally substituted with Ci-C_4-alkyl;

R^6 and R^7 are the same or different and represent, independently from each other, hydrogen, Ci-C_4-alkyl, C_{3-C6}-cycloalkyl, Ci-C_4-haloalkyl or
together with the nitrogen atom to which they are attached form a
4- to 6-membered nitrogen containing heterocyclic ring, said ring optionally containing one additional heteroatom selected from O, S, NH, NR^a in which R^a represents a Ci-C_4-alkyl or Ci-C_4-haloalkyl group;

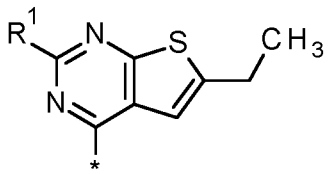
R^8 represents hydrogen or Ci-C_4-alkyl;

R^9 represents hydrogen or Ci-C_4-alkyl;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In accordance with a second embodiment of the second aspect, the present invention covers compounds of general formula (I), *supra,* in which:

X represents a group selected from: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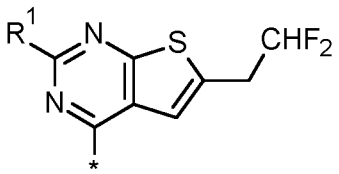
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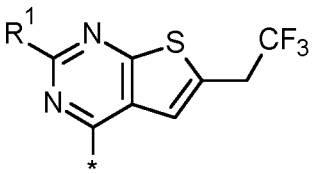
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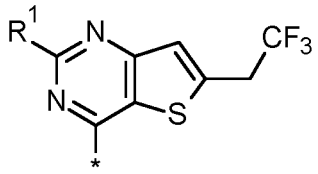
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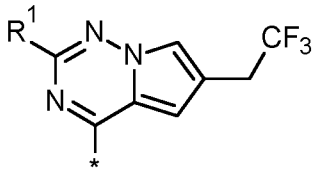
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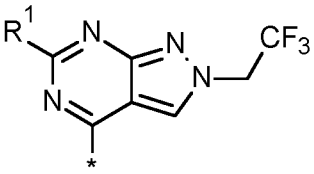
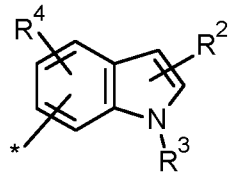

,

wherein * indicates the point of attachment of said group with the rest of the molecule;

Y represents a group


,

wherein * indicates the point of attachment of said group with the rest of the molecule;

R^1 represents hydrogen or methyl;

R^2 represents hydrogen, -CN, $-CONH_2$ or $-CO2R^9$;

R^3 represents hydrogen, methyl, C_2-C_3-hydroxyalkyl, $-CH_2-CH_2-NR^6R^7$, $-C0_2R^9$ or $-CH_2-R^5$;

R^4 represents hydrogen, methyl or methoxy;

R^5 represents $-C0_2R^9$, $-CONH_2$, pyrazolyl or methylpyrazolyl;

R^6 and R^7 are the same or different and represent, independently from each other, hydrogen, Ci_{-C4} -alkyl or

together with the nitrogen atom to which they are attached form a 4- to 6-membered nitrogen containing heterocyclic ring, said ring optionally containing one additional heteroatom selected from O, S, NH, NR^a in which R^a represents a **C1-C4-**alkyl or Ci_{-C4} -haloalkyl group;

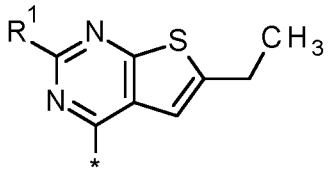
R^8 represents hydrogen or methyl;

R^9 represents hydrogen or methyl;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In accordance with a third embodiment of the second aspect, the present invention covers compounds of general formula (I), *supra,* in which:

X represents a group selected from: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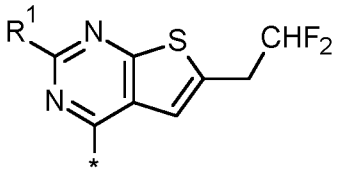
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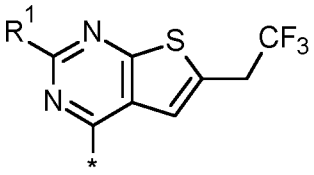
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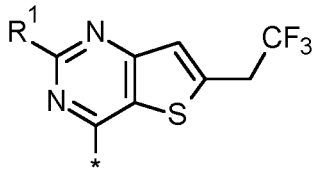
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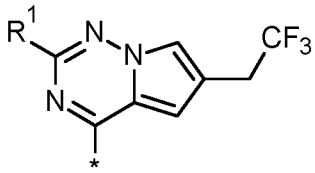
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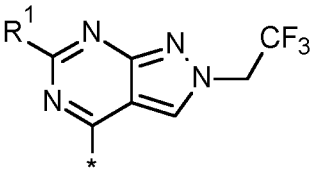
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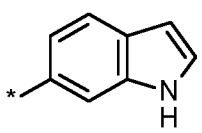
wherein * indicates the point of attachment of said group with the rest of the molecule;

Y represents a group selected from: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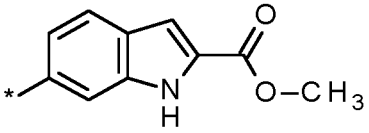
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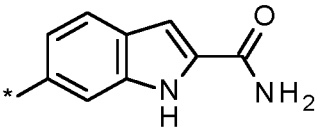
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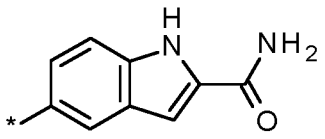
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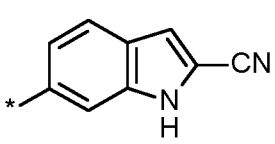
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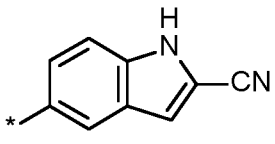
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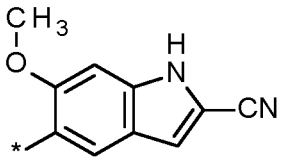
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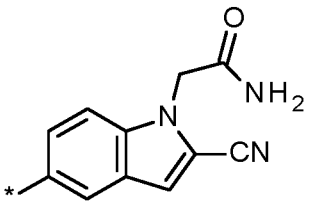
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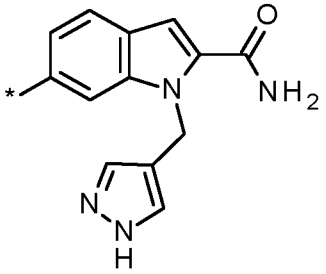
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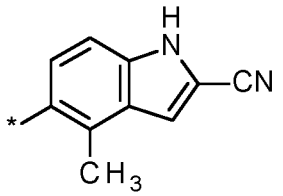
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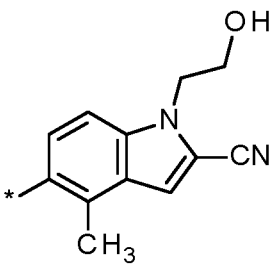
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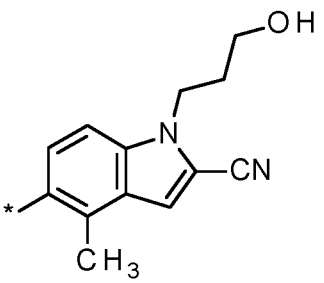
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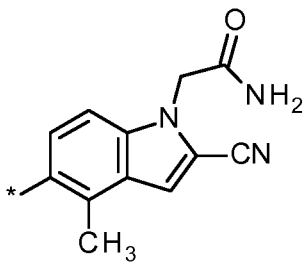
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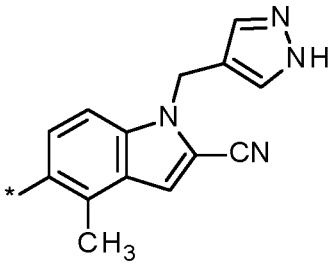
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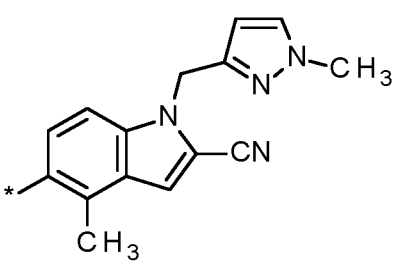
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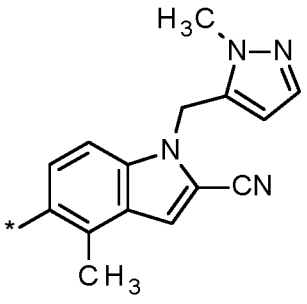
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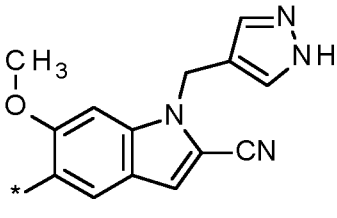
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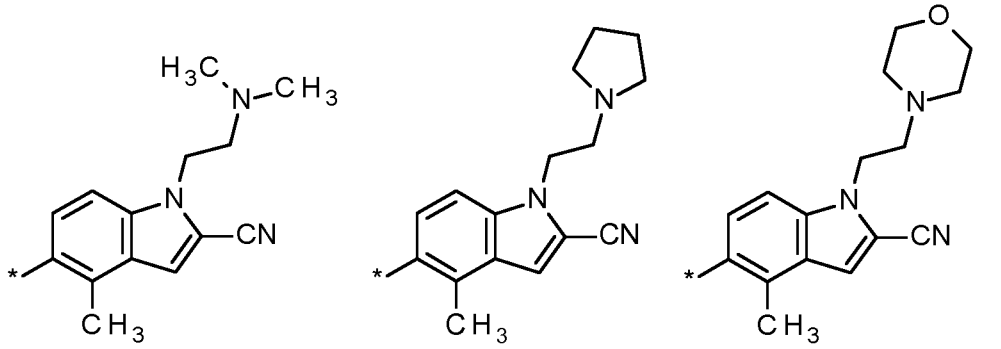


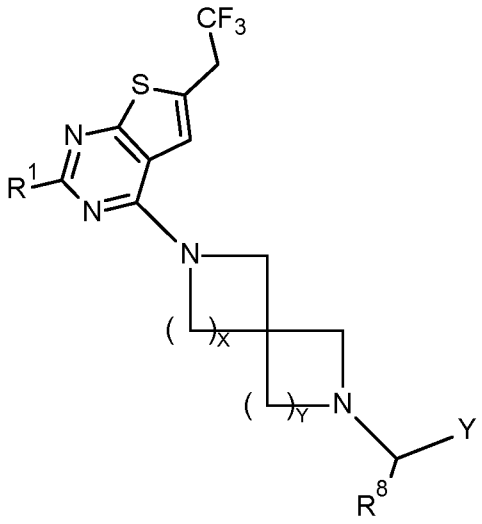
wherein: * indicates the point of attachment of said group with the rest of the molecule;

R^1 represents hydrogen or methyl;

R^8 represents hydrogen;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

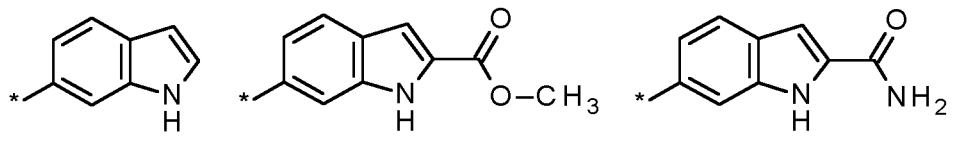
In accordance with a fourth embodiment of the second aspect, the present invention covers compounds of general formula (Ia),

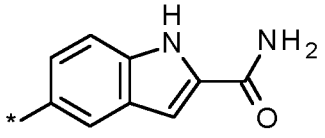


(Ia)

in which:

Y represents a group selected from:

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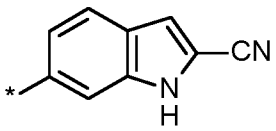
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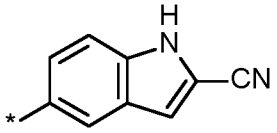
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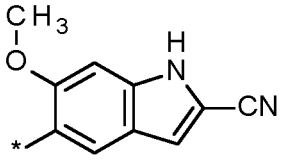
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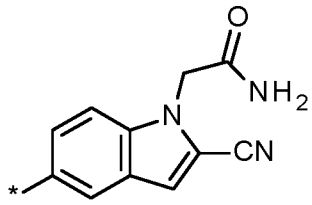
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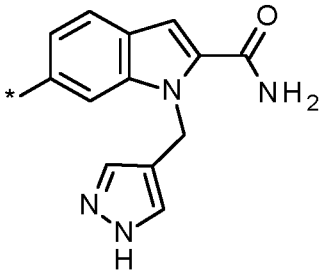
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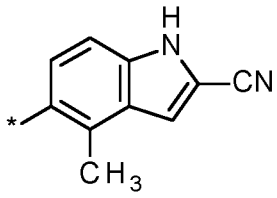
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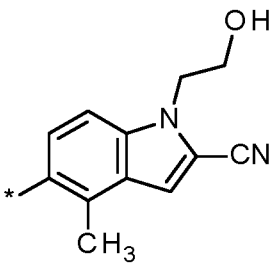
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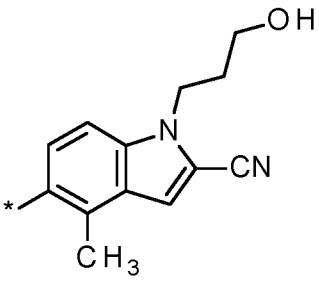
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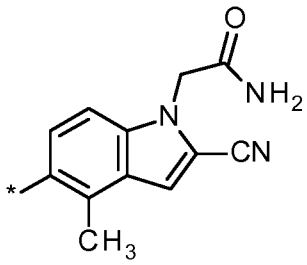
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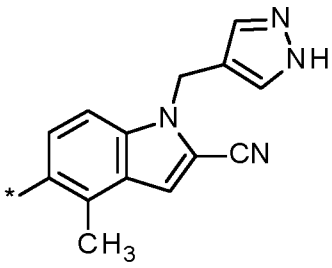
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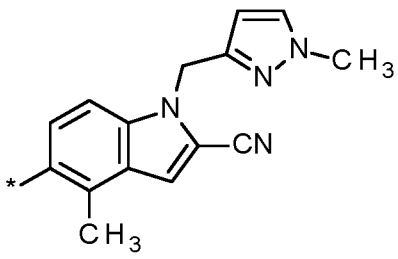
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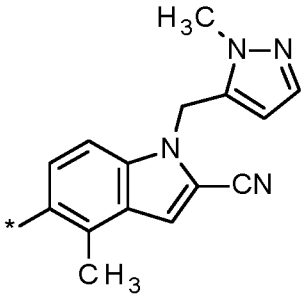
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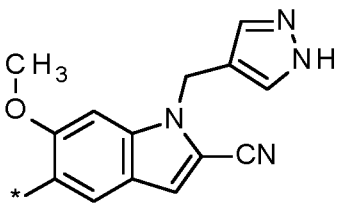
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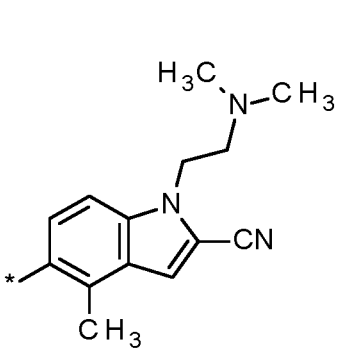
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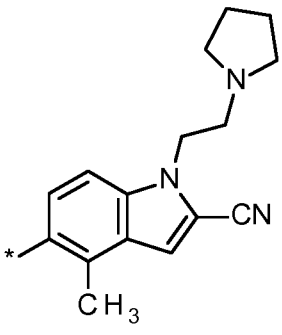
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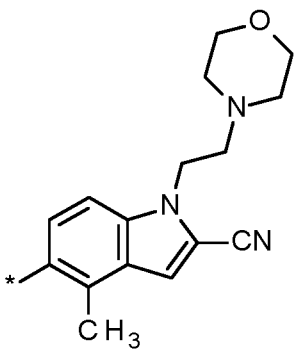

,

wherein: * indicates the point of attachment of said group with the rest of the molecule;

R^1 represents hydrogen or methyl;

R^8 represents hydrogen or methyl;

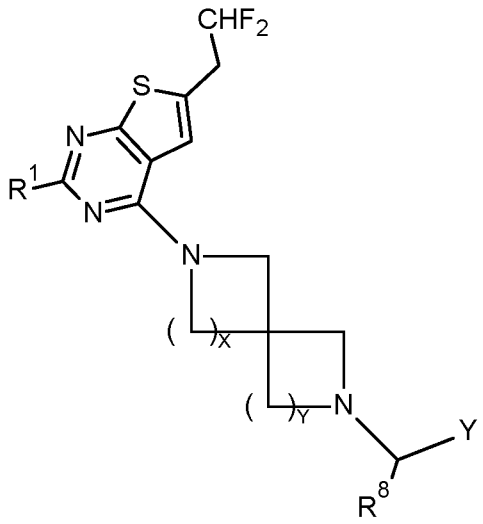
x represents 1 or 2;

y represents 1 or 2,

wherein at least one of x and y represent 2;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

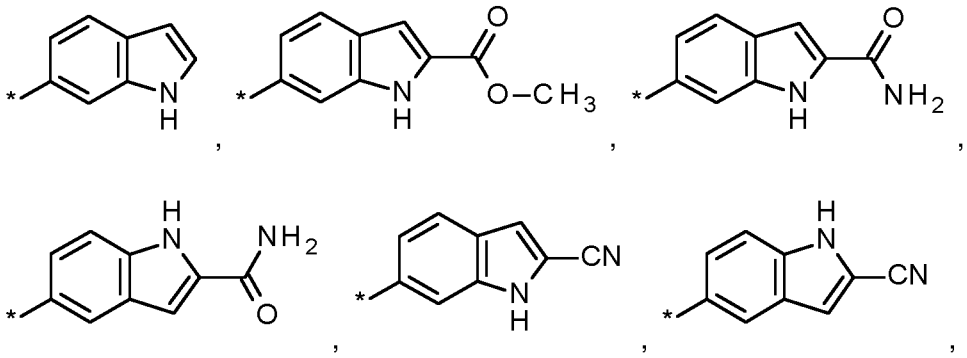
In accordance with a fifth embodiment of the second aspect, the present invention covers compounds of general formula (Id),

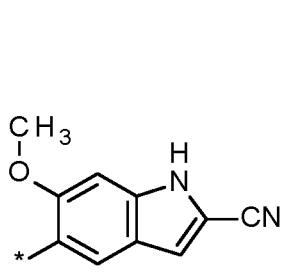
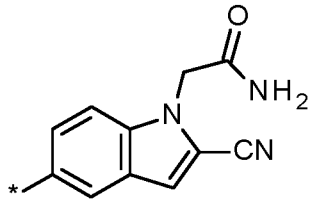
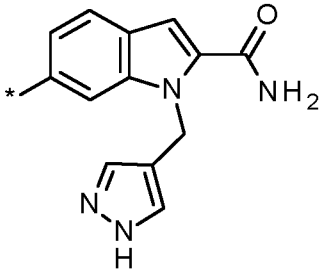
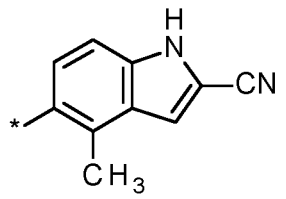
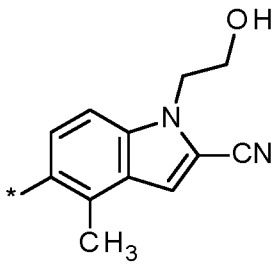
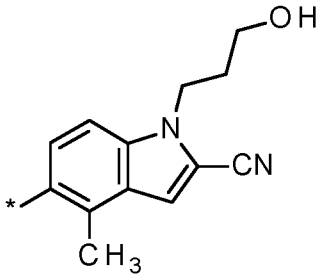
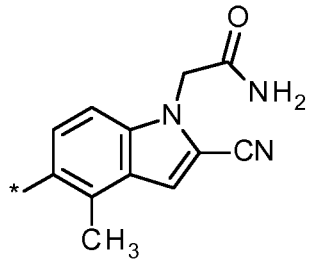
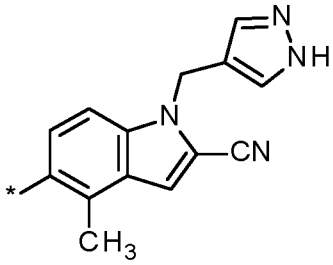
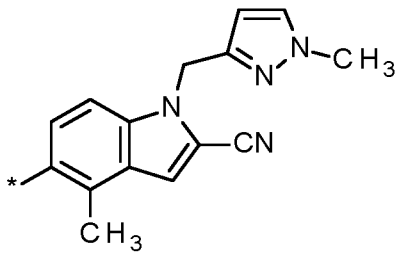
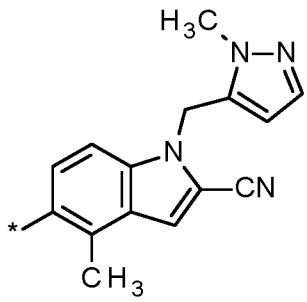
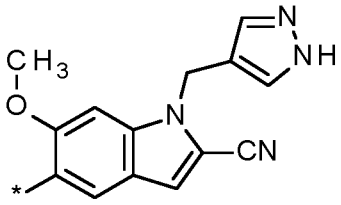
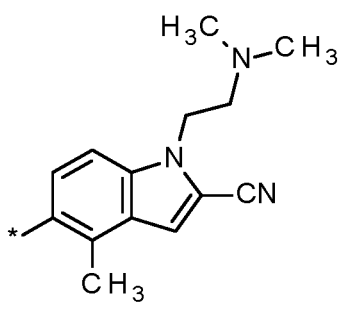
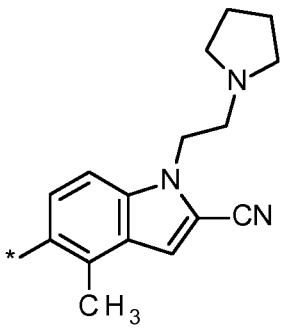
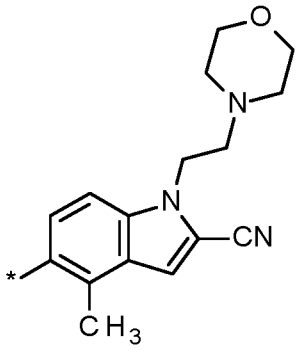


(Id)

in which:

Y represents a group selected from:



wherein: * indicates the point of attachment of said group with the rest of the molecule;

R^1 represents hydrogen or methyl;

R^8 represents hydrogen or methyl;

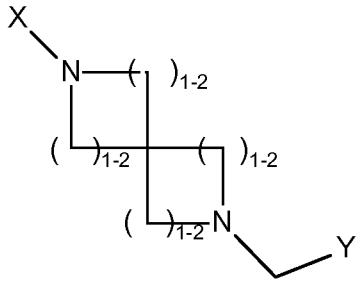
x represents 1 or 2;

y represents 1 or 2,

wherein at least one of x and y represent 2;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

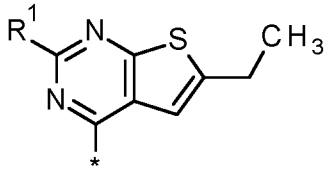
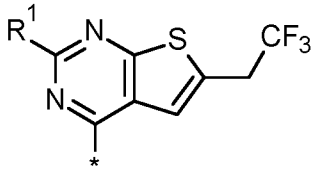
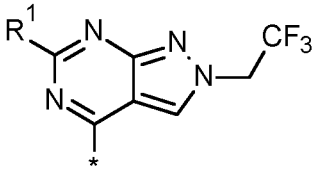
In accordance with a third aspect, the present invention covers compounds of general formula (I):



(I)

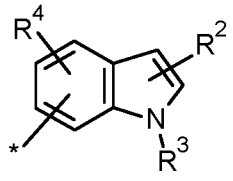
in which:

X represents a group selected from:


, 
or 
,

wherein * indicates the point of attachment of said group with the rest of the molecule;

Y represents a group


,

wherein * indicates the point of attachment of said group with the rest of the molecule;

R^1 represents hydrogen or methyl;

R^2 represents hydrogen, -CN or $-CONH_2$;

R^3 represents hydrogen, **Ci-C4**-alkyl, **C2-C4** -hydroxyalkyl or $-CH_2-R^5$;

R^4 represents hydrogen, hydroxy, halogen, methyl or methoxy;

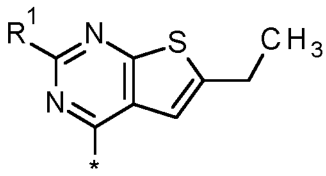
R^5 represents -CONR $^6R^7$ or 5-membered heteroaryl;

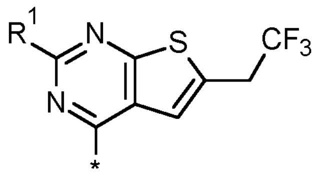
R^6 and R^7 are the same or different and represent, independently from each other, hydrogen, Ci-C4-alkyl, C3-C6 -cycloalkyl, Ci-C4-haloalkyl or together with the nitrogen atom to which they are attached form a 4- to 6-membered nitrogen containing heterocyclic ring, said ring optionally containing one additional heteroatom selected from O, S, NH, NR^a in which R^a represents a C1-C4-alkyl or Ci-C4-haloalkyl group;

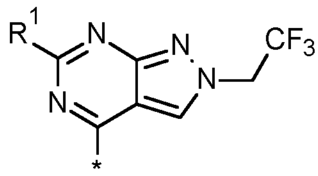
and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In accordance with a second embodiment of the third aspect, the present invention covers compounds of general formula (I), *supra,* in which:

X represents a group selected from:



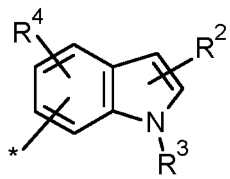
, 

or 

,

wherein * indicates the point of attachment of said group with the rest of the molecule;

Y represents a group



,

wherein * indicates the point of attachment of said group with the rest of the molecule;

R^1 represents hydrogen or methyl;

R^2 represents hydrogen, -CN or $-CONH_2$;

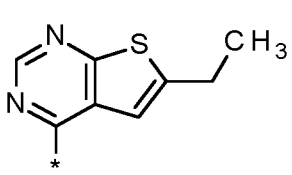
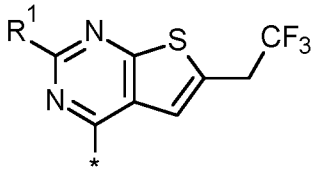
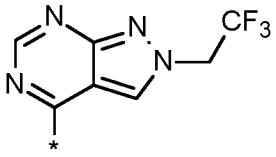
R^3 represents hydrogen, methyl or $-CH_2-CONH_2$;

R^4 represents hydrogen or methyl;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

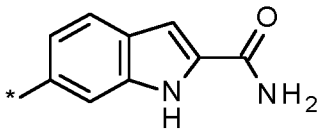
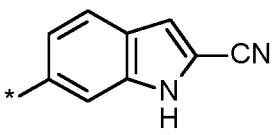
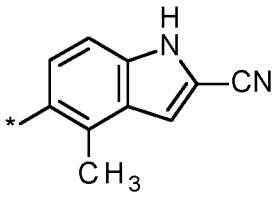
In accordance with a third embodiment of the third aspect, the present invention covers compounds of general formula (I), *supra,* in which:

X represents a group selected from:


, 
or 
,

wherein * indicates the point of attachment of said group with the rest of the molecule;

Y represents a group selected from:


, 
, 
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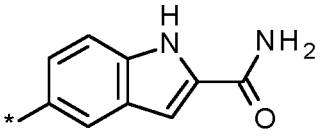
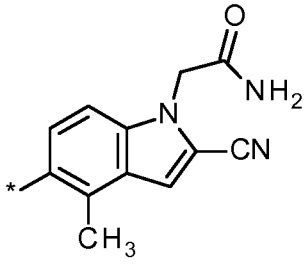
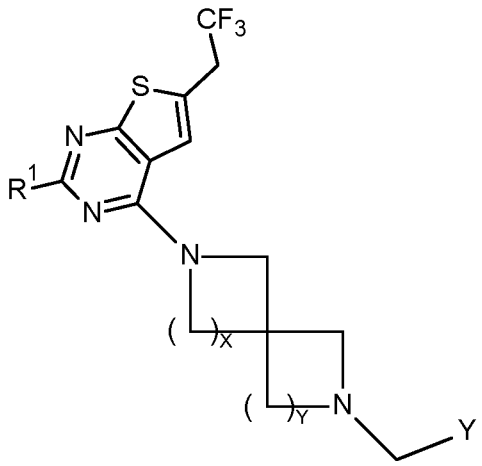

or 
,

wherein: * indicates the point of attachment of said group with the rest of the molecule;

R^1 represents hydrogen or methyl;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

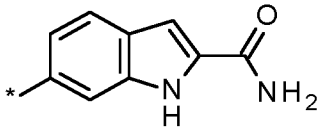
In accordance with a fourth embodiment of the third aspect, the present invention covers compounds of general formula (Ia),



(Ia)

in which:

Y represents a group selected from: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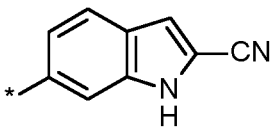
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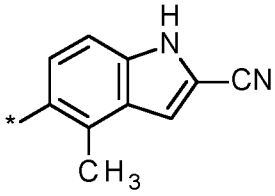
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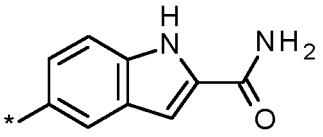
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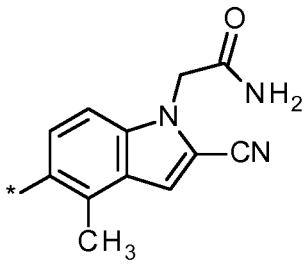

,

wherein: * indicates the point of attachment of said group with the rest of the molecule;

R^1 represents hydrogen or methyl;

x represents 1 or 2;

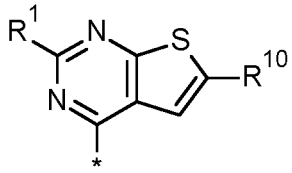
y represents 1 or 2,

wherein at least one of x and y represent 2;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

X represents a group selected from: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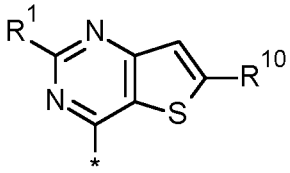
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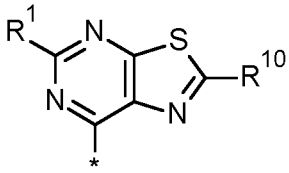
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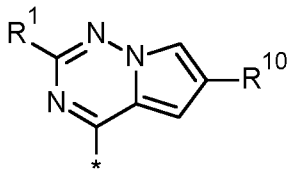
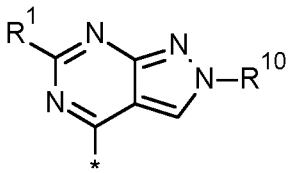
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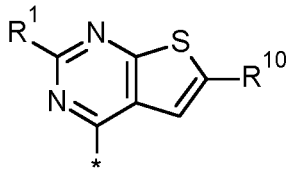
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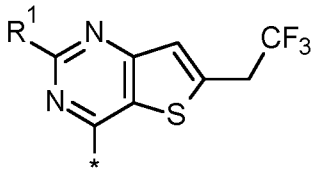
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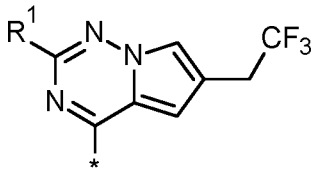
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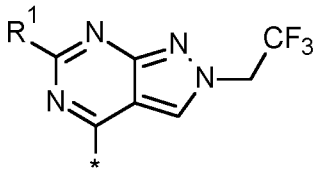
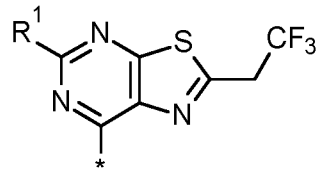
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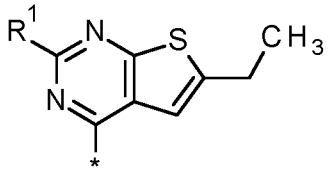
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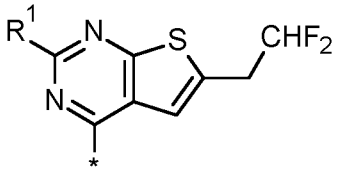
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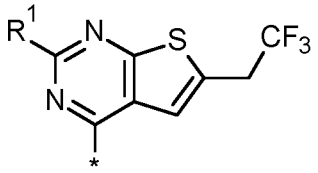
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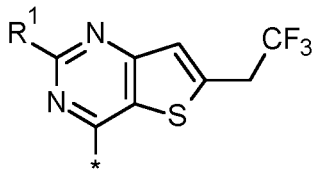
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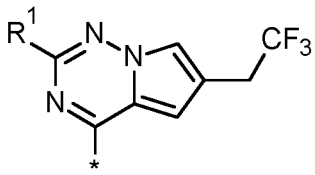
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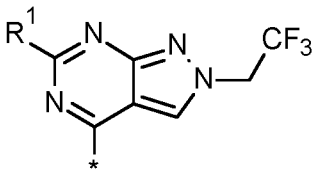
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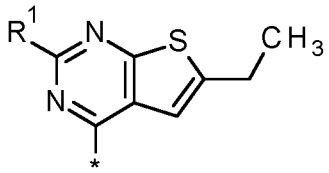
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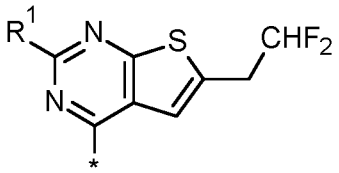
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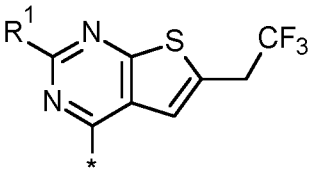
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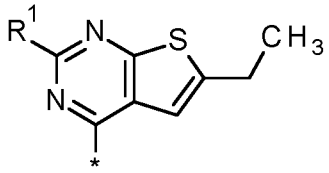
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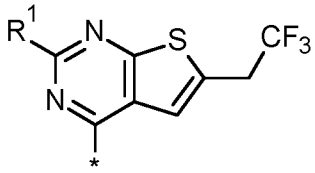
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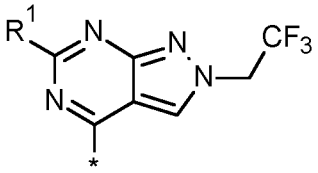
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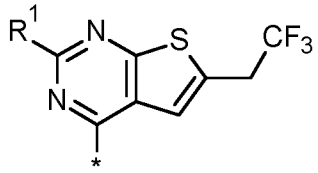
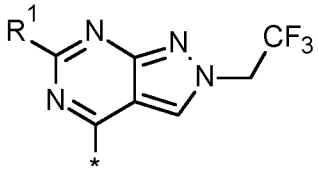

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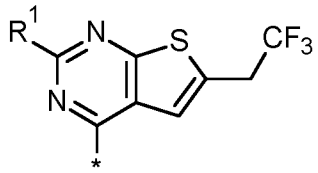
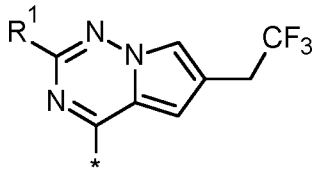
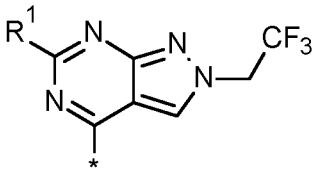

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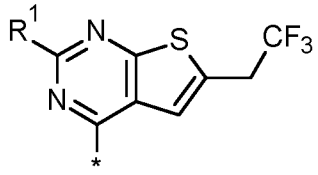
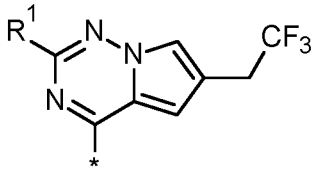

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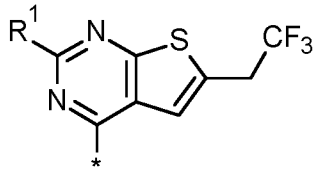

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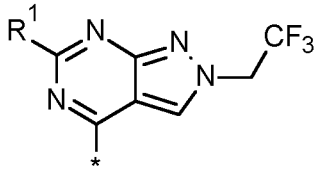

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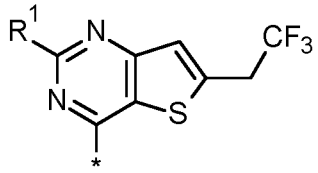

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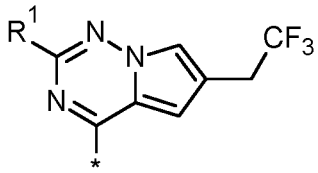

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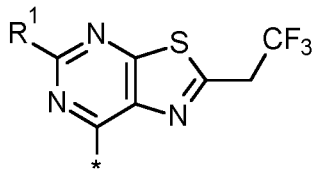

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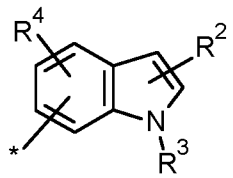

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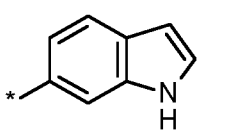

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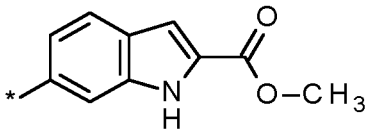

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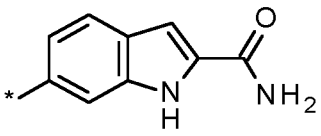

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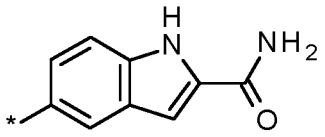

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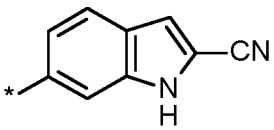

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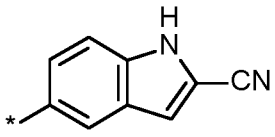

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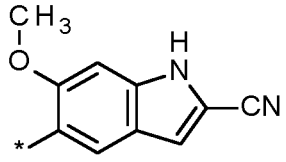

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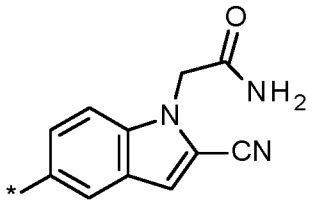

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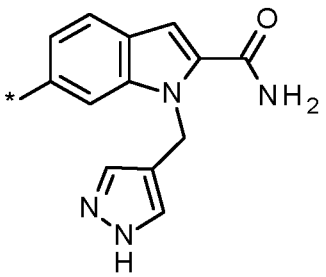

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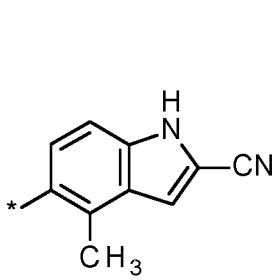

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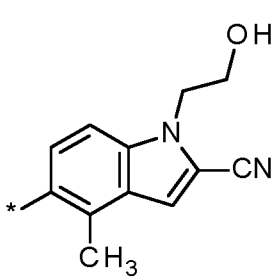

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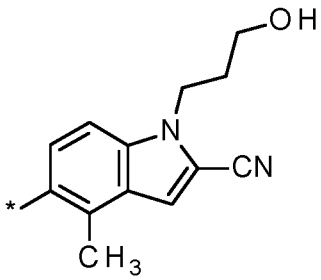

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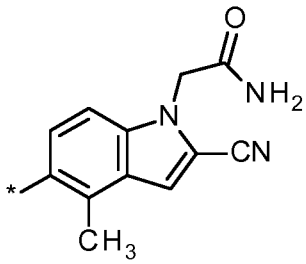
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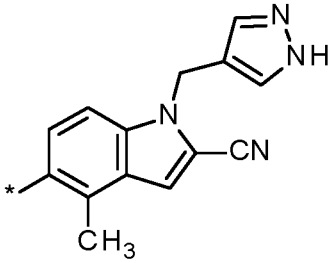
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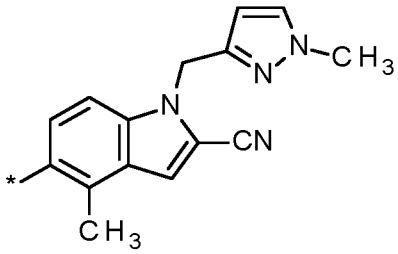
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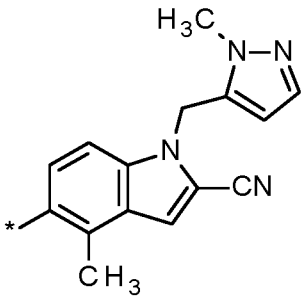
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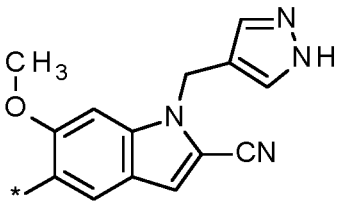
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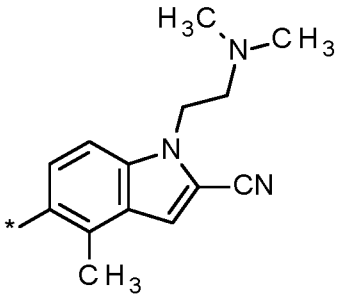
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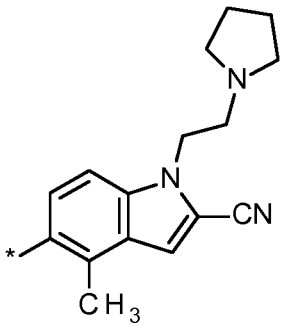
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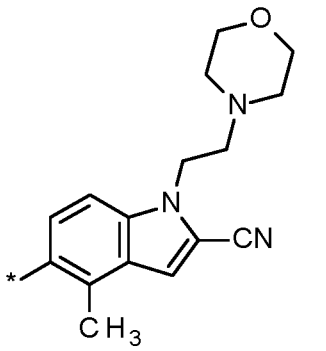
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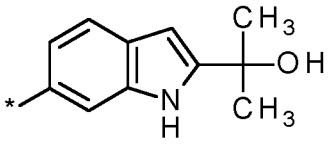
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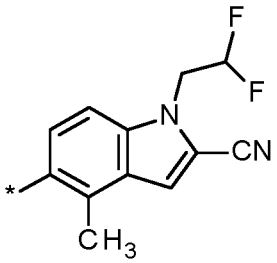
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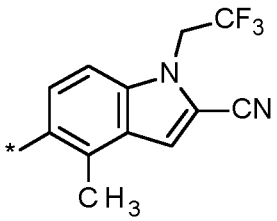
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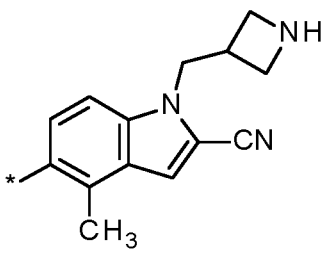
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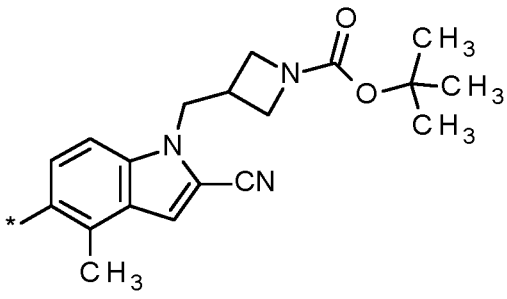
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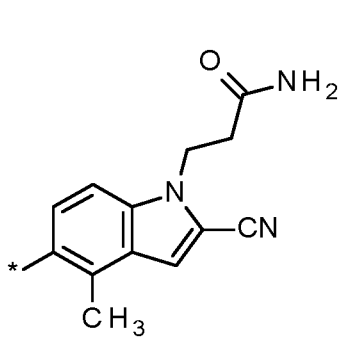
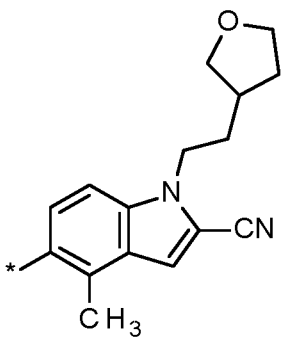
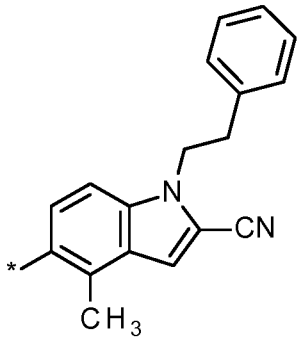
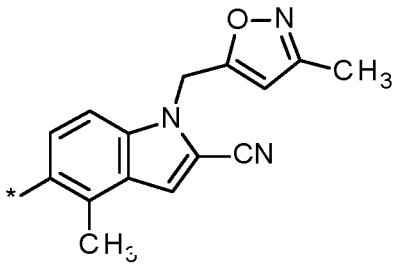
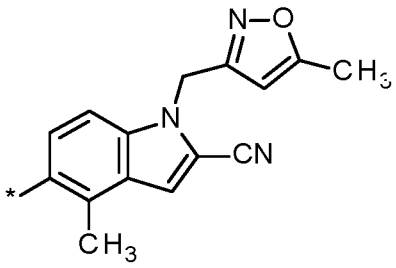
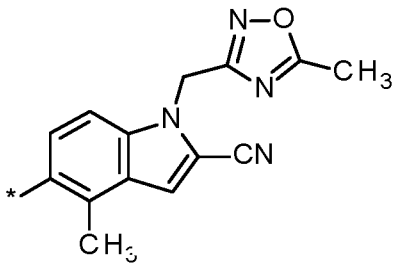
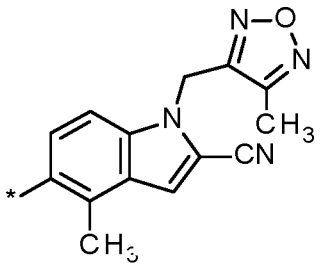








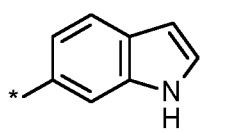
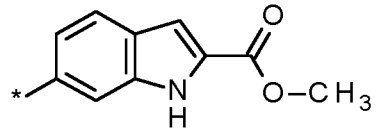
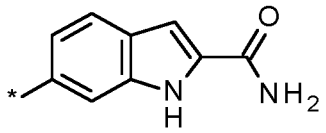
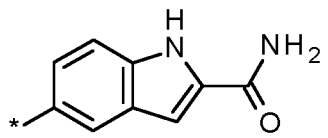
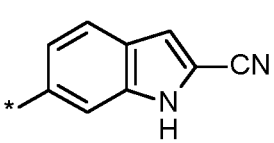
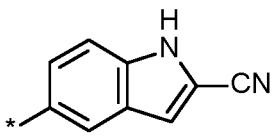
or

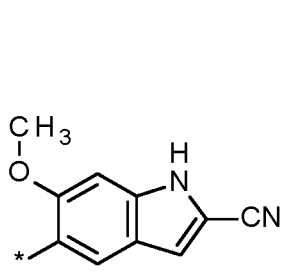
wherein * indicates the point of attachment of said group with the rest of the molecule;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

Y represents a group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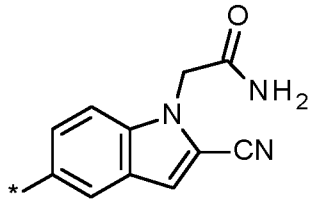
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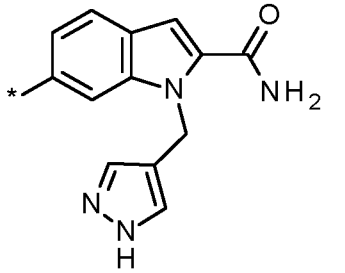
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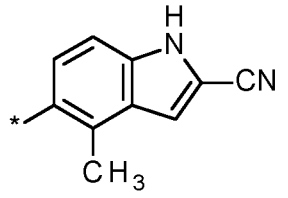
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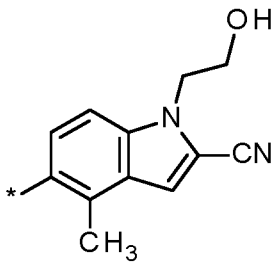
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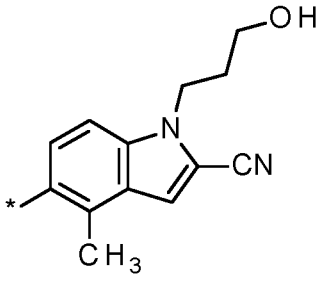
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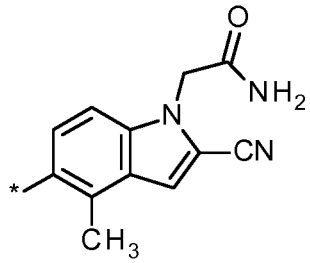
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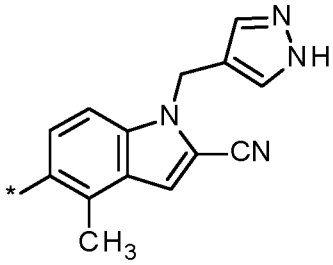
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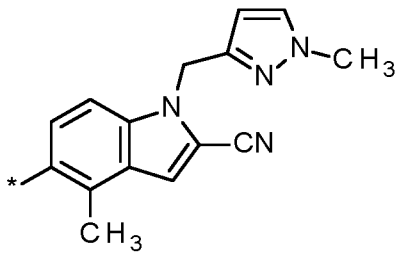
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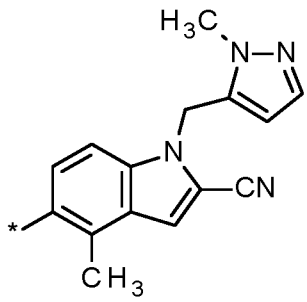
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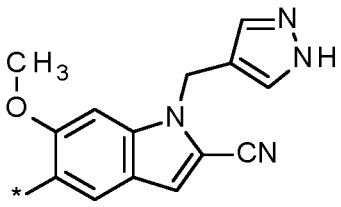
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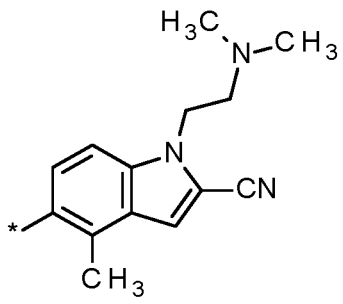
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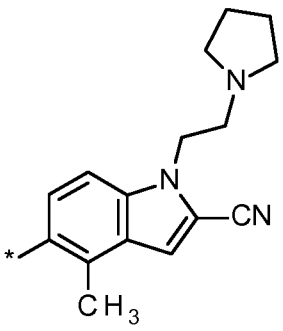
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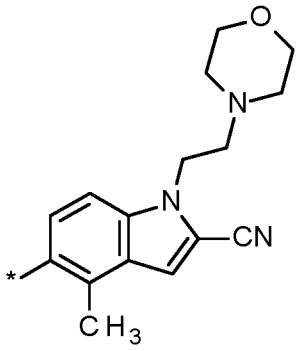
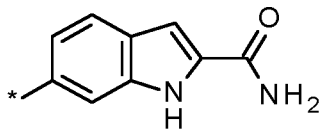

,

wherein * indicates the point of attachment of said group with the rest of the molecule;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

Y represents a group selected from: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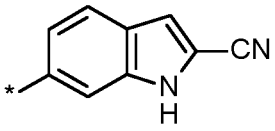
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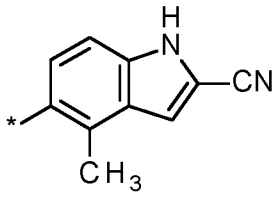
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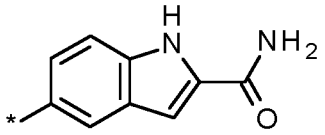
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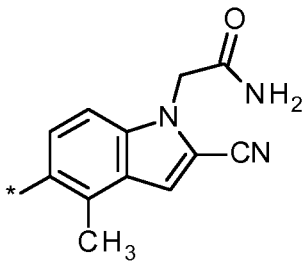
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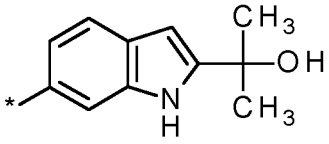
wherein: * indicates the point of attachment of said group with the rest of the molecule;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which: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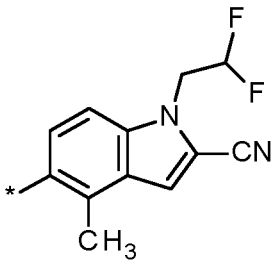
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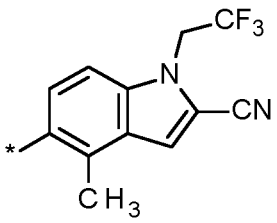
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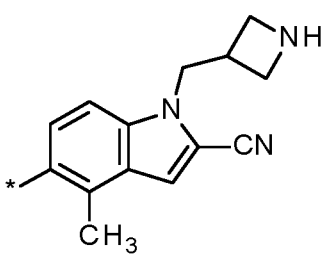
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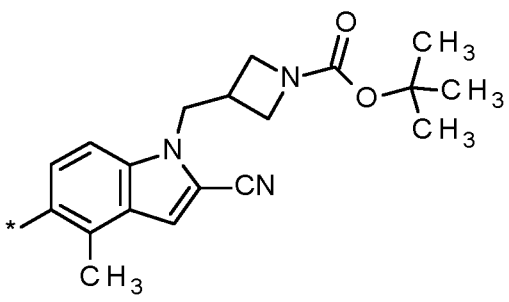
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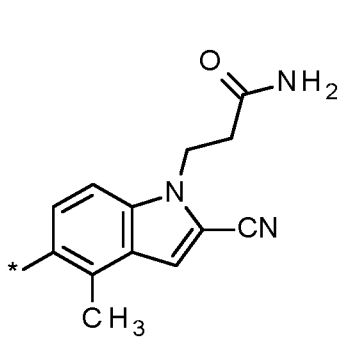
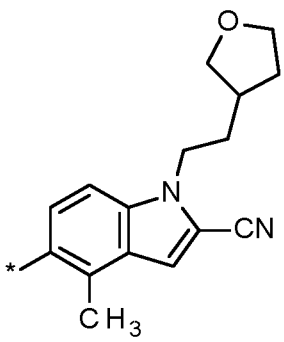
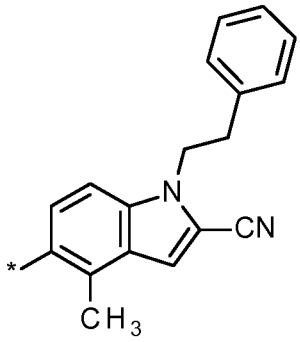
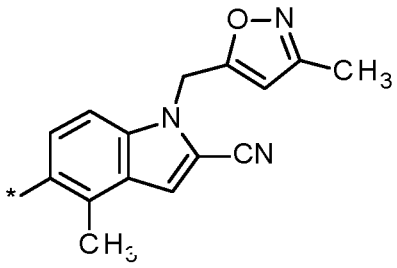
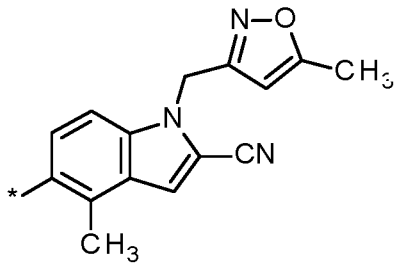
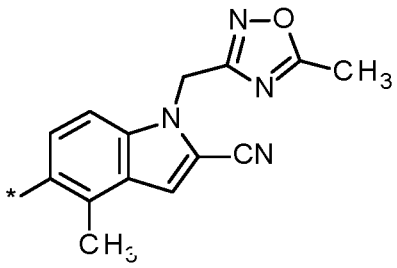
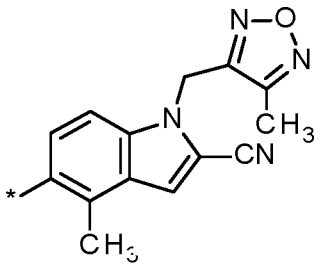
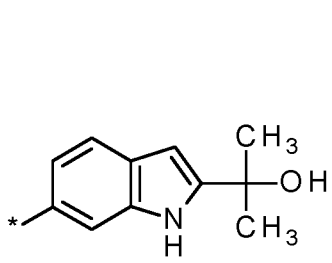
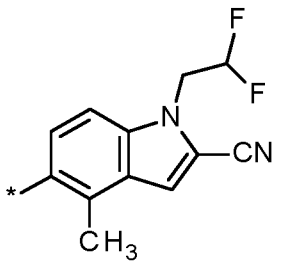
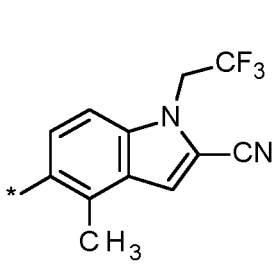
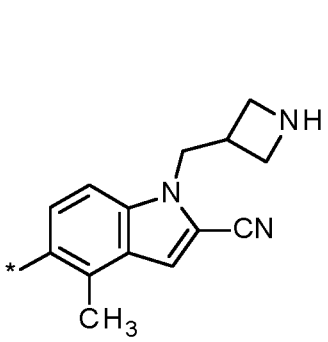
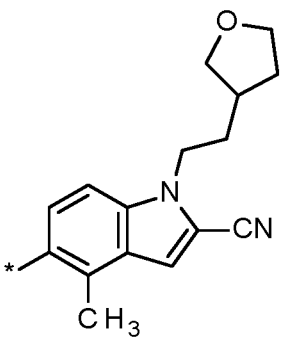
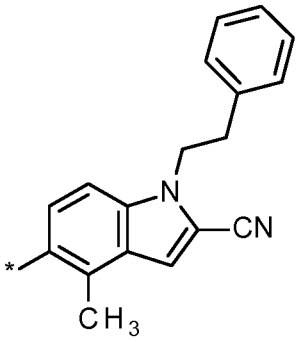
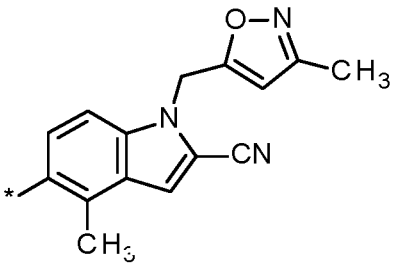
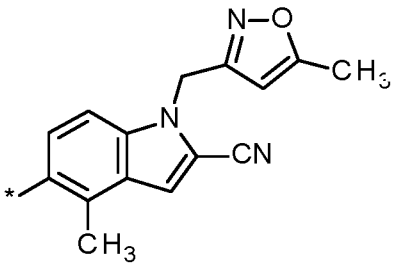
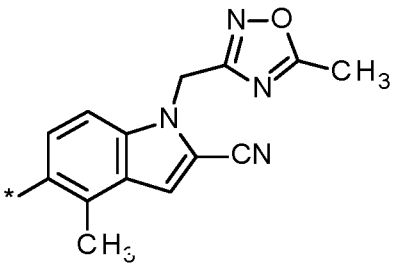
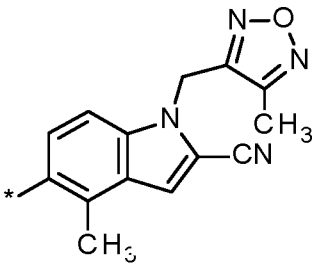








wherein: * indicates the point of attachment of said group with the rest of the molecule;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

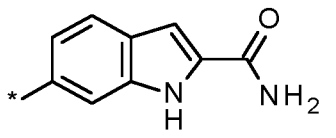
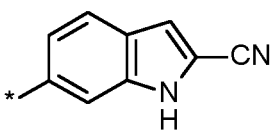
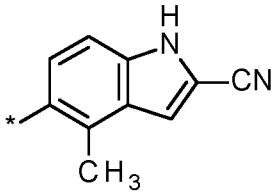








wherein: * indicates the point of attachment of said group with the rest of the molecule;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

Y represents a group selected from:

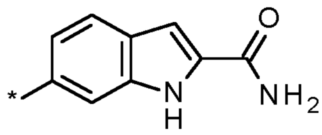




wherein: * indicates the point of attachment of said group with the rest of the molecule;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

Y represents



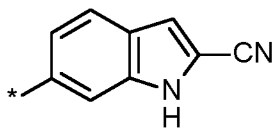
,

wherein: * indicates the point of attachment of said group with the rest of the molecule;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

Y represents



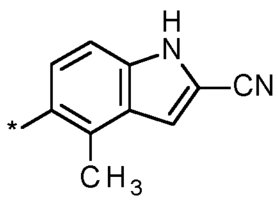
,

wherein: * indicates the point of attachment of said group with the rest of the molecule;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

Y represents



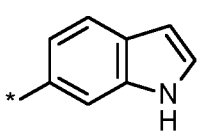
,

wherein: * indicates the point of attachment of said group with the rest of the molecule;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

Y represents a group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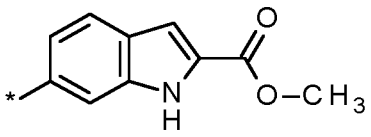
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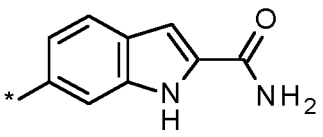
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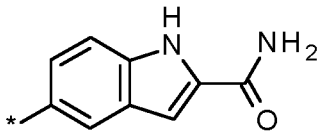
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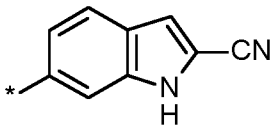
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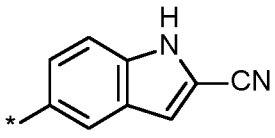
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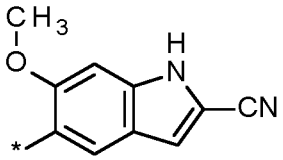
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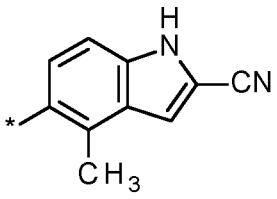
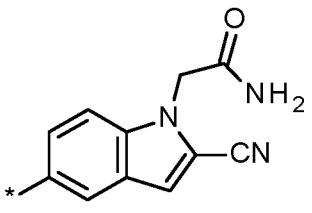

,

wherein * indicates the point of attachment of said group with the rest of the molecule;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

Y represents a group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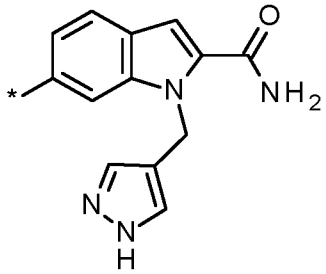
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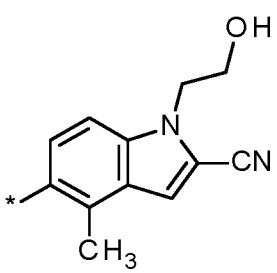
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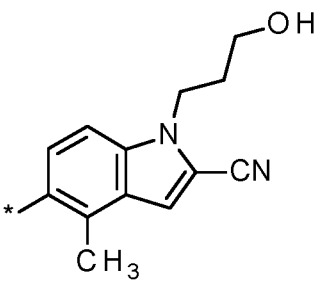
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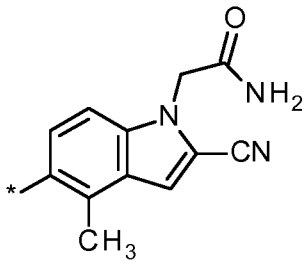
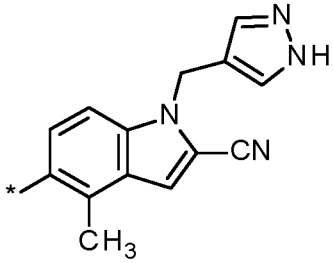
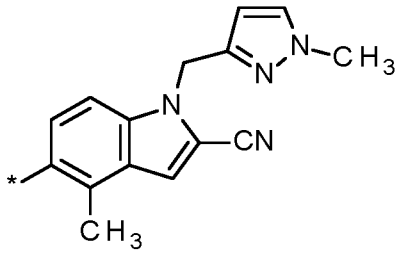
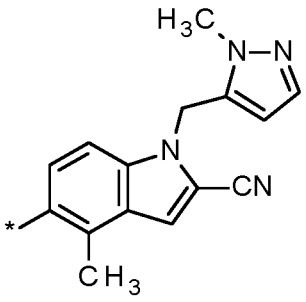
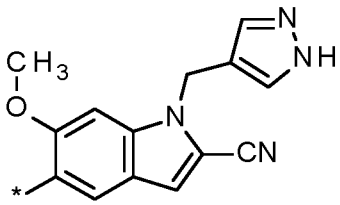
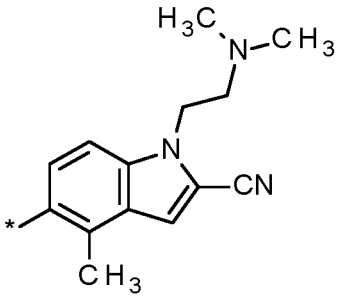
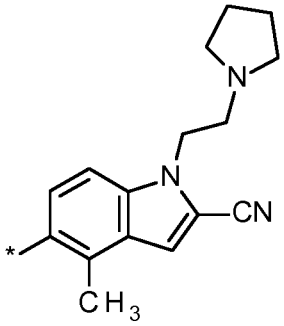
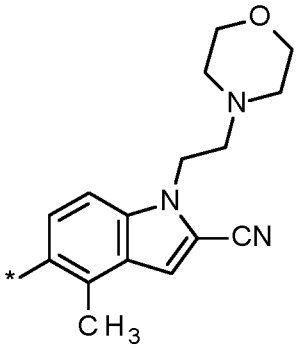









wherein * indicates the point of attachment of said group with the rest of the molecule;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

R^1 represents hydrogen or methyl;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

R^1 represents hydrogen;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

R^1 represents methyl;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

R^2 represents hydrogen, Ci-C_4-hydroxyalkyl, -CN, -$CONH_2$ or -$C0_2R^9$;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

R^2 represents -CN, -$CONH_2$ or -$C(CH_3)_2$-OH;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

R^2 represents -CN or -$CONH_2$;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

R^2 represents -CN;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

R^2 represents $-CONH_2$;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

R^2 represents $-C(CH_3)_2-OH$;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

R^3 represents hydrogen, Ci-C4-alkyl, Ci-C4-haloalkyl, C2-C4-hydroxyalkyl or $-CH_2-R^5$;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

R^3 represents hydrogen, Ci-C4-alkyl, C2-C4-hydroxyalkyl or $-CH_2-R^5$;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

R^3 represents hydrogen, methyl or $-CH_2-R^5$;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

R^3 represents hydrogen, methyl, difluoroethyl, trifluoroethyl or $-CH_2-R^5$;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

R^3 represents hydrogen or $-CH2-R^5$;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

R^3 represents hydrogen, methyl or $-CH2-CONH2$;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

R^3 represents hydrogen or methyl;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

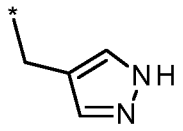
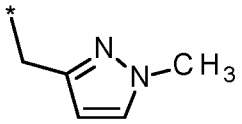
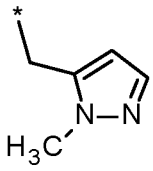
In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

R^3 represents difluoroethyl or trifluoroethyl;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

R^3 represents


, 
or 
;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

R^3 represents hydrogen;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

R^4 represents hydrogen, hydroxy, halogen, methyl or methoxy;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

R^4 represents hydrogen, hydroxy, fluoro, chloro, methyl or methoxy;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

R^4 represents hydrogen, fluoro, chloro or methyl;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

R^4 represents hydrogen or methyl;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

R^5 represents -CO_2R^9, -$CONR^6R^7$, 4- to 6-membered heterocycloalkyl optionally substituted with -CO_2R^9, phenyl or 5-membered heteroaryl,
wherein said phenyl group is optionally substituted, one or more times, independently from each other, with hydroxy, halogen, cyano, Ci-C3-alkyl, Ci-C3-haloalkyl, Ci-C3-alkoxy or Ci-C3-haloalkoxy and said 5-membered heteroaryl is optionally substituted with Ci-C4-alkyl;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

R^5 represents phenyl or 5-membered heteroaryl, wherein said phenyl group is optionally substituted, one or more times, independently from each other, with hydroxy, halogen, cyano, Ci-C3-alkyl, Ci-C3-haloalkyl, Ci-C3-alkoxy or Ci-C3-haloalkoxy and said 5-membered heteroaryl is optionally substituted with Ci-C4-alkyl;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

R^5 represents -$CONH_2$ or 5-membered heteroaryl, wherein said 5-membered heteroaryl is optionally substituted with Ci-C4-alkyl;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

R^5 represents **-CONH**$_2$;

and stereoisomers, tautomers, **N**-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

R^5 represents 5-membered heteroaryl, wherein said 5-membered heteroaryl is optionally substituted with methyl;

and stereoisomers, tautomers, **N**-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

R^5 represents pyrazolyl;

and stereoisomers, tautomers, **N**-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

R^5 represents methylpyrazolyl;

and stereoisomers, tautomers, **N**-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

R^8 represents hydrogen or **C**$_{i\text{-}C4}$ -alkyl;

and stereoisomers, tautomers, **N**-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

R^8 represents hydrogen or methyl;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of either the first, the second or the third aspect, the present invention covers compounds of formula (I), *supra,* in which:

R^8 represents hydrogen;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a particular further embodiment of the second aspect, the present invention covers combinations of two or more of the above mentioned embodiments under the heading "further embodiments of the second aspect of the present invention".

The present invention covers any sub-combination within any embodiment or aspect of the present invention of compounds of general formula (I), *supra.*

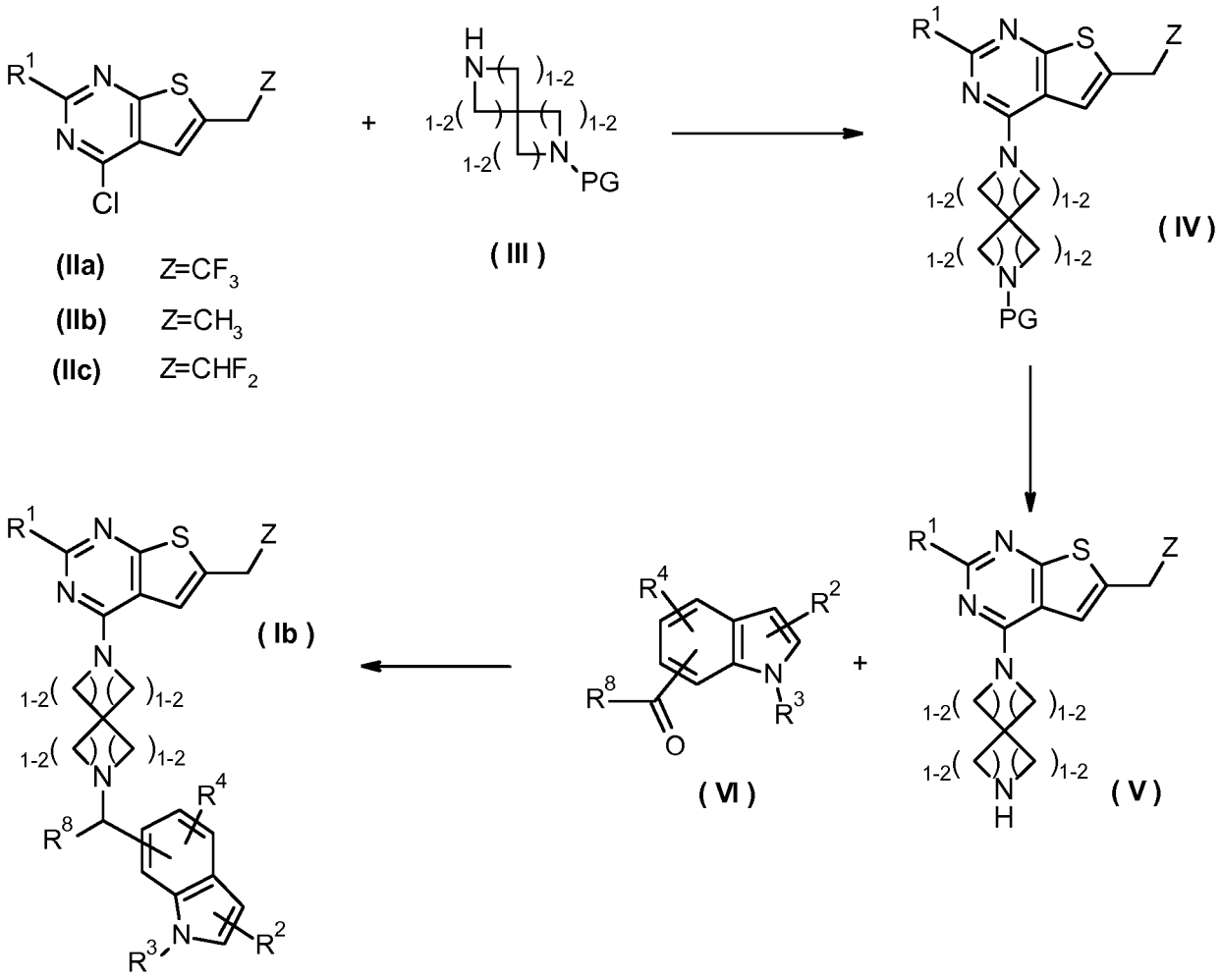
The present invention covers any sub-combination within any embodiment or aspect of the present invention of intermediate compounds of general formula (V), (VIII) and (XIII). The present invention covers the compounds of general formula (I) which are disclosed in the Example Section of this text, *infra.*

The compounds according to the invention of general formula (I) can be prepared according to the following schemes 1, 2, 3 and 4. The schemes and procedures described below illustrate synthetic routes to the compounds of general formula (I) of the invention and are not intended to be limiting. It is clear to the person skilled in the art that the order of transformations as exemplified in schemes 1, 2, 3 and 4 can be modified in various ways. The order of transformations exemplified in these schemes is therefore not intended to be limiting. In addition, interconversion of any of the substituents, R^1, R^2, R^3 or R^4 can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups, halogenation, alkylation, acylation, metallation or substitution known to the person skilled in the art. These transformations include those which introduce a functionality which allows for further interconversion of substituents. Appropriate protecting groups and their introduction and cleavage are well-known to the person skilled in the art (see for example T.W.

Greene and P.G.M. Wuts in *Protective Groups in Organic Synthesis,* 3rd edition, Wiley 1999). Specific examples are described in the subsequent paragraphs.

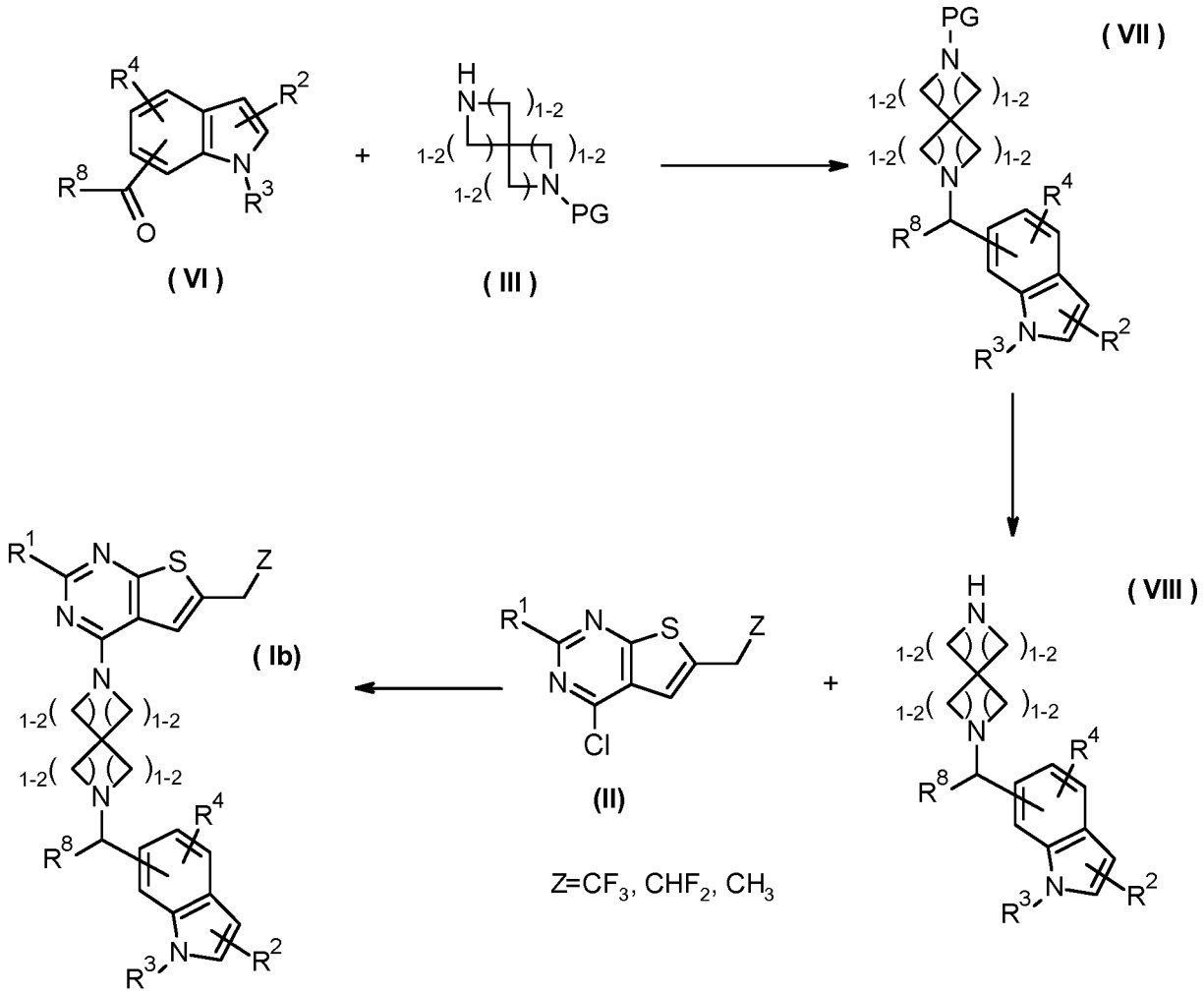
Four routes for the preparation of compounds of general formula **(I)** are described in schemes 1, 2, 3 and 4.

As outlined in scheme 1 compounds of general formula **(Ib)** can be prepared from starting materials of formula **(Ha)** or **(Mb)** by reacting with spirocyclic amines of the formula **(III)** containing a suitable protecting group PG.



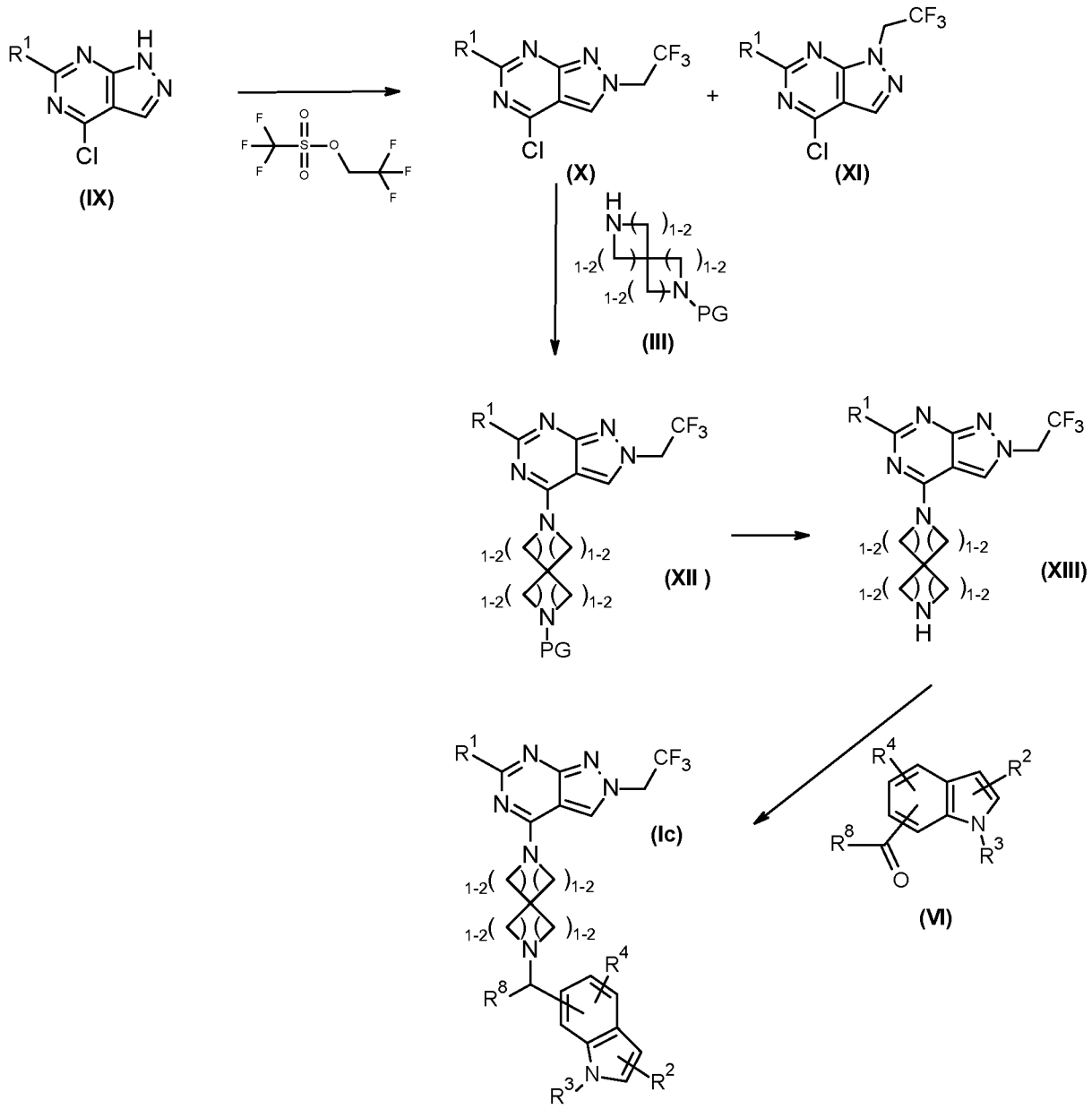
Scheme 1: Synthesis of compounds of general formula **(Ib),** in which R^1, R^2, R^3, R^4 and R^8 have the meaning as given for general formula **(I),** *supra,* from compounds of formulae **(Ha), (Mb), (Iie), (III)** and **(VI);** PG is a protecting group, e.g. Boc.

An alternative route for the synthesis of the compounds of formula **(Ib)** is shown in scheme 2.



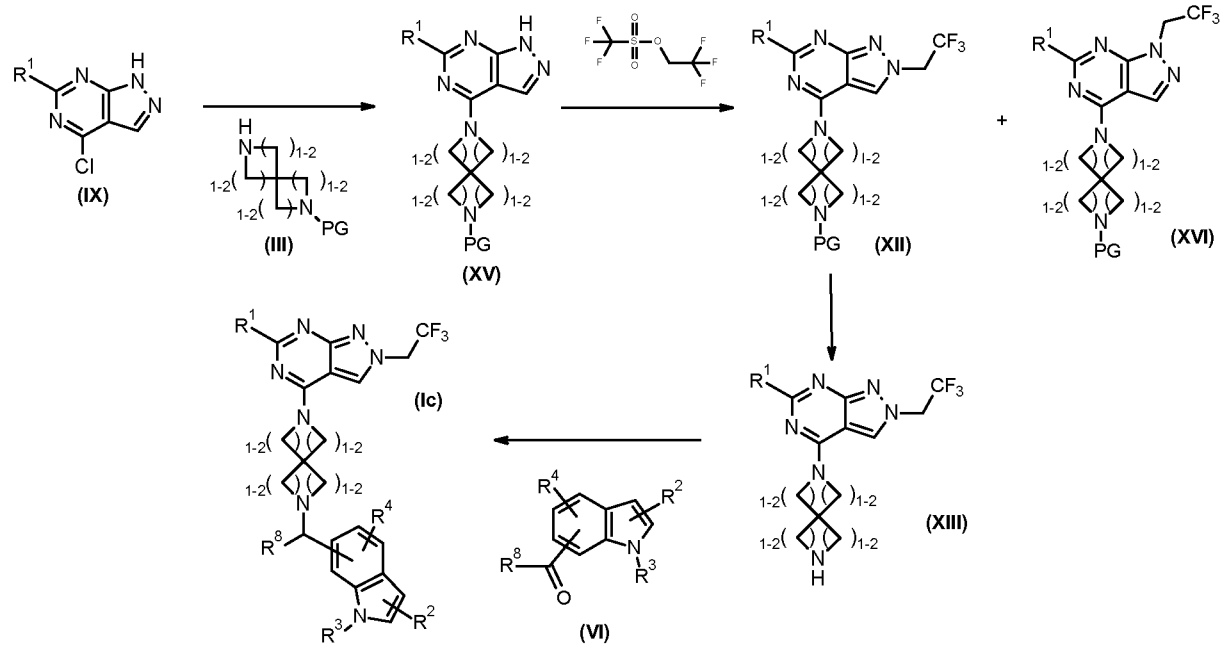
Scheme 2: Synthesis of compounds of general formula **(Ib),** in which R^1, R^2, R^3, R^4 and R^8 have the meaning as given for general formula **(I),** *supra,* from compounds of formulae **(VI), (III),** and **(II)**

The synthesis of compounds of formula **(Ic)** starting from commercially available compounds of formula **(IX),** trifluoroethylation afforded a mixture of alkylated products **(X)** and **(XI)** which can be separated. The desired compound of formula **(X)** can then be transferred to the compounds of formula **(Ic)** using a corresponding synthetic sequence as described in scheme 1.



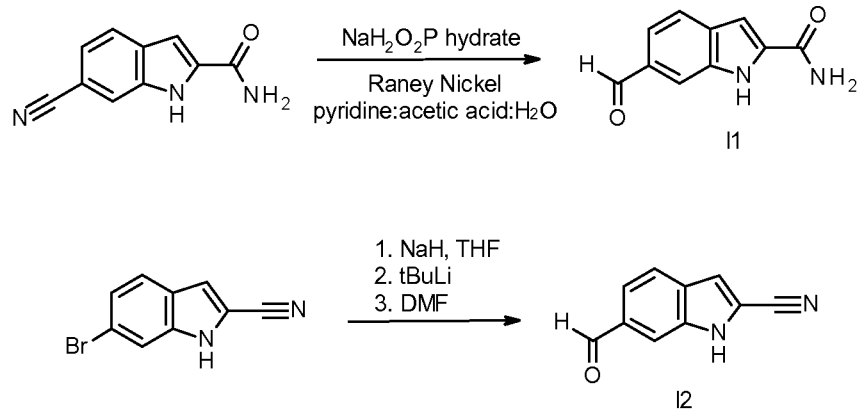
Scheme 3: Synthesis of compounds of general formula **(Ic),** in which R^1, R^2, R^3, R^4 and R^8 have the meaning as given for general formula **(I),** *supra,* from compounds of formulae **(IX), (III),** and **(VI)**

An alternative synthetic route toward compounds of formula **(Ic)** is described in scheme 4.



Scheme 4: Synthesis of compounds of general formula **(Ic),** in which R^1, R^2, R^3, R^4 and R^8 have the meaning as given for general formula **(I),** *supra,* from compounds of formulae **(IX), (III),** and **(VI)**

A synthetic approach towards the intermediates **(11)** and **(I2)** is described in scheme 5:

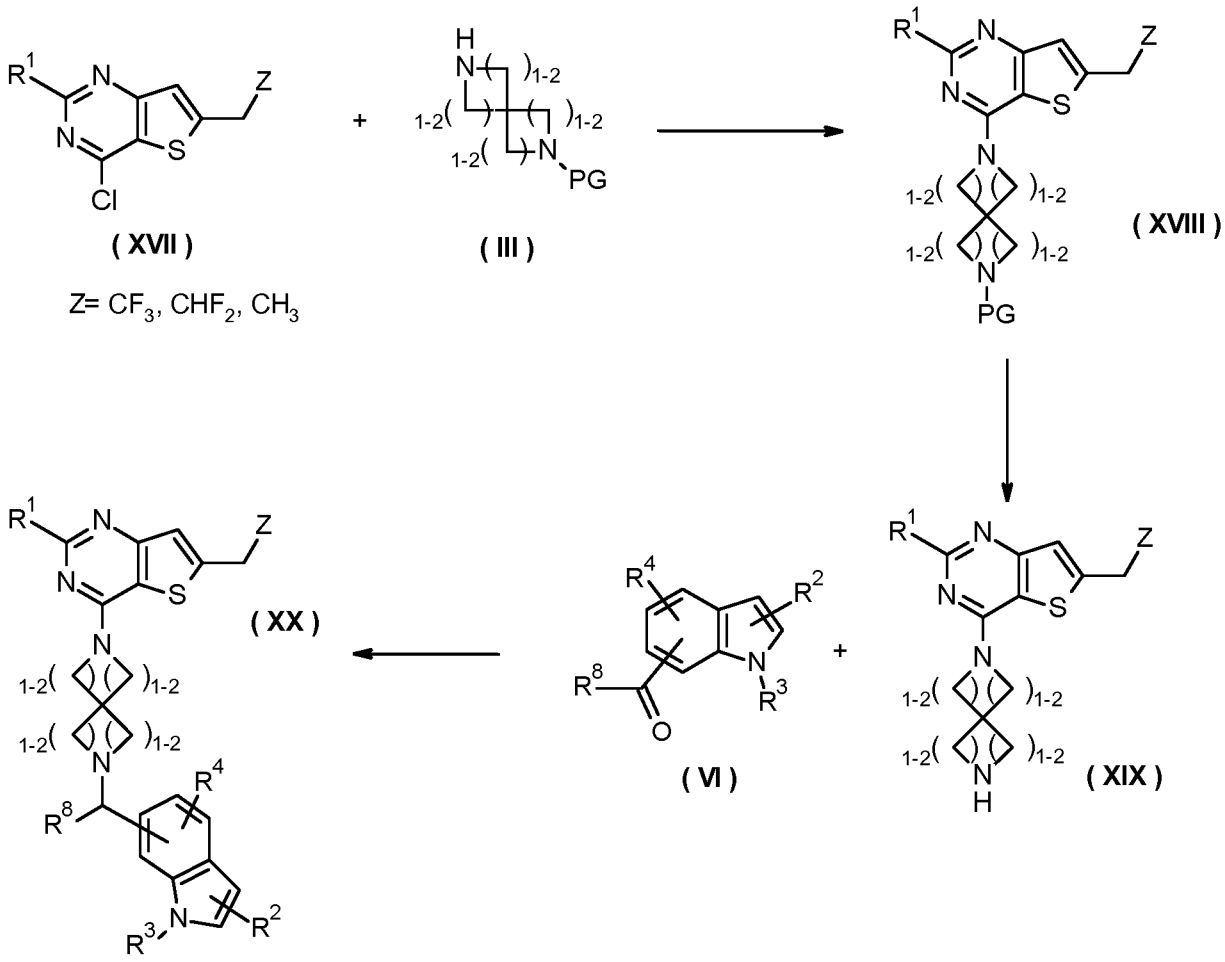


Scheme 5: Synthesis of the intermediates **(11)** and **(I2)**

The transformation of the 6-cyano-1 H-indole-2-carboxamide to the aldehyde **(11)** using sodium hypophosphite and Raney-Nickel was carried out according to a procedure described in Liebigs Ann. Chem., **1986,** 2174.

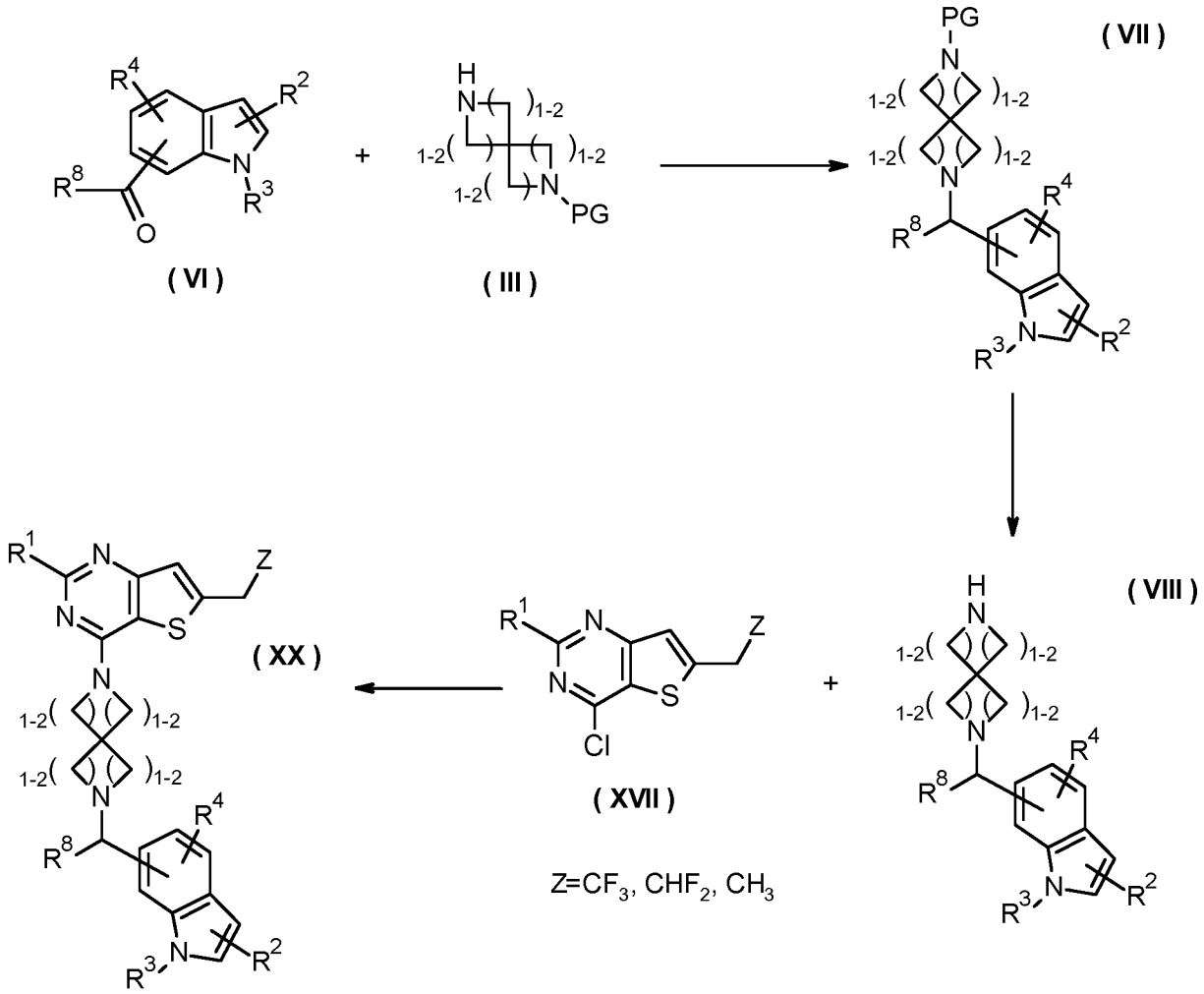
For the transformation of 6-bromo-1 H-indole-2-carbonitrile to the aldehyde **(I2)** via lithiation see Cancer Cell **2015,** 27, 589 - 602.

The synthesis of compounds of formula **(XX)** is shown in scheme **6** starting from chloro pyrimidine derivatives of formula **(XVII)** following a corresponding synthetic sequence as described in scheme 1.



Scheme 6: Synthesis of compounds of general formula **(XX),** in which R^1, R^2, R^3, R^4 and R^8 have the meaning as given for general formula **(I),** *supra,* from compounds of formulae **(XVII), (III)** and **(VI);** PG is a protecting group, e.g. Boc.

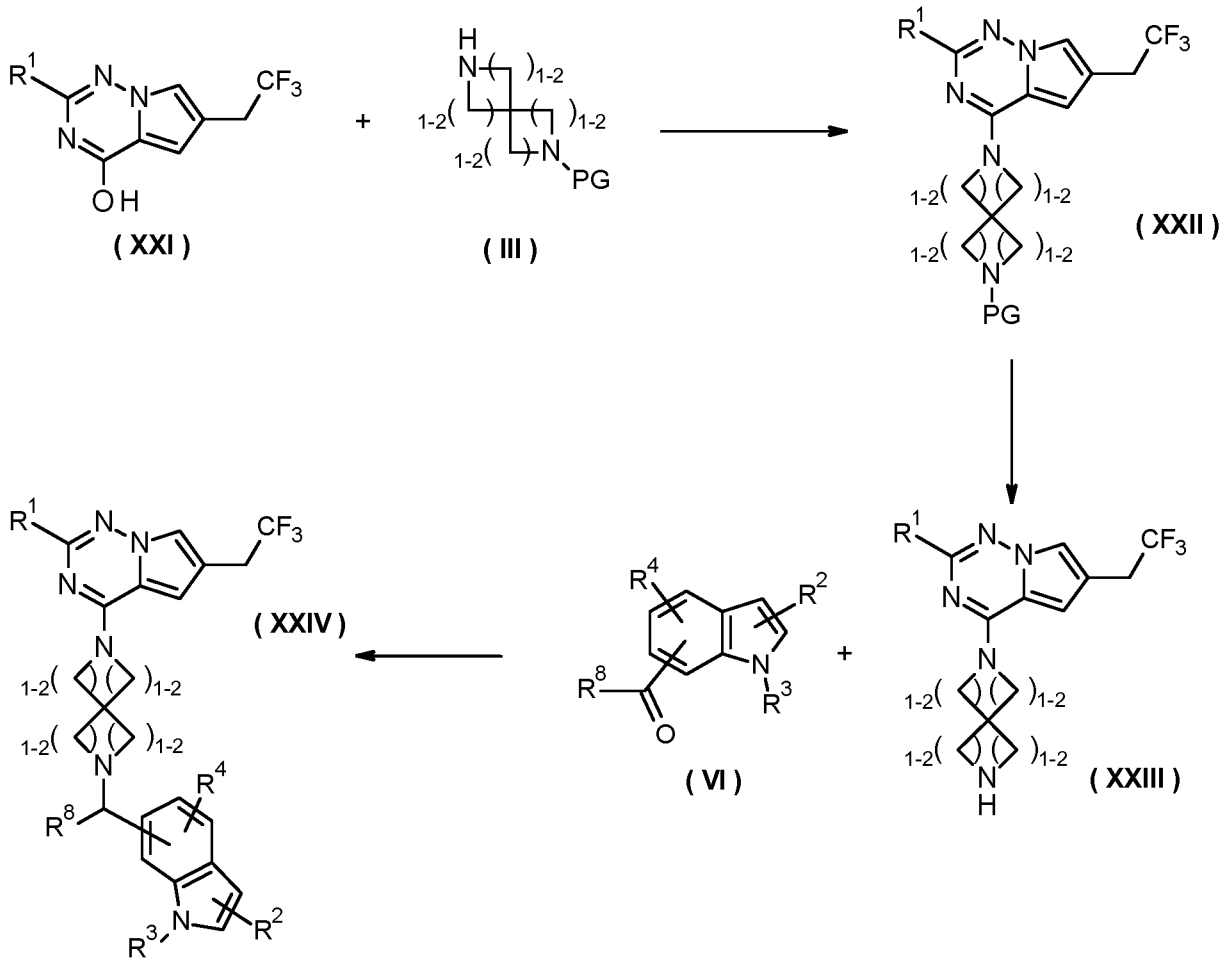
An alternative synthetic route toward compounds of formula **(XX)** is described in scheme **7.**



Scheme 7: Synthesis of compounds of general formula **(XX),** in which R^1, R^2, R^3, R^4 and R^8 have the meaning as given for general formula **(I),** *supra,* from compounds of formulae **(VI), (III)** and **(XVII).**

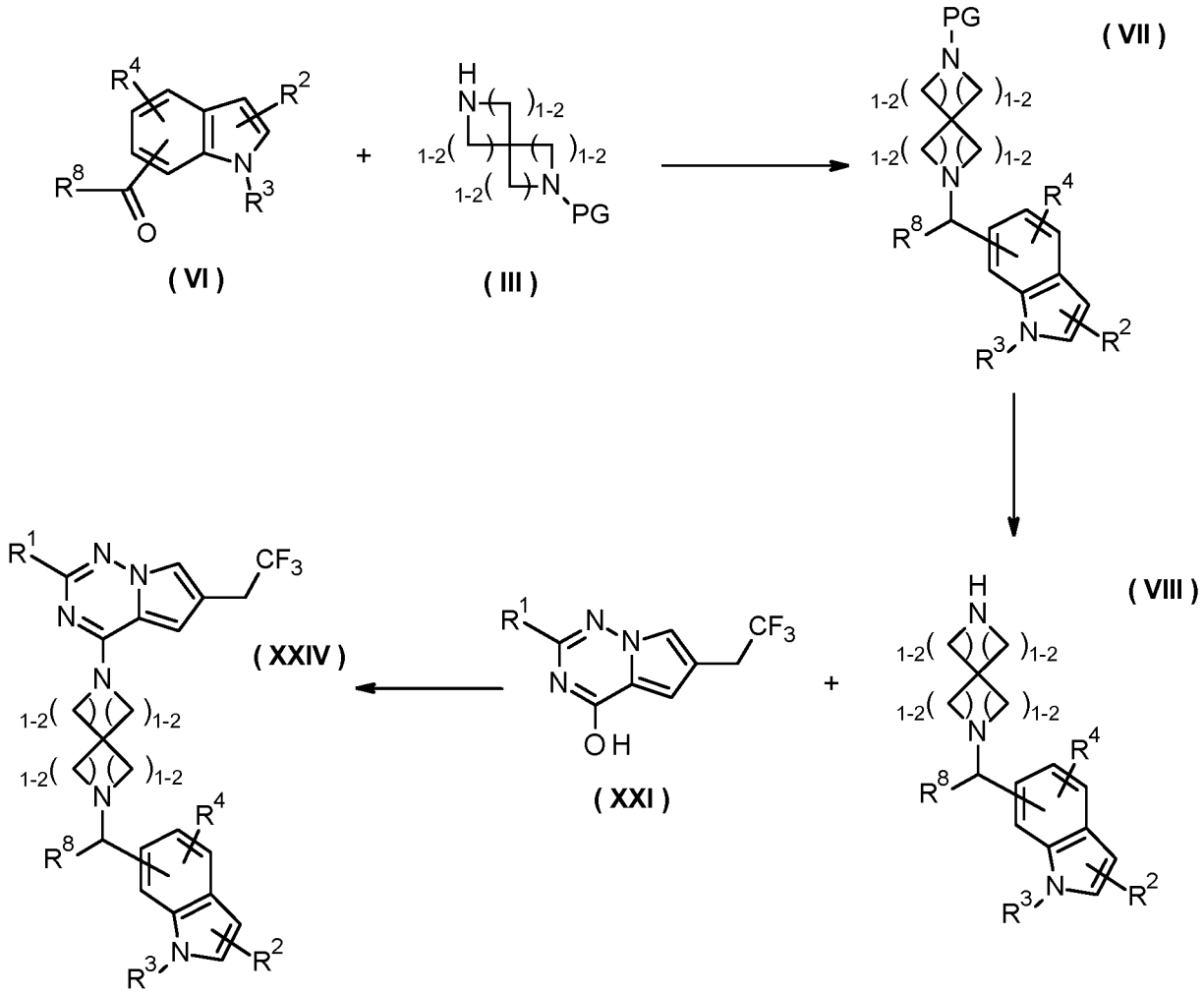
First compounds of formula **(VI)** were converted by reductive amination to the corresponding amines of formula **(VII).** After deprotection amines of formula **(VII)** were then reacted with chloro pyrimidine derivatives of formula **(XVII)** to the corresponding bicyclic amines of formula **(XX).**

The synthesis of pyrrolo[2,1-f][1 ,2,4]triazine derivatives of formula **(XXIV)** is described in scheme **8.** Pyrrolo[2,1-f][1 ,2,4]triazin-4-ol derivatives of formula **(XXVI)** can be transformed to the spirocyclic derivatives of formula **(XXII)** using e.g. PYBOP. Deprotection followed by reductive amination lead to the desired spirocyclic amine derivatives of formula **(XXIV).**



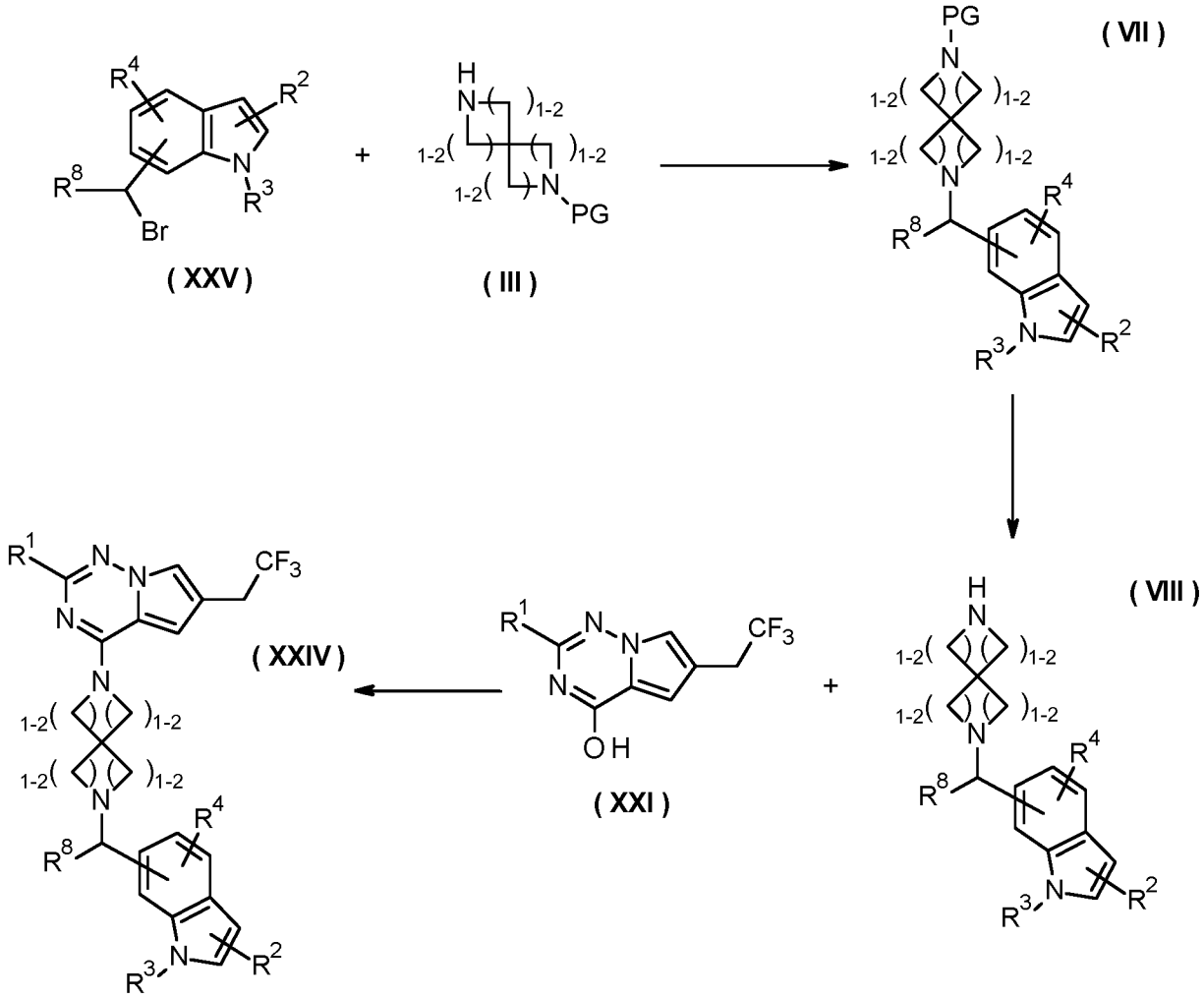
Scheme 8: Synthesis of compounds of general formula **(XXIV),** in which R^1, R^2, R^3, R^4 and R^8 have the meaning as given for general formula **(I),** *supra,* from compounds of formulae **(XXI), (III)** and **(VI);** PG is a protecting group, e.g. Boc.

An alternative synthetic route toward compounds of formula **(XXIV)** is described in scheme **9** according to the reaction sequence shown in scheme **7.**



Scheme 9: Synthesis of compounds of general formula **(XXIV),** in which R^1, R^2, R^3, R^4 and R^8 have the meaning as given for general formula **(I),** *supra,* from compounds of formulae **(VI), (III)** and **(XXI).**

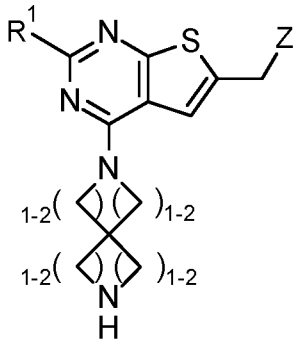
An alternative synthetic approach toward compounds of formula **(XXIV)** is described in scheme **10.** Starting from an alkylbromide of formula **(XXV)** the intermediate **(VII)** can be obtained by alkylation reaction with spirocyclic derivatives of formula **(III).** The reaction sequence can be finished according to the transformations shown in scheme **9.**



Scheme 10: Synthesis of compounds of general formula **(XXIV),** in which R^1, R^2, R^3, R^4 and R^8 have the meaning as given for general formula **(I),** *supra,* from compounds of formulae **(XXV), (III)** and **(XXI).**

The compounds are either commercially available or can be prepared according to procedures available from the public domain, as understandable to the person skilled in the art. Specific examples are described in the Experimental Section.

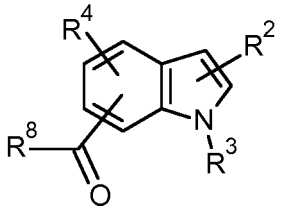
In accordance with a fourth aspect, the present invention covers methods of preparing compounds of general formula (Ib) as defined *supra,* said methods comprising the step of allowing an intermediate compound of general formula (V):



(V),

in which R^1 is as defined for the compound of general formula (I) as defined *supra,* and Z is methyl, difluoromethyl or trifluoromethyl,

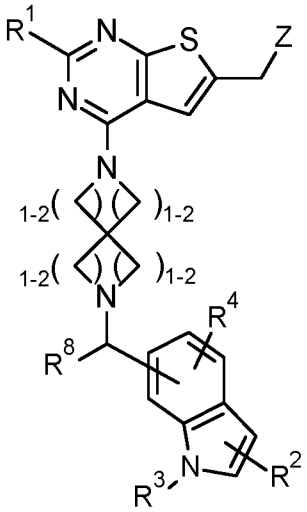
to react with a compound of general formula (VI):



(VI),

in which R^2, R^3, R^4 and R^8 are as defined for the compound of general formula (I) as defined *supra,*

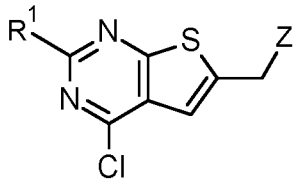
thereby giving a compound of general formula (Ib):



(Ib),

in which R^1, R^2, R^3, R^4 and R^8 and Z are as defined *supra.*

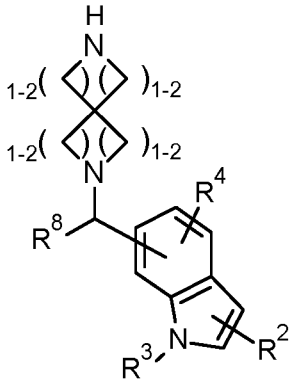
In accordance with a fifth aspect, the present invention covers methods of preparing compounds of general formula (Ib) as defined *supra,* said methods comprising the step of allowing an intermediate compound of general formula (II):



(II).

in which R^1 is as defined for the compound of general formula (I) as defined *supra,* and Z is methyl, difluoromethyl or trifluoromethyl,

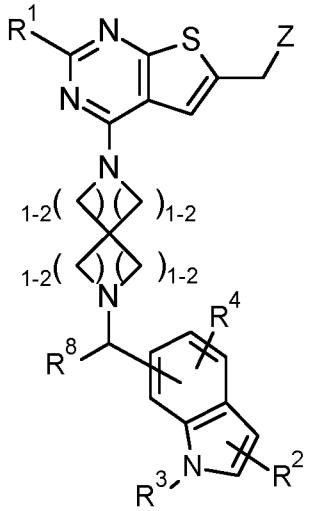
to react with a compound of general formula (VIII):



(VIII),

in which R^2, R^3, R^4 and R^8 are as defined for the compound of general formula (I) as defined *supra,*

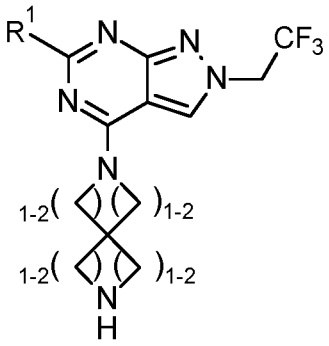
thereby giving a compound of general formula (Ib):



(Ib),

in which R^1, R^2, R^3, R^4 and R^8 and Z are as defined *supra.*

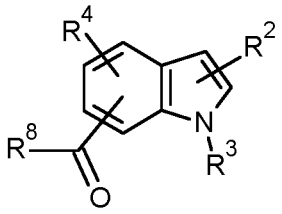
In accordance with a sixth aspect, the present invention covers methods of preparing compounds of general formula (Ic) as defined *supra,* said methods comprising the step of allowing an intermediate compound of general formula (XIII):



(XIII),

in which R^1 is as defined for the compound of general formula (I) as defined *supra,*

to react with a compound of general formula (VI):

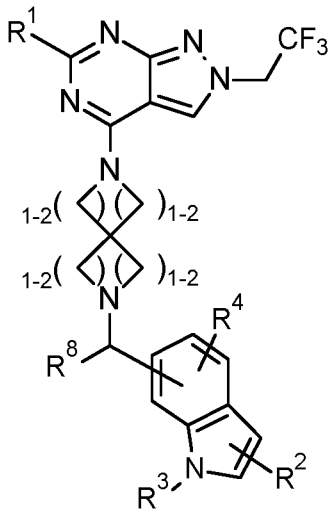


(VI)

(VI),

in which R^2, R^3, R^4 and R^8 are as defined for the compound of general formula (I) as defined *supra,*

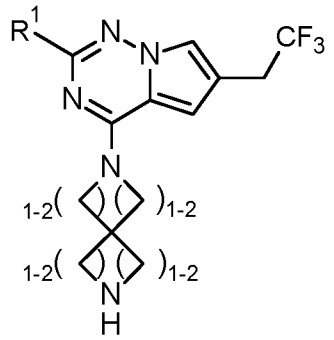
thereby giving a compound of general formula (Ic):



(Ic),

in which R^1, R^2, R^3, R^4 and R^8 are as defined *supra.*

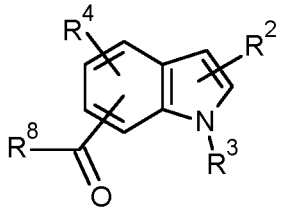
In accordance with a seventh aspect, the present invention covers methods of preparing compounds of general formula (XXIV) as defined *supra,* said methods comprising the step of allowing an intermediate compound of general formula (XXIII):



(XXIII),

in which R^1 is as defined for the compound of general formula (I) as defined *supra,*

to react with a compound of general formula (VI):

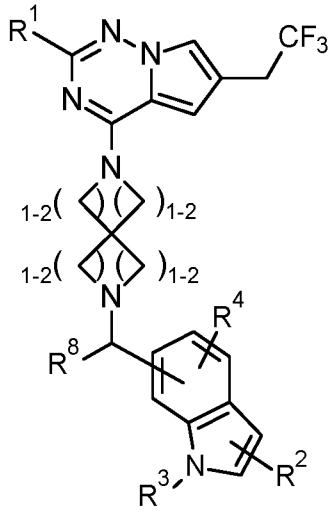


(VI)

(VI),

in which R^2, R^3, R^4 and R^8 are as defined for the compound of general formula (I) as defined *supra,*

thereby giving a compound of general formula (XXIV):



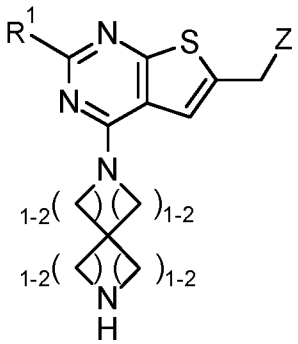
(XXIV),

in which R^1, R^2, R^3, R^4 and R^8 are as defined *supra.*

The present invention covers methods of preparing compounds of the present invention of general formula (I), said methods comprising the steps as described in the Experimental Section herein.

In accordance with a eighth aspect, the present invention covers intermediate compounds which are useful for the preparation of the compounds of general formula (I), *supra.*

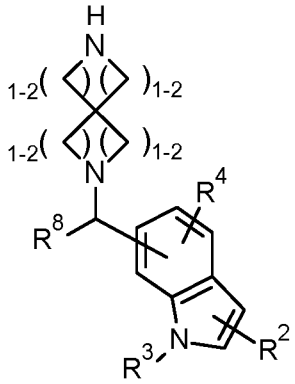
Particularly, the inventions covers the intermediate compounds of general formula (V):



(V),

in which R^1 is as defined for the compound of general formula (I) as defined *supra,* and Z is methyl, difluoromethyl or trifluoromethyl.

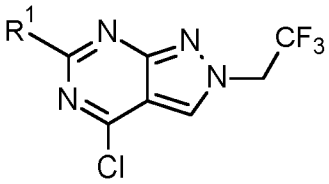
Particularly, the inventions covers the intermediate compounds of general formula (VIII):



(VIII),

in which R^2, R^3, R^4 and R^8 are as defined for the compound of general formula (I) as defined *supra.*

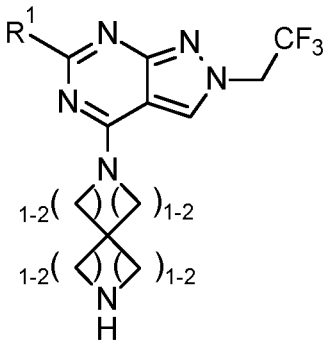
Particularly, the inventions covers the intermediate compounds of general formula (X):



(X),

in which R^1 is as defined for the compound of general formula (I) as defined *supra.*

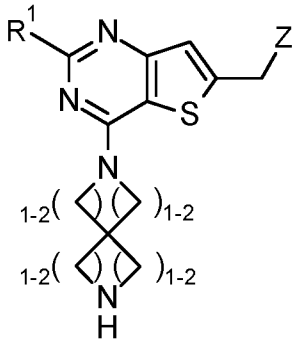
Particularly, the inventions covers the intermediate compounds of general formula (XIII):



(XIII),

in which R^1 is as defined for the compound of general formula (I) as defined *supra.*

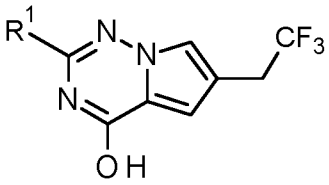
Particularly, the inventions covers the intermediate compounds of general formula (XIX):



(XIX),

in which R^1 is as defined for the compound of general formula (I) as defined *supra,* and Z is methyl, difluoromethyl or trifluoromethyl.

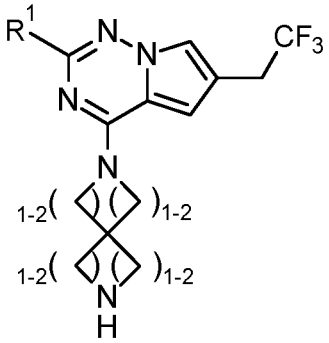
Particularly, the inventions covers the intermediate compounds of general formula (XXI):



(XXI),

in which R^1 is as defined for the compound of general formula (I) as defined *supra.*

Particularly, the inventions covers the intermediate compounds of general formula (XXIII):

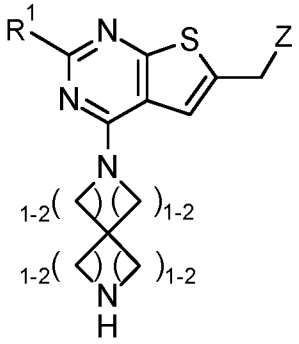


(XXIII),

in which R^1 is as defined for the compound of general formula (I) as defined *supra.*

In accordance with a ninth aspect, the present invention covers the use of said intermediate compounds for the preparation of a compound of general formula (I) as defined *supra.*

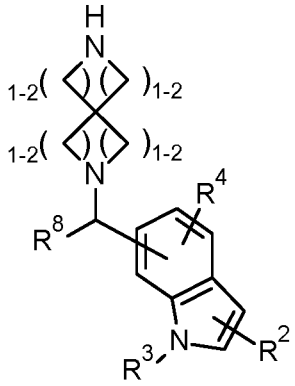
Particularly, the inventions covers the use of intermediate compounds of general formula (V):



(V),

in which R^1 is as defined for the compound of general formula (I) as defined *supra,* and Z is methyl, difluoromethyl or trifluoromethyl, for the preparation of a compound of general formula (I) as defined *supra.*

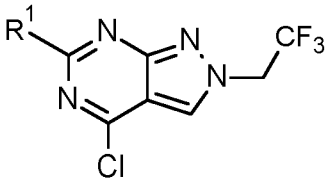
Particularly, the inventions covers the use of intermediate compounds of general formula (VIII):



(VIII),

in which R^2, R^3, R^4 and R^8 are as defined for the compound of general formula (I) as defined *supra,* for the preparation of a compound of general formula (I) as defined *supra.*

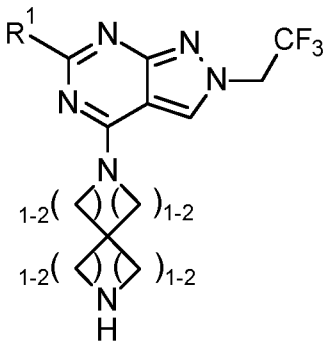
Particularly, the inventions covers the use of intermediate compounds of general formula (X):



(X),

in which R^1 is as defined for the compound of general formula (I) as defined *supra,* for the preparation of a compound of general formula (I) as defined *supra.*

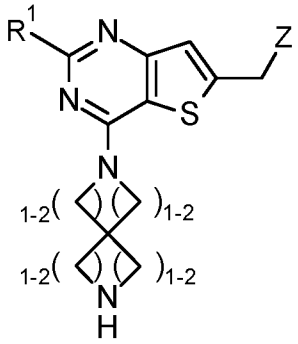
Particularly, the inventions covers the use of intermediate compounds of general formula (XIII):



(XIII),

in which R^1 is as defined for the compound of general formula (I) as defined *supra,* for the preparation of a compound of general formula (I) as defined *supra.*

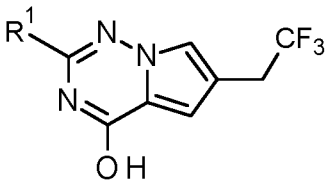
Particularly, the inventions covers the use of intermediate compounds of general formula (XIX):



(XIX),

in which R^1 is as defined for the compound of general formula (I) as defined *supra,* and Z is methyl, difluoromethyl or trifluoromethy, for the preparation of a compound of general formula (I) as defined *supra.*

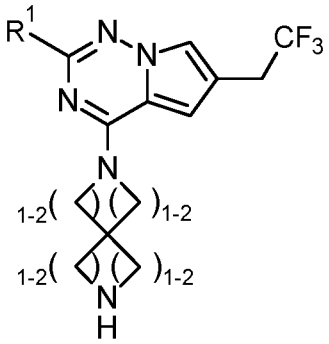
Particularly, the inventions covers the use of intermediate compounds of general formula (XXI):



(XXI),

in which R^1 is as defined for the compound of general formula (I) as defined *supra,* for the preparation of a compound of general formula (I) as defined *supra.*

Particularly, the inventions covers the use of intermediate compounds of general formula (XXIII):



(XXIII),

in which R^1 is as defined for the compound of general formula (I) as defined *supra,* for the preparation of a compound of general formula (I) as defined *supra.*

The present invention covers the intermediate compounds which are disclosed in the Example Section of this text, *infra.*

The present invention covers any sub-combination within any embodiment or aspect of the present invention of intermediate compounds of general formula (V), (VIII) and (XIII), *supra.*

The compounds of general formula (I) of the present invention can be converted to any salt, preferably pharmaceutically acceptable salts, as described herein, by any method which is known to the person skilled in the art. Similarly, any salt of a compound of general formula (I) of the present invention can be converted into the free compound, by any method which is known to the person skilled in the art.

Compounds of the present invention can be utilized to inhibit the interaction between menin and MLL-1 and decrease cell proliferation and/or cell division, and/or produce apoptosis. This method comprises administering to a mammal in need thereof, including a human, an amount

of a compound of general formula (I) of the present invention, or a pharmaceutically acceptable salt, isomer, polymorph, metabolite, hydrate, solvate or ester thereof, which is effective to treat the disorder.

Hyperproliferative disorders include, but are not limited to, for example : psoriasis, keloids, and other hyperplasias affecting the skin, benign prostate hyperplasia (BPH), solid tumours, such as cancers of the breast, respiratory tract, brain, reproductive organs, digestive tract, urinary tract, eye, liver, skin, head and neck, thyroid, parathyroid and their distant metastases. Those disorders also include lymphomas, sarcomas, and leukemias.

Examples of breast cancers include, but are not limited to, invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma *in situ,* and lobular carcinoma *in situ.*

Examples of cancers of the respiratory tract include, but are not limited to, small-cell and non-small-cell lung carcinoma, as well as bronchial adenoma and pleuropulmonary blastoma.

Examples of brain cancers include, but are not limited to, brain stem and hypophtalmic glioma, cerebellar and cerebral astrocytoma, medulloblastoma, ependymoma, as well as neuroectodermal and pineal tumour.

Tumours of the male reproductive organs include, but are not limited to, prostate and testicular cancer.

Tumours of the female reproductive organs include, but are not limited to, endometrial, cervical, ovarian, vaginal, and vulvar cancer, as well as sarcoma of the uterus.

Tumours of the digestive tract include, but are not limited to, anal, colon, colorectal, oesophageal, gallbladder, gastric, pancreatic, rectal, small-intestine, and salivary gland cancers.

Tumours of the urinary tract include, but are not limited to, bladder, penile, kidney, renal pelvis, ureter, urethral and human papillary renal cancers.

Eye cancers include, but are not limited to, intraocular melanoma and retinoblastoma.

Examples of liver cancers include, but are not limited to, hepatocellular carcinoma (liver cell carcinomas with or without fibrolamellar variant), cholangiocarcinoma (intrahepatic bile duct carcinoma), and mixed hepatocellular cholangiocarcinoma.

Skin cancers include, but are not limited to, squamous cell carcinoma, Kaposi's sarcoma, malignant melanoma, Merkel cell skin cancer, and non-melanoma skin cancer.

Head-and-neck cancers include, but are not limited to, laryngeal, hypopharyngeal, nasopharyngeal, oropharyngeal cancer, lip and oral cavity cancer and squamous cell.

Lymphomas include, but are not limited to, AIDS-related lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, Burkitt lymphoma, Hodgkin's disease, and lymphoma of the central nervous system.

Sarcomas include, but are not limited to, sarcoma of the soft tissue, osteosarcoma, malignant fibrous histiocytoma, lymphosarcoma, and rhabdomyosarcoma.

Leukemias include, but are not limited to, acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, and hairy cell leukemia.

The present invention also provides methods of treating angiogenic disorders including diseases associated with excessive and/or abnormal angiogenesis.

Inappropriate and ectopic expression of angiogenesis can be deleterious to an organism. A number of pathological conditions are associated with the growth of extraneous blood vessels. These include, for example, diabetic retinopathy, ischemic retinal-vein occlusion, and retinopathy of prematurity [Aiello *et al.,* New Engl. J. Med., **1994,** 331 , 1480 ; Peer *et al.,* Lab. Invest., **1995,** 72, 638], age-related macular degeneration (AMD) [Lopez *et al.,* Invest. Opththalmol. Vis. Sci., **1996,** 37, 855], neovascular glaucoma, psoriasis, retrolental fibroplasias, angiofibroma, inflammation, rheumatoid arthritis (RA), restenosis, in-stent restenosis, vascular graft restenosis, *etc.* In addition, the increased blood supply associated with cancerous and neoplastic tissue, encourages growth, leading to rapid tumour enlargement and metastasis. Moreover, the growth of new blood and lymph vessels in a tumour provides an escape route for renegade cells, encouraging metastasis and the consequence spread of the cancer. Thus, compounds of general formula (I) of the present invention can be utilized to treat and/or prevent any of the aforementioned angiogenesis disorders, for example by inhibiting and/or reducing blood vessel formation; by inhibiting, blocking, reducing, decreasing, *etc.* endothelial cell proliferation, or other types involved in angiogenesis, as well as causing cell death or apoptosis of such cell types.

These disorders have been well characterized in humans, but also exist with a similar etiology in other mammals, and can be treated by administering pharmaceutical compositions of the present invention.

The term "treating" or "treatment" as stated throughout this document is used conventionally, for example the management or care of a subject for the purpose of combating, alleviating, reducing, relieving, improving the condition of a disease or disorder, such as a carcinoma.

The compounds of the present invention can be used in particular in therapy and prevention, *i.e.* prophylaxis, of tumour growth and metastases, especially in solid tumours of all indications and stages with or without pre-treatment of the tumour growth.

Generally, the use of chemotherapeutic agents and/or anti-cancer agents in combination with a compound or pharmaceutical composition of the present invention will serve to:

1. yield better efficacy in reducing the growth of a tumour or even eliminate the tumour as compared to administration of either agent alone,
2. provide for the administration of lesser amounts of the administered chemotherapeutic agents,
3. provide for a chemotherapeutic treatment that is well tolerated in the patient with fewer deleterious pharmacological complications than observed with single agent chemotherapies and certain other combined therapies,
4. provide for treating a broader spectrum of different cancer types in mammals, especially humans,
5. provide for a higher response rate among treated patients,
6. provide for a longer survival time among treated patients compared to standard chemotherapy treatments,
7. provide a longer time for tumour progression, and/or
8. yield efficacy and tolerability results at least as good as those of the agents used alone, compared to known instances where other cancer agent combinations produce antagonistic effects.

In addition, the compounds of general formula (I) of the present invention can also be used in combination with radiotherapy and/or surgical intervention.

In a further embodiment of the present invention, the compounds of general formula (I) of the present invention may be used to sensitize a cell to radiation, *i.e.* treatment of a cell with a compound of the present invention prior to radiation treatment of the cell renders the cell more susceptible to DNA damage and cell death than the cell would be in the absence of any treatment with a compound of the present invention. In one aspect, the cell is treated with at least one compound of general formula (I) of the present invention.

Thus, the present invention also provides a method of killing a cell, wherein a cell is administered one or more compounds of the present invention in combination with conventional radiation therapy.

The present invention also provides a method of rendering a cell more susceptible to cell death, wherein the cell is treated with one or more compounds of general formula (I) of the present invention prior to the treatment of the cell to cause or induce cell death. In one aspect, after the cell is treated with one or more compounds of general formula (I) of the present invention, the cell is treated with at least one compound, or at least one method, or a

combination thereof, in order to cause DNA damage for the purpose of inhibiting the function of the normal cell or killing the cell.

In other embodiments of the present invention, a cell is killed by treating the cell with at least one DNA damaging agent, *i.e.* after treating a cell with one or more compounds of general formula (I) of the present invention to sensitize the cell to cell death, the cell is treated with at least one DNA damaging agent to kill the cell. DNA damaging agents useful in the present invention include, but are not limited to, chemotherapeutic agents (e.g. cis platin), ionizing radiation (X-rays, ultraviolet radiation), carcinogenic agents, and mutagenic agents.

In other embodiments, a cell is killed by treating the cell with at least one method to cause or induce DNA damage. Such methods include, but are not limited to, activation of a cell signalling pathway that results in DNA damage when the pathway is activated, inhibiting of a cell signalling pathway that results in DNA damage when the pathway is inhibited, and inducing a biochemical change in a cell, wherein the change results in DNA damage. By way of a non-limiting example, a DNA repair pathway in a cell can be inhibited, thereby preventing the repair of DNA damage and resulting in an abnormal accumulation of DNA damage in a cell.

In one aspect of the invention, a compound of general formula (I) of the present invention is administered to a cell prior to the radiation or other induction of DNA damage in the cell. In another aspect of the invention, a compound of general formula (I) of the present invention is administered to a cell concomitantly with the radiation or other induction of DNA damage in the cell. In yet another aspect of the invention, a compound of general formula (I) of the present invention is administered to a cell immediately after radiation or other induction of DNA damage in the cell has begun.

In another aspect, the cell is in vitro. In another embodiment, the cell is in vivo.

Compounds of the present invention can be utilized to inhibit the interaction between menin and MLL-1 . This method comprises administering to a mammal in need thereof, including a human, an amount of a compound of this invention, or a pharmaceutically acceptable salt, isomer, polymorph, metabolite, hydrate, solvate or ester thereof; which is effective to treat the disorder.

These disorders have been well characterized in humans, but also exist with a similar etiology in other mammals, and can be treated by administering pharmaceutical compositions of the present invention.

The term "treating" or "treatment" as used in the present text is used conventionally, *e.g.,* the management or care of a subject for the purpose of combating, alleviating, reducing, relieving, improving the condition of a disease or disorder, such as a carcinoma.

The compounds of the present invention can be used in particular in therapy and prevention, *i.e.* prophylaxis, of cancer.

In accordance with a further aspect, the present invention covers compounds of general formula (I), as described *supra,* or stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, particularly pharmaceutically acceptable salts thereof, or mixtures of same, for use in the treatment or prophylaxis of diseases, in particular cancer.

The pharmaceutical activity of the compounds according to the invention can be explained by their activity as inhibitors of the interaction between menin and MLL-1 .

In accordance with a further aspect, the present invention covers the use of compounds of general formula (I), as described *supra,* or stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, particularly pharmaceutically acceptable salts thereof, or mixtures of same, for the treatment or prophylaxis of diseases, in particular cancer, particularly acute myeloid leukemia, prostate and breast carcinoma, and hepatocellular carcinoma.

In accordance with a further aspect, the present invention covers the use of a compound of formula (I), described *supra,* or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, for the prophylaxis or treatment of diseases, in particular cancer, particularly acute myeloid leukemia, prostate and breast carcinoma, and hepatocellular carcinoma.

In accordance with a further aspect, the present invention covers the use of compounds of general formula (I), as described *supra,* or stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, particularly pharmaceutically acceptable salts thereof, or mixtures of same, in a method of treatment or prophylaxis of diseases, in particular cancer, particularly acute myeloid leukemia, prostate and breast carcinoma, and hepatocellular carcinoma.

In accordance with a further aspect, the present invention covers use of a compound of general formula (I), as described *supra,* or stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, particularly pharmaceutically acceptable salts thereof, or mixtures of same, for the preparation of a pharmaceutical composition, preferably a medicament, for the prophylaxis or treatment of diseases, in particular cancer disorders, particularly acute myeloid leukemia, prostate and breast carcinoma, and hepatocellular carcinoma.

In accordance with a further aspect, the present invention covers a method of treatment or prophylaxis of diseases, in particular cancer disorders, particularly acute myeloid leukemia, prostate and breast carcinoma, and hepatocellular carcinoma, using an effective amount of a compound of general formula (I), as described *supra,* or stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, particularly pharmaceutically acceptable salts thereof, or mixtures of same.

In accordance with a further aspect, the present invention covers pharmaceutical compositions, in particular a medicament, comprising a compound of general formula (I), as described *supra,* or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, a salt thereof, particularly a pharmaceutically acceptable salt, or a mixture of same, and one or more excipients), in particular one or more pharmaceutically acceptable excipient(s). Conventional procedures for preparing such pharmaceutical compositions in appropriate dosage forms can be utilized.

The present invention furthermore covers pharmaceutical compositions, in particular medicaments, which comprise at least one compound according to the invention, conventionally together with one or more pharmaceutically suitable excipients, and to their use for the above mentioned purposes.

It is possible for the compounds according to the invention to have systemic and/or local activity. For this purpose, they can be administered in a suitable manner, such as, for example, via the oral, parenteral, pulmonary, nasal, sublingual, lingual, buccal, rectal, vaginal, dermal, transdermal, conjunctival, otic route or as an implant or stent.

For these administration routes, it is possible for the compounds according to the invention to be administered in suitable administration forms.

For oral administration, it is possible to formulate the compounds according to the invention to dosage forms known in the art that deliver the compounds of the invention rapidly and/or in a modified manner, such as, for example, tablets (uncoated or coated tablets, for example with enteric or controlled release coatings that dissolve with a delay or are insoluble), orally-disintegrating tablets, films/wafers, films/lyophylisates, capsules (for example hard or soft gelatine capsules), sugar-coated tablets, granules, pellets, powders, emulsions, suspensions, aerosols or solutions. It is possible to incorporate the compounds according to the invention in crystalline and/or amorphised and/or dissolved form into said dosage forms.

Parenteral administration can be effected with avoidance of an absorption step (for example intravenous, intraarterial, intracardial, intraspinal or intralumbal) or with inclusion of absorption (for example intramuscular, subcutaneous, intracutaneous, percutaneous or intraperitoneal). Administration forms which are suitable for parenteral administration are, inter alia, preparations for injection and infusion in the form of solutions, suspensions, emulsions, lyophylisates or sterile powders.

Examples which are suitable for other administration routes are pharmaceutical forms for inhalation [inter alia powder inhalers, nebulizers], nasal drops, nasal solutions, nasal sprays; tablets/films/wafers/capsules for lingual, sublingual or buccal administration; suppositories; eye drops, eye ointments, eye baths, ocular inserts, ear drops, ear sprays, ear powders, ear-rinses, ear tampons; vaginal capsules, aqueous suspensions (lotions, mixturae agitandae),

lipophilic suspensions, emulsions, ointments, creams, transdermal therapeutic systems (such as, for example, patches), milk, pastes, foams, dusting powders, implants or stents.

The compounds according to the invention can be incorporated into the stated administration forms. This can be effected in a manner known per se by mixing with pharmaceutically suitable excipients. Pharmaceutically suitable excipients include, inter alia,

- fillers and carriers (for example cellulose, microcrystalline cellulose (such as, for example, Avicel®), lactose, mannitol, starch, calcium phosphate (such as, for example, Di-Cafos®)),
- ointment bases (for example petroleum jelly, paraffins, triglycerides, waxes, wool wax, wool wax alcohols, lanolin, hydrophilic ointment, polyethylene glycols),
- bases for suppositories (for example polyethylene glycols, cacao butter, hard fat),
- solvents (for example water, ethanol, isopropanol, glycerol, propylene glycol, medium chain-length triglycerides fatty oils, liquid polyethylene glycols, paraffins),
- surfactants, emulsifiers, dispersants or wetters (for example sodium dodecyl sulfate), lecithin, phospholipids, fatty alcohols (such as, for example, Lanette®), sorbitan fatty acid esters (such as, for example, Span®), polyoxyethylene sorbitan fatty acid esters (such as, for example, Tween®), polyoxyethylene fatty acid glycerides (such as, for example, Cremophor®), polyoxethylene fatty acid esters, polyoxyethylene fatty alcohol ethers, glycerol fatty acid esters, poloxamers (such as, for example, Pluronic®),
- buffers, acids and bases (for example phosphates, carbonates, citric acid, acetic acid, hydrochloric acid, sodium hydroxide solution, ammonium carbonate, trometamol, triethanolamine),
- isotonicity agents (for example glucose, sodium chloride),
- adsorbents (for example highly-disperse silicas),
- viscosity-increasing agents, gel formers, thickeners and/or binders (for example polyvinylpyrrolidone, methylcellulose, hydroxypropylmethylcellulose, hydroxypropyl-cellulose, carboxymethylcellulose-sodium, starch, carbomers, polyacrylic acids (such as, for example, Carbopol®); alginates, gelatine),
- disintegrants (for example modified starch, carboxymethylcellulose-sodium, sodium starch glycolate (such as, for example, Explotab®), cross- linked polyvinylpyrrolidone, croscarmellose-sodium (such as, for example, AcDiSol®)),

- flow regulators, lubricants, glidants and mould release agents (for example magnesium stearate, stearic acid, talc, highly-disperse silicas (such as, for example, Aerosil®)),
- coating materials (for example sugar, shellac) and film formers for films or diffusion membranes which dissolve rapidly or in a modified manner (for example polyvinylpyrrolidones (such as, for example, Kollidon®), polyvinyl alcohol, hydroxypropylmethylcellulose, hydroxypropylcellulose, ethylcellulose, hydroxypropyl-methylcellulose phthalate, cellulose acetate, cellulose acetate phthalate, polyacrylates, polymethacrylates such as, for example, Eudragit®)),
- capsule materials (for example gelatine, hydroxypropylmethylcellulose),
- synthetic polymers (for example polylactides, polyglycolides, polyacrylates, polymethacrylates (such as, for example, Eudragit®), polyvinylpyrrolidones (such as, for example, Kollidon®), polyvinyl alcohols, polyvinyl acetates, polyethylene oxides, polyethylene glycols and their copolymers and blockcopolymers),
- plasticizers (for example polyethylene glycols, propylene glycol, glycerol, triacetine, triacetyl citrate, dibutyl phthalate),
- penetration enhancers,
- stabilisers (for example antioxidants such as, for example, ascorbic acid, ascorbyl palmitate, sodium ascorbate, butylhydroxyanisole, butylhydroxytoluene, propyl gallate),
- preservatives (for example parabens, sorbic acid, thiomersal, benzalkonium chloride, chlorhexidine acetate, sodium benzoate),
- colourants (for example inorganic pigments such as, for example, iron oxides, titanium dioxide),
- flavourings, sweeteners, flavour- and/or odour-masking agents.

The present invention furthermore relates to a pharmaceutical composition which comprise at least one compound according to the invention, conventionally together with one or more pharmaceutically suitable excipient(s), and to their use according to the present invention.

In accordance with another aspect, the present invention covers pharmaceutical combinations, in particular medicaments, comprising at least one compound of general formula (I) of the present invention and at least one or more further active ingredients, in particular for the treatment and/or prophylaxis of cancer, more specifically acute myeloid leukemia, prostate and breast carcinoma, and hepatocellular carcinoma.

Particularly, the present invention covers a pharmaceutical combination, which comprises:

- one or more first active ingredients, in particular compounds of general formula (I) as defined *supra,* and
- one or more further active ingredients, in particular cancer, more specifically acute myeloid leukemia, prostate and breast carcinoma, and hepatocellular carcinoma.

The term "combination" in the present invention is used as known to persons skilled in the art, it being possible for said combination to be a fixed combination, a non-fixed combination or a kit-of-parts.

A "fixed combination" in the present invention is used as known to persons skilled in the art and is defined as a combination wherein, for example, a first active ingredient, such as one or more compounds of general formula (I) of the present invention, and a further active ingredient are present together in one unit dosage or in one single entity. One example of a "fixed combination" is a pharmaceutical composition wherein a first active ingredient and a further active ingredient are present in admixture for simultaneous administration, such as in a formulation. Another example of a "fixed combination" is a pharmaceutical combination wherein a first active ingredient and a further active ingredient are present in one unit without being in admixture.

A non-fixed combination or "kit-of-parts" in the present invention is used as known to persons skilled in the art and is defined as a combination wherein a first active ingredient and a further active ingredient are present in more than one unit. One example of a non-fixed combination or kit-of-parts is a combination wherein the first active ingredient and the further active ingredient are present separately. It is possible for the components of the non-fixed combination or kit-of-parts to be administered separately, sequentially, simultaneously, concurrently or chronologically staggered.

The compounds of the present invention can be administered as the sole pharmaceutical agent or in combination with one or more other pharmaceutically active ingredients where the combination causes no unacceptable adverse effects. The present invention also covers such pharmaceutical combinations. For example, the compounds of the present invention can be combined with known cancer agents.

Examples of cancer agents include:

131 1-chTNT, abarelix, abiraterone, aclarubicin, adalimumab, ado-trastuzumab emtansine, afatinib, aflibercept, aldesleukin, alectinib, alemtuzumab, alendronic acid, alitretinoin, altretamine, amifostine, aminoglutethimide, hexyl aminolevulinate, amrubicin, amsacrine, anastrozole, ancestim, anethole dithiolethione, anetumab ravtansine, angiotensin II, antithrombin III, aprepitant, arcitumomab, arglabin, arsenic trioxide, asparaginase, atezolizumab, axitinib, azacitidine, basiliximab, belotecan, bendamustine, besilesomab, belinostat, bevacizumab, bexarotene, bicalutamide, bisantrene, bleomycin, blinatumomab,

bortezomib, buserelin, bosutinib, brentuximab vedotin, busulfan, cabazitaxel, cabozantinib, calcitonine, calcium folinate, calcium levofolinate, capecitabine, capromab, carbamazepine carboplatin, carboquone, carfilzomib, carmofur, carmustine, catumaxomab, celecoxib, celmoleukin, ceritinib, cetuximab, chlorambucil, chlormadinone, chlormethine, cidofovir, cinacalcet, cisplatin, cladribine, clodronic acid, clofarabine, cobimetinib, copanlisib , crisantaspase, crizotinib, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, daratumumab, darbepoetin alfa, dabrafenib, dasatinib, daunorubicin, decitabine, degarelix, denileukin diftitox, denosumab, depreotide, deslorelin, dianhydrogalactitol, dexrazoxane, dibrospidium chloride, dianhydrogalactitol, diclofenac, dinutuximab, docetaxel, dolasetron, doxifluridine, doxorubicin, doxorubicin + estrone, dronabinol, eculizumab, edrecolomab, elliptinium acetate, elotuzumab, eltrombopag, endostatin, enocitabine, enzalutamide, epirubicin, epitiostanol, epoetin alfa, epoetin beta, epoetin zeta, eptaplatin, eribulin, erlotinib, esomeprazole, estradiol, estramustine, ethinylestradiol, etoposide, everolimus, exemestane, fadrozole, fentanyl, filgrastim, fluoxymesterone, floxuridine, fludarabine, fluorouracil, flutamide, folinic acid, formestane, fosaprepitant, fotemustine, fulvestrant, gadobutrol, gadoteridol, gadoteric acid meglumine, gadoversetamide, gadoxetic acid, gallium nitrate, ganirelix, gefitinib, gemcitabine, gemtuzumab, Glucarpidase, glutoxim, GM-CSF, goserelin, granisetron, granulocyte colony stimulating factor, histamine dihydrochloride, histrelin, hydroxycarbamide, 1-125 seeds, lansoprazole, ibandronic acid, ibritumomab tiuxetan, ibrutinib, idarubicin, ifosfamide, imatinib, imiquimod, improsulfan, indisetron, incadronic acid, ingenol mebutate, interferon alfa, interferon beta, interferon gamma, iobitridol, iobenguane (1231), iomeprol, ipilimumab, irinotecan, Itraconazole, ixabepilone, ixazomib, lanreotide, lansoprazole, lapatinib, lasocholine, lenalidomide, lenvatinib, lenograstim, lentinan, letrozole, leuprorelin, levamisole, levonorgestrel, levothyroxine sodium, lisuride, lobaplatin, lomustine, lonidamine, masoprocol, medroxyprogesterone, megestrol, melarsoprol, melphalan, mepitiostane, mercaptopurine, mesna, methadone, methotrexate, methoxsalen, methylaminolevulinate, methylprednisolone, methyltestosterone, metirosine, mifamurtide, miltefosine, miriplatin, mitobronitol, mitoguazone, mitolactol, mitomycin, mitotane, mitoxantrone, mogamulizumab, molgramostim, mopidamol, morphine hydrochloride, morphine sulfate, nabilone, nabiximols, nafarelin, naloxone + pentazocine, naltrexone, nartograstim, necitumumab, nedaplatin, nelarabine, neridronic acid, netupitant/palonosetron, nivolumab, pentetreotide, nilotinib, nilutamide, nimorazole, nimotuzumab, nimustine, nintedanib, nitracrine, nivolumab, obinutuzumab, octreotide, ofatumumab, olaparib, olaratumab, omacetaxine mepesuccinate, omeprazole, ondansetron, oprelvekin, orgotein, orilotimod, osimertinib, oxaliplatin, oxycodone, oxymetholone, ozogamicine, p53 gene therapy, paclitaxel, palbociclib, palifermin, palladium-103 seed, palonosetron, pamidronic acid, panitumumab, panobinostat, pantoprazole, pazopanib, pegaspargase, PEG-epoetin beta (methoxy PEG-epoetin beta), pembrolizumab, pegfilgrastim, peginterferon alfa-2b, pembrolizumab, pemetrexed,

pentazocine, pentostatin, peplomycin, Perflubutane, perfosfamide, Pertuzumab, picibanil, pilocarpine, pirarubicin, pixantrone, plerixafor, plicamycin, poliglusam, polyestradiol phosphate, polyvinylpyrrolidone + sodium hyaluronate, polysaccharide-K, pomalidomide, ponatinib, porfimer sodium, pralatrexate, prednimustine, prednisone, procarbazine, procodazole, propranolol, quinagolide, rabeprazole, racotumomab, radium-223 chloride, radotinib, raloxifene, raltitrexed, ramosetron, ramucirumab, ranimustine, rasburicase, razoxane, refametinib , regorafenib, risedronic acid, rhenium-186 etidronate, rituximab, rolapitant, romidepsin, romiplostim, romurtide, roniciclib , samarium (153Sm) lexidronam, sargramostim, satumomab, secretin, siltuximab, sipuleucel-T, sizofiran, sobuzoxane, sodium glycididazole, sonidegib, sorafenib, stanozolol, streptozocin, sunitinib, talaporfin, talimogene laherparepvec, tamibarotene, tamoxifen, tapentadol, tasonermin, teceleukin, technetium (99mTc) nofetumomab merpentan, 99mTc-HYNIC-[Tyr3]-octreotide, tegafur, tegafur + gimeracil + oteracil, temoporfin, temozolomide, temsirolimus, teniposide, testosterone, tetrofosmin, thalidomide, thiotepa, thymalfasin, thyrotropin alfa, tioguanine, tocilizumab, topotecan, toremifene, tositumomab, trabectedin, trametinib, tramadol, trastuzumab, trastuzumab emtansine, treosulfan, tretinoin, trifluridine + tipiracil, trilostane, triptorelin, trametinib, trofosfamide, thrombopoietin, tryptophan, ubenimex, valatinib , valrubicin, vandetanib, vapreotide, vemurafenib, vinblastine, vincristine, vindesine, vinflunine, vinorelbine, vismodegib, vorinostat, vorozole, yttrium-90 glass microspheres, zinostatin, zinostatin stimalamer, zoledronic acid, zorubicin.

Based upon standard laboratory techniques known to evaluate compounds useful for the treatment of cancer, by standard toxicity tests and by standard pharmacological assays for the determination of treatment of the conditions identified above in mammals, and by comparison of these results with the results of known active ingredients or medicaments that are used to treat these conditions, the effective dosage of the compounds of the present invention can readily be determined for treatment of each desired indication. The amount of the active ingredient to be administered in the treatment of one of these conditions can vary widely according to such considerations as the particular compound and dosage unit employed, the mode of administration, the period of treatment, the age and sex of the patient treated, and the nature and extent of the condition treated.

The total amount of the active ingredient to be administered will generally range from about 0.001 mg/kg to about 200 mg/kg body weight per day, and preferably from about 0.01 mg/kg to about 20 mg/kg body weight per day. Clinically useful dosing schedules will range from one to three times a day dosing to once every four weeks dosing. In addition, it is possible for "drug holidays", in which a patient is not dosed with a drug for a certain period of time, to be beneficial to the overall balance between pharmacological effect and tolerability. It is possible

for a unit dosage to contain from about 0.5 mg to about 1500 mg of active ingredient, and can be administered one or more times per day or less than once a day. The average daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous and parenteral injections, and use of infusion techniques will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily rectal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily vaginal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily topical dosage regimen will preferably be from 0.1 to 200 mg administered between one to four times daily. The transdermal concentration will preferably be that required to maintain a daily dose of from 0.01 to 200 mg/kg. The average daily inhalation dosage regimen will preferably be from 0.01 to 100 mg/kg of total body weight.

Of course the specific initial and continuing dosage regimen for each patient will vary according to the nature and severity of the condition as determined by the attending diagnostician, the activity of the specific compound employed, the age and general condition of the patient, time of administration, route of administration, rate of excretion of the drug, drug combinations, and the like. The desired mode of treatment and number of doses of a compound of the present invention or a pharmaceutically acceptable salt or ester or composition thereof can be ascertained by those skilled in the art using conventional treatment tests.

EXPERIMENTAL SECTION

The ^{1}H-NMR data of the examples are listed in the form of ^{1}H-NMR peaklists. For each signal peak the δ value in ppm is given, followed by the signal intensity, reported in round brackets. The δ value-signal intensity pairs from different peaks are separated by commas. Therefore, a peaklist is described by the general form: δ_1 (intensityi), **δ2 (1ntensit.y2), ... ,** δ_i (intensity,), ... , δ_n (intensity$_n$).

The intensity of a sharp signal correlates with the height (in cm) of the signal in a printed NMR spectrum. When compared with other signals, this data can be correlated to the real ratios of the signal intensities. In the case of broad signals, more than one peak, or the center of the signal along with their relative intensity, compared to the most intense signal displayed in the spectrum, are shown. A ^{1}H-NMR peaklist is similar to a classical ^{1}H-NMR readout, and thus usually contains all the peaks listed in a classical NMR interpretation. Moreover, similar to classical ^{1}H-NMR printouts, peaklists can show solvent signals, signals derived from stereoisomers of target compounds (also the subject of the invention), and/or peaks of impurities. The peaks of stereoisomers, and/or peaks of impurities are typically displayed with a lower intensity compared to the peaks of the target compounds (e.g., with a purity of >90%). Such stereoisomers and/or impurities may be typical for the particular manufacturing process,

and therefore their peaks may help to identify the reproduction of our manufacturing process on the basis of "by-product fingerprints". An expert who calculates the peaks of the target compounds by known methods (MestReC, ACD simulation, or by use of empirically evaluated expectation values), can isolate the peaks of target compounds as required, optionally using additional intensity filters. Such an operation would be similar to peak-picking in classical ^{1}H-NMR interpretation. A detailed description of the reporting of NMR data in the form of peaklists can be found in the publication "Citation of NMR Peaklist Data within Patent Applications" (cf. Research Disclosure Database Number 605005, 2014, 01 Aug 2014, or http://www.researchdisclosure.com/searching-disclosures). In the peak picking routine, as described in the Research Disclosure Database Number 605005, the parameter "MinimumHeight" can be adjusted between 1% and 4%. Depending on the chemical structure and/or depending on the concentration of the measured compound it may be reasonable to set the parameter "MinimumHeight" <1%.

Chemical names were generated using the ACD/Name software from ACD/Labs. In some cases generally accepted names of commercially available reagents were used in place of ACD/Name generated names.

The following table 1 lists the abbreviations used in this paragraph and in the Examples section as far as they are not explained within the text body. Other abbreviations have their meanings customary *per se* to the skilled person.

Table 1: Abbreviations

The following table lists the abbreviations used herein.

Abbreviation	Meaning
Boc	*tert*-butoxycarbonyl
c	concentration
DAD	diode array detector
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
DIPEA	diisopropylethylamine
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
ELSD	Evaporative Light Scattering Detector
ent	enantiomer
ESI	electrospray (ES) ionisation
h	hour(s)
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid

Abbreviation	Meaning
HPLC	high performance liquid chromatography
LC-MS	liquid chromatography mass spectrometry
min	minute(s)
M	molar
MS	mass spectrometry
NMP	1-methylpyrrolidin-2-one
NMR	nuclear magnetic resonance spectroscopy: chemical shifts (δ) are given in ppm. The chemical shifts were corrected by setting the DMSO signal to 2.50 ppm unless otherwise stated.
PDA	Photo Diode Array
Pd/C	palladium on activated charcoal
prep.	preparative
PTFE	polytetrafluoroethylene
PyBOP	(benzotriazol-l-yloxy)tripyrrolidinophosphonium hexafluorophosphate
r.t. or rt or RT	room temperature
Rt	retention time (as measured either with HPLC or UPLC) in minutes
SQD	Single-Quadru pole-Detector
THF	tetrahydrofuran
UPLC	ultra performance liquid chromatography

Other abbreviations have their meanings customary per se to the skilled person.

The various aspects of the invention described in this application are illustrated by the following examples which are not meant to limit the invention in any way.

The example testing experiments described herein serve to illustrate the present invention and the invention is not limited to the examples given.

EXPERIMENTAL SECTION - GENERAL PART

All reagents, for which the synthesis is not described in the experimental part, are either commercially available, or are known compounds or may be formed from known compounds by known methods by a person skilled in the art.

The compounds and intermediates produced according to the methods of the invention may require purification. Purification of organic compounds is well known to the person skilled in the

art and there may be several ways of purifying the same compound. In some cases, no purification may be necessary. In some cases, the compounds may be purified by crystallization. In some cases, impurities may be stirred out using a suitable solvent. In some cases, the compounds may be purified by chromatography, particularly flash column chromatography, using for example prepacked silica gel cartridges, e.g. Biotage SNAP cartidges KP-Sil® or KP-NH® in combination with a Biotage autopurifier system (SP4® or Isolera Four®) and eluents such as gradients of hexane/ethyl acetate or DCM/methanol. In some cases, the compounds may be purified by preparative HPLC using for example a Waters autopurifier equipped with a diode array detector and/or on-line electrospray ionization mass spectrometer in combination with a suitable prepacked reverse phase column and eluents such as gradients of water and acetonitrile which may contain additives such as trifluoroacetic acid, formic acid or aqueous ammonia.

In some cases, purification methods as described above can provide those compounds of the present invention which possess a sufficiently basic or acidic functionality in the form of a salt, such as, in the case of a compound of the present invention which is sufficiently basic, a trifluoroacetate or formate salt for example, or, in the case of a compound of the present invention which is sufficiently acidic, an ammonium salt for example. A salt of this type can either be transformed into its free base or free acid form, respectively, by various methods known to the person skilled in the art, or be used as salts in subsequent biological assays. It is to be understood that the specific form (e.g. salt, free base etc.) of a compound of the present invention as isolated and as described herein is not necessarily the only form in which said compound can be applied to a biological assay in order to quantify the specific biological activity.

Analytical LC-MS methods:

Method 1: Instrument: Waters Acquity UPLCMS Single Quad; column: Kinetex 2.6 µm, 50x2.1 mm; Eluent A: water + 0.05 % formic acid (99%); Eluent B: acetonitrile + 0.05 % formic acid (99%); gradient: 0-1.9 1-99% B, 1.9-2.1 99% B; flow 1.3 ml/min; temperature: 60°C; DAD scan: 200-400 nm.

Method 2: Instrument: Agilent 1290 UPLCMS 6230 TOF; column: BEH C 18 1.7 µm, 50x2.1 mm; Eluent A: water + 0.05 % formic acid (99%); Eluent B: acetonitrile + 0.05 % formic acid (99%); gradient: 0-1.7 2-90% B, 1.7-2.0 90% B; flow 1.2 ml/min; temperature: 60°C; DAD scan: 190-400 nm.

Method 3: Instrument MS: Waters ZQ; instrument HPLC: Waters UPLC Acquity; column: Acquity BEH C18 (Waters), 50mm x 2.1 mm, 1.7µm; eluent A: water +0,1% ammonia, eluent B:

acetonitrile (Sigma-Aldrich); gradient: O.Omin 99% A - 1.6min 1% A - 1.8min 1% A - 1.81 min 99% A - 2.0min 99% A; oven: 60°C; flow: 0.800 ml/min; UV-detection PDA 210-400nm

Method 4: Shimadzu LCMS-2020; instrument HPLC: Waters UPLC Acquity; column: Kinetex 2.6u XB-C18, 50mm x 3mm, 2.6 µm; eluent A: water +0.05% TFA, eluent B: acetonitrile; gradient: O.Omin 100% A - 4.8 min 100% A - 4.9min 5% A; oven: 40°C; flow: 1.5 ml/min;

Method 5: Column: XBridge BEH C18 2.5 µm 2.1 x 50 mm, Waters Acquity Quaternary pump (flow 0.8 ml/min), Waters Acquity Autosampler, Waters Acquity QDa, Waters Acquity PDA, run time: 1.35 min, solvents: A) 10 mM ammonium bicarbonate pH 10, B) MeCN, gradient: 2-98% B in 0.80 min, hold at 98% B to 1.35 min

Method 6: Column: XBridge BEH C18 2.5 µm 2.1 x 50 mm, Waters Acquity Binary pump (flow 0.8 ml/min), Waters Acquity Autosampler, Waters Acquity SQD, Waters Acquity PDA, run time: 1.30 min, solvents: A) 10 mM ammonium bicarbonate pH 10, B) MeCN, gradient: 2-98% B in 0.80 min, hold at 98% B to 1.30 min

Method 7: Column: XBridge BEH C18 2.5 µm 2.1 x 50 mm, Waters Acquity Binary pump (flow 0.8 ml/min), Waters Acquity Autosampler, Waters Acquity SQD, Waters Acquity PDA, run time: 4.80 min, solvents: A) 10 mM ammonium bicarbonate pH 10, B) MeCN, gradient: 2-98% B in 4.00 min, hold @ 98% B to 4.70 min

Method 8: Instrument: Waters Acquity UPLCMS SingleQuad; Column: Acquity UPLC BEH C18 1.7 µm, 50x2.1 mm; eluent A: water + 0.2 vol % aqueous ammonia (32%), eluent B: acetonitrile; gradient: 0-1.6 min 1-99% B, 1.6-2.0 min 99% B; flow 0.8 ml/min; temperature: 60 °C; DAD scan: 210-400 nm.

Method 9: Column: XBridge BEH C18 2.5 µm 2.1 x 50 mm, Waters Acquity Quaternary pump (flow 0.8 ml/min), Waters Acquity Autosampler, Waters Acquity QDa, Waters Acquity PDA, run time: 4.8 min, solvents: A) 10 mM ammonium bicarbonate pH 10, B) MeCN, gradient: 2-98% B in 4.00 min, hold at 98% B to 4.605 min

Method 10: Column: XBridge BEH C18 2.5 µm 2.1 x 50 mm, Waters Acquity Binary pump (Flow 0.8 ml/min), Waters Acquity Autosampler, Waters Acquity SQD, Waters Acquity PDA, Run Time: 4.80 min, solvents: A) 10 mM ammonium bicarbonate pH 10, B) MeCN, gradient: 20-70% B in 3.50 min, 70-98% B to 4.00 min, 98% B @ 4.60 min

Method 11: Column: XBridge BEH C18 2.5 µm 2.1 x 50 mm, Waters Acquity Quaternary pump (flow 0.8 ml/min), Waters Acquity Autosampler, Waters Acquity QDa, Waters Acquity PDA, run time: 4.8 min, solvents: A) 10 mM ammonium bicarbonate pH 10, B) MeCN, gradient: 2-98% B in 4.00 min, hold at 98% B to 4.60 min

Method 12: Instrument: Waters Acquity UPLCMS SingleQuad; Column: Acquity UPLC BEH C18 1.7 µm, 50x2.1 mm; eluent A: water + 0.1 vol % formic acid (99%), eluent B: acetonitrile;

gradient: 0-1.6 min 1-99% B, 1.6-2.0 min 99% B; flow 0.8 ml/min; temperature: 60 °C; DAD scan: 210-400 nm.

Method 13: Instrument: Waters Acquity UPLCMS SingleQuad; Colum: Acquity UPLC BEH C18 1.7 50x2.1 mm; eluent A: water + 0.2 vol % aqueous ammonia (32%), eluent B: acetonitrile; gradient: 0-1.6 min 1-99% B, 1.6-2.0 min 99% B; flow 0.8 ml/min; temperature: 60 °C; DAD scan: 210-400 nm.

Analytical methods preparative HPLC:

Method A: instrument: Sepiatec: Prep SFC100; column: Chiralpak IC 5µm 250x30mm; eluent A: CO_2, eluent B: 2-propanol + 0.4 Vol-% diethylamine (99%); isokratic: 36%B; flow 100.0 ml/min temperature: 40°C; BPR: 150bar; MWD @ 254nm

Method B: instrument: Sepiatec: Prep SFC100; column: Chiralpak IA 5µm 250x30mm; eluent A: CO_2, eluent B: methanol + 0.2 Vol-% aqueous ammonia (32%); isokratic: 46%B; flow 100.0 ml/min temperature: 40°C; BPR: 150bar; MWD @ 254nm

Method C: instrument: Labomatic HD5000, Labocord-5000; Gilson GX-241 , Labcol Vario 4000, column: Chiralpak IE 5µ 250x30mm; eluent A: tert.-butylmethylether + 0.1 Vol-% diethylamine (99%); eluent B: ethanol; isokratic: 90%A+10%B; flow 50.0 ml/min; UV 254 nm.

Method D: Instrument: Labomatic HD5000, Labocord-5000; Gilson GX-241 , Labcol Vario 4000, column: Chiralpak ID 5µ 250x30mm; eluent A: tert.-butylmethylether + 0.1 Vol-% diethylamine (99%); Eluent B: ethanol; isokratic: 90%A+10%B; flow 40.0 ml/min; UV 280 nm

Method E: Instrument: Labomatic HD5000, Labocord-5000; Gilson GX-241 , Labcol Vario 4000, column: Chiralpak IF 5µ 250x20mm; eluent A: hexane + 0.1 Vol-% diethylamine (99%); eluent B: 2-propanol; gradient: 20 - 50% B in 20 min; flow 20.0 ml/min; UV 254 nm

Method F: Instrument: Labomatic HD5000, Labocord-5000; Gilson GX-241 , Labcol Vario 4000, column: YMC - cellulose SC 5µ 250x30mm; eluent A: hexane + 0.1 Vol-% diethylamine (99%); eluent B: ethanol; gradient: 20-50%B in 20 min; flow 40.0 ml/min; UV 280 nm

Method G: Instrument: Labomatic HD5000, Labocord-5000; Gilson GX-241 , Labcol Vario 4000, column: Chiralpak IE 5µ 250x30mm; eluent A: MtBE + 0.1 Vol-% diethylamine (99%); eluent B: ethanol; isokratic: 90%A+10%B; flow 40.0 ml/min; UV 280 nm

Method H: Instrument: Labomatic HD5000, Labocord-5000; Gilson GX-241 , Labcol Vario 4000, column: Chiralpak IA 5µm 250x30mm; Eluent A: MTBE + 0.1 Vol-% diethylamine (99%); isokratic: 100%A; flow 50.0 ml/min; detection: UV 280 nm

Method I: Instrument: Labomatic HD5000, Labocord-5000; Gilson GX-241 , Labcol Vario 4000, column: Chiralpak IA 5µm 250x30mm; Eluent A: MTBE + 0.1 Vol-% diethylamine (99%); Eluent B: ethanol; isokratic: 90%A + 10% B; flow 50.0 ml/min; detection UV 280 nm

Method J: Instrument: Labomatic HD5000, Labocord-5000; Gilson GX-241 , Labcol Vario 4000, column: YMC Amylose SA 5µm 250x30mm; Eluent: hexane + 0.1 Vol-% diethylamine (99%)/ethanol 50:50; flow 40.0 ml/min; detection UV 280 nm

Analytical methods chiral HPLC:

Method 4: instrument: Agilent: 1260, Aurora SFC-Modul; column: Chiralpak IC 5µm 100x4.6mm; eluent A: CO_2, eluent B: 2-propanol + 0.2 Vol-% diethylamine (99%); isokratic: 36%B; flow 4.0 ml/min; temperature: 37.5°C; BPR: 100bar; MWD @ 254nm

Method 5: instrument: Agilent: 1260, Aurora SFC-Modul; column: Chiralpak IA 5µm 100x4.6mm; eluent A: CO2, eluent B: methanol + 0.2 Vol-% aqueous ammonia (32%); isokratic: 46%B; flow 4.0 ml/min; temperature: 37.5°C; BPR: 100bar; MWD @ 254nm

Method 6: instrument: Agilent HPLC 1260; column: Chiralpak IE 3µ 100x4,6mm; eluent A: tert-butylmethylether + 0.1 Vol-% diethylamine (99%); eluent B: ethanol; isokratic: 90%A+10%B; flow 1.4 ml/min; temperatur: 25 °C; DAD 254 nm

Method 7: Instrument: Agilent HPLC 1260; Saule: Chiralpak ID 3µ 100x4,6mm; eluent A: tert-butylmethylether + 0.1 Vol-% diethylamine (99%); Eluent B: ethanol; isokratic: 90%A+10%B; flow 1.4 ml/min; temperature: 25 °C; DAD 280 nm

Method 8: Instrument: Agilent HPLC 1260; column: Chiralpak IF 3µ 100x4,6mm; eluent A: hexane + 0.1 Vol-% diethylamine (99%); eluent B: 2-propanol; gradient: 5 - 30% B in 7 min; flow 1.4 ml/min; temperature: 25 °C; DAD 254 nm

Method 9: Instrument: Agilent HPLC 1260; column: YMC - cellulose SC 3µ 100x4,6mm; eluent A: hexane + 0.1 Vol-% diethylamine (99%); eluent B: ethanol; gradient: 20-50%B in 7Min; flow 1.4 ml/min; temperature: 25 °C; DAD 280 nm

Method 10: Instrument: Agilent HPLC 1260; column: Chiralpak IE 3µ 100x4,6mm; eluent A: MtBE + 0.1 Vol-% diethylamine (99%); eluent B: ethanol; isokratic: 90%A+10%B; flow 1.4 ml/min; temperature: 25 °C; DAD 280 nm

Method 11: Instrument: Agilent HPLC 1260; column: Chiralpak IA 3µm 100x4.6mm; Eluent A: MTBE + 0.1 Vol-% diethylamine (99%); isokratic: 100%A; flow 1.4 ml/min; temperature: 25 °C; detection DAD 280 nm

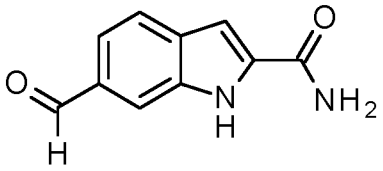
Method 12: Instrument: Agilent HPLC 1260; column: Chiralpak IA 3µm 100x4,6mm; Eluent A: MTBE + 0.1 Vol-% diethylamin (99%); Eluent B: ethanol; isokratic: 90%A + 10% B; flow: 1.4 ml/min; temperature: 25 °C; detection DAD 280 nm

Method 13: Instrument: Agilent HPLC 1260; column: YMC Amylose SA 3µm 100x4,6mm; Eluent: hexane + 0.1 Vol-% diethylamine (99%)/ethanol 50:50; flow 1.4 ml/min; temperature: 25 °C; detection DAD 254 nm

EXPERIMENTAL SECTION - INTERMEDIATES

Intermediate 11

6-formyl-1 H-indole-2-carboxamide



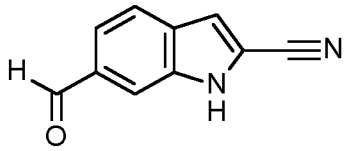
To a mixture of 1.5 ml pyridine, 0.75 ml acetic acid und 0.75 ml water was added 100 mg (0.535 mmol) 6-cyano-1 H-indole-2-carboxamide [CAS 877998-60-2], 161.5 mg (1.52 mmol) sodium hypophosphite monohydrate [CAS 10039-56-2] and then 78.4 mg (1.34 mmol) Raney-Nickel in one portion and the suspension was stirred at 45°C for 2 h. The mixture was filtered through a PTFE-filter and the filter cake was rinsed with ethyl acetate (10ml). The filtrate was quenched with water and extracted into ethyl acetate. The organic phase was isolated, dried over a hydrophobic filter paper and evaporated. The residue was purified using preparative HPLC. The product rich fractions were pooled and evaporated to yield 6-formyl-1 H-indole-2-carboxamide (intermediate 11) as a yellow solid (61.5 mg, 61 %).

LC-MS (method 2): Rt = 0.51 min; MS (ESIpos): m/z = 189 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 2.323 (0.82), 2.327 (1.15), 2.332 (0.79), 2.518 (4.50), 2.523 (3.10), 2.665 (0.84), 2.669 (1.15), 2.674 (0.80), 7.225 (6.00), 7.228 (5.98), 7.541 (4.96), 7.545 (4.83), 7.562 (6.15), 7.566 (6.21), 7.577 (2.53), 7.771 (5.98), 7.792 (4.94), 7.987 (7.19), 7.990 (7.05), 8.156 (2.45), 10.013 (16.00), 12.165 (3.01).

Intermediate I2

6-formyl-1 H-indole-2-carbonitrile



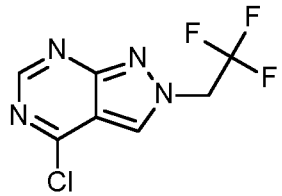
6-Bromo-1 H-indole-2-carbonitrile (300 mg, 1.289 mmol) was dissolved in 12.5 ml THF. The schlenk tube was flushed with argon and sodium hydride (123.8 mg, 3.09 mmol, 60% suspension in oil) was added. After stirring for 10 min the mixture was cooled to -90°C (ethanol/N2(liq.)) and tert-butyl lithium (1.5 ml, 2.58 mmol) was added dropwise to maintain the temperature between -95°C- -90°C. The reaction was stirred for 1h before DMF (496 µl, 6.45 mmol) was added and the reaction was allowed to warm to -70°C. The temperature was kept for 30min and then allowed to warm to RT. The reaction was quenched with acetic acid (369 µl, 6.45 mmol), stirred for 10min and then partitioned between ethyl acetate and saturated NaHCC>3 solution (precipitation). The yellow precipitate was filtered through a PTFE-filter. The filtrate was extracted twice with ethyl acetate, the organic layer was isolated, dried over a hydrophobic filter paper and concentrated in vacuo. The crude product was purified using preparative HPLC. The product rich fractions were pooled and evaporated to yield 6-formyl-1H-indole-2-carbonitrile (intermediate **I2)** as a yellow solid (37.3 mg, 16.8%).

LC-MS (method 2): Rt = 0.77 min; MS (ESIpos): m/z = 171 $[M+H]^+$

1H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.472 (11.60), 7.474 (11.84), 7.61 1 (4.76), 7.615 (4.91), 7.633 (5.66), 7.636 (6.04), 7.822 (7.39), 7.843 (6.09), 8.059 (7.99), 10.056 (16.00).

Intermediate I3

4-chloro-2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidine



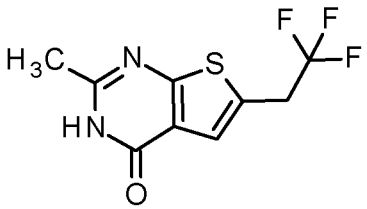
To a suspension of 4 g (25.9 mmol) 4-chloro-1 H-pyrazolo[3,4-d]pyrimidine [CAS 5399-92-8] in 22 ml DMF was added 5.6 ml (39 mmol) 2,2,2-trifluoroethyl trifluoromethanesulfonate and 7.15 g potassium carbonate (51.8 mmol). The mixture was stirred for 5 min. at 0°C , followed by 17 h at RT. All volatile components were evaporated, water was added and the suspension freeze dried. The residue was purified by silica gel column chromatography to give the desired 4-chloro-2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidine (intermediate **I3)** (1.08g, 15%) and 4-chloro-1 -(2,2,2-trifluoroethyl)-1 H-pyrazolo[3,4-d]pyrimidine (1.1g, 16%).

LC-MS (method 2): Rt = 0.66 min; MS (ESIpos): m/z = 237 $[M+H]^+$

^{1}H-NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 1.268 (4.69), 2.055 (7.25), 5.074 (4.57), 5.095 (13.00), 5.114 (12.98), 5.135 (4.20), 8.319 (12.47), 8.925 (16.00).

Intermediate I4

2-methyl-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4(3H)-one



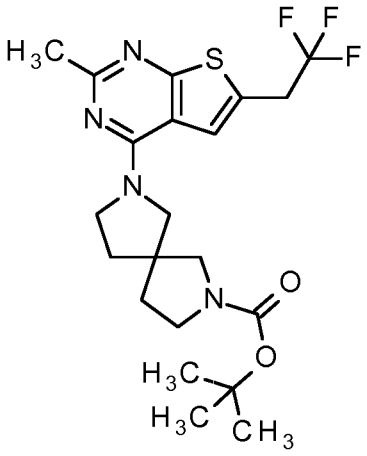
7g 2-amino-5-(2,2,2-trifluoroethyl)thiophene-3-carboxamide (31.2 mmol) was refluxed in a mixture of triethyl orthoacetate (24ml) and acetic acid (18ml) for 16h. After cooling to RT water was added and the mixture was extracted with ethyl acetate (3x). The combined organic extracts were evaporated. The residue was purified by silica gel column chromatography to give the desired intermediate **I4** (4.5g, 44%).

LC-MS (method 2): Rt = 0.74 min; MS (ESIpos): m/z = 249 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 2.355 (16.00), 2.518 (0.92), 2.522 (0.60), 3.990 (0.72), 4.018 (2.09), 4.046 (2.00), 4.073 (0.64), 7.333 (3.50).

Intermediate I5

tert-butyl 7-[2-methyl-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]nonane-2-carboxylate



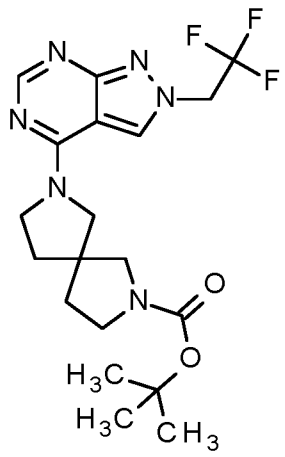
To a suspension of 200 mg (604 µmol) 2-methyl-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4(3H)-one (intermediate **14)** in 13 ml acetonitrile was given 137 mg (604 µmol) tert-butyl 2,7-diazaspiro[4.4]nonane-2-carboxylate [CAS 236406-49-8], 377 mg PyBOP (725 µmol) [CAS 128625-52-5] and 170 µl (1.2 mmol) triethylamine. The mixture was stirred for 3 h at 80°C. The residue was filtered and purified by preparative HPLC to yield 245 mg (84 %) of the desired product.

LC-MS (method 2): Rt = 1.2 min; MS (ESIpos): m/z = 457 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.389 (12.24), 1.406 (9.63), 1.866 (0.71), 1.886 (1.02), 1.905 (0.74), 1.986 (0.69), 2.417 (16.00), 2.518 (1.78), 2.523 (1.25), 3.233 (0.69), 3.259 (2.09), 3.281 (1.47), 3.308 (0.67), 3.374 (1.30), 3.687 (0.58), 3.847 (0.48), 3.972 (0.67), 4.000 (1.85), 4.028 (1.76), 4.055 (0.56), 7.640 (1.90).

Intermediate I6

tert-butyl 7-[2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]nonane-2-carboxylate



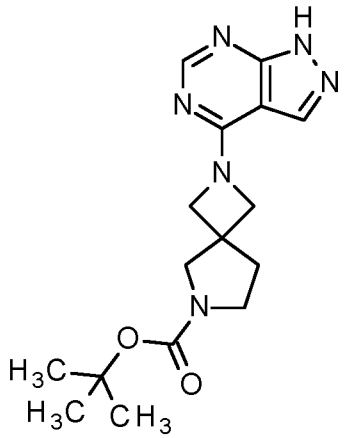
To a suspension of 2.16 g (4.52 mmol) tert-butyl 7-(1 H-pyrazolo[3,4-d]pyrimidin-4-yl)-2,7-diazaspiro[4.4]nonane-2-carboxylate (intermediate **I8)** in 19 ml DMF was added 780 µl (5.4 mmol) 2,2,2-trifluoroethyl trifluoromethanesulfonate and 1.25 g potassium carbonate (9.04 mmol). The mixture was stirred for 5 min. at 0°C followed by 23 h at RT after having added additional 0.4 ml. 2,2,2-trifluoroethyl trifluoromethanesulfonate after 3h. The solvent was removed by evaporation and the crude mixture was filtered and purified by preparative HPLC to yield 394 mg (18 %) of the desired product (intermediate **I6).** 643 mg (33%) of tert-butyl 7-[1-(2,2,2-trifluoroethyl)-1 H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]nonane-2-carboxylate were also obtained.

LC-MS (method 2): Rt = 0.79 min; MS (ESIpos): m/z = 427 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.922 (0.42), 0.937 (0.42), 1.390 (16.00), 1.408 (13.01), 1.899 (1.17), 1.935 (0.75), 1.950 (0.64), 1.963 (0.81), 1.980 (0.98), 1.996 (0.44), 2.074 (0.72), 2.094 (1.23), 2.112 (0.70), 2.518 (2.55), 2.523 (1.77), 2.674 (0.48), 3.268 (2.56), 3.294 (1.92), 3.353 (1.26), 3.370 (1.19), 3.386 (1.01), 3.401 (1.02), 3.583 (0.56), 3.613 (1.38), 3.648 (0.72), 3.726 (3.59), 3.749 (1.54), 3.766 (0.73), 3.861 (0.78), 3.878 (1.52), 3.896 (0.75), 4.134 (0.92), 5.310 (0.42), 5.320 (0.45), 5.342 (1.33), 5.359 (1.89), 5.382 (1.51), 5.404 (0.42), 8.208 (3.07), 8.234 (3.86), 8.341 (1.01), 8.566 (0.47), 8.735 (1.95), 8.766 (1.54).

Intermediate I7

tert-butyl 2-(1H-pyrazolo[3,4-d]pyrimidin-4-yl)-2,6-diazaspiro[3.4]octane-6-carboxylate



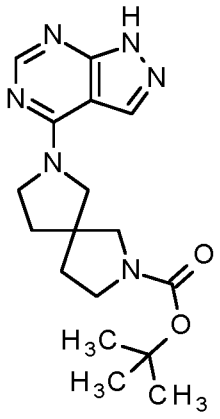
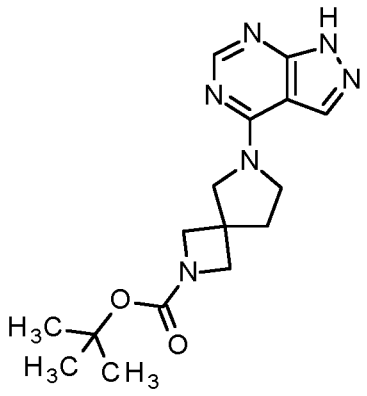
To a suspension of 500 mg (3.24 mmol) 4-chloro-1 H-pyrazolo[3,4-d]pyrimidine [CAS 5399-92-8] in 20 ml tetrahydrofuran was added 1.7 ml ethyldiisopropylamine (9.7 mmol), followed by 755 mg (3.56 mmol) tert-butyl 2,6-diazaspiro[3.4]octane-6-carboxylate [CAS 885270-86-0]. The reaction mixture was stirred for 3 h at 80°C. The solvent was removed by evaporation and the crude product was used without further purification (1.33 g, 99%). A small amout was further purified by preparative HPLC to give analytically pure intermediate **I7.**

LC-MS (method 2): Rt = 0.65 min; MS (ESIpos): m/z = 331 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.932 (0.41), 0.949 (0.41), 1.405 (16.00), 1.427 (0.41), 2.144 (0.62), 2.326 (0.43), 2.518 (1.84), 2.522 (1.24), 2.668 (0.43), 3.504 (0.44), 8.006 (1.33), 8.206 (6.85), 13.484 (0.49).

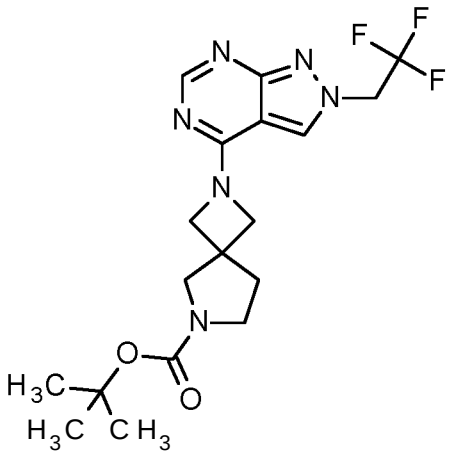
The following intermediates **I8** and **I9** were prepared using respectively commercially available tert-butyl 2,7-diazaspiro [4.4]nonane-2-carboxylate [CAS 236406-49-8] and commercially available tert-butyl 2,6-diazaspiro[3.4]octane-2-carboxylate [CAS 885270-84-8] by reacting

with commercially available 4-chloro-1 H-pyrazolo[3,4-d]pyrimidine [CAS 5399-92-8] according to the preparation of intermediate **I7.**

Inter-mediate	Structure Name	Analytical Data
I8	 tert-butyl 7-(1H-pyrazolo[3,4-d]pyrimidin-4-yl)-2,7-diazaspiro[4.4]nonane-2-carboxylate	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.389 (16.00), 1.408 (13.68), 1.894 (1.23), 1.930 (0.86), 1.948 (1.11), 1.965 (0.58), 2.062 (0.61), 2.079 (1.15), 2.097 (0.66), 2.518 (1.82), 2.523 (1.32), 3.257 (2.88), 3.282 (1.19), 3.311 (0.61), 3.358 (1.33), 3.370 (1.25), 3.575 (0.44), 3.604 (1.15), 3.635 (0.81), 3.720 (0.70), 3.738 (1.30), 3.755 (1.79), 3.770 (0.88), 3.889 (0.80), 3.907 (1.51), 3.924 (0.76), 8.142 (1.06), 8.187 (2.91), 8.210 (2.18), 13.442 (0.81). LC-MS (method 2): Rt = 0.70 min; MS (ESIpos): m/z = 345 [M+H]+
I9	 tert-butyl 6-(1H-pyrazolo[3,4-d]pyrimidin-4-yl)-2,6-diazaspiro[3.4]octane-2-carboxylate	^{1}H-NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 1.451 (4.42), 1.455 (0.55), 1.469 (16.00), 1.625 (0.44), 3.048 (0.42), 3.847 (0.73), 3.849 (0.75), 3.925 (0.45), 3.943 (0.57), 3.984 (1.09), 4.005 (0.77), 8.019 (0.58), 8.438 (0.75). LC-MS (method 2): Rt = 0.65 min; MS (ESIpos): m/z = 331 [M+H]+

Intermediate 110

tert-butyl 2-[2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin -4-yl]-2,6-diazaspiro[3.4]octane-6-carboxylate

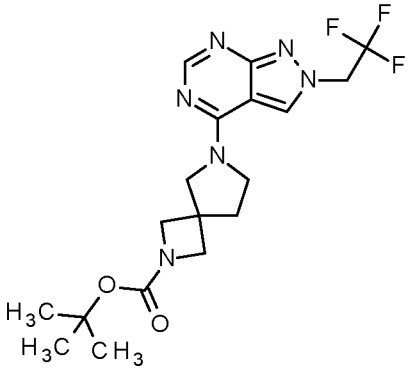


A suspension of 459 mg (1.33 mmol) tert-butyl 2-(1 H-pyrazolo[3,4-d]pyrimidin-4-yl)-2,6-diazaspiro[3.4]octane-6-carboxylate (intermediate **I7)** in 5.9 ml DMF was cooled to 0°C. 231 µl (1.6 mmol) 2,2,2-trifluoroethyl trifluoromethanesulfonate was added followed by 369 mg (9.04 mmol) potassium carbonate. The mixture was stirred for 5 min at 0°C followed by 17 h at RT. The residue was filtered and purified by preparative HPLC to yield 148 mg (26 %) of the desired product. Furthermore 144 mg (20%) of tert-butyl 2-[1-(2,2,2-trifluoroethyl)-1 H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,6-diazaspiro[3.4]octane-6-carboxylate were isolated.

LC-MS (method 2): Rt = 0.76 min; MS (ESIpos): m/z = 413 $[M+H]^+$

^{1}H-NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 1.484 (16.00), 2.214 (0.71), 3.633 (0.40), 4.310 (0.86), 4.931 (0.43), 4.951 (1.24), 4.972 (1.20), 7.941 (2.47), 8.481 (4.05).

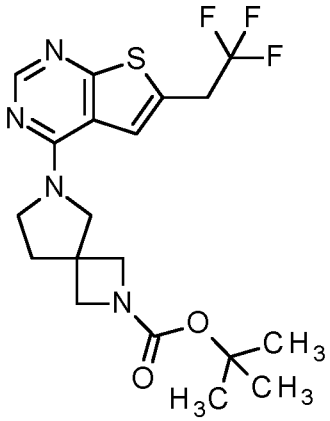
The following intermediate **111** was prepared using intermediate **I9** by reacting with 2,2,2-trifluoroethyl trifluoromethanesulfonate according to the preparation of intermediate **110.**

Inter-mediate	Structure Name	Analytical Data
I11	 tert-butyl 6-[2-(2,2,2-	LC-MS (method 2): Rt = 0.71 min; MS (ESIpos): m/z = 413 $[M+H]^+$ ^{1}H-NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 1.451 (0.13), 1.462 (0.32), 1.476 (16.00), 1.491 (0.09), 1.633 (0.18), 1.664 (0.55), 2.251 (0.10), 2.267 (0.18), 2.284 (0.11), 2.389 (0.15), 2.406 (0.25), 2.416 (0.12), 2.421 (0.14), 3.863 (0.39), 3.881 (0.71), 3.898 (0.38), 3.917 (0.22), 3.939 (0.37), 3.965 (0.54), 3.977 (0.66), 3.997

Inter¬ mediate	Structure Name	Analytical Data
	trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,6-diazaspiro[3.4]octane-2-carboxylate	(1.29), 4.016 (0.36), 4.948 (0.14), 4.966 (0.36), 4.987 (0.36), 5.007 (0.13), 8.052 (0.30), 8.072 (0.21), 8.486 (0.52).

Intermediate 112

tert-butyl 6-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,6-diazaspiro[3.4]octane-2-carboxylate



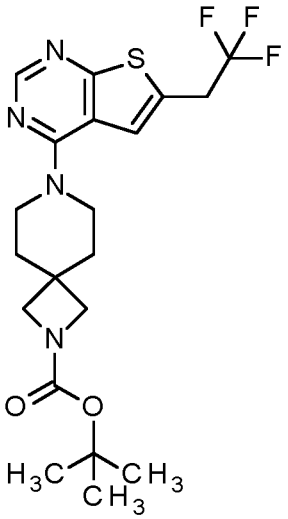
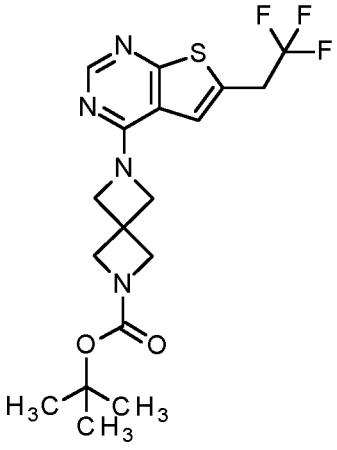
To a suspension of 6 g (23.75 mmol) 4-chloro-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidine, [CAS 1628317-85-0] in 60 ml tetrahydrofuran was added 12.41 ml DIPEA (71.2 mmol), followed by 6.05 g (28.5 mmol) tert-butyl 2,6-diazaspiro[3.4]octane-2-carboxylate [CAS 885270-84-8] and the mixture was stirred for 8 h at 80°C in capped microwave vials. The reaction mixture was treated with water and saturated ammonium chloride solution, extracted with ethyl acetate (3x), dried and concentrated in vacuo to yield 10.07 g (99 %) of the desired product.

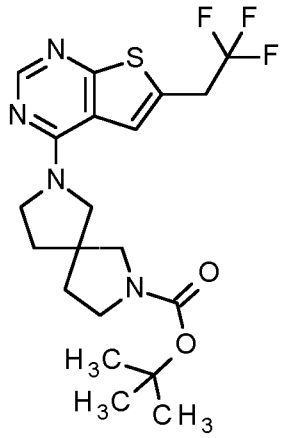
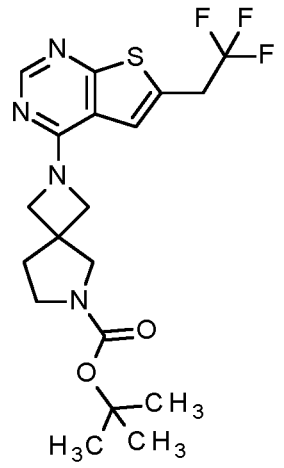
LC-MS (method 2): Rt = 1.20 min; MS (ESIpos): m/z = 429 $[M+H]^+$

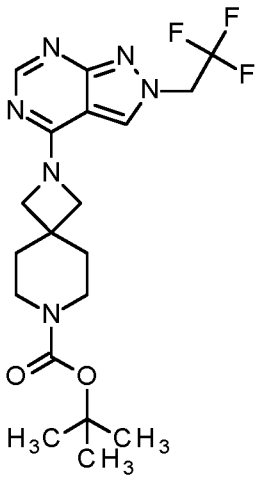
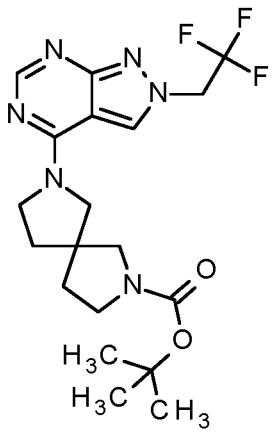
^{1}H-NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 1.439 (0.24), 1.441 (0.27), 1.462 (16.00), 1.623 (0.37), 2.261 (0.35), 2.279 (0.70), 2.295 (0.36), 3.607 (0.27), 3.632 (0.79), 3.658 (0.76), 3.683 (0.25), 3.888 (0.35), 3.905 (0.68), 3.914 (1.00), 3.922 (0.40), 3.935 (1.73), 3.972 (2.19), 3.978 (1.67), 3.994 (0.90), 7.345 (1.03), 8.444 (1.89).

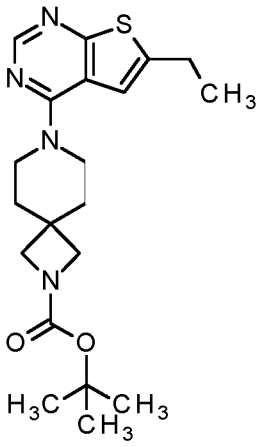
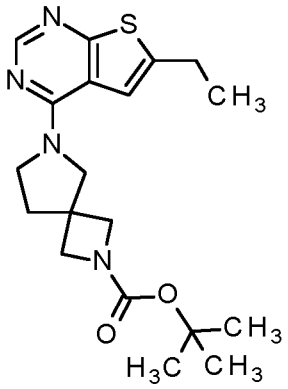
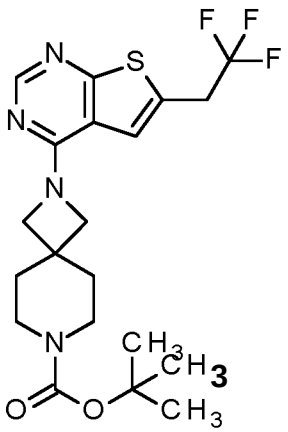
The following intermediates **113-121** were prepared using corresponding intermediates **I3,** 4-chloro-6-ethylthieno[2,3-d]pyrimidine [CAS 81136-42-7] or 4-chloro-6-(2,2,2-

trifluoroethyl)thieno[2,3-d]pyrimidine [CAS 1628317-85-0] respectively by reacting with corresponding commercially available spirocyclic amines according to the preparation of **112.**

Inter-mediate	Structure Name	Analytical Data
I13	 tert-butyl 7-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate	LC-MS (method 2): Rt = 1.31 min; MS (ESIpos): m/z = 443 $[M+H]^+$ ^{1}H-NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 1.393 (16.00), 3.666 (5.83), 3.715 (0.84), 8.408 (2.01).
I14	 tert-butyl 6-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,6-diazaspiro[3.3]heptane-2-carboxylate	^{1}H-NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 1.388 (16.00), 1.506 (1.27), 4.100 (5.62), 4.452 (2.13), 7.020 (0.87), 8.380 (2.06). LC-MS (method 2): Rt = 1.15 min; MS (ESIpos): m/z = 415 [M+H]+

Inter¬ mediate	Structure Name	Analytical Data
115	 tert-butyl 7-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]nonane-2-carboxylate	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.172 (0.75), 1.352 (0.48), 1.389 (16.00), 1.405 (12.65), 1.871 (1.06), 1.888 (1.24), 1.912 (0.89), 1.930 (0.44), 1.987 (2.22), 2.001 (0.89), 2.518 (1.32), 2.523 (0.89), 3.242 (0.65), 3.268 (1.89), 3.288 (1.83), 3.372 (1.84), 3.716 (0.63), 3.860 (0.50), 4.016 (1.06), 4.035 (0.76), 4.042 (2.48), 4.070 (2.35), 4.098 (0.74), 7.709 (2.38), 8.326 (6.03). LC-MS (Method 1): Rt = 1.26 min; MS (ESIpos): m/z = 443 $[M+H]^+$
116	 tert-butyl 2-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,6-diazaspiro[3.4]octane-6-carboxylate	^{1}H-NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 1.267 (0.44), 1.464 (2.36), 1.483 (16.00), 1.613 (1.10), 2.054 (0.82), 2.188 (0.79), 3.454 (0.45), 3.501 (0.48), 3.595 (0.95), 3.600 (0.95), 3.619 (1.74), 3.635 (0.83), 3.644 (1.57), 3.670 (0.46), 4.289 (0.54), 4.310 (1.05), 4.345 (0.61), 7.1 10 (2.10), 8.455 (3.24). LC-MS (Method 1): Rt = 1.22 min; MS (ESIpos): m/z = 429 $[M+H]^+$

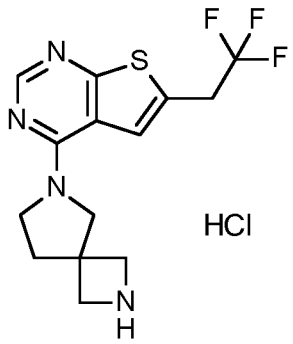
Inter-mediate	Structure Name	Analytical Data
I17	 tert-butyl 2-[2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]nonane-7-carboxylate	^{1}H-NMR (400 MHz, DMSO-d6) delta [ppm]: 1.154 (0.57), 1.172 (1.12), 1.190 (0.58), 1.379 (0.90), 1.384 (3.04), 1.402 (16.00), 1.748 (1.01), 1.756 (1.00), 1.987 (2.28), 2.518 (0.59), 3.299 (0.49), 3.934 (1.06), 4.017 (0.52), 4.035 (0.52), 4.163 (1.01), 5.366 (0.77), 5.389 (0.72), 8.211 (3.01), 8.595 (1.94). LC-MS (method 2): Rt = 0.81 min; MS (ESIpos): m/z = 427 $[M+H]^+$
I18	 tert-butyl 7-[2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]nonane-2-carboxylate	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.389 (16.00), 1.408 (13.46), 1.899 (1.21), 1.934 (0.77), 1.950 (0.61), 1.962 (0.83), 1.979 (1.05), 1.996 (0.44), 2.076 (0.66), 2.093 (1.27), 2.111 (0.72), 2.318 (0.44), 2.323 (0.99), 2.327 (1.43), 2.331 (1.05), 2.336 (0.50), 2.518 (8.17), 2.523 (5.63), 2.660 (0.44), 2.665 (0.99), 2.669 (1.43), 2.673 (0.99), 2.678 (0.44), 3.268 (2.70), 3.294 (2.04), 3.385 (1.27), 3.401 (1.16), 3.583 (0.61), 3.613 (1.43), 3.648 (0.77), 3.726 (3.70), 3.748 (1.60), 3.765 (0.77), 3.860 (0.83), 3.878 (1.60), 3.895 (0.77), 5.319 (0.44), 5.341 (1.32), 5.359 (1.93), 5.381 (1.60), 5.403 (0.44), 8.208 (3.20), 8.233 (4.25), 8.734 (2.04), 8.765 (1.60). LC-MS (method 2): Rt = 0.77 min; MS (ESIpos): m/z = 427 $[M+H]^+$

Inter-mediate	Structure Name	Analytical Data
I19	 tert-butyl 7-(6-ethylthieno[2,3-d]pyrimidin-4-yl)-2,7-diazaspiro[3.5]nonane-2-carboxylate	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.263 (1.62), 1.282 (3.82), 1.301 (1.69), 1.364 (0.42), 1.373 (0.60), 1.386 (16.00), 1.767 (0.82), 1.780 (1.48), 1.794 (0.83), 1.987 (0.60), 2.896 (0.84), 2.899 (0.85), 2.915 (0.82), 2.917 (0.82), 3.621 (0.52), 3.751 (0.53), 7.258 (1.17), 8.332 (2.52). LC-MS (method 2): Rt = 1.30 min; MS (ESIpos): m/z = 389 $[M+H]^+$
I20	 tert-butyl 6-(6-ethylthieno[2,3-d]pyrimidin-4-yl)-2,6-diazaspiro[3.4]octane-2-carboxylate	^{1}H-NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 1.275 (1.55), 1.294 (3.44), 1.312 (1.47), 1.385 (16.00), 2.178 (0.80), 2.824 (0.70), 2.827 (0.70), 2.843 (0.69), 3.828 (0.94), 3.849 (1.49), 3.888 (1.61), 3.899 (1.39), 3.910 (0.81), 7.018 (1.08), 8.322 (1.96). LC-MS (method 2): Rt = 1.13 min; MS (ESIpos): m/z = 375 $[M+H]^+$
I21		^{1}H-NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 1.439 (0.13), 1.457 (0.16), 1.462 (0.33), 1.480 (16.00), 1.615 (0.11), 1.637 (0.09), 1.829 (0.66), 1.843 (1.04), 1.857 (0.65), 3.449 (0.64), 3.599 (0.25), 3.624 (0.71), 3.649 (0.69), 3.674 (0.23), 4.134 (0.97), 7.135 (0.97), 8.442 (1.97). LC-MS (method 2): Rt = 1.23 min; MS (ESIpos): m/z = 443 $[M+H]^+$

Inter¬ mediate	Structure Name	Analytical Data
	tert-butyl 2-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]nonane-7-carboxylate	

Intermediate 122

4-(2,6-diazaspiro[3.4]oct-6-yl)-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidine hydrochloride

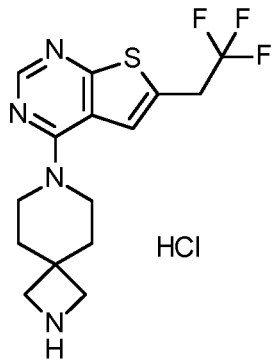
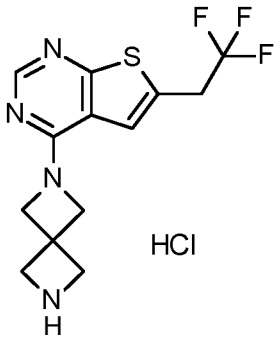


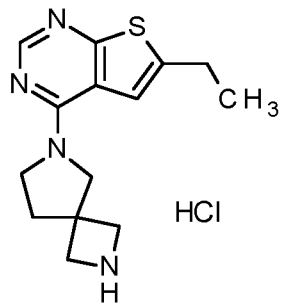
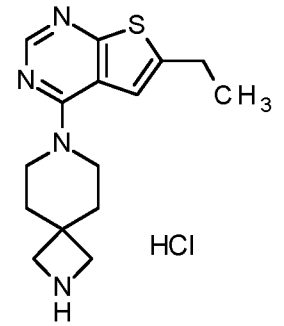
To a suspension of 9.23g (21.5 mmol) tert-butyl 6-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,6-diazaspiro[3.4]octane-2-carboxylate (intermediate **112)** in 45 ml dichloromethane and 30 ml methanol was added 8 ml of a solution of 4M hydrochloride in dioxane. The mixture was stirred for 1 h at RT. All solvent was removed by evaporation to yield 10 g (101.8 %) of the desired product which was used without further purification.

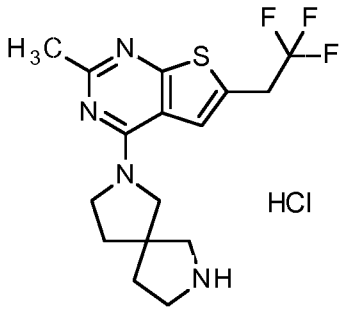
LC-MS (method 1): Rt = 0.56 min; MS (ESIpos): m/z = 329 $[M+H]^+$

^{1}H-NMR (500 MHz, DMSO-d6) δ [ppm]: 1.231 (0.99), 2.332 (3.12), 2.354 (1.67), 2.358 (1.95), 2.361 (2.16), 2.365 (1.53), 2.515 (5.54), 2.518 (5.05), 2.522 (3.88), 2.631 (1.09), 2.635 (1.53), 2.639 (1.14), 3.101 (0.49), 3.114 (0.49), 3.713 (0.42), 3.857 (1.51), 3.902 (2.50), 3.923 (4.40), 3.932 (3.80), 3.946 (2.71), 3.971 (1.53), 3.980 (1.33), 4.054 (4.32), 4.078 (4.87), 4.101 (7.39), 4.123 (6.74), 4.144 (2.60), 4.338 (3.49), 4.485 (3.15), 7.306 (3.30), 7.313 (0.81), 7.317 (0.99), 7.738 (10.87), 8.482 (16.00), 9.150 (1.14), 9.384 (0.91).

The following intermediates were prepared analogous to intermediate **I22** starting from **I5, 113, 114, 119, 120** respectively.

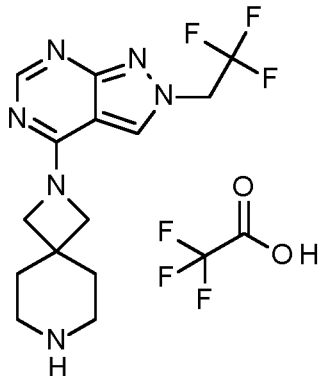
Inter¬ mediate	Structure Name	Analytical Data
123	 HCl 4-(2,7-diazaspiro[3.5]non-7-yl)-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidine hydrochloride	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.231 (0.56), 1.904 (4.66), 1.918 (6.09), 1.931 (5.41), 2.323 (1.07), 2.327 (1.48), 2.331 (1.17), 2.522 (16.00), 2.665 (1.87), 2.669 (2.26), 2.673 (1.87), 3.164 (0.95), 3.565 (2.67), 3.754 (5.73), 3.770 (9.59), 3.785 (6.48), 3.806 (6.26), 3.820 (7.67), 3.834 (7.19), 3.902 (14.23), 4.072 (1.70), 4.100 (3.96), 4.128 (3.79), 4.156 (1.43), 7.680 (6.26), 8.441 (11.41), 8.449 (0.78), 9.107 (1.41). LC-MS (method 2): Rt = 0.58 min; MS (ESIpos): m/z = 343 [M+H]$^+$
124	 HCl 4-(2,6-diazaspiro[3.3]hept-2-yl)-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidine hydrochloride	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.230 (1.27), 2.318 (0.69), 2.322 (1.52), 2.326 (2.14), 2.331 (1.45), 2.336 (0.69), 2.518 (9.11), 2.522 (6.13), 2.659 (0.73), 2.664 (1.60), 2.668 (2.10), 2.673 (1.49), 2.678 (0.69), 3.163 (0.76), 3.299 (2.07), 3.310 (2.14), 3.395 (0.40), 3.551 (1.27), 3.662 (0.40), 3.674 (0.44), 3.676 (0.47), 3.698 (0.47), 3.700 (0.44), 3.712 (0.44), 3.729 (0.54), 3.740 (0.51), 3.751 (0.47), 4.003 (9.98), 4.079 (3.77), 4.093 (3.77), 4.107 (5.12), 4.118 (3.66), 4.136 (5.22), 4.149 (7.18), 4.168 (4.21), 4.184 (5.84), 4.200 (3.08), 4.341 (0.73), 4.561 (0.73), 7.408 (3.37), 7.424 (7.29), 8.136 (0.58), 8.311 (3.41), 8.431 (7.33), 8.443 (16.00), 8.958 (0.47). LC-MS (method 2): Rt = 0.49 min; MS (ESIpos): m/z = 315 [M+H]$^+$

Inter-mediate	Structure Name	Analytical Data
I25	 HCl 4-(2,6-diazaspiro[3.4]oct-6-yl)-6-ethylthieno[2,3-d]pyrimidine hydrochloride	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.281 (1.61), 1.286 (7.12), 1.300 (3.65), 1.305 (16.00), 1.318 (1.79), 1.324 (7.11), 2.302 (1.48), 2.318 (3.07), 2.322 (3.04), 2.327 (2.46), 2.332 (2.06), 2.337 (1.83), 2.518 (4.94), 2.523 (3.34), 2.665 (0.80), 2.669 (1.08), 2.674 (0.76), 2.902 (1.63), 2.904 (1.68), 2.921 (4.61), 2.923 (4.72), 2.940 (4.63), 2.941 (4.66), 2.960 (1.50), 3.163 (1.18), 3.892 (1.84), 3.904 (1.88), 3.911 (2.12), 3.921 (2.77), 3.932 (2.42), 3.939 (2.12), 3.950 (1.72), 3.960 (1.48), 4.037 (1.46), 4.054 (2.35), 4.067 (2.33), 4.078 (2.28), 4.096 (1.99), 7.453 (4.50), 8.485 (1.55), 8.491 (7.65). LC-MS (method 2): Rt = 0.47 min; MS (ESIpos): m/z = 275 $[M+H]^+$
I26	 HCl 4-(2,7-diazaspiro[3.5]non-7-yl)-6-ethylthieno[2,3-d]pyrimidine hydrochloride	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.281 (1.61), 1.286 (7.12), 1.300 (3.65), 1.305 (16.00), 1.319 (1.83), 1.324 (7.11), 1.351 (0.58), 2.303 (1.50), 2.319 (3.07), 2.322 (3.04), 2.327 (2.46), 2.332 (2.06), 2.336 (1.84), 2.518 (4.94), 2.523 (3.34), 2.665 (0.80), 2.669 (1.08), 2.674 (0.76), 2.904 (1.68), 2.922 (4.81), 2.941 (4.66), 2.959 (1.54), 3.163 (1.18), 3.892 (1.84), 3.911 (2.12), 3.921 (2.77), 3.932 (2.42), 3.938 (2.12), 3.949 (1.74), 3.960 (1.48), 4.018 (0.61), 4.037 (1.46), 4.054 (2.35), 4.067 (2.33), 4.078 (2.28), 4.096 (1.99), 4.476 (0.83), 7.453 (4.50), 8.491 (7.65), 9.186 (0.60), 9.361 (0.60). LC-MS (method 2): Rt = 0.54 min; MS (ESIpos): m/z = 289 $[M+H]^+$

Inter¬ mediate	Structure Name	Analytical Data
127	 4-[2,7-diazaspiro[4.4]non-2-yl]-2-methyl-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidine hydrochloride	^{1}H-NMR (500 MHz, DMSO-d6) δ [ppm]: 1.938 (0.53), 1.953 (1.08), 1.963 (0.99), 1.968 (0.74), 1.979 (1.87), 1.994 (1.01), 2.011 (0.41), 2.018 (0.92), 2.033 (1.87), 2.047 (1.25), 2.059 (1.29), 2.073 (0.85), 2.083 (0.51), 2.365 (0.78), 2.514 (5.65), 2.521 (16.00), 3.153 (0.62), 3.164 (0.87), 3.176 (1.29), 3.188 (1.43), 3.200 (0.88), 3.227 (1.02), 3.239 (1.52), 3.251 (1.40), 3.262 (0.88), 3.274 (0.60), 3.283 (0.76), 3.297 (1.75), 3.309 (2.70), 3.321 (1.71), 3.335 (0.74), 3.428 (0.42), 3.457 (0.58), 3.468 (0.64), 3.489 (0.71), 3.498 (0.72), 3.510 (0.67), 3.662 (1.89), 3.666 (1.87), 3.674 (1.92), 3.696 (1.87), 3.702 (1.96), 3.708 (1.91), 3.712 (1.91), 4.017 (0.62), 4.058 (0.97), 4.080 (2.14), 4.102 (2.03), 4.124 (0.79), 5.758 (3.07), 7.784 (1.06), 9.404 (0.55). LC-MS (method 2): Rt = 0.55 min; MS (ESIpos): m/z = 357 $[M+H]^+$

Intermediate I28

4-(2,7-diazaspiro[3.5]non-2-yl)-2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidine trifluoroacetate



A suspension of 1.81 g (3.82 mmol) tert-butyl 2-[2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]nonane-7-carboxylate (intermediate 117) in 13 ml dichloromethane was cooled to 0°C and 80 µl water and 4.4 ml trifluoroacetic acid were added.

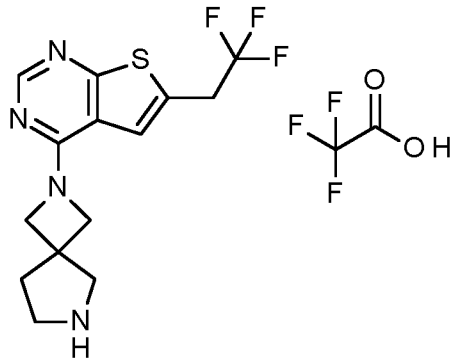
The mixture was stirred for 1 h at RT. All volatile ingredients were removed by evaporation to yield 3.73 g (199 %, salt residues) of the desired product.

LC-MS (method 1): Rt = 0.30 min; MS (ESIpos): m/z = 327 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.107 (7.83), 1.154 (1.29), 1.172 (2.49), 1.189 (1.20), 1.239 (1.98), 1.255 (1.81), 1.270 (1.12), 1.352 (1.03), 1.531 (6.02), 1.742 (0.43), 1.778 (1.46), 1.840 (1.55), 1.854 (1.81), 1.869 (1.46), 1.899 (0.52), 1.986 (5.33), 2.031 (10.15), 2.327 (4.82), 2.331 (3.35), 2.518 (15.91), 2.523 (11.01), 2.669 (4.99), 2.673 (3.53), 3.070 (3.53), 3.126 (3.53), 3.637 (2.75), 3.763 (0.77), 3.778 (0.60), 3.863 (3.61), 3.999 (0.77), 4.016 (1.38), 4.034 (1.46), 4.262 (14.02), 4.434 (14.19), 4.951 (4.22), 4.974 (4.22), 5.228 (2.75), 5.251 (2.67), 5.286 (2.49), 5.309 (2.32), 5.503 (3.44), 5.525 (7.48), 5.547 (7.05), 5.568 (2.92), 5.758 (9.38), 7.956 (1.46), 8.160 (0.52), 8.219 (0.52), 8.325 (0.69), 8.340 (1.29), 8.543 (3.61), 8.627 (9.12), 8.915 (16.00).

Intermediate I29

4-(2,6-diazaspiro[3.4]oct-2-yl)-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidine trifluoroacetate



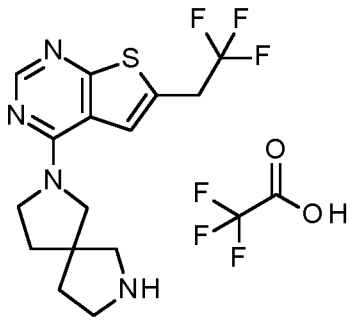
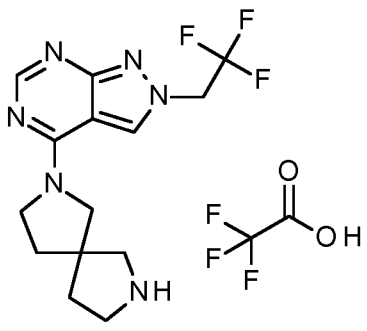
To a suspension of 1 g (2.33 mmol) tert-butyl 2-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,6-diazaspiro[3.4]octane-6-carboxylate (intermediate **116)** in 8 ml dichloromethane was added 4 ml trifluoroacetic acid. The mixture was stirred for 17 h at RT. All volatile ingredients were removed by evaporation to yield 2 g (174 %, salt residues) of the desired product.

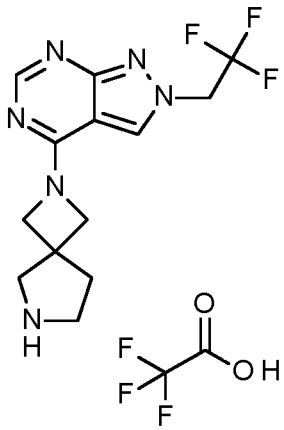
LC-MS (method 2): Rt = 0.47 min; MS (ESIpos): m/z = 329 $[M+H]^+$

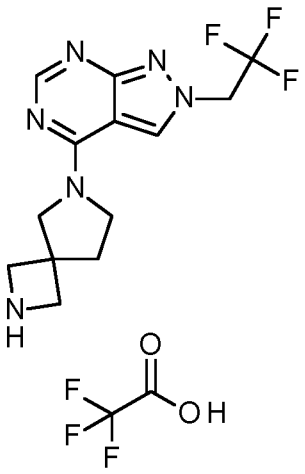
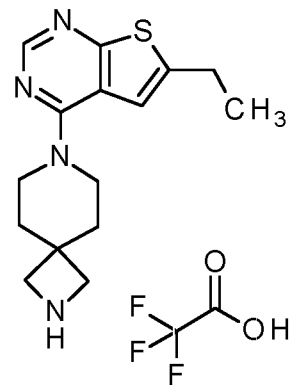
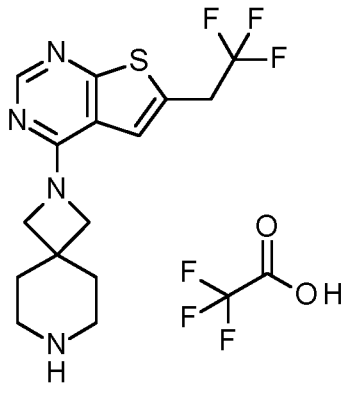
^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.232 (0.60), 1.240 (0.54), 1.828 (1.30), 2.256 (2.54), 2.275 (5.36), 2.297 (16.00), 2.323 (0.67), 2.327 (0.86), 2.331 (0.60), 2.518 (3.22), 2.523 (2.21), 2.665 (0.60), 2.669 (0.81), 2.674 (0.57), 3.214 (0.78), 3.231 (1.93), 3.246 (2.57), 3.261 (1.84), 3.278 (0.68), 3.444 (2.44), 3.459 (4.31), 3.473 (2.37), 3.844 (0.69), 4.053 (1.30), 4.080 (3.60), 4.108 (3.43), 4.136 (1.11), 4.391 (1.03), 7.124 (0.68), 7.142 (1.70), 7.160 (3.17), 7.163 (2.95),

7.180 (3.85), 7.230 (3.36), 7.234 (1.15), 7.248 (3.54), 7.267 (1.42), 7.352 (6.52), 8.391 (14.67), 8.852 (1.54).

The following intermediates were prepared analogous to intermediate **I29** starting from **115, 118, 110, 111 , 119** or **121** respectively.

Inter-mediate	Structure Name	Analytical Data
I30	 4-[2,7-diazaspiro[4.4]non-2-yl]-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidine trifluoroacetate	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.351 (0.83), 1.531 (1.30), 1.938 (0.99), 1.957 (1.57), 1.971 (2.00), 1.990 (3.97), 2.002 (2.05), 2.009 (2.37), 2.019 (3.75), 2.038 (2.34), 2.052 (1.94), 2.071 (1.73), 2.083 (1.73), 2.518 (5.46), 2.522 (3.78), 3.155 (0.80), 3.171 (1.57), 3.185 (2.48), 3.200 (3.01), 3.214 (1.54), 3.229 (1.60), 3.243 (2.88), 3.258 (2.34), 3.273 (1.54), 3.287 (1.09), 3.296 (1.30), 3.313 (3.14), 3.328 (4.82), 3.343 (2.88), 3.361 (1.09), 3.777 (0.96), 3.889 (1.62), 4.029 (1.86), 4.057 (5.16), 4.084 (4.85), 4.111 (1.54), 7.694 (6.04), 8.379 (16.00), 8.927 (1.89). LC-MS (method 2): Rt = 0.55 min; MS (ESIpos): m/z = 343 $[M+H]^+$
I31	 4-[2,7-diazaspiro[4.4]non-2-yl]-2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidine trifluoroacetate	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.107 (11.67), 1.192 (0.57), 1.208 (0.64), 1.532 (0.89), 1.962 (0.45), 1.981 (0.76), 1.994 (1.15), 2.014 (2.23), 2.022 (1.34), 2.033 (1.59), 2.041 (3.06), 2.059 (3.25), 2.066 (2.42), 2.073 (1.72), 2.084 (2.23), 2.105 (1.72), 2.124 (1.66), 2.142 (0.76), 2.156 (0.45), 2.197 (0.76), 2.211 (1.02), 2.228 (1.85), 2.246 (1.34), 2.261 (1.78), 2.278 (1.08), 2.292 (0.76), 2.318 (1.21), 2.323 (2.61), 2.327 (3.76), 2.331 (2.61), 2.518 (12.75), 2.523 (8.73), 2.548 (0.51), 2.660 (1.21), 2.665 (2.68), 2.669 (3.76), 2.673 (2.61), 3.184 (0.51), 3.197 (0.89), 3.214 (1.34), 3.229 (1.59), 3.243 (1.08),

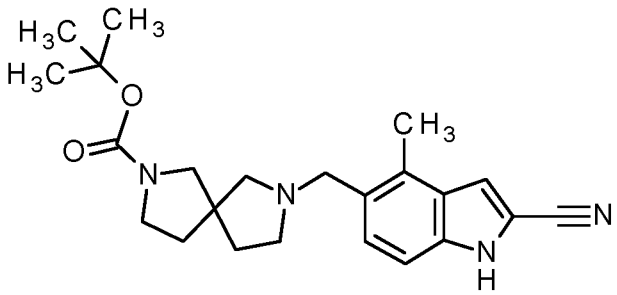
Inter¬ mediate	Structure Name	Analytical Data
		3.262 (2.29), 3.276 (4.46), 3.290 (2.74), 3.327 (2.29), 3.343 (2.93), 3.357 (2.80), 3.372 (1.66), 3.852 (1.59), 3.885 (2.93), 3.930 (1.98), 3.948 (4.91), 3.985 (3.19), 4.012 (4.46), 4.028 (2.04), 4.134 (2.17), 4.928 (1.02), 4.951 (1.59), 4.974 (1.59), 4.996 (1.02), 5.265 (0.89), 5.287 (1.47), 5.310 (1.40), 5.333 (0.76), 5.367 (0.83), 5.389 (0.76), 5.479 (1.59), 5.501 (4.14), 5.522 (4.78), 5.542 (3.12), 5.563 (1.02), 5.758 (16.00), 6.973 (0.51), 7.100 (0.57), 7.228 (0.51), 8.340 (2.42), 8.418 (0.57), 8.566 (1.15), 8.655 (7.14), 8.699 (0.57), 9.002 (1.15), 9.059 (4.40), 9.130 (5.93). LC-MS (method 2): Rt = 0.46 min; MS (ESIpos): m/z = 327 $[M+H]^+$
132	 4-(2,6-diazaspiro[3.4]oct-2-yl)-2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidine trifluoroacetate	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.106 (12.89), 1.779 (2.42), 2.297 (3.79), 2.316 (8.67), 2.326 (3.29), 2.333 (5.09), 2.518 (8.56), 2.522 (5.67), 2.664 (1.52), 2.668 (2.02), 2.673 (1.52), 3.230 (1.73), 3.245 (2.28), 3.283 (1.59), 3.502 (2.20), 3.516 (4.44), 3.526 (4.12), 3.540 (2.09), 4.405 (1.63), 4.434 (4.01), 4.465 (4.08), 4.493 (1.70), 4.613 (0.94), 4.641 (6.39), 4.672 (0.87), 5.508 (2.09), 5.530 (5.56), 5.552 (5.27), 5.574 (1.81), 5.758 (16.00), 8.608 (9.93), 8.758 (0.40), 8.879 (14.48), 8.980 (2.02), 9.007 (1.91). LC-MS (method 2): Rt = 0.21 min; MS (ESIpos): m/z = 313 $[M+H]^+$

Inter-mediate	Structure Name	Analytical Data
I33	 4-(2,6-diazaspiro[3.4]oct-6-yl)-2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidine trifluoroacetate	^{1}H-NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 1.770 (16.00), 2.207 (0.86), 2.224 (1.66), 2.242 (0.91), 2.440 (0.75), 2.458 (1.41), 2.475 (0.75), 3.552 (1.27), 3.571 (1.49), 3.646 (1.37), 3.666 (1.84), 3.768 (1.98), 3.786 (2.43), 3.804 (2.17), 3.822 (2.40), 3.838 (2.18), 3.854 (0.79), 3.925 (2.70), 4.022 (3.15), 4.929 (0.67), 4.949 (1.92), 4.970 (1.90), 4.985 (0.67), 8.035 (1.49), 8.124 (1.73), 8.466 (8.52). LC-MS (method 2): Rt = 0.18 min; MS (ESIpos): m/z = 313 $[M+H]^+$
I34	 4-(2,7-diazaspiro[3.5]non-7-yl)-6-ethylthieno[2,3-d]pyrimidine trifluoroacetate	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.106 (1.51), 1.240 (0.64), 1.255 (0.68), 1.272 (7.79), 1.290 (16.00), 1.309 (7.73), 1.351 (0.46), 1.871 (3.96), 1.885 (4.75), 1.899 (4.04), 2.518 (1.74), 2.523 (1.22), 2.895 (1.33), 2.911 (3.79), 2.913 (3.87), 2.930 (3.69), 2.932 (3.84), 2.950 (1.21), 3.770 (6.21), 3.774 (5.94), 3.785 (11.52), 3.801 (8.29), 6.614 (0.63), 7.311 (5.51), 8.396 (11.18), 8.763 (0.86). LC-MS (method 2): Rt = 0.55 min; MS (ESIpos): m/z = 289 $[M+H]^+$
I35	 4-(2,7-diazaspiro[3.5]non-2-yl)-	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.240 (0.54), 1.256 (0.42), 1.825 (0.43), 1.970 (3.43), 1.984 (5.31), 1.997 (3.61), 2.296 (12.93), 2.322 (0.46), 2.326 (0.60), 2.331 (0.42), 2.518 (2.38), 2.522 (1.71), 2.664 (0.45), 2.668 (0.60), 2.673 (0.43), 3.094 (3.49), 4.027 (1.39), 4.055 (3.50), 4.083 (3.40), 4.111 (1.38), 7.122 (0.55), 7.141 (1.39), 7.159 (2.73), 7.161 (2.88), 7.173 (0.78), 7.179 (3.33), 7.183 (1.90), 7.229 (2.88), 7.233

Inter¬ mediate	Structure Name	Analytical Data
	6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidine trifluoroacetate	(0.97), 7.247 (2.97), 7.262 (0.56), 7.266 (1.23), 7.426 (6.19), 8.375 (16.00), 8.496 (1.47). LC-MS (method 2): Rt = 0.55 min; MS (ESIpos): m/z = 343 $[M+H]^+$

Intermediate I36

tert-butyl 7-[(2-cyano-4-methyl-1H-indol-5-yl)methyl]-2,7-diazaspiro[4.4]nonane-2-carboxylate



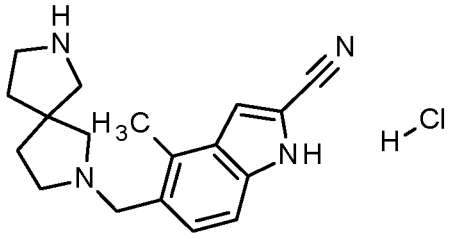
To a stirring solution of tert-butyl 2,7-diazaspiro[4.4]nonane-2-carboxylate, 73.7 mg (0.326 mmol), and 5-formyl-4-methyl-1 H-indole-2-carbonitrile, 60.0 mg (0.326 mmol), in dichloromethane, 2.30 mlml, was added sodium triacetoxyborohydride, 207 mg (0.977 mmol). Stirring continued at room temperature for 18 hours. The mixture was quenched with water and stirred at room temperature for 30 minutes. The product was extracted with dichloromethane, the organics were dried over sodium sulphate and concentrated under vacuum to give the desired product, 131 mg (102%) and was used in the next step without any purification.

1H NMR (400 MHz, CDCh3): δ [ppm] = 1.43 (s, 9H), 1.70-1.81 (m, 4H), 2.36-2.68 (m, 7H), 3.12-3.36 (m, 4H), 3.67 (s, 2H), 7.12-7.18 (m, 1H), 7.21 (s, 1H), 7.31 (d, 1H), 8.78 (d, 1H).

LC-MS (method 6): Rt = 0.96 min., 90%. MS (ESIpos): m/z = (M+H)+ 395.

Intermediate I37

5-(2,7-diazaspiro[4.4]non-2-ylmethyl)-4-methyl-1H-indole-2-carbonitrile hydrochloride



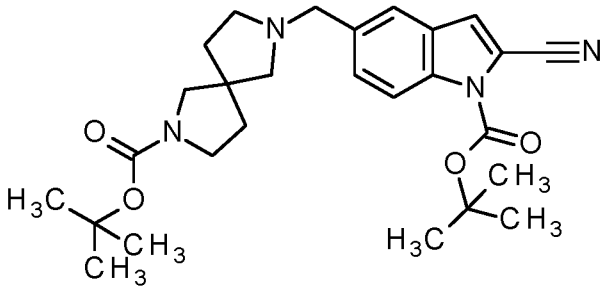
To a stirring solution of tert-butyl 7-[(2-cyano-4-methyl-1 H-indol-5-yl)methyl]-2,7-diazaspiro[4.4]nonane-2-carboxylate (intermediate **I36),** 131 mg (0.332 mmol), in 1,4-dioxane, 0.260 ml, was added hydrochloric acid (4 M in 1,4-dioxane), 1.50 ml (6.00 mmol). Stirring continued at room temperature for 2 hours. The reaction mixture was concentrated under vacuum to give the desired product, 88.0 mg (72% yield), and was used in the next step without purification.

1H NMR (400 MHz, DMSO-d6): δ [ppm] = 1.88-2.24 (m, 4H), 2.61 (s, 3H), 3.10-3.51 (m, 8H), 4.38-4.52 (m, 2H), 7.32 (d, 1H), 7.54 (s, 1H), 7.56 (d, 1H), 9.10-9.40 (m, 2H), 10.95 (d, 1H).

LC-MS (method 6): Rt = 0.64 min., 81%. MS (ESIpos): m/z = (M+H)+ 295.

Intermediate I38

tert-butyl 5-{[7-(tert-butoxycarbonyl)-2,7-diazaspiro[4.4]non-2-yl]methyl}-2-cyano-1H-indole-1 -carboxylate

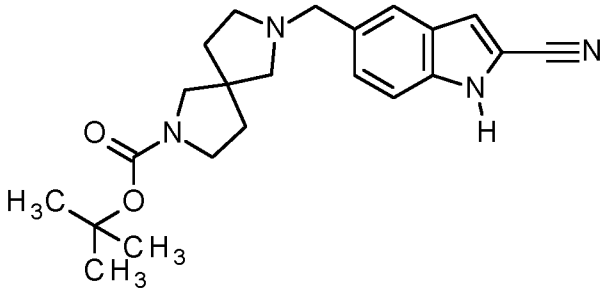


tert-Butyl 2,7-diazaspiro[4.4]nonane-2-carboxylate, 71.0 mg (0.316 mmol), was added to a solution of tert-butyl 5-(bromomethyl)-2-cyano-1 H-indole-1 -carboxylate (intermediate **I60),** 145 mg (0.316 mmol), in tetrahydrofuran, 6.00 ml, followed by potassium carbonate, 131 mg (0.947 mmol), under argon at room temperature. The reaction was heated at 50 °C for 16 hours, then quenched with water, and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered, and concentrated under vacuum. Purification by dry flash chromatography on silica gel 60 (eluent: heptane-ethyl acetate; 6:4, then ethyl acetate-methanol; 95:5) gave the desired product, 130 mg (86% yield).

LC-MS (method 5): Rt = 1.10 min. MS (ESIpos): m/z = (M+H)+ 481 .

Intermediate 139

tert-butyl 7-[(2-cyano-1H-indol-5-yl)methyl]-2,7-diazaspiro[4.4]nonane-2-carboxylate

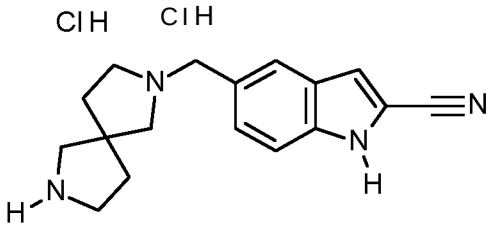


Sodium hydroxide (4 M in water), 1.69 ml (6.76 mmol), was added drop-wise to a solution of tert-butyl 5-{[7-(tert-butoxycarbonyl)-2,7-diazaspiro[4.4]non-2-yl]methyl}-2-cyano-1 H-indole-1-carboxylate (intermediate **I38),** 130 mg (0.27 mmol), in methanol, 5.00 ml, under argon at 0 °C. The reaction was stirred at 0 °C for 1 hour, and allowed to warm to room temperature. The reaction was diluted with water, and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered, and concentrated to give the desired product, 91.0 mg (88% yield). The product was used directly in the next step without purification.

LC-MS (method 5): Rt = 0.89 min., 68%. MS (ESIpos): m/z = (M+H)+ 381 .

Intermediate I40

5-(2,7-diazaspiro[4.4]non-2-ylmethyl)-1 H-indole-2-carbonitrile dihydrochloride



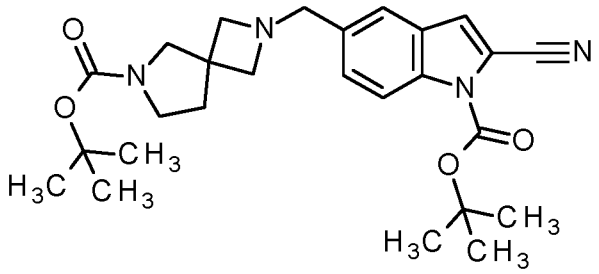
Hydrogen chloride (4 M in 1,4-dioxane), 3.00 ml, was added to tert-butyl 7-[(2-cyano-1 H-indol-5-yl)methyl]-2,7-diazaspiro[4.4]nonane-2-carboxylate (intermediate **I39),** 130 mg (0.342 mmol), at room temperature. The reaction was stirred for 45 minutes at room temperature, and concentrated to give the desired product, 160 mg (100% yield).

1H NMR (400 MHz, DMSO-d6): δ [ppm] = 1.33-1 .39 (m, 1H), 1.56 (s, 2H), 1.89-1 .95 (m, 2H), 2.14 (d, 1H), 2.84-2.93 (m, 2H), 3.19 (d, 2H), 3.68 (dt, 3H), 4.22-4.27 (m, 2H), 7.41 (m, 1H), 7.52 (q, 1H), 7.78-8.00 (m, 1H), 9.20 (br s, 1H), 10.60 (d, 1H).

LC-MS (method 5): Rt = 0.62 min., 85%. MS (ESIpos): m/z = (M+H)+ 299.

Intermediate 141

tert-butyl 5-{[6-(tert-butoxycarbonyl)-2,6-diazaspiro[3.4]oct-2-yl]methyl}-2-cyano-1 H-indole-1 -carboxylate

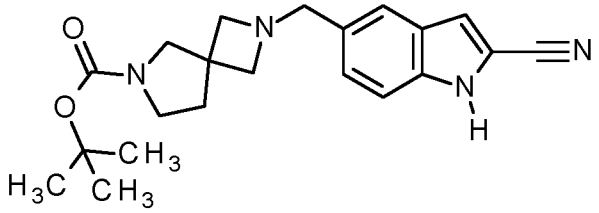


tert-Butyl 2,6-diazaspiro[3.4]octane-6-carboxylate, 81.0 mg (0.380 mmol), was added to a solution of tert-butyl 5-(bromomethyl)-2-cyano-1 H-indole-1 -carboxylate (intermediate **I60),** 150 mg (0.380 mmol), in tetrahydrofuran, 6.00 ml, followed by potassium carbonate, 158 mg (1.14 mmol), at room temperature under argon . The reaction was heated at 50 °C for 16 hours, then quenched with water, and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered, and concentrated to give a residue. Purification by dry flash chromatography on silica gel 60 (eluent: heptane-ethyl acetate; 6:4, then ethyl acetate-methanol; 19:1) gave the desired product, 110 mg (62% yield).

LC-MS (method 5): Rt = 1.01 min., 83%. MS (ESI pos): m/z = (M+H)+ 467.

Intermediate I42

tert-butyl 2-[(2-cyano-1 H-indol-5-yl)methyl]-2,6-diazaspiro[3.4]octane-6-carboxylate

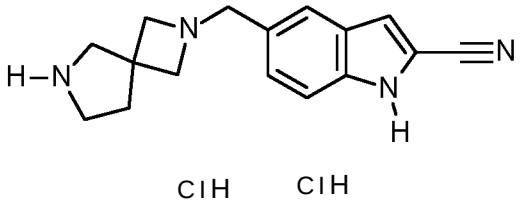


Sodium hydroxide (4 M in water), 1.47 ml (5.89 mmol), was added drop-wise to a solution of tert-butyl 5-{[6-(tert-butoxycarbonyl)-2,6-diazaspiro[3.4]oct-2-yl]methyl}-2-cyano-1 H-indole-1 -carboxylate (intermediate **141),** 110 mg (0.236 mmol), in methanol, 3.00 ml, under argon at 0 °C. The reaction was stirred at 0 °C for 30 minutes. The reaction was diluted with water, and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered, and concentrated to give the desired product, 83 mg (96% yield). The product was used directly in the next step without purification.

LC-MS (method 5): Rt = 0.82 min., 81%. MS (ESI pos): m/z = (M+H)+ 367.

Intermediate I43

5-(2,6-diazaspiro[3.4]oct-2-ylmethyl)-1 H-indole-2-carbonitrile dihydrochloride

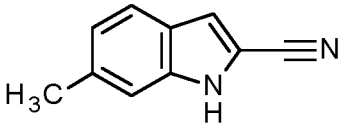


Hydrogen chloride (4 M in 1,4-dioxane), 3.00 ml, was added tert-butyl 2-[(2-cyano-1 H-indol-5-yl)methyl]-2,6-diazaspiro[3.4]octane-6-carboxylate (intermediate **I42),** 83.0 mg (0.226 mmol), at room temperature. The reaction was stirred for 50 minutes at room temperature, and concentrated to give the desired product (103 mg, 100%). The product was used directly in the next step without purification.

LC-MS (method 5): Rt = 0.56 min., 81%. MS (ESIpos): m/z = (M+H)+ 267.

Intermediate I44

6-methyl-1H-indole-2-carbonitrile



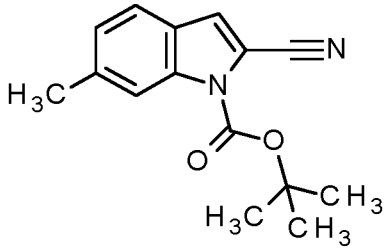
Phosphorus oxychloride, 2.68 ml (28.7 mmol), was added drop-wise to a suspension of 6-methyl-1 H-indole-2-carboxamide [CAS 893730-34-2], 1.00 g (5.74 mmol), under argon at room temperature. The reaction was heated at 80 °C for 16 hours, and concentrated under vacuum. The residue was suspended in water and basified with potassium carbonate. The precipitate was collected by filtration, washed with water, and dried to give the desired product, 900 mg (100% yield).

1H NMR (400 MHz, CDCh3): δ [ppm] = 2.47 (s, 3H), 7.05 (d, 1H), 7.15 (s, 1H), 7.19 (s, 1H), 7.54 (d, 1H), 8.47 (br s, 1H).

LC-MS (method 5): Rt = 0.81 min., 92%. MS (ESIneg): m/z = (M-H)- 155.

Intermediate I45

tert-butyl 2-cyano-6-methyl-1 H-indole-1 -carboxylate



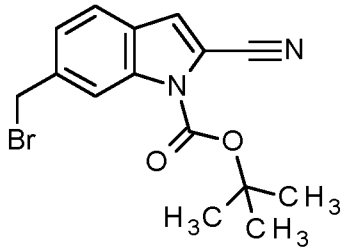
4-Dimethylaminopyridine, 106 mg (0.86 mmol), was added to a solution of 6-methyl-1 H-indole-2-carbonitrile (intermediate **I44),** 900 mg (5.76 mmol), in acetonitrile, 20.0 mil, followed by di-tert-butyl dicarbonate, 1.51 g (6.92 mmol), under argon at room temperature. The reaction was stirred at room temperature for 64 hours, then quenched with water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, and concentrated to give the desired product, 1.40 g (95%).

1H NMR (400 MHz, CDCh3): δ [ppm] = 1.71 (s, 9H), 2.50 (s, 3H), 7.15 (d, 1H), 7.29 (s, 1H), 7.49 (d, 1H), 8.07 (s, 1H).

LC-MS (method 5): Rt = 1.01 and 1.02 min., 95% non-ionising.

Intermediate I46

tert-butyl 6-(bromomethyl)-2-cyano-1 H-indole-1 -carboxylate



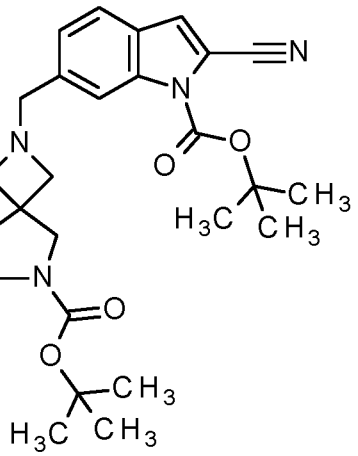
N-Bromosuccinimide, 833 mg (4.68 mmol), was added to a solution of tert-butyl 2-cyano-6-methyl-1 H-indole-1 -carboxylate (intermediate **I45),** 1.00 g (3.90 mmol), in carbon tetrachloride, 20.0 ml, followed by 2,2'-azobisisobutyronitrile, 32.0 mg (0.195 mmol), under argon at room temperature. The reaction was heated at 80 °C for 16 hours, and concentrated to give a residue. Purification by flash chromatography on silica gel 60 (eluent: heptane-ethyl acetate; 9:1) gave the desired product, 1.3 g (99%, 96:4 product-starting material by 1H NMR).

1H NMR (400 MHz, CDCh3): δ [ppm] = 1.73 (m, 9H), 4.63 (s, 2H), 7.31-7.33 (m, 1H), 7.37 (dd, 1H), 7.62 (m, 1H), 8.32 (s, 1H).

LC-MS (method 5): Rt = 0.99 and 1.03 min., 99% non-ionising.

Intermediate I47

tert-butyl 6-{[6-(tert-butoxycarbonyl)-2,6-diazaspiro[3.4]oct-2-yl]methyl}-2-cyano-1H-indole-1 -carboxylate

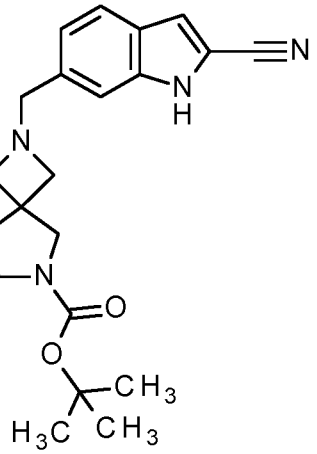


tert-Butyl 2,6-diazaspiro[3.4]octane-6-carboxylate, 32.0 mg (0.149 mmol), was added to a solution of tert-butyl 6-(bromomethyl)-2-cyano-1 H-indole-1 -carboxylate (intermediate **I46),** 50.0 mg (0.149 mmol), in tetrahydrofuran, 5.00 ml, followed by potassium carbonate, 62.0 mg (0.447 mmol), at room temperature under argon. The reaction was heated at 50 °C for 16 hours, then quenched with water, and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered, and concentrated to give a residue. Purification by dry flash chromatography on silica gel 60 (eluent: heptane-ethyl acetate-triethylamine; 30:19:1) gave the desired product, 50 mg (72% yield).

LC-MS (method 5): Rt = 1.02 min., 75%. MS (ESIpos): m/z = (M+H)+ 467.

Intermediate I48

tert-butyl 2-[(2-cyano-1 H-indol-6-yl)methyl]-2,6-diazaspiro[3.4]octane-6-carboxylate



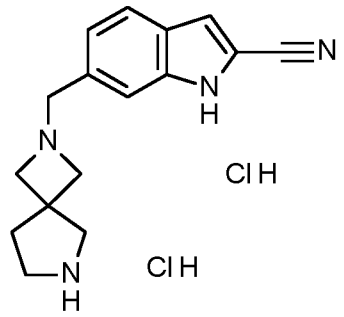
Sodium hydroxide (4 M in water), 0.67 ml (2.68 mmol), was added drop-wise to a solution of tert-butyl 6-{[6-(tert-butoxycarbonyl)-2,6-diazaspiro[3.4]oct-2-yl]methyl}-2-cyano-1 H-indole-1 -

carboxylate (intermediate **147),** 50.0 mg (0.107 mmol), in methanol, 1.00 ml, under argon at 0 °C. The reaction was stirred at 0 °C for 1 hour, and allowed to warm to room temperature. The reaction was diluted with water, and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered, and concentrated to give the desired product, 33 mg (84% yield). The product was used directly in the next step without purification.

LC-MS (method 5): Rt = 0.85 min., 77%. MS (ESIpos): m/z = (M+H)+ 367.

Intermediate I49

6-(2,6-diazaspiro[3.4]oct-2-ylmethyl)-1 H-indole-2-carbonitrile dihydrochloride

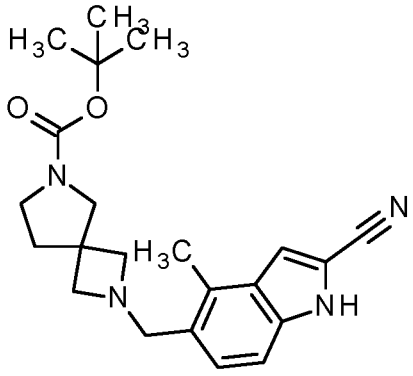


Hydrogen chloride (4M in 1,4-dioxane), 1.00 ml, was added to tert-butyl 2-[(2-cyano-1 H-indol-6-yl)methyl]-2,6-diazaspiro[3.4]octane-6-carboxylate (intermediate **I48),** 33.0 mg (0.09 mmol), at room temperature. The reaction was stirred for 45 minutes at room temperature, and concentrated to give the desired product (160 mg, 100% yield). The product was used directly in the next step without purification.

LC-MS (method 5): Rt = 0.58 min., 89%. MS (ESIpos): m/z = (M+H)+ 267.

Intermediate I50

tert-butyl 2-[(2-cyano-4-methyl-1 H-indol-5-yl)methyl]-2,6-diazaspiro[3.4]octane-6-carboxylate



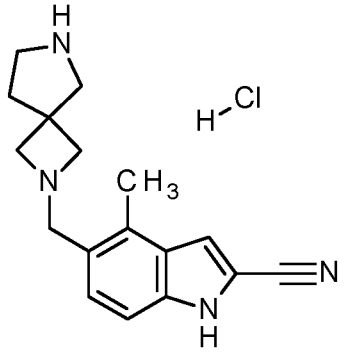
To a stirring solution of tert-butyl 2,6-diazaspiro[3.4]octane-6-carboxylate, 69.2 mg (0.326 mmol), and 5-formyl-4-methyl-1 H-indole-2-carbonitrile, 60.0 mg (0.326 mmol), in dichloromethane, 2.30 ml, was added sodium triacetoxyborohydride, 207 mg (0.977 mmol). Stirring continued at room temperature for 18 hours. The mixture was quenched with water and stirred at room temperature for 30 minutes. The product was extracted with dichloromethane, the organics were dried over sodium sulphate and concentrated under vacuum to give the desired product, 101 mg (81% yield) and was used in the next step without purification.

1H NMR (400 MHz, CDCl3): δ [ppm] = 1.44 (s, 9H), 1.98-2.03 (m, 2H), 2.50 (s, 3H), 3.98 (s, 4H), 3.27-3.49 (m, 2H), 3.42 (d, 2H), 3.70 (s, 2H), 7.12 (dd, 1H), 7.19 (s, 1H), 7.27 (d, 1H), 9.18 (d, 1H).

LC-MS (method 6): Rt = 0.86 min., 90%. MS (ESIpos): m/z = (M+H)+ 381 .

Intermediate 151

5-(2,6-diazaspiro[3.4]oct-2-ylmethyl)-4-methyl-1 H-indole-2-carbonitrile hydrochloride



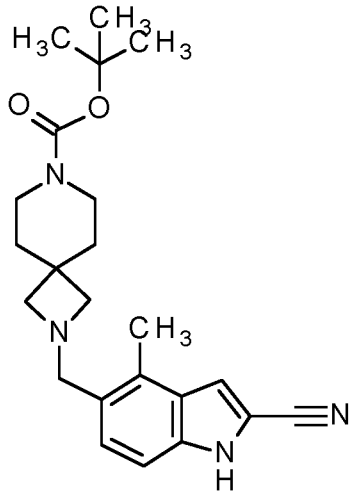
To a stirring solution of tert-butyl 2-[(2-cyano-4-methyl-1 H-indol-5-yl)methyl]-2,6-diazaspiro[3.4]octane-6-carboxylate (intermediate **I50),** 101 mg (0.265 mmol), in 1,4-dioxane, 0.422 ml, was added hydrochloric acid (4 M in 1,4-dioxane), 1.50 ml (6.00 mmol). Stirring continued at room temperature for 2 hours. The reaction mixture was concentrated under vacuum to give the desired product, 70.5 mg (94% yield), and was used in the next step without purification.

1H NMR (400 MHz, DMSO-d6): δ [ppm] = 2.16-2.78 (m, 2H), 2.59 (s, 3H), 3.06-3.16 (m, 2H), 3.46-3.47 (m, 2H), 3.86-3.90 (m, 1H), 3.99-4.04 (m, 1H), 4.15-4.22 (m, 2H), 4.50-4.48 (m, 2H), 7.31 (d, 1H), 7.47 (d, 1H), 7.53 (s, 1H), 9.32 (s, 1H), 9.43 (s, 1H), 11.16 (s, 1H).

LC-MS (method 6): Rt = 0.59 min., 97%. MS (ESIpos): m/z = (M+H)+ 281 .

Intermediate I52

tert-butyl 2-[(2-cyano-4-methyl-1H-indol-5-yl)methyl]-2,7-diazaspiro[3.5]nonane-7-carboxylate



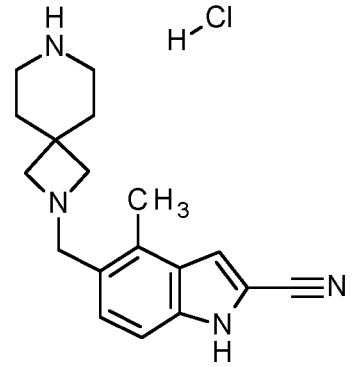
To a stirring solution of tert-butyl 2,7-diazaspiro[3.5]nonane-7-carboxylate, 73.7 mg (0.326 mmol), and 5-formyl-4-methyl-1 H-indole-2-carbonitrile, 60.0 mg (0.326 mmol), in dichloromethane, 2.30 ml, was added sodium triacetoxyborohydride, 207 mg (0.977 mmol). Stirring continued at room temperature for 18 hours. The mixture was quenched with water and stirred at room temperature for 30 minutes. The product was extracted with dichloromethane, the organics were dried over sodium sulphate and concentrated under vacuum to give the desired product, 85.0 mg (66%) and was used in the next step without purification.

1H NMR (400 MHz, CDCl3): δ [ppm] = 1.44 (s, 9H), 1.67-1 .69 (m, 4H), 2.49 (s, 3H), 3.06 (s, 2H), 3.29-3.32 (m, 4H), 3.73 (s, 2H), 7.12 (d, 1H), 7.18 (s, 1H), 7.28 (d, 1H), 9.08 (br s, 1H).

LC-MS (method 6): Rt = 0.64 min., 75%. MS (ESIpos): m/z = (M+H)+ 395.

Intermediate I53

5-(2,7-diazaspiro[3.5]non-2-ylmethyl)-4-methyl-1H-indole-2-carbonitrile hydrochloride



To a stirring solution of tert-butyl 2-[(2-cyano-4-methyl-1 H-indol-5-yl)methyl]-2,7-diazaspiro[3.5]nonane-7-carboxylate (intermediate **I52),** 70.0 mg (0.177 mmol), in 1,4-dioxane,

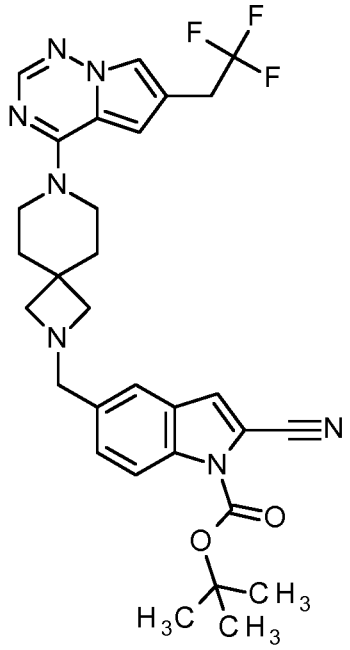
1.34 ml, was added hydrochloric acid (4 M in 1,4-dioxane), 3.61 ml (14.4 mmol). Stirring continued at room temperature for 2 hours. The reaction mixture was concentrated under vacuum to give the desired product, 77.0 mg (118%), and was used in the next step without purification.

1H NMR (400 MHz, DMSO-d6): δ [ppm] = 1.93-2.11 (m, 4H), 2.59 (s, 3H), 2.97 (d, 4H), 3.83-3.93 (m, 4H), 4.45 (d, 2H), 7.31 (d, 1H), 7.50-7.53 (m, 2H), 8.84 (s, 2H), 11.05 (s, 1H).

LC-MS (method 6): Rt = 0.63 min., 78%. MS (ESIpos): m/z = (M+H)+ 295.

Intermediate I54

tert-butyl 2-cyano-5-({7-[6-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}methyl)-1H-indole-1-carboxylate



To a stirring solution of tert-butyl 7-[6-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (intermediate **I93),** 87.4 mg (0.205 mmol), in 1,4-dioxane, 0.200 ml, was added hydrochloric acid (4 M in 1,4-dioxane), 0.510 ml (2.04 mmol). Stirring continued at room temperature for 2 hours. The reaction mixture was concentrated under vacuum to give 4-(2,7-diazaspiro[3.5]non-7-yl)-6-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazine hydrochloride (1:1). Assumed quantitative and was used in the next step without purification.

UPLC1-MS (method 6): Rt = 0.62 min., 58%. MS (ESIpos): m/z = (M+H)+ 326.

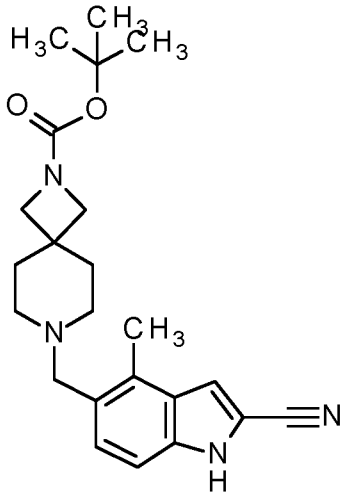
A stirred mixture of 4-(2,7-diazaspiro[3.5]non-7-yl)-6-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazine hydrochloride, -74.2 mg (assumed 0.205 mmol), tert-butyl 5-(bromomethyl)-2-cyano-1H-indole-1-carboxylate (intermediate **I60),** 58.7 mg (0.175 mmol), and potassium carbonate, 113 mg (0.818 mmol), in tetrahydrofuran, 5.00 ml, was heated to 50 °C for 4 hours.

The mixture was cooled to room temperature and partitioned between water and ethyl acetate. The product was extracted with ethyl acetate, the combined organics were dried over sodium sulphate and concentrated under vacuum to give the desired product, 117 mg (99% yield) yield and was used directly in the next step without purification.

LC-MS (method 6): Rt = 1.04 min., 45%. MS (ESIpos): m/z = (M+H)+ 580.

Intermediate I55

tert-butyl 7-[(2-cyano-4-methyl-1H-indol-5-yl)methyl]-2,7-diazaspiro[3.5]nonane-2-carboxylate



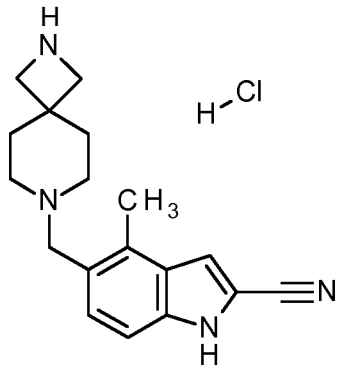
To a stirring solution of tert-butyl 2,7-diazaspiro[3.5]nonane-2-carboxylate, 64.6 mg (0.285 mmol), and 5-formyl-4-methyl-1 H-indole-2-carbonitrile, 52.6 mg (0.285 mmol), in dichloromethane, 2.00 ml, was added sodium triacetoxyborohydride, 181 mg (0.856 mmol). Stirring continued at room temperature for 18 hours. The mixture was quenched with water and stirred at room temperature for 30 minutes. The product was extracted with dichloromethane, the organics were dried over sodium sulphate and concentrated under vacuum to give the desired product, 70.0 mg (62% yield) and was used in the next step without purification.

1H NMR (400 MHz, CDCh3): δ [ppm] = 1.43 (s, 9H), 1.67-1 .73 (m, 4H), 2.25-2.43 (m, 4H), 2.52 (s, 3H), 3.50 (s, 2H), 3.60 (s, 4H), 7.17 (d, 1H), 7.22 (s, 1H), 7.30 (d, 1H), 8.57 (s, 1H).

LC-MS (method 6): Rt = 0.94 min., 69%. MS (ESIpos): m/z = (M+H)+ 395.

Intermediate I56

5-(2,7-diazaspiro[3.5]non-7-ylmethyl)-4-methyl-1H-indole-2-carbonitrile hydrochloride



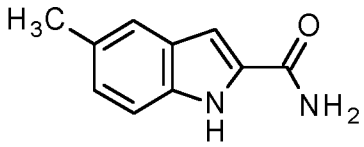
To a stirring solution of tert-butyl 7-[(2-cyano-4-methyl-1 H-indol-5-yl)methyl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (intermediate **I55),** 70.0 mg (0.177 mmol), in 1,4-dioxane, 1.34 ml, was added hydrochloric acid (4 M in 1,4-dioxane), 3.61 ml (14.4 mmol). Stirring continued at room temperature for 2 hours. The reaction mixture was concentrated under vacuum to give the desired product, 81.0 mg (113%), and was used in the next step without purification.

1H NMR (400 MHz, DMSO-d6): δ [ppm] = 1.95 (t, 2H), 2.13 (d, 2H), 2.56 (s, 3H), 3.02 (q, 2H), 2.22 (d, 2H), 3.65 (t, 2H), 3.77 (t, 2H), 4.28 (d, 2H), 7.33 (d, 1H), 7.54-7.56 (m, 2H), 9.18 (s, 2H), 10.17 (s, 1H)

LC-MS (method 6): Rt = 0.60 min., 80%. MS (ESIpos): m/z = (M+H)+ 295.

Intermediate I57

5-methyl-1H-indole-2-carboxamide



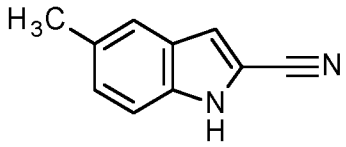
Thionyl chloride, 0.60 ml (8.22 mmol), was added drop-wise to a solution of 5-methyl-1 H-indole-2-carboxylic acid [CAS 10241-97-1], 1.20 g (6.85 mmol), in chloroform, 12.0 ml, under argon at room temperature. The reaction was heated at 60 °C for 2 hours. The reaction was quenched by drop-wise addition into ammonium hydroxide and ice. The precipitate was collected by filtration, washed once with water, and dried to give the desired product, 910 mg (76% yield).

1H NMR (400 MHz, DMSO-d6): δ [ppm] = 2.32 (s, 3H), 6.86-6.98 (m, 2H), 7.25-7.32 (m, 3H), 7.89 (s, 1H), 11.38 (s, 1H).

LC-MS (method 5): Rt = 0.64 min., 100%. Non-ionising.

Intermediate 158

5-methyl-1H-indole-2-carbonitrile



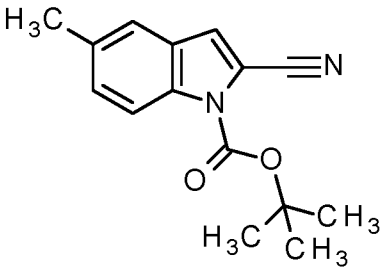
Phosphorus oxychloride, 2.40 ml (26.1 mmol), was added drop-wise to a suspension of 5-methyl-1 H-indole-2-carboxamide (intermediate **I57),** 910 mg (5.22 mmol), under argon at room temperature. The reaction was heated at 80 °C for 7 hours, and quenched by drop-wise addition to ice-water. After stirring for 1 hour, the mixture was basified with sodium hydrogen carbonate. The precipitate was collected by filtration, washed with water, and dried to give the desired product, 609 mg (75%).

1H NMR (400 MHz, CDCh3): δ [ppm] = 2.44 (s, 3H), 7.1 1 (d, 1H), 7.21 (dd, 1H), 7.29 (s, 1H), 7.44 (s, 1H), 8.45 (br s, 1H).

LC-MS (method 5): Rt = 0.81 min., 96%. MS (ESIneg): m/z = (M-H)- 155.

Intermediate I59

tert-butyl 2-cyano-5-methyl-1 H-indole-1 -carboxylate



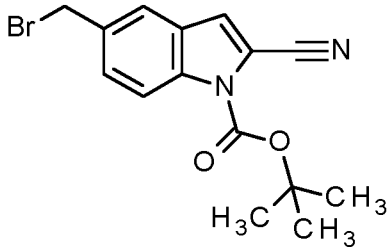
4-Dimethylaminopyridine, 71.5 mg (0.590 mmol), was added to a solution of 5-methyl-1 H-indole-2-carbonitrile (intermediate **I58),** 609 mg (3.90 mmol), in acetonitrile, 15.0 ml, followed by di-tert-butyl dicarbonate, 1.02 g (4.68 mmol), under argon at room temperature. The reaction was stirred at room temperature for 16 hours, then quenched with water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated to give the desired product, 976 mg (92% yield).

1H NMR (400 MHz, CDCh3): δ [ppm] = 1.71 (s, 9H), 2.44 (s, 3H), 7.25 (s, 1H), 7.31 (dd, 1H), 7.39 (s, 1H), 8.09 (d, 1H).

LC-MS (method 5): Rt = 1.02 min., 94%. Non-ionising.

Intermediate I60

tert-butyl 5-(bromomethyl)-2-cyano-1 H-indole-1 -carboxylate



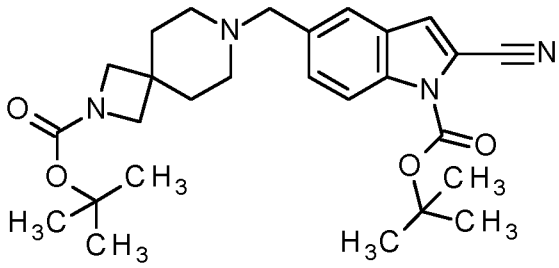
N-Bromosuccinimide, 450 mg (2.53 mmol), was added to a solution of tert-butyl 2-cyano-5-methyl-1 H-indole-1 -carboxylate (intermediate **I59),** 540 mg (2.1 1 mmol), in carbon tetrachloride, 20.0 ml, followed by 2,2'-azobisisobutyronitrile, 17.3 mg (0.105 mmol), under argon at room temperature. The reaction was heated at 80 °C for 16 hours, and concentrated under vacuum. Purification by flash chromatography on silica gel 60 (eluent: heptane-ethyl acetate; 9:1) gave the desired product, 578 mg (82%, 85:15 product-starting material by 1H NMR).

1H NMR (400 MHz, CDCh3): δ [ppm] = 1.72 (s, 9H), 4.60 (s, 2H), 7.31 (s, 1H), 7.53 (dd, 1H), 7.64 (s, 1H), 8.21 (d, 1H).

LC-MS (method 5): Rt = 0.98 min., 72% non-ionising.

Intermediate 161

tert-butyl 5-{[2-(tert-butoxycarbonyl)-2,7-diazaspiro[3.5]non-7-yl]methyl}-2-cyano-1 H-indole-1 -carboxylate

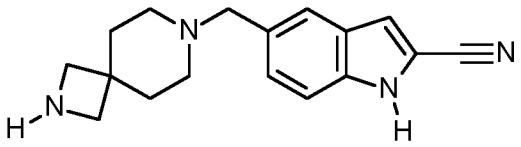


tert-Butyl 2,7-diazaspiro[3.5]nonane-2-carboxylate, 86.0 mg (0.380 mmol), was added to a solution of tert-butyl 5-(bromomethyl)-2-cyano-1 H-indole-1 -carboxylate (intermediate **I60),** 150 mg (0.380 mmol), in tetrahydrofuran, 7.50 ml, followed by potassium carbonate, 158 mg (1.14 mmol), at room temperature under argon. The reaction was heated at 50 °C for 16 hours, then quenched with water, and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered, and concentrated under vacuum. Purification by dry flash chromatography on silica gel 60 (eluent: heptane-ethyl acetate; 6:4, then ethyl acetate-methanol; 95:5) gave the desired product, 113 mg (62% yield).

LC-MS (method 5): Rt = 1.09 min., 96%. MS (ESIpos): m/z = (M+H)+ 481 .

Intermediate 162

5-(2,7-diazaspiro[3.5]non-7-ylmethyl)-1 H-indole-2-carbonitrile dihydrochloride



cm cm

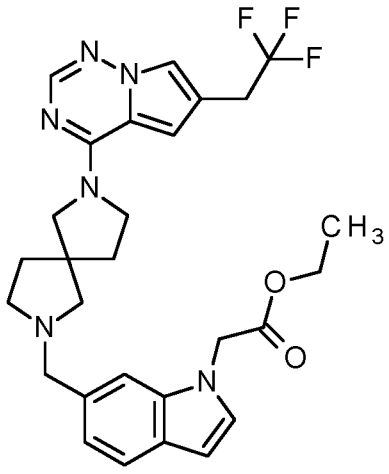
Hydrogen chloride (4 M in 1,4-dioxane), 3.00 ml, was added to tert-butyl 7-[(2-cyano-1 H-indol-5-yl)methyl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (intermediate **161),** 106 mg (0.279 mmol), at room temperature. The reaction was stirred for 45 minutes at room temperature, and concentrated to give the desired product, 160 mg (100%).

1H NMR (400 MHz, DMSO-d6): δ [ppm] = 1.56 (s, 2H), 1.87-1 .95 (m, 2H), 2.14 (d, 2H), 2.89 (q, 2H), 3.20 (d, 2H), 3.69 (dt, 4H), 4.23-4.27 (m, 2H), 7.42-7.43 (m, 1H), 7.51 (s, 1H), 7.83 (s, 1H), 9.08 (br s, 2H), 10.50 (br s, 1H).

LC-MS (method 5): Rt = 0.59 min., 73%. MS (ESIpos): m/z = (M+H)+ 381 .

Intermediate I63

ethyl [6-({7-[6-(2,2,2-trifluoroethyl)pyrrolo[2,1 -n[1,2,4]triazin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indol-1 -yl]acetate



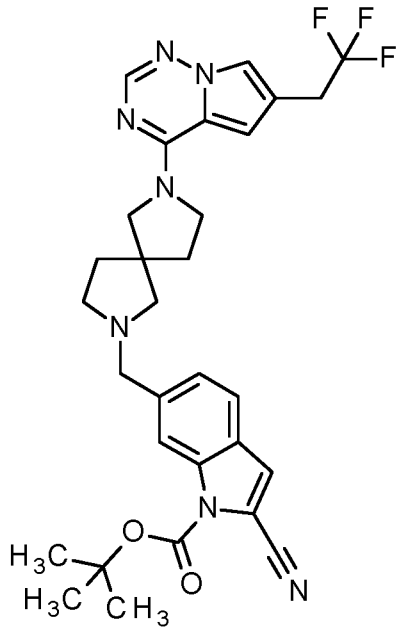
To a stirring solution of 4-[7-(1 H-indol-6-ylmethyl)-2,7-diazaspiro[4.4]non-2-yl]-6-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1 ,2,4]triazine (example **79),** 57.0 mg (0.125 mmol), in N,N-dimethylformamide, 0.500 ml, at 0 °C was added sodium hydride (60% in oil), 6.00 mg (0.150 mmol). After stirring for 30 minutes, ethyl chloroacetate, 16.1 µl (0.150 mmol), was added and the mixture was stirred at 0 °C for 1 hour. The reaction mixture was quenched with water and

extracted with ethyl acetate. The combined organics were washed with brine, dried over magnesium sulphate and concentrated under vacuum to give the desired product, 66.0 mg (97% yield) and was used directly in the next step without purification.

LC-MS (method 6): Rt = 0.90 min., 67%. MS (ESIpos): m/z = (M+H)+ 541 .

Intermediate I64

tert-butyl 2-cyano-6-({7-[6-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-1-carboxylate

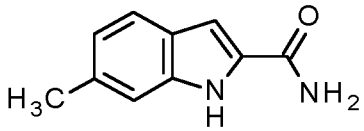


A suspension of tert-butyl 6-(bromomethyl)-2-cyano-1H-indole-1-carboxylate (intermediate **I46),** 50 mg (0.149 mmol), 4-(2,7-diazaspiro[4.4]non-2-yl)-6-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazine hydrochloride (intermediate **1106),** 70.2 mg (194 mmol), and potassium carbonate, 61.8 mg (0.447 mmol), in tetrahydrofuran, 5.00 ml, was heated at 50 °C for 18 hours. The reaction was cooled to room temperature, diluted with water and extracted into ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and concentrated to give a residue. The residue was purified by flash chromatography on silica gel 60 (eluent: heptanes-ethyl acetate/2% triethylamine 7:3 to 2-propanol-ethyl acetate/2% triethylamine 1:9) to give tert-butyl 2-cyano-6-({7-[6-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-1-carboxylate, 36 mg (42% yield), which was used without further purification.

LC-MS (method 6): Rt = 1.04 min., 57%. MS (ESIpos): m/z = (M+H)+ 580.

Intermediate I65

6-methyl-1H-indole-2-carboxamide

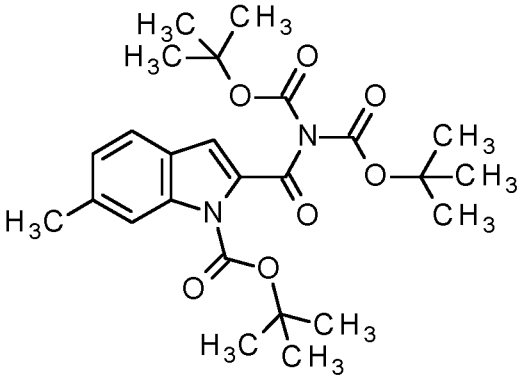


Thionyl chloride, 4.50 ml (61.6 mmol), was added drop-wise to a solution of 6-methyl-1 H-indole-2-carboxylic acid [CAS 18474-59-4], 1.20 g (6.85 mmol), in chloroform, 180 ml, under argon at room temperature. The reaction was heated at 60 °C for 2 hours. The reaction was quenched by drop-wise addition into ammonium hydroxide and ice, with ice bath cooling. The precipitate was collected by filtration, washed once with water, and dried to give the desired product, 7.95 g (89% yield). The product was used directly in the next step without purification.

LC-MS (method 5): Rt = 0.60 min., 100%. MS (ESIneg): m/z = (M-H)- 173.

Intermediate I66

tert-butyl 2-[bis(tert-butoxycarbonyl)carbamoyl]-6-methyl-1 H-indole-1 -carboxylate



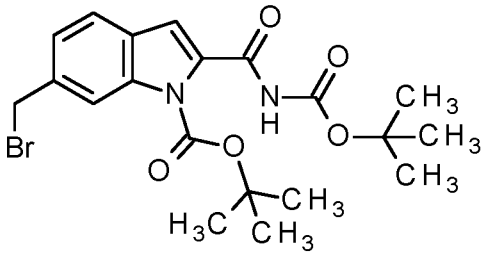
To a solution of 6-methyl-1 H-indole-2-carboxamide (intermediate **I65),** 1.00 g (5.74 mmol), in acetonitrile, 20.0 ml, was added 4-dimethylaminopyridine, 105 mg (0.861 mmol), and di-tert-butyl dicarbonate, 1.50 g (6.89 mmol), and stirred at room temperature for 18 hours. The reaction was diluted with water and brine, extracted into ethyl acetate, the combined organic layers dried over sodium sulfate, filtered and concentrated to give a residue. The residue was purified by flash chromatography on silica gel 60 (eluent: ethyl acetate-heptane 2:8) to give the desired product, 710 mg (33% yield).

1H NMR (400 MHz, CDCh3): δ [ppm] = 1.42 (s, 18H), 1.62 (s, 9H), 2.48 (s, 3H), 6.86 (s, 1H), 7.08 (d, 1H), 7.44 (d, 1H), 8.01 (s, 1H);

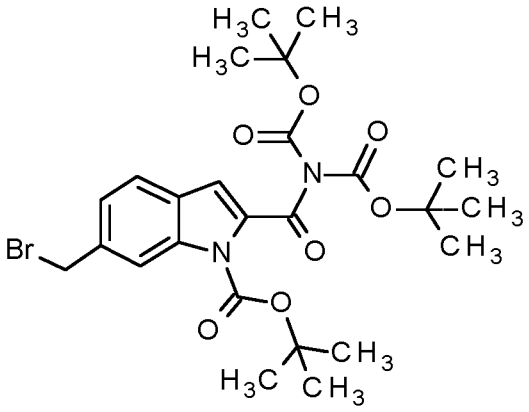
LC-MS (method 5): Rt = 1.14 min., 88%. MS (ESIpos): m/z = (M+H)+ no ionisation.

Intermediate I67 and intermediate I68

tert-butyl 6-(bromomethyl)-2-[(tert-butoxycarbonyl)carbamoyl]-1 H-indole-1 -carboxylate (I67)



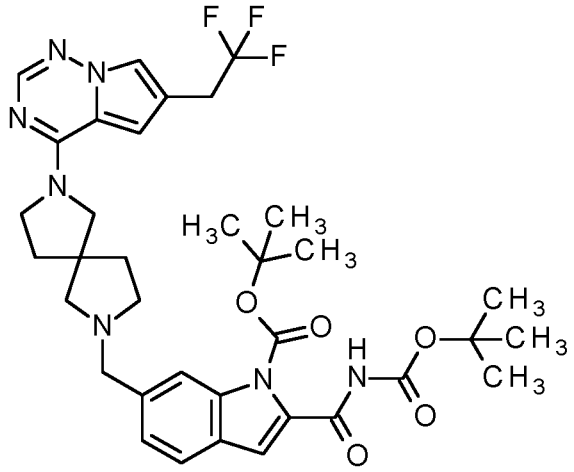
tert-butyl 2-[bis(tert-butoxycarbonyl)carbamoyl]-6-(bromomethyl)-1 H-indole-1 -carboxylate (I68)



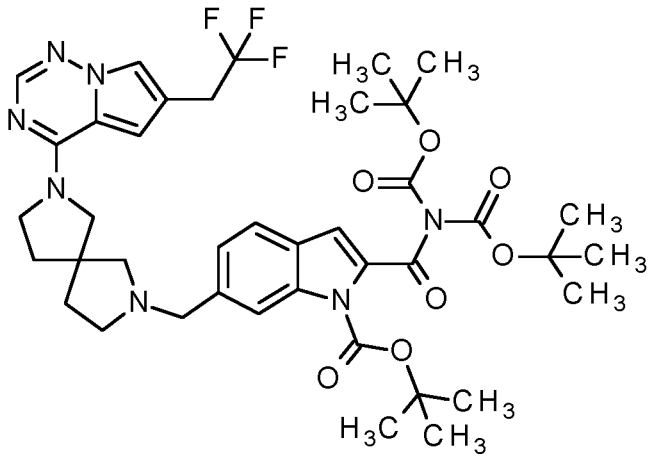
To a solution of tert-butyl 2-[(di-tert-butoxycarbonyl)carbamoyl]-6-methyl-1 H-indole-1 -carboxylate (intermediate **I66),** 200 mg (0.534 mmol), and N-bromosuccinimide, 114 mg (0.641 mmol), in carbon tetrachloride, 15.0 ml, was added 2,2'-azobisisobutyronitrile, 4.39 mg (26.7 μηοl), and heated at 80 °C for 18 hours. The reaction was cooled to room temperature and concentrated under vacuum to give a residue. A portion of the residue (190 mg), was purified by flash chromatography on silica gel 60 (eluent: ethyl acetate-heptane 1:99 to 25:75) to give a 2:1 mixture of tert-butyl 6-(bromomethyl)-2-[(tert-butoxycarbonyl)carbamoyl]-1 H-indole-1-carboxylate (I67) and tert-butyl 2-[bis(tert-butoxycarbonyl)carbamoyl]-6-(bromomethyl)-1 H-indole-1 -carboxylate **(I68),** 67.4 mg.

Intermediate I69 and intermediate I70

tert-butyl 4-{[2-cyano-4-methyl-5-({2-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indol-1 -yl]methyl}-1 H-pyrazole-1 -carboxylate (I69)



tert-butyl 2-[bis(tert-butoxycarbonyl)carbamoyl]-6-({7-[6-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-1-carboxylate (I70)



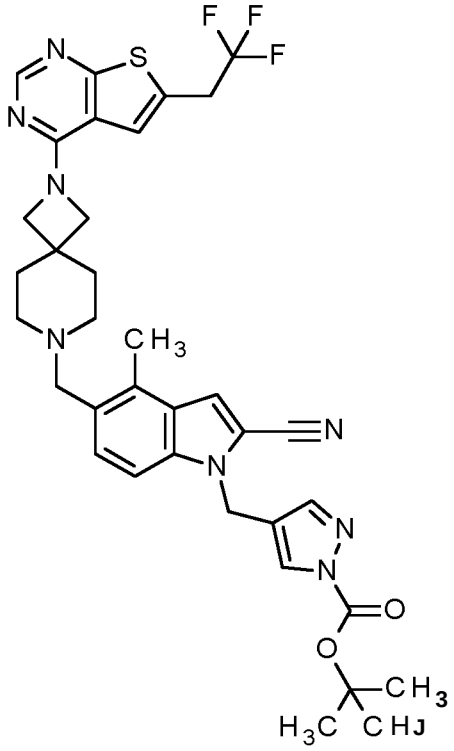
tert-butyl 2-[bis(tert-butoxycarbonyl)carbamoyl]-6-(bromomethyl)-1H-indole-1-carboxylate (intermediate I68) and tert-butyl 6-(bromomethyl)-2-[(tert-butoxycarbonyl)carbamoyl]-1H-indole-1-carboxylate (intermediate I67), 67.4 mg (0.149 mmol), was added 4-(2,7-diazaspiro[4.4]non-2-yl)-6-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazine hydrochloride (intermediate 106), 48.3 mg (0.133 mmol), potassium carbonate, 103 mg (0.743 mmol), and tetrahydrofuran, 2.35 ml, and heated at 40 °C for 1 hour, then at reflux for 4 hours. The reaction was cooled to room temperature, water added and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and concentrated to give a residue. The residue was purified by flash chromatography on silica gel 60 (eluent: dichloromethane-12% ammonia/methanol 1:0 to 39:1) to give a 1.13:1 mixture of the desired products, 32.9 mg (30% over 2 steps).

1H NMR (400 MHz, CDCh3, assumed 1:1 mixture): δ [ppm] = 1.38 (s, 9H), 1.41 (s, 18H), 1.60 (s, 18H), 1.82-2.01 (m, 10H), 2.43-2.58 (m, 2H), 2.67-2.83 (m, 2H), 3.39 (qn, 4H), 3.53 (d, 2H), 3.61-3.69 (m, 2H), 3.73 (s, 4H), 3.75-3.84 (m, 2H), 3.91-4.01 (m, 2H), 5.54 (br s, 2H), 6.65 (br d, 2H), 6.81 (d, 2H), 7.25 (m, masked by solvent peak assumed 2H), 7.45-7.51 (m, 4H), 7.79 (s, 2H), 7.99 (br s, 1H), 8.10 (d, 2H);

LC-MS (method 6): Rt = 0.99 min., 51%. MS (ESIpos): m/z = (M+H)+ 698, Rt = 1.14 min., 44%. MS (ESIpos): m/z = (M+H)+ 798.

Intermediate 171

tert-butyl 4-{[2-cyano-4-methyl-5-({2-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin -4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indol-1 -yl]methyl}-1 H-pyrazole-1 -carboxylate



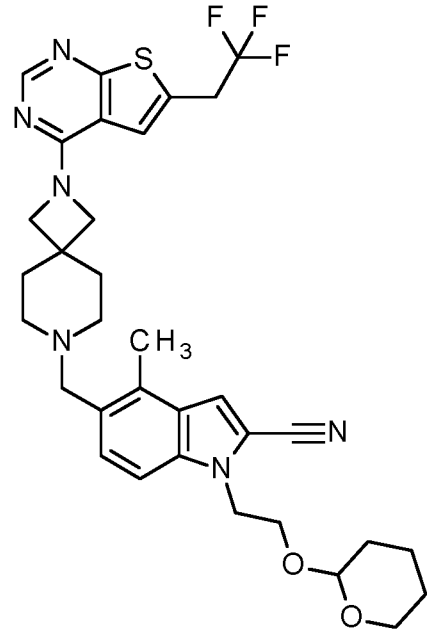
To a solution of 4-methyl-5-({2-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carbonitrile (example **29)** (95.0 mg, 186 μηηοl) in DMF (2 ml) was added caesium carbonate (182 mg, 558 μηηοl) and then tert-butyl 4-(bromomethyl)-l H-pyrazole-1 -carboxylate [CAS 530144-72-0] (72.9 mg, 279 μπιοl). After stirring for 4 h at RT the reaction mixture was diluted with water and extracted 3x with ethyl acetate. The collected organic phases were dried with sodium sulfate. After removal of the solvent by evaporation 132 mg crude product were obtained which was used without further purification. A sample (25 mg) of the crude proct was purified by prep. HPLC. The product rich fractions were pooled, the solvent was removed under reduced pressure and freeze dried to yield the desired product (10 mg, 7 % yield).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.363 (0.53), 1.535 (16.00), 1.754 (0.81), 2.322 (0.41), 2.326 (0.51), 2.332 (0.45), 2.518 (1.40), 2.522 (0.89), 3.495 (1.37), 4.045 (0.65), 4.072 (0.63), 5.436 (1.52), 7.314 (0.65), 7.335 (0.69), 7.480 (1.00), 7.554 (0.65), 7.576 (0.49), 7.587 (1.44), 7.589 (1.35), 7.680 (1.44), 8.232 (1.29), 8.31 1 (2.60).

LC-MS (method 8): Rt = 1.54 min; MS (ESIpos): m/z = 691 [M+H]+

Intermediate 172

4-methyl-1-[2-(tetrahydro-2H^yran-2-yloxy)ethyl]-5-({2-[6-(2,2,2-trifluoroeth^ l)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carbonitrile



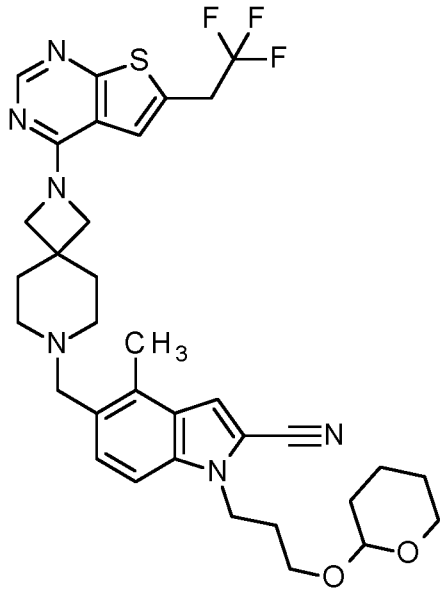
To a stirred solution of 4-methyl-5-({2-[6-(2 ,2,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carbonitrile (example **29)** (100 mg, 196 μηηοl) in DMF (2.0 ml) was added 2-(2-bromoethoxy)tetrahydro-2H-pyran (44.4 μl, 0.294 mmol) followed by caesium carbonate (191 .4 mg, 0.588 mmol). The reaction mixture was stirred overnight at RT. The reaction mixture was filtered, evaporated and and purified by preparative HPLC. The desired product was obtained as a solid (18 mg, 14 % yield).

LC-MS (method 8): Rt = 1.56 min; m/z = 639 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.145 (1.09), 1.268 (1.87), 1.354 (3.90), 1.375 (5.15), 1.458 (1.56), 1.474 (2.42), 1.505 (1.17), 1.608 (1.64), 1.624 (1.40), 1.760 (7.34), 2.323 (5.23), 2.327 (6.48), 2.331 (5.46), 2.665 (3.67), 2.669 (4.84), 2.673 (3.59), 3.226 (5.31), 3.245 (2.73), 3.253 (2.50), 3.275 (0.86), 3.471 (0.94), 3.506 (9.05), 3.540 (0.94), 3.632 (1.09), 3.641 (1.80), 3.657 (2.26), 3.669 (2.26), 3.682 (1.40), 3.850 (2.42), 3.860 (2.97), 3.877 (2.26), 4.020 (2.42), 4.047 (5.46), 4.076 (5.31), 4.103 (2.26), 4.464 (6.01), 4.474 (4.37), 4.487 (4.68), 4.498 (3.98), 7.284 (4.76), 7.305 (6.17), 7.417 (5.23), 7.439 (3.82), 7.482 (7.96), 7.508 (11.55), 8.313 (16.00).

Intermediate I73

4-methyl-1-[3-(tetrahydro-2H^yran-2-yloxy)prop yl]-5-({2-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carbonitrile



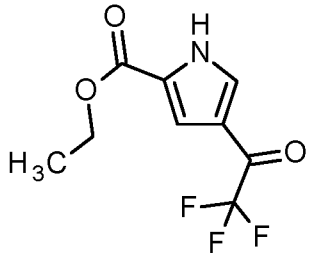
According to the preparation of intermediate **I72,** intermediate **I73** was prepared starting from example **29** (100 mg, 196 μηοl) by reacting with 2-(3-bromopropoxy)tetrahydro-2H-pyran (50 μl, 290 μηοl). After purification by preparative HPLC the desired product was obtained as a solid (23 mg, 17 % yield).

LC-MS (method 8): Rt = 1.61 min; m/z = 653 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.145 (0.87), 1.266 (0.46), 1.426 (7.01), 1.437 (6.55), 1.563 (1.74), 1.580 (3.19), 1.609 (1.62), 1.696 (2.43), 1.709 (2.72), 1.762 (9.91), 2.004 (4.52), 2.019 (6.61), 2.034 (4.64), 2.074 (1.57), 2.327 (5.86), 2.669 (3.54), 3.188 (1.45), 3.203 (2.96), 3.213 (2.38), 3.229 (3.30), 3.244 (1.51), 3.364 (2.96), 3.377 (3.13), 3.502 (15.25), 3.577 (1.74), 3.591 (3.54), 3.604 (2.84), 3.616 (3.25), 3.632 (2.90), 3.660 (3.25), 3.680 (1.91), 4.020 (3.07), 4.048 (6.90), 4.076 (6.67), 4.103 (2.90), 4.371 (4.41), 4.388 (8.35), 4.405 (4.29), 4.463 (6.38), 7.295 (4.93), 7.316 (7.54), 7.383 (6.78), 7.404 (4.23), 7.484 (9.45), 7.527 (13.80), 8.313 (16.00).

Intermediate I74

ethyl 4-(trifluoroacetyl)-1H-pyrrole-2-carboxylate

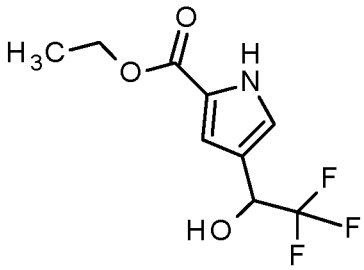


To a stirred solution of ethyl 1H-pyrrole-2-carboxylate [CAS 2199-43-1], 100 g (719 mmol), in N,N-dimethylformamide, 1.00 L, was added trifluoroacetic anhydride, 132 ml (934 mmol). The mixture was heated to 80 °C for 18 hours. The mixture was allowed to cool to room temperature and then poured in to water and stirred for 15 minutes. The resultant precipitate was collected by filtration under vacuum then dried in a vacuum oven overnight (50 °C) to give the desired product, 82.0 g (49%), as a 1:2 mixture of isomers, ethyl 4-(trifluoroacetyl)-1 H-pyrrole-2-carboxylate and ethyl 3-(trifluoroacetyl)-1 H-pyrrole-2-carboxylate. A second crop gave the desired product, 10.4 g (6%), as a 5:1 mixture of isomers (ethyl 4-(trifluoroacetyl)-1 H-pyrrole-2-carboxylate and ethyl 3-(trifluoroacetyl)-1 H-pyrrole-2-carboxylate) which was used in the next step without purification.

Desired isomer: ethyl 4-(trifluoroacetyl)-1 H-pyrrole-2-carboxylate: 1H NMR (400 MHz, CDCI-3): δ [ppm] = 1.38 (t, 3H), 4.38 (q, 2H), 7.42 (s, 1H), 7.73 (s, 1H), 9.91 (br s, 1H); LC-MS (method 6): Rt = 0.76 min., 99%. MS (ESIneg) m/z = (M-H)- 234. Undesired isomer: ethyl 3-(trifluoroacetyl)-l H-pyrrole-2-carboxylate: 1H NMR (400 MHz, CDCh3): δ [ppm] = 1.39 (t, 3H), 4.37 (q, 2H), 6.95 (dd, 1H), 7.14-7.16 (m, 1H), 10.00 (br s, 1H).

Intermediate I75

ethyl 4-[(1S)-2,2,2-trifluoro-1 -hydroxyethyl]-1 H-pyrrole-2-carboxylate



To a stirred solution of a 5:1 mixture of ethyl 4-(trifluoroacetyl)-1 H-pyrrole-2-carboxylate and ethyl 3-(trifluoroacetyl)-1 H-pyrrole-2-carboxylate, 10.4 g (44.2 mmol), in methanol, 68.0 ml, and tetrahydrofuran, 160 ml, was added sodium borohydride, 2.51 g (66.3 mmol) in portions at 0 °C under argon. The reaction mixture was stirred at 0 °C for 1 hour. The reaction mixture was diluted with water and the product was extracted into ethyl acetate. The combined organics were washed with brine, dried over sodium sulfate and concentrated under vacuum. The

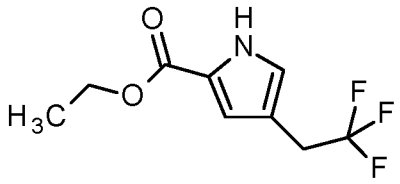
residue was purified by flash chromatography on silica gel 60 (eluent: heptane-ethyl acetate 85:15 to 60:30) to give the desired product, 5.80 g (55% yield).

1H NMR (400 MHz, CDCh3): δ [ppm] = 1.35 (t, 3H), 4.32 (q, 2H), 4.97-5.03 (m, 1H), 6.99 (s, 1H), 7.08 (s, 1H), 9.15 (br s, 1H);

LC-MS (method 6): Rt = 0.65 min., 97%. MS (ESIneg) m/z = (M-H)- 236.

Intermediate I76

ethyl 4-(2,2,2-trifluoroethyl)-1 H-pyrrole-2-carboxylate



To a stirred solution of ethyl 4-(2,2,2-trifluoro-1-hydroxyethyl)-1 H-pyrrole-2-carboxylate (intermediate **I75),** 10.7 g (45.1 mmol), and triethylamine, 9.43 ml (67.7 mmol), in dichloromethane, 550 ml, was added methanesulfonyl chloride, 5.24 ml (67.7 mmol). The reaction mixture was stirred at 0 °C for 2 hours. The reaction was quenched with water and extracted with dichloromethane. The organics were dried over magnesium sulfate and concentrated under vacuum keeping below 30 °C. The residue was used directly in the next step without purification.

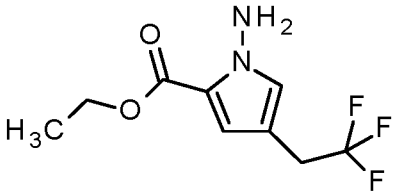
To a solution of ethyl 4-{2,2,2-trifluoro-1-[(methylsulfonyl)oxy]ethyl}-1 H-pyrrole-2-carboxylate (assumed 45.1 mmol), in ethanol, 535 ml, was added sodium borohydride, 2.56 g (67.7 mmol), in portions at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour. The reaction was quenched with water and extracted with ethyl acetate. The organics were dried over magnesium sulfate and concentrated under vacuum to give the desired product, 8.60 g (86% yield). The product was used in the next step without purification.

1H NMR (400 MHz, CDCh3): δ [ppm] = 1.35 (t, 3H), 3.25 (q, 2H), 4.31 (q, 2H), 6.86 (s, 1H), 6.90 (s, 1H), 9.13 (br s, 1H);

LC-MS (method 5): Rt = 0.79 min., 75%. MS (ESIneg) m/z = (M-H)- 220.

Intermediate I77

ethyl 1-amino-4-(2,2,2-trifluoroethyl)-1 H-pyrrole-2-carboxylate



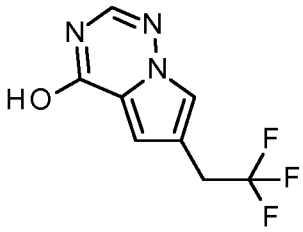
To a vigorously stirred mixture of ethyl 4-(2,2,2-trifluoroethyl)-1 H-pyrrole-2-carboxylate (intermediate **I76),** 8.60 g (38.9 mmol), ammonium chloride, 12.9 g (241 mmol), aqueous sodium hydroxide (28%), 112 ml, Aliquat-336 (methyl tri-n-octylammonium chloride), 437 mg (1.08 mmol), ammonium hydroxide (28%), 36.0 ml, and tert-butyl methyl ether, 258 ml, was added drop-wise sodium hypochlorite solution (9%), 260 ml. The reaction mixture was then stirred at room temperature for 18 hours. The phases were separated and the aqueous discarded. To the vigorously stirred organic phase was added ammonium chloride, 12.9 g (241 mmol), aqueous sodium hydroxide (28%), 112 ml, Aliquat-336 (methyl tri-n-octylammonium chloride), 437 mg (1.08 mmol), and ammonium hydroxide (28%), 36.0 ml. Sodium hypochlorite solution (9%), 260 ml, was added drop-wise and stirred for a further 18 hours. The reaction mixture was diluted with diethyl ether and the phases separated. The organics were washed with 10% sodium thiosulfate solution, dried over magnesium sulphate and concentrated under vacuum to give the desired product, 7.60 g (79% yield). The product was used in the next step without purification.

1H NMR (400 MHz, CDCh3): δ [ppm] = 1.34 (t, 3H), 3.18 (q, 2H), 4.28 (q, 2H), 5.54 (s, 2H), 6.77 (d, 1H), 6.91 (d, 1H);

LC-MS (method 7): Rt = 2.07 min., 79%. MS (ESIpos): m/z = (M+H)+ 237.

Intermediate I78

6-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazin-4-ol



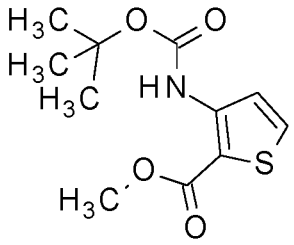
A solution of ethyl 1-amino-4-(2,2,2-trifluoroethyl)-1 H-pyrrole-2-carboxylate (intermediate **I77),** 1.14 g (4.83 mmol), formamidinium acetate, 552 mg (5.31 mmol), and N,N-diisopropylethylamine, 32.0 ml, in 1-butanol, 32.0 ml, was heated to reflux (120 °C) for 18 hours. The reaction mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel 60 (eluent: heptane-ethyl acetate 3:2 to 0:1) to give the desired product, 802 mg (77% yield).

1H NMR (400 MHz, CDCh3): δ [ppm] = 3.34-3.43 (m, 2H), 7.04 (s, 1H), 7.43 (d, 1H), 7.55 (s, 1H), 10.20 (br s, 1H);

LC-MS (method 6): Rt = 0.56 min., 89%. MS (ESIpos): m/z = (M+H)+ 218.

Intermediate I79

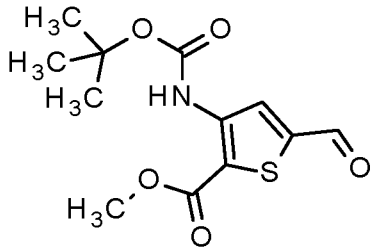
2-amino-5-(2,2-difluoroethyl)thiophene-3-carboxamide



Into a 5000-ml 4-necked round-bottom flask, was placed methyl 3-aminothiophene-2-carboxylate (300 g, 1.91 mol, 1.00 equiv) [CAS 22288-78-4], dichloromethane (3000 mL), TEA (288 g, 2.85 mol, 1.50 equiv), 4-dimethylaminopyridine (25 g, 204.63 mmol, 0.11 equiv), Di-ie/f-butyl dicarbonate (534 g, 2.45 mol, 1.28 equiv). The resulting solution was stirred overnight at room temperature. The reaction was then quenched by the addition of 2 L of water. The resulting solution was extracted with 500 ml of dichloromethane and the organic layers combined. The resulting mixture was washed with 1x1000 ml of brine. The resulting mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:50). This resulted in 200 g (41%) of methyl 3-[[(tert-butoxy)carbonyl]amino]thiophene-2-carboxylate as a white solid.

Intermediate I80

methyl 3-[(tert-butoxycarbonyl)amino]-5-formylthiophene-2 -carboxylate

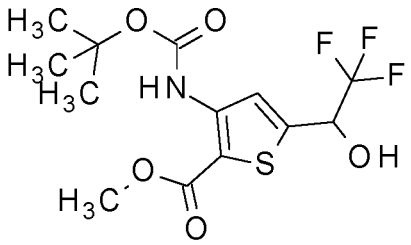


Into a 10-L 4-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed diisopropylamine (280 g, 2.77 mol, 3.60 equiv), tetrahydrofuran (3000 ml). This was followed by the addition of n-BuLi (1000 ml, 3.20 equiv) dropwise with stirring at -30°C and stirred 30 min at 0°C. To this was added a solution of methyl 3-[[(tert-

butoxy)carbonyl]amino]thiophene-2-carboxylate (intermediate **179)** (200 g, 777.28 mmol, 1.00 equiv) in tetrahydrofuran (500 ml) dropwise with stirring at -78°C and stirred 1 h. To the mixture was added piperidine-1 -carbaldehyde (532 g, 4.70 mol, 6.00 equiv) dropwise with stirring at -78°C. The resulting solution was stirred for 1 h at -78°C. The reaction was then quenched by the addition of 2 L of NH_4Cl (aq). The resulting solution was extracted with 2x2 L of ethyl acetate and the organic layers combined. The resulting mixture was washed with 2x500 ml of hydrogen chloride (3 mol/L). The resulting mixture was washed with 2x500 ml of brine. The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:20). This resulted in 200 g (90%) of methyl 3-[[(tert-butoxy)carbonyl]amino]-5-formylthiophene-2-carboxylate as a light yellow solid.

Intermediate 181

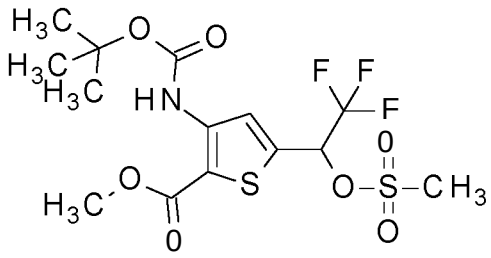
methyl 3-[(tert-butoxycarbonyl)amino]-5-(2,2,2-trifluoro-1 -hydroxyethyl)thiophene-2-carboxylate



Into a 3000-ml 4-necked round-bottom flask, was placed methyl 3-[[(tert-butoxy)carbonyl]amino]-5-formylthiophene-2-carboxylate (intermediate **I80)** (120 g, 420.59 mmol , 1.00 equiv), tetrahydrofuran (1500 ml), TBAF (31 g, 118.56 mmol, 0.28 equiv). This was followed by the addition of trimethyl(trifluoromethyl)silane [CAS 81290-20-21(120 g, 845.07 mmol, 2.00 equiv) dropwise with stirring at 0°C. The resulting solution was stirred overnight at room temperature. The reaction was then quenched by the addition of 1 L of water. The resulting solution was extracted with 2x500 ml of ethyl acetate and the organic layers combined. The resulting mixture was washed with 1x500 ml of water and 1x500 ml of brine. The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 160 g (crude) of desired product as red oil.

Intermediate I82

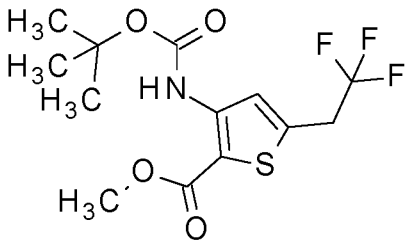
methyl 3-[(tert-butoxycarbonyl)amino]-5-{2,2,2-trifluoro-1 -[(methylsulfonyl)oxy]ethyl}-thiophene-2-carboxylate



Into a 3000-ml 4-necked round-bottom flask, was placed methyl 3-[[(tert-butoxy)carbonyl]amino]-5-(2,2,2-trifluoro-1-hydroxyethyl)thiophene-2-carboxylate (intermediate **181)** (160 g, 450.29 mmol, 1.00 equiv), dichloromethane (1600 ml), triethylamine (67.7 g, 669.04 mmol, 1.50 equiv). This was followed by the addition of methanesulfonyl chloride (61.5 g, 1.20 equiv) dropwise with stirring at OoC. The resulting solution was stirred overnight at room temperature. The reaction was then quenched by the addition of 1 L of water. The resulting solution was extracted with 1x500 ml of dichloromethane and the organic layers combined. The resulting mixture was washed with 1x500 ml of brine. The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:10). This resulted in 90 g (46%) of the desired product as a yellow solid.

Intermediate I83

methyl 3-[(tert-butoxycarbonyl)amino]-5-(2,2,2-trifluoroethyl)thiophene-2-carboxylate

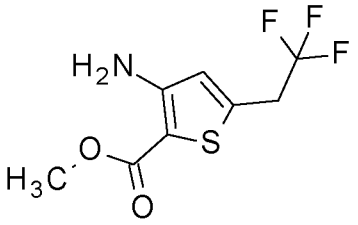


Into a 2000-ml 4-necked round-bottom flask purged and maintained with an inert atmosphere of hydrogen, was placed methyl 3-[[(tert-butoxy)carbonyl]amino]-5-[2,2,2-trifluoro-1-(methanesulfonyloxy)ethyl]thiophene-2-carboxylate (intermediate **I82)** (90 g, 207.65 mmol, 1.00 equiv), ethyl acetate (900 ml), palladium carbon (40 g). The flask was evacuated and flushed three times with air, followed by flushing with hydrogen. The resulting solution was stirred for 2 days at room temperature. The solids were filtered out and washed with 500 ml of water. The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:20). This resulted in 50 g (71%) of the desired product as a white solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ [ppm]: 9.13 (s, 1H), 7.89 (s, 1H), 3.88 (s, 3H), 3.56 (q, 2H), 1,53 (s, 9H).

Intermediate I84

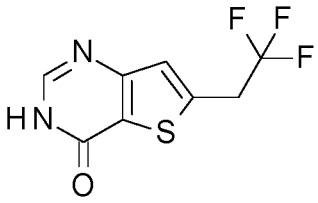
methyl 3-amino-5-(2,2,2-trifluoroethyl)thiophene-2-carboxylate



Into a 1000-ml 4-necked round-bottom flask, was placed methyl 3-[[(tert-butoxy)carbonyl]amino]-5-(2,2,2-trifluoroethyl)thiophene-2-carboxylate (intermediate **I83)** (50 g, 147.35 mmol, 1.00 equiv), dichloromethane (500 ml), trifluoroacetic acid (80 ml, 7.30 equiv). The resulting solution was stirred for 4 h at room temperature. The resulting mixture was concentrated under vacuum. The resulting solution was diluted with 500 ml of ethyl acetate. The pH value of the solution was adjusted to 8 with sodium bicarbonate (aq). The resulting solution was extracted with 2x300 ml of ethyl acetate and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 32 g (91%) of the desired product as a yellow solid.

Intermediate I85

6-(2,2,2-trifluoroethyl)thieno[3,2-d]pyrimidin-4(3H)-one



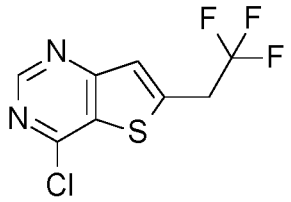
Into a 500-ml round-bottom flask, was placed methyl 3-amino-5-(2,2,2-trifluoroethyl)thiophene-2-carboxylate (intermediate **I84)** (32 g, 133.77 mmol, 1.00 equiv), 2-methoxyethan-1-ol (300 ml), acetic acid; methanimidamide (55.7 g, 535.02 mmol, 4.00 equiv). The resulting solution was stirred for 4 h at 120°C. The reaction mixture was cooled. The resulting mixture was concentrated under vacuum. The reaction was then quenched by the addition of 300 ml of water/ice and stirred 30 min. The solids were collected by filtration and washed with 1x100 ml

of water. This resulted in 20 g (64% yield) of 6-(2,2,2-trifluoroethyl)-3H,4H-thieno[3,2-d]pyrimidin-4-one as a grey solid.

LC-MS (method 4): Rt = 0.74 min; MS (ESIpos): m/z = 235 [M+H]+

Intermediate 186

4-chloro-6-(2,2,2-trifluoroethyl)thieno[3,2 -d]pyrimidine



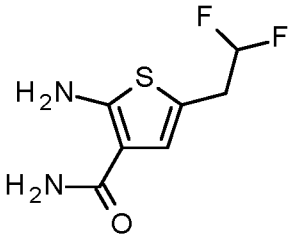
Into a 500-ml round-bottom flask, was placed 6-(2,2,2-trifluoroethyl)-3H,4H-thieno[3,2-d]pyrimidin-4-one (intermediate **185)** (20 g, 85.40 mmol, 1.00 equiv), methylbenzene (300 ml), DIEA (40 ml, 3.60 equiv), phosphorus oxychloride (40 ml, 2.94 equiv). The resulting solution was stirred for 4 h at 80°C. The reaction mixture was cooled. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:10). This resulted in 11 g (51%) of 4-chloro-6-(2,2,2-trifluoroethyl)thieno[3,2-d]pyrimidine as a light yellow solid.

LC-MS (method 4): Rt = 2.13 min; MS (ESIpos): m/z = 253 [M+H]+

^{1}H-NMR (300 MHz, DMSO-d6) δ [ppm]: 9.06 (s, 1H), 7.79 (s, 1H), 4.37 (q, 2H).

Intermediate I87

2-amino-5-(2,2-difluoroethyl)thiophene-3-carboxamide



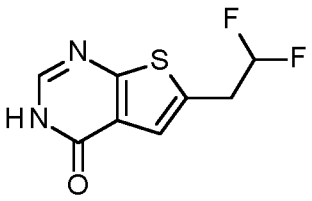
4,4-difluorobutanal (4.94 g, 45.7 mmol) was dissolved in DMF (40 ml), 2-cyanoacetamide (3.84 g, 45.7 mmol), sulfur (1.47 g, 45.7 mmol) and triethylamine (8.1 ml) were added. The mixture was stirred for 20.5 h at RT. All solvents were evaporated and the crude reaction product was used without further purification (13.0 g, 104% yield).

LC-MS (method 8): Rt = 0.69 min; MS (ESIpos): m/z = 207 [M+H]+

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.158 (3.84), 1.177 (8.12), 1.194 (3.95), 2.518 (1.16), 2.523 (0.82), 2.728 (12.76), 2.888 (16.00), 3.048 (1.08), 3.058 (1.07), 3.067 (1.55), 3.085 (1.64), 3.091 (1.70), 3.102 (1.67), 3.137 (0.60), 3.147 (0.57), 3.585 (3.82), 5.973 (0.50), 6.103 (0.46), 6.1 14 (0.99), 6.124 (0.45), 6.255 (0.46), 6.900 (2.85), 7.215 (2.57), 7.950 (2.02).

Intermediate I88

6-(2,2-difluoroethyl)thieno[2,3-d]pyrimidin -4(3H)-one



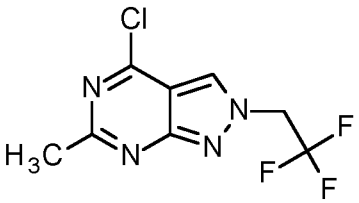
2-Amino-5-(2,2-difluoroethyl)thiophene-3-carboxamide (intermediate **I87)** (13.1 g, 75 % purity, 47.6 mmol) was dissolved in acetic acid (30 ml) and (diethoxymethoxy)ethane (40 ml, 240 mmol) was added. The mixture was refluxed for 18h. After cooling to RT all solvents were evaporated. 50 ml tert.-butylmethylether was added and the suspension was stirred for 15 min. The precipitate was filtered off, washed 3x with tert.-butylmethylether water (5 ml each) and dried in the vacuum thereafter to yield the desired product (5.04 g, 49% yield).

LC-MS (method 8): Rt = 0.45 min; MS (ESIpos): m/z = 217 [M+H]+

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.907 (2.24), 2.518 (2.68), 2.522 (1.72), 3.463 (2.40), 3.471 (2.49), 3.507 (4.78), 3.516 (4.86), 3.552 (2.36), 3.561 (2.34), 6.167 (0.94), 6.178 (2.05), 6.188 (0.92), 6.308 (1.80), 6.318 (3.87), 6.328 (1.79), 6.448 (0.87), 6.458 (1.86), 6.468 (0.87), 7.312 (11.63), 8.105 (16.00), 12.505 (0.85).

Intermediate I89

4-chloro-6-methyl-2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidine



To a stirred solution of 4-chloro-6-methyl-1 H-pyrazolo[3,4-d]pyrimidine (2.00 g, 97 % purity, 11.5 mmol) [CAS 30129-53-4] in DMF (9.2 ml) under argon at 0°C was added 2,2,2-trifluoroethyl trifluoromethanesulfonate (2.5 ml, 17 mmol) followed by potassium carbonate (3,2 g, 23,015 mmol). The mixture was stirred for 16h at RT. The suspension was filtrated through

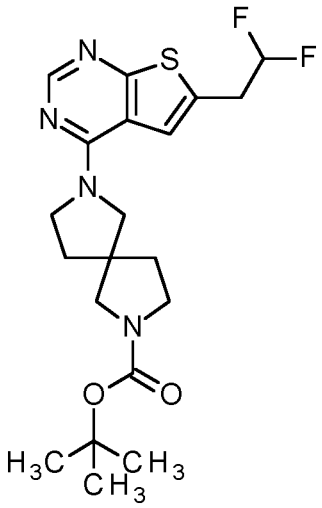
celite and evaporated off. The orange residue was purified by flash chromatography (Biotage Isolera: 100 g KP-Sil 0-60% Hex:EtOAc gradient). 1.05 g (29% yield) of the desired product were obtained as an off white solid. Furthermore fractions containing 4-chloro-6-methyl-1-(2,2,2-trifluoroethyl)-1 H-pyrazolo[3,4-d]pyrimidine as a side product were pooled and evaporated to yield 1.34 g of the undesired isomer 4-chloro-6-methyl-1-(2,2,2-trifluoroethyl)-1H-pyrazolo[3,4-d]pyrimidine as an off white solid. Analytical data for intermediate **I89:**

LC-MS (method 2): Rt = 0.74 min; MS (ESIpos): m/z = 251 [M+H]+

1H-NMR (400 MHz, CHLOROFORM-d) delta [ppm]: 1.267 (0.54), 1.594 (6.29), 2.054 (1.03), 2.687 (3.48), 2.705 (0.45), 2.815 (16.00), 4.962 (0.82), 4.983 (1.05), 5.005 (0.84), 5.021 (1.12), 5.040 (3.28), 5.061 (3.25), 5.081 (1.05), 8.176 (0.83), 8.233 (3.65).

Intermediate I90

tert-butyl 7-[6-(2,2-difluoroethyl)thieno[2,3-d]pyrimi din-4-yl]-2,7-diazaspiro[4.4]nonane-2-carboxylate



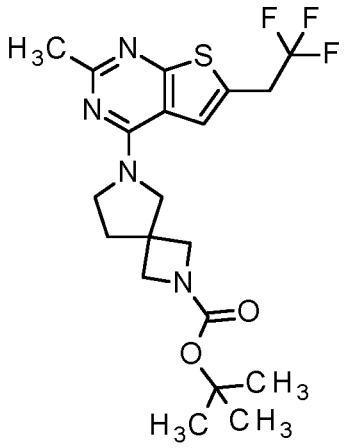
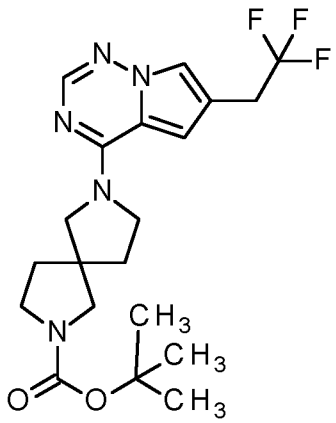
To a solution of tert-butyl 2,7-diazaspiro[4.4]nonane-2-carboxylate (1.26 g, 5.55 mmol) in 7.5 ml acetonitrile was given 6-(2,2-difluoroethyl)thieno[2,3-d]pyrimidin-4(3H)-one (intermediate **I88)** (1.20 g, 5.55 mmol), 3.47 g PyBOP (6.66 mmol) [CAS 128625-52-5] and 1.5 ml (11 mmol) triethylamine. The mixture was stirred for 22 h at 80°C. The solvent was removed by evaporation, water was added and the mixture was extracted 3x with ethyl acetate. The combined organic layers were washed with brine and dried. The crude product was purified by column chromatography to yield 1.81 g (73 % yield) of the desired product.

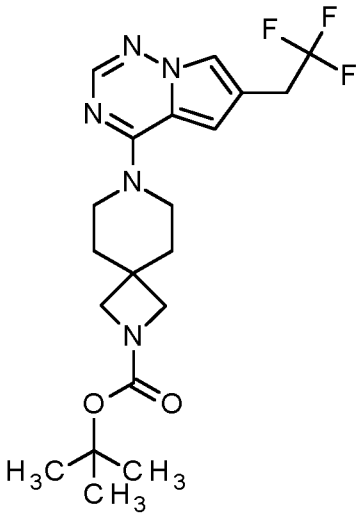
LC-MS (method 8): Rt = 1.26 min; MS (ESIpos): m/z = 425 [M+H]+

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.154 (3.07), 1.172 (6.35), 1.190 (3.21), 1.389 (16.00), 1.405 (13.26), 1.867 (1.43), 1.881 (1.44), 1.907 (1.21), 1.987 (13.16), 2.327 (0.53), 2.523 (1.73), 2.669 (0.52), 3.238 (0.74), 3.266 (2.42), 3.282 (2.16), 3.374 (2.38), 3.471 (1.06), 3.480

(1.10), 3.515 (2.09), 3.525 (2.10), 3.560 (1.08), 3.570 (1.02), 3.717 (0.80), 3.857 (0.63), 3.999 (1.00), 4.017 (2.89), 4.035 (2.84), 4.053 (0.94), 6.188 (0.74), 6.318 (0.74), 6.328 (1.49), 6.338 (0.68), 6.468 (0.68), 7.604 (2.76), 8.302 (6.23).

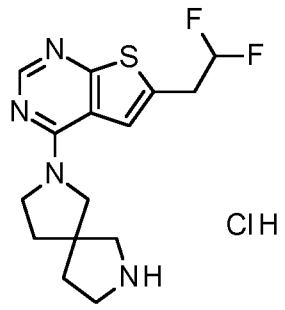
The following intermediates were prepared analogous to intermediate **I90** starting from intermediate **I4** or **I78** by reacting with the corresponding spirocyclic amines.

Inter-mediate	Structure Name	Analytical Data
I91	 tert-butyl 6-[2-methyl-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,6-diazaspiro[3.4]octane-2-carboxylate	1H-NMR (400 MHz, DMSO-d6) delta [ppm]: 1.383 (16.00), 2.172 (0.32), 2.416 (5.86), 2.518 (0.49), 2.522 (0.32), 3.798 (0.41), 3.816 (0.45), 3.891 (0.51), 3.907 (0.53), 3.997 (0.68), 4.025 (0.63), 7.641 (0.67). LC-MS (method 12): Rt = 1.26 min; MS (ESIpos): m/z = 443 [M+H]+
I92	 tert-butyl 7-[6-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazin-4-yl]-2,7-diazaspiro[4.4]nonane-2-	1H NMR (400 MHz, CDCl3): δ [ppm] = 1.46 (s, 9H), 1.80-2.18 (m, 4H), 3.32-3.50 (m, 6H), 3.74-4.08 (m, 4H), 6.68 (d, 1H), 7.53 (d, 1H), 7.83 (s, 1H); LC-MS (method 6): Rt = 0.86 min.. MS (ESIpos): m/z = (M+H)+ 426.

Inter¬ mediate	Structure Name	Analytical Data
	carboxylate	
193	 tert-butyl 7-[6-(2,2,2-trifluoroethyl)pyrrolo[2, 1-f][1 ,2,4]triazin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate	1H NMR (400 MHz, CDCh3): δ [ppm] = 1.45 (s, 9H), 1.86-1 .92 (m, 4H), 3.37-3.46 (m, 2H), 3.72 (s, 4H), 3.87-3.93 (m, 4H), 6.62 (s, 1H), 7.54 (s, 1H), 7.87 (s, 1H) UPLC1-MS (method 6): Rt = 0.62 min., 58%. MS (ESIpos): m/z = (M+H)+ 326.

Intermediate I94

4-[-2,7-diazaspiro[4.4]non-2-yl]-6-(2,2-difluoroethyl)thieno[2,3-d]pyrimidine hydrochloride

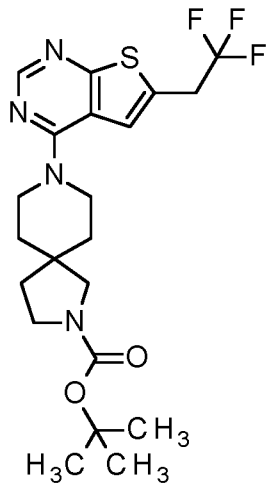


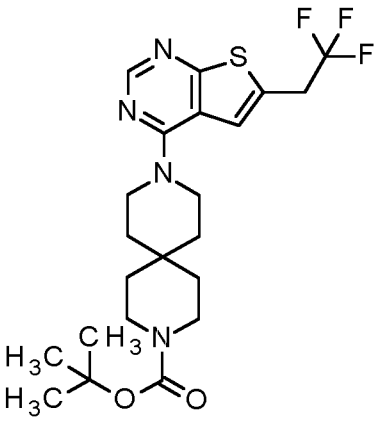
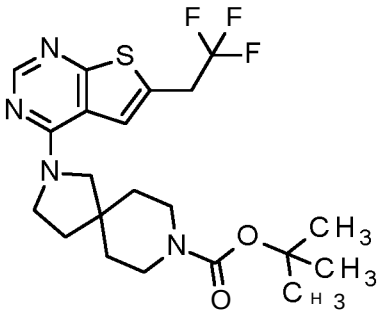
To a solution of tert-butyl 7-[6-(2,2-difluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]-nonane-2-carboxylate (1.81 g, 4.26 mmol) (intermediate **I90)** in 25 ml methanol were added 10 ml of a solution of 4M hydrochloride in dioxane. The mixture was stirred for 16.5 h at RT. All solvent was removed by evaporation to yield 1.58 g (99 % yield) of the desired product as a lightbrown solid which was used without further purification.

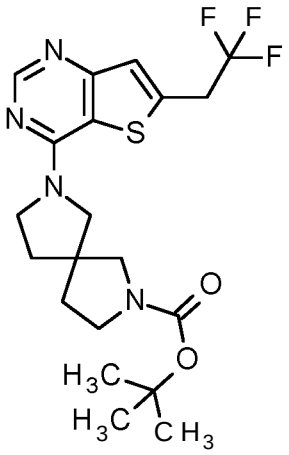
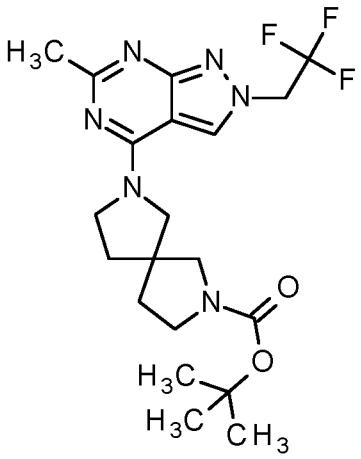
LC-MS (method 8): Rt = 0.90 min; MS (ESIpos): m/z = 326 [M+H]+

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.825 (0.93), 1.926 (0.42), 1.945 (1.00), 1.959 (1.05), 1.978 (2.10), 1.997 (1.13), 2.005 (0.99), 2.024 (2.03), 2.042 (1.50), 2.056 (1.43), 2.075 (1.05), 2.154 (0.60), 2.518 (3.67), 2.522 (2.28), 3.076 (0.44), 3.138 (0.49), 3.154 (0.90), 3.162 (0.81), 3.168 (1.34), 3.183 (1.75), 3.198 (0.96), 3.215 (0.85), 3.229 (1.43), 3.243 (1.16), 3.257 (0.82), 3.277 (0.91), 3.294 (1.93), 3.310 (2.84), 3.326 (1.86), 3.343 (0.82), 3.495 (1.74), 3.504 (2.11), 3.514 (2.30), 3.523 (2.01), 3.549 (4.01), 3.554 (11.60), 3.563 (16.00), 3.582 (10.52), 3.594 (3.67), 3.604 (3.94), 3.611 (3.68), 3.639 (5.02), 3.651 (10.08), 3.901 (1.92), 6.240 (0.54), 6.379 (1.07), 6.519 (0.51), 7.410 (0.42), 7.542 (0.48), 7.544 (0.42), 7.705 (2.50), 7.707 (2.55), 7.729 (0.71), 7.969 (0.68), 7.989 (0.62), 8.452 (6.74), 9.453 (0.80).

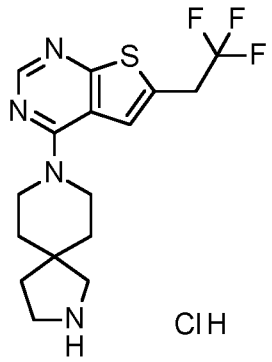
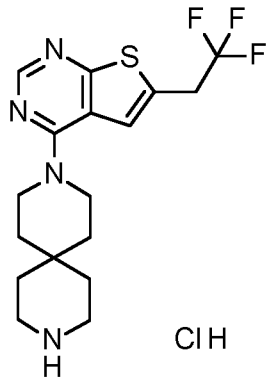
The following intermediates were prepared analogous to intermediate **112** starting from 4-chloro-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidine or intermediate **I86** or intermediate **I89** by reacting with the corresponding spirocyclic amines.

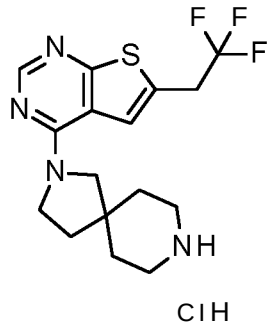
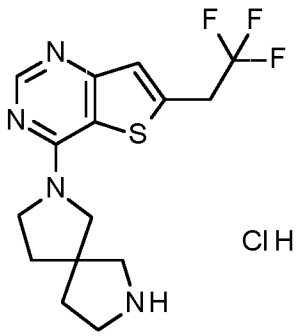
Inter-mediate	Structure Name	Analytical Data
I95	 tert-butyl 8-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,8-diazaspiro[4.5]decane-2-carboxylate	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.172 (0.70), 1.352 (0.68), 1.382 (2.67), 1.400 (16.00), 1.613 (1.24), 1.622 (1.44), 1.638 (0.87), 1.777 (0.54), 1.795 (1.02), 1.812 (0.54), 1.987 (1.35), 2.331 (0.49), 2.518 (2.49), 2.522 (1.66), 2.673 (0.51), 3.035 (0.52), 3.167 (1.27), 3.179 (1.35), 3.825 (0.52), 3.837 (0.49), 3.854 (0.43), 3.867 (0.44), 3.880 (0.48), 4.070 (1.10), 4.098 (1.04), 7.634 (1.89), 8.379 (3.98). LC-MS (method 8): Rt = 1.41 min; MS (ESIpos): m/z = 457 [M+H]+

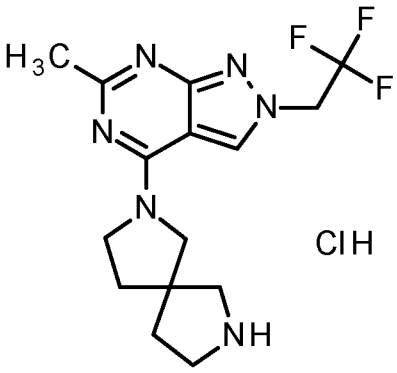
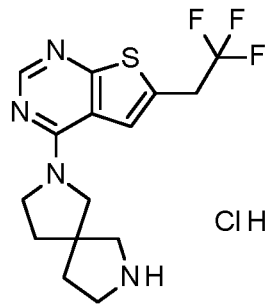
Inter¬ mediate	Structure Name	Analytical Data
196	 tert-butyl 9-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-3,9-diazaspiro[5.5]undecane-3-carboxylate	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.933 (0.74), 0.949 (0.74), 1.379 (1.06), 1.386 (0.57), 1.397 (16.00), 1.443 (0.81), 1.457 (1.05), 1.471 (0.81), 1.569 (0.79), 1.584 (1.02), 1.597 (0.81), 1.988 (0.56), 2.518 (2.02), 2.523 (1.38), 2.674 (0.42), 3.828 (0.83), 3.842 (1.02), 3.856 (0.80), 4.068 (0.67), 4.096 (0.64), 7.638 (1.22), 8.366 (2.81). LC-MS (method 8): Rt = 1.47 min; MS (ESIpos): m/z = 471 [M+H]+
197	 tert-butyl 2-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,8-diazaspiro[4.5]decane-8-carboxylate	1H-NMR (400 MHz, DMSO-d6) delta [ppm]: 1.401 (16.00), 1.477 (0.16), 1.498 (0.42), 1.516 (0.72), 1.529 (0.74), 1.546 (0.41), 1.569 (0.16), 1.920 (0.28), 2.323 (0.16), 2.327 (0.22), 2.331 (0.16), 2.518 (0.93), 2.523 (0.63), 2.665 (0.16), 2.669 (0.23), 2.673 (0.16), 3.369 (0.69), 3.381 (0.70), 3.629 (0.27), 3.842 (0.16), 4.01 1 (0.25), 4.039 (0.71), 4.067 (0.68), 4.094 (0.22), 7.733 (0.51), 8.318 (2.59). LC-MS (method 8): Rt = 1.39 min; MS (ESIpos): m/z = 457 [M+H]+

Inter¬ mediate	Structure Name	Analytical Data
198	 tert-butyl 7-[6-(2,2,2-trifluoroethyl)thieno[3,2-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]nonane-2-carboxylate	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.172 (0.66), 1.352 (0.60), 1.389 (16.00), 1.405 (14.49), 1.871 (0.86), 1.897 (1.00), 1.930 (0.78), 1.945 (0.59), 1.987 (2.41), 2.003 (1.62), 2.326 (0.73), 2.331 (0.56), 2.665 (0.56), 2.669 (0.74), 2.673 (0.59), 3.233 (0.78), 3.259 (1.72), 3.292 (1.96), 3.362 (2.28), 3.740 (0.76), 3.913 (0.73), 4.017 (0.41), 4.127 (0.97), 4.155 (2.75), 4.183 (2.65), 4.210 (0.88), 5.758 (0.43), 7.391 (4.78), 8.377 (5.80). LC-MS (method 8): Rt = 1.28 min; MS (ESIpos): m/z = 443 [M+H]+
199	 tert-butyl 7-[6-methyl-2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]nonane-2-carboxylate	1H-NMR (400 MHz, DMSO-d6) delta [ppm]: 1.389 (16.00), 1.408 (12.97), 1.869 (0.68), 1.887 (1.18), 1.908 (1.24), 1.926 (0.92), 1.939 (0.90), 1.957 (0.90), 1.974 (0.40), 2.057 (0.56), 2.074 (1.10), 2.084 (1.56), 2.093 (0.62), 2.323 (0.44), 2.327 (0.64), 2.331 (0.52), 2.347 (9.40), 2.357 (8.16), 2.518 (1.98), 2.523 (1.36), 2.665 (0.40), 2.669 (0.58), 2.674 (0.76), 3.252 (1.26), 3.259 (0.98), 3.267 (1.86), 3.287 (1.50), 3.294 (0.78), 3.304 (0.62), 3.367 (1.08), 3.381 (0.94), 3.397 (0.96), 3.562 (0.48), 3.592 (1.22), 3.620 (0.56), 3.630 (0.58), 3.697 (2.79), 3.714 (0.70), 3.732 (1.24), 3.749 (0.60), 3.833 (0.74), 3.850 (1.42), 3.867 (0.70), 5.296 (1.14), 5.314 (1.78), 5.336 (1.42), 5.358 (0.40), 8.649 (1.96), 8.681 (1.30). LC-MS (method 2): Rt = 0.78 min; MS (ESIpos): m/z = 441 [M+H]+

The following intermediates were prepared analogous to intermediate **122** starting from intermediate **115, I95, 196, 197, 198 or I99** respectively.

Inter-mediate	Structure Name	Analytical Data
I100	 8-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,8-diazaspiro[4.5]decane hydrochloride	1H-NMR (400 MHz, DMSO-d6) delta [ppm]: 1.033 (0.79), 1.050 (1.64), 1.068 (0.83), 1.170 (0.76), 1.350 (1.88), 1.679 (0.84), 1.695 (1.26), 1.712 (2.91), 1.729 (4.34), 1.740 (5.18), 1.750 (4.37), 1.767 (3.33), 1.783 (1.31), 1.800 (1.05), 1.811 (0.72), 1.830 (0.96), 1.873 (4.17), 1.892 (7.93), 1.906 (3.83), 1.910 (4.55), 1.985 (1.40), 2.000 (0.68), 2.327 (0.77), 2.518 (3.13), 2.523 (2.07), 2.669 (0.79), 3.017 (0.73), 3.032 (1.42), 3.055 (4.29), 3.069 (6.75), 3.084 (3.62), 3.162 (14.91), 3.223 (1.29), 3.241 (2.91), 3.257 (3.65), 3.271 (2.68), 3.289 (0.98), 3.426 (0.83), 3.443 (0.83), 3.884 (0.93), 3.907 (3.23), 3.924 (6.06), 3.934 (6.07), 3.949 (3.20), 3.972 (0.94), 3.984 (0.66), 4.096 (1.77), 4.124 (4.94), 4.151 (4.71), 4.179 (1.53), 4.677 (4.22), 7.721 (8.79), 8.520 (16.00), 9.506 (2.39). LC-MS (method 2): Rt = 0.61 min; MS (ESIpos): m/z = 357 $[M+H]^+$
I101	 3-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-3,9-diazaspiro[5.5]undecane hydrochloride	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.033 (0.84), 1.051 (1.68), 1.068 (0.84), 1.253 (2.23), 1.270 (2.90), 1.285 (1.90), 1.301 (1.86), 1.351 (1.15), 1.626 (6.61), 1.640 (8.51), 1.653 (6.70), 1.691 (5.81), 1.705 (8.07), 1.719 (6.03), 2.518 (5.26), 2.523 (3.49), 3.058 (6.61), 3.103 (0.44), 3.163 (9.06), 3.426 (0.80), 3.444 (0.88), 3.876 (6.36), 3.891 (7.80), 3.904 (6.28), 4.078 (2.98), 4.106 (7.07), 4.134 (9.04), 4.162 (10.56), 4.177 (10.92), 7.686 (8.75), 8.481 (16.00), 8.809 (2.36). LC-MS (method 2): Rt = 0.63 min; MS

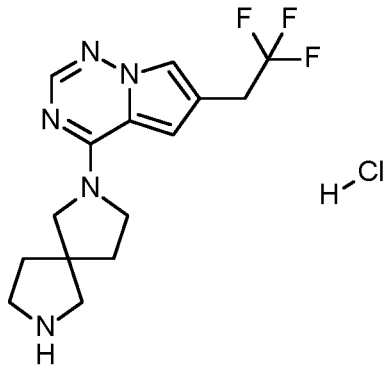
Inter¬ mediate	Structure Name	Analytical Data
		(ESIpos): m/z = 371 $[M+H]^+$
1102	 2-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,8-diazaspiro[4.5]decane hydrochloride	1H-NMR (400 MHz, DMSO-d6) delta [ppm]: 1.252 (3.82), 1.269 (5.43), 1.282 (3.50), 1.299 (3.36), 1.652 (0.93), 1.727 (1.32), 1.739 (2.29), 1.760 (4.25), 1.775 (7.79), 1.796 (7.21), 1.810 (4.07), 1.832 (2.14), 1.907 (0.71), 1.916 (2.00), 1.932 (1.93), 1.991 (3.04), 2.322 (1.46), 2.327 (2.00), 2.332 (1.46), 2.518 (1.50), 2.522 (7.36), 2.664 (1.50), 2.669 (2.11), 2.673 (1.46), 3.120 (9.32), 3.201 (0.96), 3.327 (0.96), 3.384 (0.82), 3.478 (0.61), 3.497 (0.64), 3.564 (0.75), 3.592 (0.86), 3.603 (0.86), 3.741 (3.79), 4.031 (2.75), 4.060 (3.46), 4.068 (3.79), 4.096 (7.64), 4.124 (7.00), 4.151 (2.61), 7.401 (2.61), 7.840 (1.25), 8.137 (1.50), 8.463 (16.00), 8.881 (1.86). LC-MS (method 8): Rt = 1.15 min; MS (ESIpos): m/z = 357 [M+H]+
1103	 4-[2,7-diazaspiro[4.4]non-2-yl]-6-(2,2,2-trifluoroethyl)thieno[3,2-d]pyrimidine hydrochloride	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.033 (0.49), 1.051 (1.00), 1.068 (0.47), 1.253 (0.41), 1.270 (0.53), 1.351 (0.66), 1.953 (0.52), 1.972 (1.00), 1.986 (1.11), 2.004 (1.91), 2.023 (1.13), 2.066 (0.88), 2.153 (0.64), 2.180 (0.60), 2.518 (4.16), 2.523 (2.67), 3.163 (16.00), 3.187 (1.33), 3.202 (1.51), 3.216 (1.08), 3.231 (0.55), 3.263 (1.35), 3.278 (2.64), 3.295 (3.23), 3.309 (2.34), 3.326 (0.99), 3.409 (0.44), 3.427 (0.77), 3.444 (0.80), 3.462 (0.53), 3.469 (0.42), 3.686 (2.31), 3.698 (2.38), 4.106 (0.71), 4.183 (0.67), 4.356 (1.15), 4.384 (3.11), 4.412 (2.95), 4.439 (0.97), 7.660 (6.53), 8.835 (7.72), 9.541 (1.05). LC-MS (method 8): Rt = 1.24 min; MS (ESIpos): m/z = 343 [M+H]+

Inter-mediate	Structure Name	Analytical Data
I104	 4-[2,7-diazaspiro[4.4]non-2-yl]-6-methyl-2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidine hydrochloride	1H-NMR (400 MHz, DMSO-d6) delta [ppm]: 1.658 (0.42), 1.672 (0.83), 1.691 (1.75), 1.709 (2.29), 1.727 (2.02), 1.744 (1.21), 1.751 (1.67), 1.769 (0.77), 1.783 (0.46), 1.878 (0.94), 1.895 (2.08), 1.908 (1.88), 1.923 (1.33), 1.954 (0.46), 2.017 (0.79), 2.035 (1.73), 2.042 (1.48), 2.059 (1.27), 2.073 (0.83), 2.083 (3.08), 2.322 (1.15), 2.326 (1.65), 2.331 (1.81), 2.339 (16.00), 2.349 (15.98), 2.518 (4.44), 2.522 (3.06), 2.539 (0.90), 2.644 (1.17), 2.664 (1.29), 2.671 (3.48), 2.687 (1.06), 2.699 (3.06), 2.713 (2.77), 2.727 (1.56), 2.734 (2.73), 2.760 (0.83), 2.836 (1.08), 2.844 (1.27), 2.860 (3.37), 2.877 (4.06), 2.895 (1.67), 3.228 (0.96), 3.255 (1.69), 3.509 (2.04), 3.538 (2.60), 3.586 (0.81), 3.619 (2.77), 3.639 (2.69), 3.648 (2.21), 3.661 (1.60), 3.674 (2.40), 3.699 (2.23), 3.720 (1.29), 3.737 (1.46), 3.756 (1.10), 3.763 (1.02), 3.782 (1.42), 3.804 (1.25), 3.823 (0.83), 3.832 (0.75), 3.850 (0.77), 5.279 (1.83), 5.301 (5.37), 5.323 (5.15), 5.345 (1.65), 8.643 (6.96), 8.684 (0.60). LC-MS (method 2): Rt = 0.24 min; MS (ESIpos): m/z = 341 [M+H]+
I105	 4-[2,7-diazaspiro[4.4]non-2-yl]-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidine hydrochloride	1H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.950 (0.75), 1.964 (0.78), 1.969 (0.54), 1.983 (1.52), 2.002 (0.82), 2.011 (0.70), 2.030 (1.42), 2.047 (1.01), 2.062 (0.95), 2.080 (0.68), 2.518 (1.98), 2.522 (1.30), 3.058 (0.69), 3.162 (2.41), 3.174 (0.91), 3.189 (1.19), 3.204 (0.67), 3.215 (0.57), 3.230 (0.95), 3.244 (0.75), 3.259 (0.48), 3.273 (0.65), 3.291 (1.27), 3.306 (1.89), 3.321 (1.15), 3.339 (0.41), 3.564 (16.00), 3.918 (0.75), 4.059 (0.75), 4.086 (1.97), 4.114 (1.88), 4.142 (0.62), 7.820 (1.02), 8.492 (5.05), 9.495 (0.54).

Inter¬ mediate	Structure Name	Analytical Data
		LC-MS (method 13): Rt = 0.97 min; MS (ESIpos): m/z = 343 [M+H]+

Intermediate 1106

4-[2,7-diazaspiro[4.4]non-2-yl]-6-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazine hydrochloride



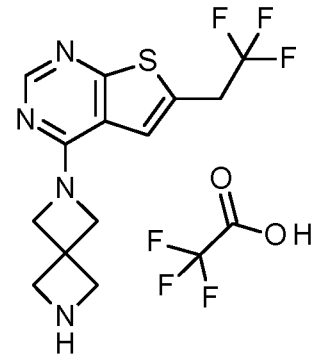
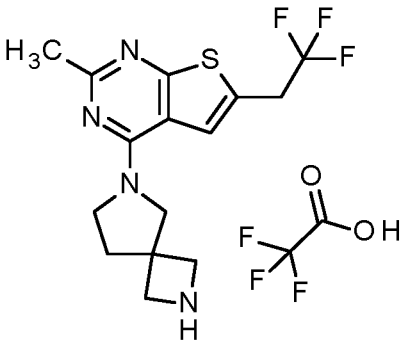
To a stirred solution of tert-butyl 7-[6-(2,2,2-trifluoroethyl)pyrrolo[2,1-fl[1 ,2,4]triazin-4-yl]-2,7-diazaspiro[4.4]nonane-2-carboxylate (intermediate **I92),** 879 mg (2.07 mmol), in 1,4-dioxane, 2.00 ml, was added hydrochloric acid (4 M in 1,4-dioxane), 5.17 ml (20.7 mmol). Stirring continued for 30 minutes. The mixture was concentrated under vacuum to give the desired product, 932 mg (103% combined yield). Used in the next step without purification.

1H NMR (400 MHz, MeOD-d3): δ [ppm] = 2.13-2.40 (m, 4H), 3.38-3.51 (m, 4H), 3.60-3.78 (m, 2H), 3.85-3.95 (m, 2H), 4.20-4.31 (m, 2H), 7.51 (d, 1H), 7.97 (s, 1H), 7.98 (d, 1H);

LC-MS (method 9): Rt = 1.58 min., 95%. MS (ESIpos): m/z = (M+H)+ 326.

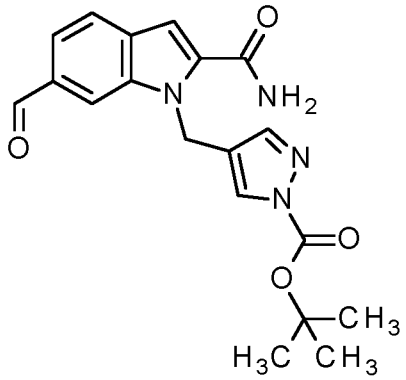
The following intermediates were prepared analogous to intermediate **I29** starting from **114** or **191 .**

Inter-mediate	Structure Name	Analytical Data

Inter¬ mediate	Structure Name	Analytical Data
1107	 4-(2,6-diazaspiro[3.3]hept-2-yl)-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidine trifluoroacetate	1H-NMR (400 MHz, DMSO-d6) delta [ppm]: 1.352 (0.97), 1.820 (0.91), 2.296 (13.50), 2.323 (0.59), 2.327 (0.80), 2.331 (0.57), 2.518 (3.20), 2.523 (2.1 1), 2.665 (0.57), 2.669 (0.79), 2.673 (0.57), 4.068 (1.68), 4.096 (4.87), 4.123 (4.67), 4.151 (1.56), 4.188 (6.52), 4.204 (11.89), 4.219 (6.38), 4.536 (1.96), 6.331 (0.67), 7.124 (0.59), 7.141 (1.51), 7.161 (3.00), 7.179 (3.48), 7.229 (2.98), 7.234 (1.01), 7.248 (3.20), 7.266 (1.24), 7.373 (8.66), 8.384 (16.00), 8.606 (1.68). LC-MS (method 2): Rt = 0.50 min; MS (ESIpos): m/z = 315 $[M+H]^+$
1108	 4-(2,6-diazaspiro[3.4]oct-6-yl)-2-methyl-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidine trifluoroacetate	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.107 (3.95), 2.294 (1.33), 2.318 (0.80), 2.323 (0.98), 2.327 (1.14), 2.331 (0.82), 2.467 (16.00), 2.523 (3.04), 2.665 (0.70), 2.669 (0.96), 2.673 (0.69), 3.839 (0.77), 3.918 (0.67), 3.946 (1.44), 3.956 (1.33), 3.975 (0.98), 4.018 (1.86), 4.047 (2.75), 4.074 (2.99), 4.101 (1.10), 6.978 (1.02), 7.105 (1.14), 7.233 (0.99), 7.638 (3.22), 8.668 (0.40). LC-MS (method 8): Rt = 1.01 min; MS (ESIpos): m/z = 343 [M+H]+

Intermediate 1109

tert-butyl 4-[(2-carbamoyl-6-formyl-1 H-indol-1 -yl)methyl]-1 H-pyrazole-1 -carboxylate



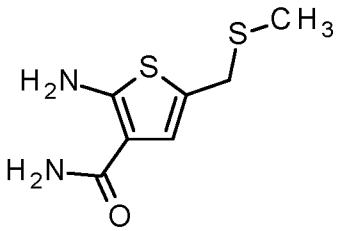
6-formyl-1 H-indole-2-carboxamide (100 mg, 531 μηηοI, intermediate **11)** was added to DMF (2 ml). Then caesium carbonate (519 mg, 1.59 mmol) was added and then tert-butyl 4-(bromomethyl)-1 H-pyrazole-1-carboxylate (208 mg, 797 μηιοI) [CAS 530144-72-0]. The mixture was stirred for 22 h at RT. The reaction mixture was quenched with water, and extracted 3x with ethyl acetate. The organic layer was dried over sodium sulfate, filtered, and concentrated. The crude product was purified by RP-HPLC which gave the desired product as a white solid, 29 mg (12% yield).

LC-MS (method 13): Rt = 0.96 min; MS (ESIneg): m/z = 367 [M-H]-¹H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.499 (16.00), 2.518 (0.73), 2.523 (0.50), 2.540 (0.44), 5.697 (1.87), 5.785 (0.50), 7.454 (1.63), 7.605 (0.72), 7.608 (0.68), 7.626 (0.86), 7.629 (0.86), 7.813 (0.95), 7.833 (0.76), 8.401 (1.03), 10.075 (0.48), 10.094 (1.93).

Intermediates for foreign application

Intermediate 11 10

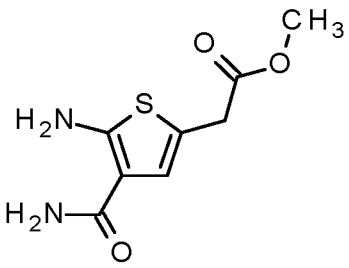
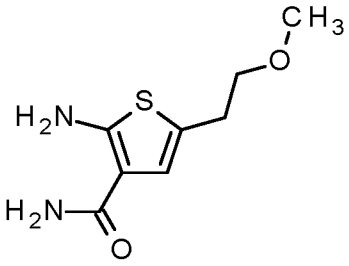
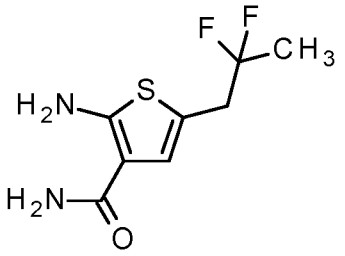
2-amino-5-[(methylsulfanyl)methyl]thiophene-3-carboxamide



3-(methylsulfanyl)propanal (10.7 g, 103 mmol) [CAS 3268-49-3] was dissolved in DMF (83 ml), 2-cyanoacetamide (8.64 g, 103 mmol), sulfur (3.29 g, 103 mmol) and triethylamine (17 ml) were added. The mixture was stirred for 24 h at RT. All solvents were evaporated and the crude reaction product was used without further purification.

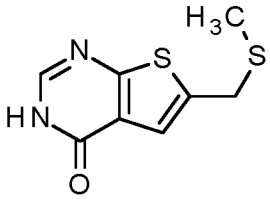
LC-MS (method 8): Rt = 0.70 min; MS (ESIpos): m/z = 202 [M+H]+

The following intermediates were prepared analogous to intermediate **1110** starting from the corresponding aldehydes.

Inter-mediate	Structure Name	Analytical Data
I111	 methyl (5-amino-4-carbamoylthiophen-2-yl)acetate	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 3.58 - 3.60 (m, 2H), 3.62 (s, 3H), 6.46 - 7.39 (m, 5H). LC-MS (method 1): Rt = 0.61 min; MS (ESIpos): m/z = 215 $[M+H]^+$
I112	 2-amino-5-(2-methoxyethyl)thiophene-3-carboxamide	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 2.69 - 2.74 (m, 2H), 3.25 (s, 3H), 3.44 (t, 2H), 6.43 - 7.27 (m, 5H). LC-MS (method 1): Rt = 0.63 min; MS (ESIpos): m/z = 201 $[M+H]^+$
I113	 2-amino-5-(2,2-difluoropropyl)thiophene-3-carboxamide	LC-MS (method 8): Rt = 0.75 min; MS (ESIpos): m/z = 221 $[M+H]^+$

Intermediate 1114

6-[(methylsulfanyl)methyl]thieno[2,3-d]pyrimidin-4(3H)-one

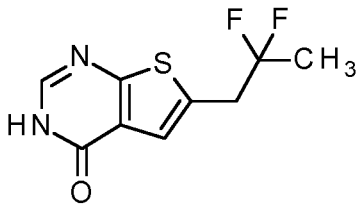


2-amino-5-[(methylsulfanyl)methyl]thiophene-3-carboxamide (20.0 g, 98.9 mmol, intermediate **1110)** was dissolved in acetic acid (50 ml) and (diethoxymethoxy)ethane (69 ml, 410 mmol) was added. The mixture was refluxed for 4h. After cooling to RT 100 mg hexane/ ethyl acetate (1:1) was added and after stirring for 30 min at 0°C the precipitate was filtered off. The product was washed with 50 ml hexane/ ethyl acetate (1:1) and dried in vacuum to yield the desired product as a beige colored solid (7.3 g, 35% yield).

LC-MS (method 2): Rt = 0.62 min; MS (ESIpos): m/z = 213 [M+H]+

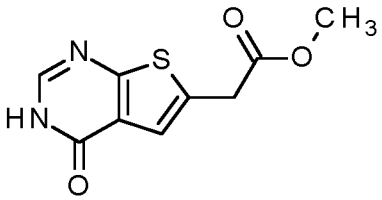
1H-NMR (400 MHz, DMSO-d6) delta [ppm]: 1.907 (0.58), 2.016 (16.00), 2.048 (0.26), 2.518 (1.63), 2.522 (1.06), 3.584 (0.31), 3.991 (4.88), 3.993 (5.20), 7.253 (3.28), 8.087 (1.39), 8.096 (1.48), 12.490 (0.26).

The following intermediate was prepared analogous to intermediate **11 14** starting from the corresponding intermediate **11 13.**

Inter-mediate	Structure Name	Analytical Data
I115	 6-(2,2-difluoropropyl)thieno[2,3-d]pyrimidin-4(3H)-one	1H-NMR (400 MHz, DMSO-d6) delta [ppm]: 1.593 (6.55), 1.640 (13.49), 1.687 (6.10), 2.083 (0.51), 2.518 (2.18), 2.522 (1.39), 3.528 (3.39), 3.568 (6.75), 3.609 (3.19), 7.288 (9.41), 8.106 (16.00), 12.486 (1.05). LC-MS (method 1): Rt = 0.67 min; MS (ESIpos): m/z = 231 $[M+H]^+$

Intermediate 11 16

methyl (4-oxo-3,4-dihydrothieno[2,3-d]pyrimidin-6-yl)acetate

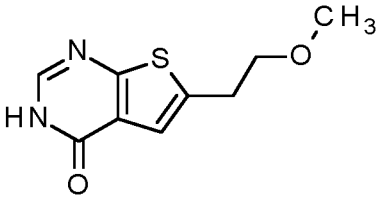


A mixture of methyl (5-amino-4-carbamoylthiophen-2-yl)acetate (2.14 g, 9.89 mmol, intermediate **111 1)** in 8.5 ml acetic acid was treated with trimethoxymethane (6.5 ml, 59 mmol) in the microwave at 120 °C for 5 h. The crude reaction mixture was evaporated to dryness. MTBE (30 ml) was added and the resulting mixture was filtered and washed with MTBE. After drying of the solid 2.08 g (85 % purity, 80 % yield) of the desired product was obtained.

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 3.66 (s, 3H), 4.05 (d, 2H), 7.26 (s, 1H), 8.09 (s, 1H), 12.46 (br s, 1H).

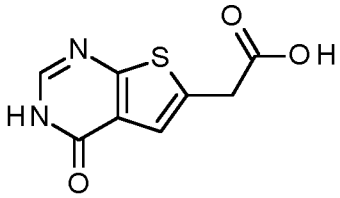
LC-MS (method 12: Rt = 0.64 min; MS (ESIpos): m/z = 225 $[M+H]^+$

The following intermediate was prepared analogous to intermediate 11 **16** starting from the corresponding intermediate 11 **12.**

Inter-mediate	Structure Name	Analytical Data
I117	 6-(2-methoxyethyl)thieno[2,3-d]pyrimidin-4(3H)-one	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 3.06 (td, 2H), 3.28 (s, 3H), 3.58 (t, 2H), 7.16 (t, 1H), 8.06 (s, 1H), 12.42 (br s, 1H). LC-MS (method 12): Rt = 0.68 min; MS (ESIpos): m/z = 211 $[M+H]^+$

Intermediate 11 18

(4-0X0-3,4-dihydrothieno[2,3-d]pyrimidin-6-yl)acetic acid



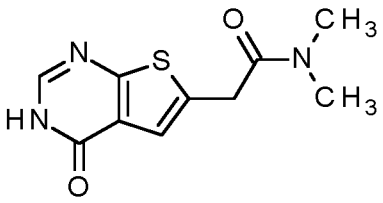
To a solution of methyl (4-oxo-3,4-dihydrothieno[2,3-d]pyrimidin-6-yl)acetate (2.08 g, 85 % purity, 7.88 mmol, intermediate 11 **16)** in THF (80 ml) was added a solution of lithium hydroxide (566 mg, 23.7 mmol) in water (16 ml). The mixture was stirred at room temperature for 2 h. The reaction mixture was then diluted with water (60 ml) and brine (60 ml). It was acidified with hydrochloric acid (pH 1.8) and extracted with ethyl acetate. The extracts were dried over anhydrous sodium sulfate and concentrated under vacuum to give 1.88 g (94 % purity, 106 % yield) of the desired product (intermediate **1118).**

LC-MS (method 12): Rt = 0.50 min; MS (ESIneg): m/z = 209 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 3.93 (d, 2H), 7.21 - 7.25 (m, 1H), 8.08 (s, 1H), 12.45 (br s, 1H), 12.72 (br s, 1H).

Intermediate 1119

N,N-dimethyl-2-(4-oxo-3,4-dihydrothieno[2,3-d]pyrimidin-6-yl)acetamide



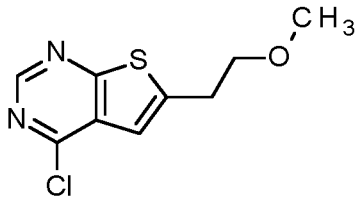
To a solution of (4-oxo-3,4-dihydrothieno[2,3-d]pyrimidin-6-yl)acetic acid (359 mg, 96 % purity, 1.64 mmol, intermediate **1118)** in DMF (25 ml) was added a potaasium carbonate (340 mg, 2.46 mmol), N-methylmethanamine hydrochloride (176 mg, 2.13 mmol), and HATU (873 mg, 2.30 mmol). The mixture was stirred at room temperature for 21 h. The solvent was removed by evaporation, water (30 ml) and brine (30 ml) were added and the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine and dried over sodium sulfate. The crude product was purified by column chromatography on silica gel to yield 93.0 mg (24 % yield) of the desired product (intermediate **1119).**

LC-MS (method 12): Rt = 0.48 min; MS (ESIpos): m/z = 238 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 2.85 (s, 3H), 3.05 (s, 3H), 4.03 (s, 2H), 7.18 (s, 1H), 8.06 (s, 1H), 12.40 (br s, 1H).

Intermediate 1120

4-chloro-6-(2-methoxyethyl)thieno[2,3-d]pyrimidine



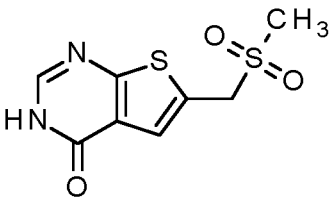
Into flask, was placed 6-(2-methoxyethyl)thieno[2,3-d]pyrimidin-4(3H)-one (3.65 g, 17.3 mmol, intermediate **1117),** DMF (67 µl) and phosphorus oxychloride (15 ml, 160 mmol). The resulting solution was stirred for 2 h at 110°C. The reaction mixture was cooled. The resulting mixture was concentrated under vacuum. The reaction was then quenched with ice water. The mixture was extracted with ethyl acetate. The extracts were dried over anhydrous sodium sulfate and concentrated under vacuum. The resulting material was purified by flash chromatography on silica gel 60 (eluent: hexane-ethyl acetate) to give 3.02 g (100 % purity, 76 % yield) of the desired product (intermediate **1120).**

LC-MS (method 12): Rt = 1.05 min; MS (ESIpos): m/z = 229 [M+H]+

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 3.24 (td, 2H), 3.30 (s, 3H), 3.66 (t, 2H), 7.37 (t, 1H), 8.87 (s, 1H).

Intermediate 1121

6-[(methylsulfonyl)methyl]thieno[2,3-d]pyrimidin-4(3H)-one

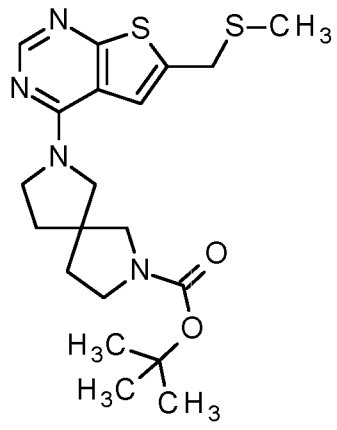


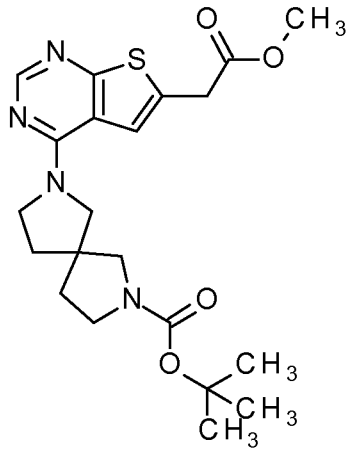
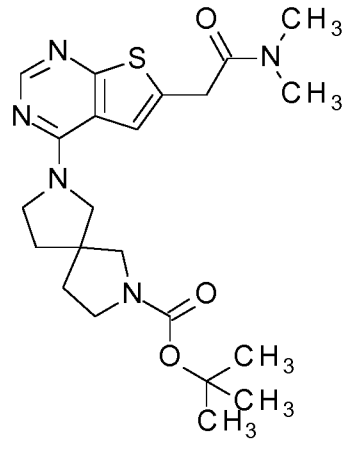
6-[(methylsulfanyl)methyl]thieno[2,3-d]pyrimidin-4(3H)-one (2.90 g, 13.7 mmol, intermediate **1114**) was dissolved in chloroform (72 ml) and cooled to 0°C. 3-Chloroperbenzoic acid (7.65 g, 77 % purity, 34.2 mmol) was added and stirred for 2h at 0°C and then additional 16h at RT. The reaction mixture was quenched with water, and extracted 2x with ethyl acetate. The organic layers were combined and evaporated. The crude product was purified by RP-column chromatography (BIOTAGE ISOLERA, SNAP C18 Biotage cartridge) to yield the desired product 470 mg (13% yield).

LC-MS (method 1): Rt = 0.35 min; MS (ESIneg): m/z = 245 [M-H]-

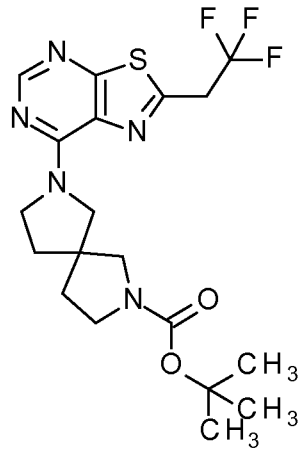
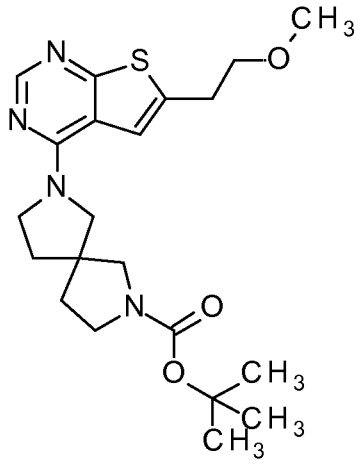
1H-NMR (400 MHz, DMSO-d6) delta [ppm]: 2.518 (0.93), 2.523 (0.67), 2.993 (16.00), 4.862 (7.01), 7.333 (0.97), 7.445 (6.03), 8.123 (1.51), 8.147 (8.73), 12.569 (0.71).

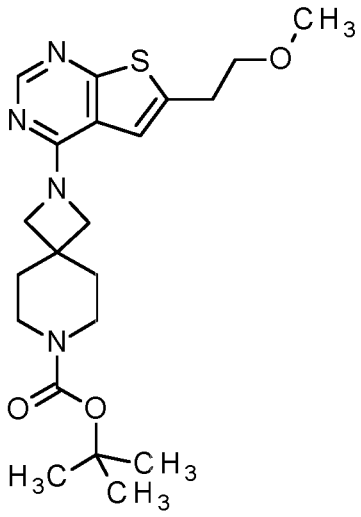
The following intermediates were prepared analogous to intermediate **I90** starting from the corresponding 6-substituted thieno[2,3-d]pyrimidin-4(3H)-ones **1121**, **1116** and **1119** by reacting with the corresponding spirocyclic amines.

Inter-mediate	Structure Name	Analytical Data
I122		^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.172 (0.70), 1.352 (0.68), 1.382 (2.67), 1.400 (16.00), 1.613 (1.24), 1.622 (1.44), 1.638 (0.87), 1.777 (0.54), 1.795 (1.02), 1.812 (0.54), 1.987 (1.35), 2.331 (0.49), 2.518 (2.49), 2.522 (1.66), 2.673 (0.51), 3.035 (0.52), 3.167 (1.27), 3.179 (1.35), 3.825 (0.52), 3.837 (0.49), 3.854 (0.43), 3.867 (0.44), 3.880 (0.48), 4.070 (1.10),

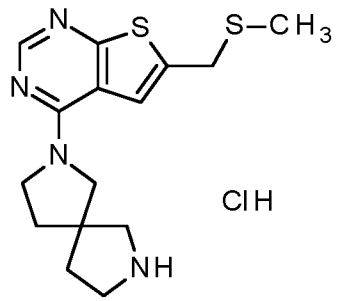
Inter-mediate	Structure Name	Analytical Data
	tert-butyl 7-{6-[(methylsulfanyl)methyl]thieno[2,3-d]pyrimidin-4-yl}-2,7-diazaspiro[4.4]nonane-2-carboxylate	4.098 (1.04), 7.634 (1.89), 8.379 (3.98). LC-MS (method 8): Rt = 1.41 min; MS (ESIpos): m/z = 457 [M+H]+
I123	 tert-butyl (7-[6-(2-methoxy-2-oxoethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]nonane-2-carboxylate	LC-MS (method 13): Rt = 1.19 min; MS (ESIpos): m/z =433 [M+H]+ ^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.40 (d, 9H), 1.82 - 1.93 (m, 2H), 1.99 (br s, 2H), 3.22 - 3.31 (m, 2H), 3.36 (br dd, 2H), 3.66 (s, 7H), 4.05 (s, 2H), 7.56 (s, 1H), 8.29 (s, 1H).
I124	 tert-butyl 7-{6-[2-(dimethylamino)-2-oxoethyl]thieno[2,3-d]pyrimidin-4-yl}-2,7-diazaspiro[4.4]nonane-2-carboxylate	LC-MS (method 13): Rt = 1.07 min; MS (ESIpos): m/z = 446 [M+H]$^+$ ^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.38 - 1.42 (m, 9H), 1.82 - 1.93 (m, 2H), 1.99 (br s, 2H), 2.85 (s, 3H), 3.06 (s, 3H), 3.23 - 3.31 (m, 2H), 3.35 - 3.41 (m, 2H), 3.59 - 3.97 (m, 4H), 4.03 (s, 2H), 7.48 (s, 1H), 8.27 (s, 1H).

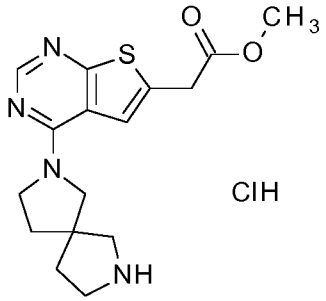
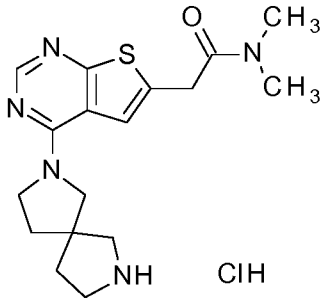
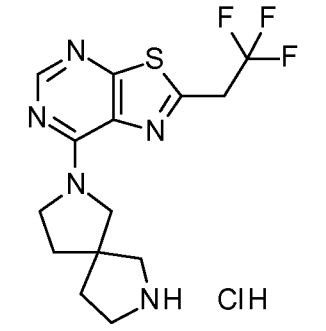
The following intermediates were prepared analogous to intermediate **112** starting from 7-chloro-2-(2,2,2-trifluoroethyl)-[1,3]thiazolo[5,4-d]pyrimidine (CAS # 1935198-98-3) and the intermediate **1120** by reacting with the corresponding spirocyclic amines.

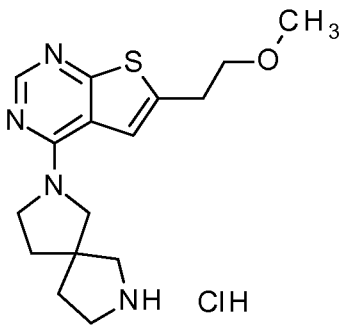
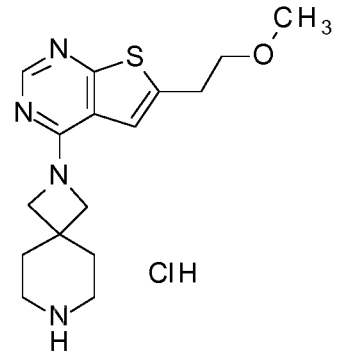
Inter-mediate	Structure Name	Analytical Data
I125	 tert-butyl 7-[2-(2,2,2-trifluoroethyl)[1,3]thiazolo[5,4-d]pyrimidin-7-yl]-2,7-diazaspiro[4.4]nonane-2-carboxylate	LC-MS (method 12): Rt = 1.37 min; MS (ESIneg): m/z = 442 $[M+H]^-$ ^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.39 (br d, 10H), 1.84 - 2.08 (m, 5H), 3.21 - 3.31 (m, 3H), 3.35 - 3.41 (m, 2H), 3.65 (br d, 1H), 3.77 (br s, 1H), 4.04 (d, 1H), 4.18 (br s, 1H), 4.37 (q, 2H), 8.39 (br d, 1H).
I126	 tert-butyl 7-[6-(2-methoxyethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]nonane-2-	LC-MS (method 12): Rt = 1.15 min; MS (ESIpos): m/z = 419 $[M+H]^+$ ^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.40 (d, 9H), 1.82 - 1.93 (m, 2H), 1.99 (s, 2H), 3.09 (t, 2H), 3.21 - 3.31 (m, 5H), 3.35 - 3.42 (m, 2H), 3.59 (t, 2H), 3.70 (br s, 2H), 3.85 (br s, 2H), 7.43 (s, 1H), 8.26 (s, 1H).

Inter¬ mediate	Structure Name	Analytical Data
	carboxylate	
11 27	 tert-butyl 2-[6-(2-methoxyethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]nonane-7-carboxylate	LC-MS (method 12): Rt = 1.16 min; MS (ESIpos): m/z = 419 $[M+H]^+$ ^{1}H-NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 1.47 (s, 9H), 1.82 (br t, 4H), 3.11 (t, 2H), 3.39 (s, 3H), 3.43 (br s, 4H), 3.66 (t, 2H), 4.11 (br s, 4H), 6.95 (s, 1H), 8.39 (s, 1H).

The following intermediates were prepared analogous to intermediate 11 06 starting from intermediates 11 22, 11 23, 11 24 ,11 25, 11 26, and 11 27 respectively.

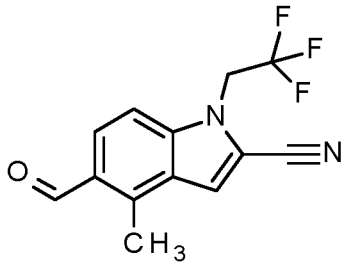
Inter-mediate	Structure Name	Analytical Data
I128	 4-[2,7-diazaspiro[4.4]non-2-yl]-	LC-MS (method 8): Rt = 0.94 min; MS (ESIpos): m/z = 322 $[M+H]^+$

Inter-mediate	Structure Name	Analytical Data
	6-[(methylsulfanyl)methyl]thieno[2,3-d]pyrimidine hydrochloride	
I129	 methyl {4-[2,7-diazaspiro[4.4]non-2-yl]thieno[2,3-d]pyrimidin-6-yl}acetate hydrochloride	LC-MS (method 13): Rt = 0.86 min; MS (ESIpos): m/z = 333 $[M+H]^+$ ^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.90 - 2.12 (m, 3H), 2.12 - 2.25 (m, 1H), 3.14 - 3.35 (m, 5H), 3.68 (s, 3H), 3.77 - 4.05 (m, 4H), 4.12 (s, 2H), 7.73 (br s, 1H), 8.55 (s, 1H), 9.60 (br s, 2H).
I130	 2-{4-[2,7-diazaspiro[4.4]non-2-yl]thieno[2,3-d]pyrimidin-6-yl}-N,N-dimethylacetamide hydrochloride	LC-MS (method 13): Rt = 0.73 min; MS (ESIpos): m/z =346 $[M+H]^+$ ^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.91 - 2.13 (m, 4H), 2.18 (br s, 1H), 2.87 (s, 3H), 3.08 (s, 3H), 3.14 - 3.26 (m, 4H), 3.27 - 3.35 (m, 3H), 3.94 (br s, 4H), 4.11 (s, 2H), 7.66 (br s, 1H), 8.54 (s, 1H), 9.52 (br s, 2H).
I131	 7-[2,7-diazaspiro[4.4]non-2-yl]-	LC-MS (method 13): Rt = 0.98 min; MS (ESIpos): m/z = 344 $[M+H]^+$ ^{1}H-NMR (600 MHz, DMSO-d6) δ [ppm]: 1.93 - 2.04 (m, 2H), 2.05 - 2.24 (m, 2H), 3.16 - 3.25 (m, 2H), 3.29 (br d, 2H), 3.68 - 3.83 (m, 2H), 4.12 - 4.23 (m, 2H), 4.39 (q, 2H), 8.42 - 8.50 (m, 1H), 9.35 - 9.59 (m, 2H).

Inter-mediate	Structure Name	Analytical Data
	2-(2,2,2-trifluoroethyl)[1,3]thiazolo[5,4-d]pyrimidine hydrochloride	
I132	 4-[2,7-diazaspiro[4.4]non-2-yl]-6-(2-methoxyethyl)thieno[2,3-d]pyrimidine hydrochloride	LC-MS (method 12): Rt = 0.86 min; MS (ESIpos): m/z = 319 $[M+H]^+$ ^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.92 - 2.12 (m, 3H), 2.18 (br s, 1H), 3.12 - 3.20 (m, 3H), 3.21 - 3.36 (m, 7H), 3.62 (t, 2H), 3.79 - 4.12 (m, 4H), 7.63 (br s, 1H), 8.56 (s, 1H), 9.55 (br s, 2H).
I133	 4-(2,7-diazaspiro[3.5]non-2-yl)-6-(2-methoxyethyl)thieno[2,3-d]pyrimidine hydrochloride	LC-MS (method 13): Rt = 0.84 min; MS (ESIpos): m/z =319 $[M+H]^+$ ^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 2.03 (br t, 4H), 3.06 (br s, 4H), 3.11 - 3.17 (m, 2H), 3.29 (s, 3H), 3.61 (t, 2H), 3.88 - 4.70 (m, 4H), 7.31 (s, 1H), 8.54 (s, 1H), 9.19 (br s, 2H).

Intermediate 1134

5-formyl-4-methyl-1-(2,2,2-trifluoroethyl)-1 H-indole-2-carbonitrile



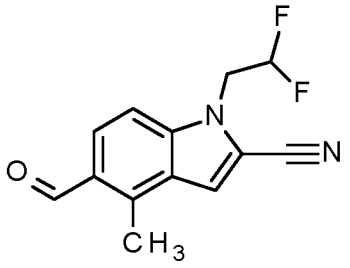
5-Formyl-4-methyl-1 H-indole-2-carbonitrile (250 mg, 1.36 mmol, CAS # 1857296-22-0) was added to DMF (13 ml). Then caesium carbonate (884 mg, 2.71 mmol) was added and then 2,2,2-trifluoroethyl trifluoromethanesulfonate (310 µl, 96 % purity, 2.0 mmol). The mixture was stirred for 16 h at RT. The reaction mixture was evaporated under reduced pressure. The resulting crude product was purified by RP-HPLC which gave the desired product (203 mg, 56 % yield, intermediate **1134).**

LC-MS (method 13): Rt = 1.15 min; MS (ESIpos): m/z =267 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 2.87 (s, 3H), 5.46 (d, 2H), 7.80 (d, 1H), 7.91 (d, 1H), 8.03 (s, 1H), 10.38 (s, 1H).

Intermediate 1135

1-(2,2-difluoroethyl)-5-formyl-4-methyl-1 H-indole-2-carbonitrile



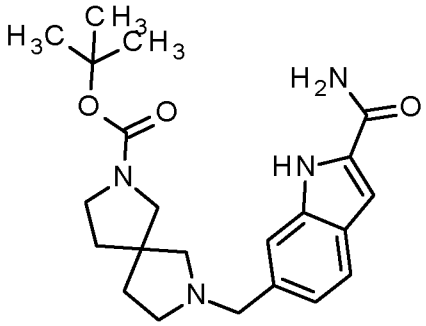
5-Formyl-4-methyl-1 H-indole-2-carbonitrile (150 mg, 814 µmol, CAS # 1857296-22-0) was added to DMF (7.5 ml). Then caesium carbonate (531 mg, 1.63 mmol) was added and then 2,2-difluoroethyl trifluoromethanesulfonate (170 µl, 98 % purity, 1.2 mmol). The mixture was stirred for 45 h at 60°C. The reaction mixture was evaporated under reduced pressure. The resulting crude product was purified by RP-HPLC which gave the desired product (109 mg, 90 % purity, 49 % yield, intermediate **1135).**

LC-MS (method 13): Rt = 1.06 min; MS (ESIpos): m/z = 249 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 2.86 (s, 3H), 4.91 (td, 2H), 6.35 - 6.66 (m, 1H), 7.68 (d, 1H), 7.86 (d, 1H), 7.95 (s, 1H), 10.37 (s, 1H).

Intermediate 1136

tert-butyl 7-[(2-carbamoyl-1H-indol-6-yl)methyl]-2,7-diazaspiro[4.4]nonane-2-carboxylate

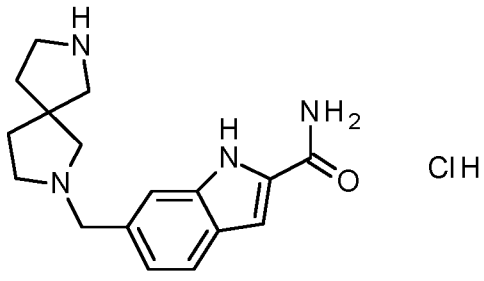


To a stirring solution of 6-formyl-1 H-indole-2-carboxamide (1.00 g, 5.31 mmol) in 12 ml dichloromethane was added triethylamine (1.6 ml, 12 mmol). Then tert-butyl 2,7-diazaspiro[4.4]nonane-2-carboxylate (1.20 g, 5.31 mmol) and sodium triacetoxyborohydride (2.08 g, 9.83 mmol) was added. Stirring continued at room temperature for 18 hours. The mixture was quenched with water and extracted 3x with ethyl acetate. The combined organic extracts were dried over sodium sulphate and concentrated under vacuum to give the desired product, 2.4 g (113%), which was used in the next step without further purification.

LC-MS (method 8): Rt = 1.13 min; MS (ESIpos): m/z = 399 $[M+H]^+$

Intermediate 1137

6-(2,7-diazaspiro[4.4]non-2-ylmethyl)-1 H-indole-2-carboxamide hydrochloride



To a stirring solution of tert-butyl 7-[(2-carbamoyl-1 H-indol-6-yl)methyl]-2,7-diazaspiro[4.4]nonane-2-carboxylate (3.50 g, 7.90 mmol) (intermediate **IXX)** in methanol (79 ml), was added hydrochloric acid (4 M in 1,4-dioxane), 14 ml (55 mmol). Stirring continued at room temperature for 2 days. The reaction mixture was concentrated under vacuum to give the desired product, 3.3 g (125% yield), and was used without further purification.

1H-NMR (400 MHz, DMSO-d6) delta [ppm]: 1.929 (0.59), 1.945 (0.61), 1.963 (0.53), 2.008 (0.51), 2.021 (0.77), 2.028 (0.85), 2.040 (0.56), 2.047 (0.46), 2.061 (0.56), 2.083 (0.73), 2.093

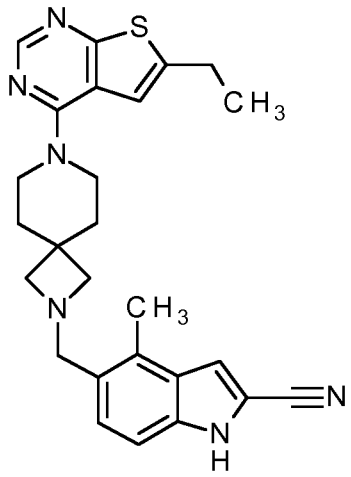
(0.81), 2.107 (1.00), 2.128 (0.72), 2.518 (1.24), 2.523 (0.81), 3.058 (1.14), 3.136 (0.45), 3.162 (16.00), 3.180 (1.65), 3.197 (1.37), 3.209 (1.04), 3.233 (0.54), 3.250 (0.85), 3.268 (1.12), 3.280 (1.06), 3.290 (0.98), 3.306 (0.56), 3.393 (0.40), 3.461 (0.53), 3.476 (0.56), 3.492 (0.45), 3.563 (1.50), 3.882 (0.67), 4.385 (0.56), 4.398 (0.57), 4.470 (0.69), 4.483 (0.51), 4.501 (0.46), 4.800 (0.74), 7.140 (2.07), 7.145 (2.07), 7.324 (1.21), 7.345 (1.37), 7.434 (0.65), 7.614 (2.44), 7.649 (2.12), 7.670 (1.87), 8.066 (0.54), 11.901 (1.04).

LC-MS (method 8): Rt = 0.79 min; MS (ESIpos): m/z = 299 $[M+H]^+$

EXPERIMENTAL SECTION - EXAMPLES

Example 1

5-{[7-(6-ethylthieno[2,3-d]pyrimidin-4-yl)-27-diazaspiro[3.5]non-2-yl]methyl}-4 -methyl-1H-indole-2-carbonitrile



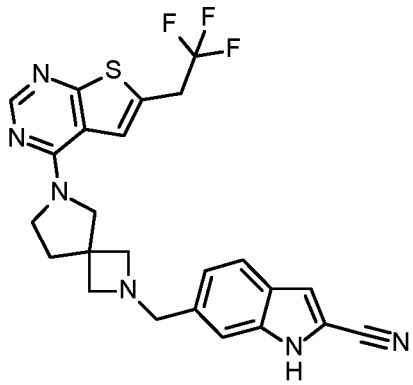
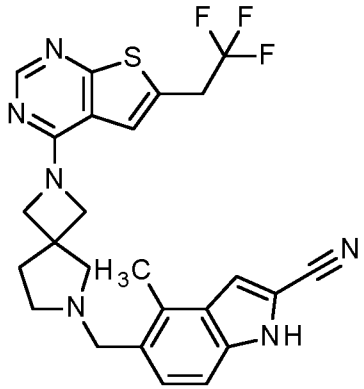
To a suspension of 150 mg (462 μηηοl) 4-(2,7-diazaspiro[3.5]non-7-yl)-6-ethylthieno[2,3-d]pyrimidine hydrochloride (intermediate **I34)** in 5.8 ml dichloromethane was added 109 μl triethylamine (785 μηηοl) followed by 85 mg (462 μηηοl) 5-formyl-4-methyl-1 H-indole-2-carbonitrile (CAS[1 857296-22-0], for preparation see Cancer Cell **2015,** 27, 589) and 166 mg (785 μηηοl) sodium triacetoxyborohydride (CAS[56553-60-7]) and the mixture was stirred for 17 h at RT. The reaction mixture was treated with 1M solution of sodium hydroxide, extracted with dichloromethane (2x) and the combined collected organic phases were concentrated in vacuo. The residue was purified by preparative HPLC to yield 151 mg (68%) of the desired product.

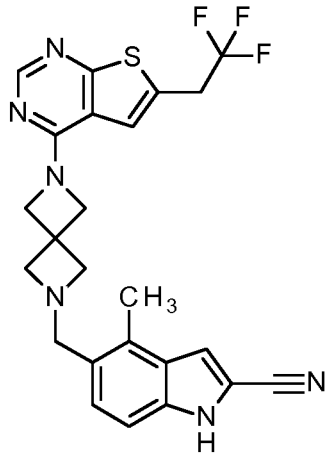
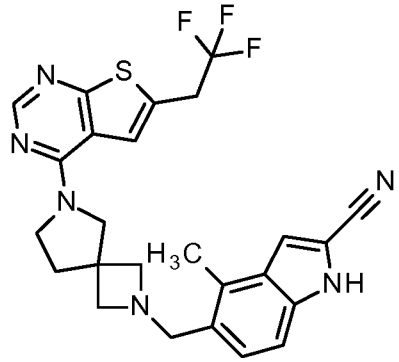
LC-MS (method 2): R_t = 0.78 min; m/z = 457 $(M+H)^+$

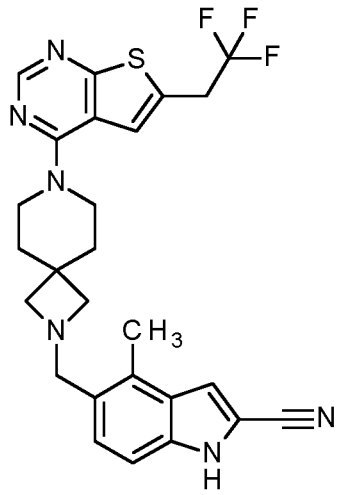
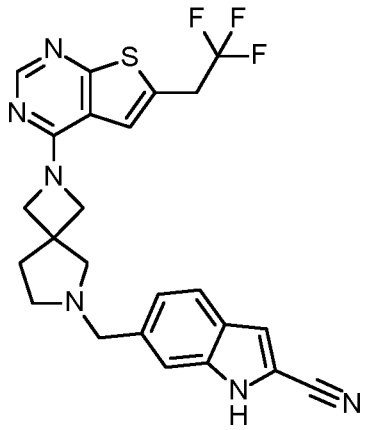
^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.258 (6.51), 1.277 (16.00), 1.295 (6.38), 1.767 (2.50), 1.780 (3.10), 1.794 (2.56), 2.323 (0.47), 2.327 (0.67), 2.332 (0.46), 2.477 (14.15), 2.518 (2.57),

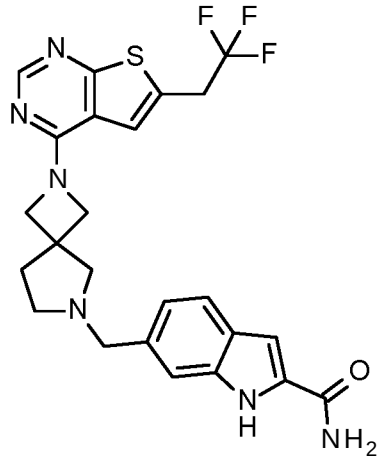
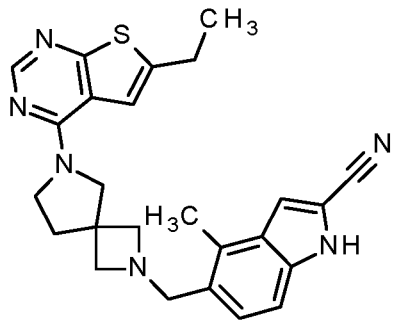
2.523 (1.94), 2.665 (0.47), 2.669 (0.68), 2.673 (0.45), 2.867 (0.94), 2.870 (0.98), 2.886 (2.91), 2.889 (2.94), 2.905 (2.77), 2.907 (2.81), 2.924 (0.91), 2.926 (0.91), 2.996 (13.74), 3.663 (5.92), 3.718 (2.57), 3.731 (3.12), 3.744 (2.50), 7.21 1 (1.38), 7.231 (2.82), 7.237 (2.41), 7.240 (4.23), 7.243 (2.30), 7.270 (3.65), 7.292 (1.84), 7.435 (4.63), 7.437 (4.56), 8.310 (10.85), 12.233 (0.88).

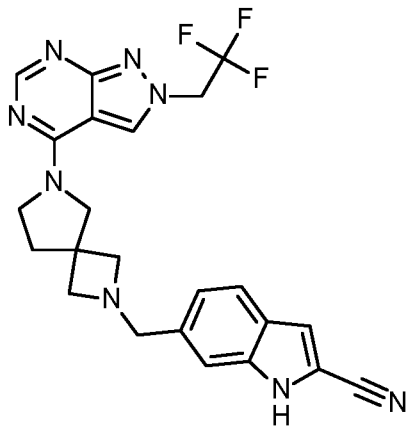
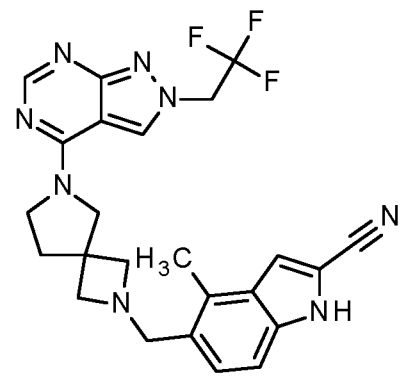
The following examples were prepared analogous to the preparation of example **1** starting from the corresponding intermediates **I22, I29, I24, I23, I33, I27** by reacting with the corresponding aldehydes.

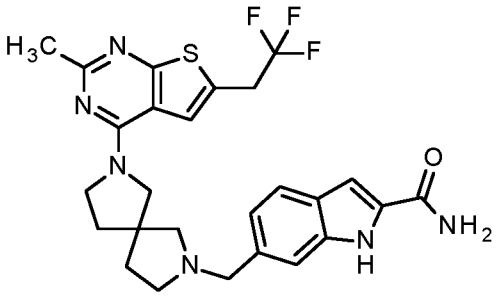
Example	Structure Name	Analytical Data
2	 6-({6-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,6-diazaspiro[3.4]oct-2-yl}methyl)-1 H-indole-2-carbonitrile	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 2.518 (3.93), 2.523 (2.81), 2.540 (16.00), 3.208 (11.02), 3.700 (7.09), 4.056 (1.92), 4.084 (1.82), 7.074 (2.11), 7.077 (2.12), 7.094 (2.14), 7.098 (2.25), 7.293 (1.07), 7.306 (5.85), 7.308 (6.18), 7.351 (3.49), 7.580 (3.22), 7.602 (2.83), 7.71 1 (2.11), 8.318 (13.50). LC-MS (method 2): R_t = 0.79 min; m/z = 483 $(M+H)^+$
3	 4-methyl-5-({2-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 2.082 (2.35), 2.100 (4.90), 2.117 (2.63), 2.323 (0.68), 2.327 (0.92), 2.331 (0.68), 2.523 (3.33), 2.530 (2.26), 2.548 (3.28), 2.564 (1.81), 2.665 (0.86), 2.669 (1.00), 2.673 (0.72), 2.756 (3.18), 3.657 (11.84), 4.002 (1.57), 4.030 (4.36), 4.057 (4.20), 4.085 (1.46), 4.250 (1.29), 7.216 (2.65), 7.238 (5.56), 7.271 (7.24), 7.292 (3.28), 7.422 (8.16), 7.445 (9.56), 8.305 (16.00),

Example	Structure Name	Analytical Data
	yl]-2,6-diazaspiro[3.4]oct-6-yl}methyl)-1H-indole-2-carbonitrile	12.254 (1.15) LC-MS (method 2): R_t = 0.77 min; m/z = 497 $(M+H)^+$
4	 4-methyl-5-({6-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,6-diazaspiro[3.3]hept-2-yl}methyl)-1H-indole-2-carbonitrile	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 2.074 (0.62), 2.472 (16.00), 2.518 (3.55), 2.522 (2.52), 3.611 (6.27), 4.009 (0.81), 4.037 (2.26), 4.065 (2.15), 7.211 (1.15), 7.232 (3.44), 7.250 (4.75), 7.272 (1.50), 7.437 (9.38), 7.439 (8.79), 8.315 (11.62), 12.250 (1.03). LC-MS (method 2): R_t = 0.75 min; m/z = 483 $(M+H)^+$
5	 4-methyl-5-({6-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,6-diazaspiro[3.4]oct-2-yl}methyl)-1H-indole-2-carbonitrile	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 2.480 (11.87), 2.518 (2.60), 2.523 (1.79), 2.540 (16.00), 3.183 (5.53), 3.666 (4.67), 4.053 (1.30), 4.080 (1.24), 7.207 (1.19), 7.228 (2.07), 7.275 (2.82), 7.297 (1.54), 7.437 (3.88), 7.439 (3.73), 7.701 (1.53), 8.312 (8.62). LC-MS (method 2): R_t = 0.79 min; m/z = 497 $(M+H)^+$

Example	Structure Name	Analytical Data
6	 4-methyl-5-({7-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}methyl)-1H-indole-2-carbonitrile	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.784 (2.72), 1.793 (3.19), 1.798 (3.42), 1.802 (3.28), 1.812 (2.76), 2.478 (16.00), 2.518 (3.33), 2.523 (2.36), 2.540 (5.81), 3.005 (14.14), 3.667 (6.29), 3.756 (2.79), 3.764 (3.13), 3.770 (3.43), 3.783 (2.71), 4.071 (2.28), 4.099 (2.17), 7.211 (1.53), 7.233 (2.85), 7.272 (3.96), 7.294 (1.96), 7.436 (4.65), 7.439 (4.90), 7.608 (4.31), 8.364 (13.11), 12.231 (1.03). LC-MS (method 2): R_t = 0.85 min; m/z = 511 $(M+H)^+$
7	 6-({2-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,6-diazaspiro[3.4]oct-6-yl}methyl)-1H-indole-2-carbonitrile	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 2.109 (1.46), 2.126 (3.13), 2.144 (1.71), 2.518 (1.69), 2.523 (1.26), 2.540 (0.43), 2.553 (1.51), 2.570 (2.62), 2.588 (1.30), 2.781 (3.40), 3.700 (6.57), 4.007 (1.01), 4.034 (2.83), 4.062 (2.70), 4.090 (0.92), 4.269 (0.80), 7.129 (2.46), 7.133 (2.35), 7.150 (2.60), 7.153 (2.60), 7.324 (6.45), 7.326 (7.25), 7.378 (3.98), 7.433 (5.60), 7.601 (3.66), 7.622 (3.29), 8.314 (16.00), 12.295 (0.72). LC-MS (method 2): R_t = 0.76 min; m/z = 483 $(M+H)^+$

Example	Structure Name	Analytical Data
8	 6-({2-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,6-diazaspiro[3.4]oct-6-yl}methyl)-1 H-indole-2-carboxamide	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.020 (0.71), 2.074 (0.50), 2.104 (2.14), 2.121 (4.26), 2.138 (2.33), 2.331 (0.99), 2.518 (4.88), 2.523 (3.48), 2.540 (2.67), 2.561 (3.67), 2.577 (1.83), 2.669 (1.43), 2.673 (1.03), 2.769 (4.94), 3.297 (0.56), 3.655 (7.77), 4.005 (1.43), 4.033 (3.98), 4.060 (3.82), 4.088 (1.30), 4.266 (1.21), 6.995 (3.14), 6.998 (3.11), 7.016 (3.26), 7.019 (3.32), 7.073 (5.44), 7.313 (1.62), 7.346 (5.81), 7.435 (7.58), 7.514 (4.69), 7.535 (4.26), 7.920 (1.55), 8.311 (16.00), 8.324 (0.75), 8.558 (0.43), 11.469 (3.36). LC-MS (method 2): R_t = 0.64 min; m/z = 501 $(M+H)^+$
9	 5-{[6-(6-ethylthieno[2,3-d]pyrimidin-4-yl)-2,6-diazaspiro[3.4]oct-2-yl]methyl}-4-methyl-1 H-indole-2-carbonitrile	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.260 (6.04), 1.279 (13.11), 1.297 (6.16), 2.119 (0.90), 2.136 (1.63), 2.152 (0.91), 2.479 (16.00), 2.518 (3.33), 2.523 (2.50), 2.540 (0.69), 2.860 (0.93), 2.879 (2.70), 2.898 (2.65), 2.916 (0.87), 3.159 (1.17), 3.175 (7.82), 3.197 (0.90), 3.666 (6.56), 3.745 (0.79), 3.865 (1.18), 7.206 (1.62), 7.227 (2.79), 7.278 (3.87), 7.299 (2.14), 7.354 (2.95), 7.435 (4.85), 7.437 (4.64), 8.246 (12.45), 12.231 (1.08). LC-MS (method 2): R_t = 0.72 min; m/z = 443 $(M+H)^+$

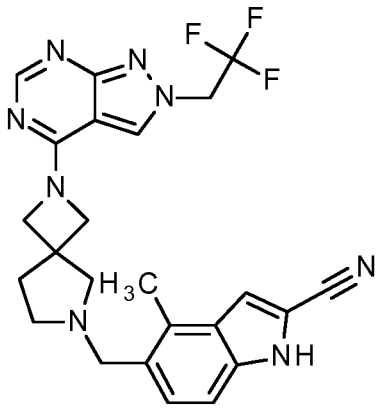
Example	Structure Name	Analytical Data
10	 6-({6-[2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,6-diazaspiro[3.4]oct-2-yl}methyl)-1H-indole-2-carbonitrile	1H-NMR (500 MHz, DMSO-d6) δ [ppm]: -0.030 (6.43), -0.016 (4.78), 2.101 (3.81), 2.115 (7.52), 2.129 (4.38), 2.133 (6.49), 2.246 (2.73), 2.260 (5.41), 2.274 (2.73), 2.335 (1.14), 2.339 (2.51), 2.343 (3.42), 2.347 (2.39), 2.350 (1.08), 2.521 (3.07), 2.609 (1.20), 2.613 (2.56), 2.616 (3.42), 2.620 (2.51), 2.624 (1.14), 3.145 (2.85), 3.154 (6.15), 3.167 (9.28), 3.184 (9.62), 3.199 (5.98), 3.202 (6.43), 3.216 (12.19), 3.230 (11.90), 3.244 (4.84), 3.452 (1.20), 3.636 (3.81), 3.650 (7.35), 3.664 (3.99), 3.681 (13.84), 3.689 (16.00), 3.753 (3.25), 3.770 (15.43), 3.780 (3.53), 3.896 (14.18), 5.297 (1.48), 5.316 (4.61), 5.336 (6.72), 5.355 (5.07), 5.372 (1.48), 7.067 (5.30), 7.084 (5.52), 7.285 (10.93), 7.331 (8.60), 7.335 (7.35), 7.563 (4.90), 7.570 (5.92), 7.579 (4.61), 7.586 (5.35), 8.187 (15.54), 8.194 (12.36), 8.287 (2.85), 8.288 (2.73), 8.693 (8.83), 8.793 (11.96), 12.258 (4.67). LC-MS (method 2): R_t = 0.47 min; m/z = 467 $(M+H)^+$
11	 4-methyl-5-({6-[2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,6-	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 2.100 (1.07), 2.118 (2.17), 2.135 (1.13), 2.240 (0.76), 2.257 (1.54), 2.274 (0.79), 2.484 (16.00), 2.518 (2.29), 2.523 (1.67), 3.138 (1.03), 3.155 (3.11), 3.167 (3.18), 3.185 (1.33), 3.192 (1.62), 3.210 (3.67), 3.223 (3.66), 3.241 (1.36), 3.640 (1.23), 3.659 (5.50), 3.672 (5.33), 3.757 (1.00), 3.772 (5.14), 3.790 (0.89), 3.896 (4.07), 5.316 (0.48), 5.339 (1.94), 5.361 (2.94),

Example	Structure Name	Analytical Data
	diazaspiro[3.4]oct-2-yl}methyl)-1H-indole-2-carbonitrile	5.383 (1.96), 5.406 (0.50), 7.205 (1.01), 7.211 (1.19), 7.226 (1.87), 7.232 (2.22), 7.273 (5.54), 7.294 (2.83), 7.437 (4.84), 8.207 (7.49), 8.209 (6.04), 8.711 (2.96), 8.799 (3.84). LC-MS (method 2): R_t = 0.47 min; m/z = 481 $(M+H)^+$
12	 6-({7-[2-methyl-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carboxamide	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.753 (0.44), 1.787 (0.66), 1.803 (1.21), 1.822 (1.29), 1.838 (0.64), 1.977 (0.51), 2.323 (0.46), 2.327 (0.68), 2.332 (0.49), 2.405 (16.00), 2.454 (0.79), 2.518 (2.37), 2.523 (1.81), 2.540 (0.87), 2.546 (1.18), 2.569 (1.18), 2.585 (0.69), 2.636 (0.68), 2.660 (0.61), 2.665 (0.70), 2.669 (0.85), 2.673 (0.66), 3.610 (0.65), 3.642 (1.68), 3.665 (1.86), 3.697 (0.96), 3.971 (0.45), 3.999 (1.18), 4.026 (1.13), 6.996 (1.56), 6.999 (1.52), 7.016 (1.63), 7.019 (1.62), 7.062 (2.34), 7.064 (2.57), 7.067 (2.51), 7.309 (0.84), 7.338 (2.42), 7.496 (2.00), 7.517 (1.79), 7.615 (2.91), 7.911 (0.81), 11.451 (1.68). LC-MS (method 2): R_t = 0.66 min; m/z = 529 $(M+H)^+$
12.1	6-({7-[2-methyl-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carboxamide (ent-1)	separation of example **12** by chiral chromatography afforded **12.1** and its enantiomer **12.2**. prep. HPLC (method C) analyt. HPLC (method 6): R_t = 2.36 min optical rotation: $[\alpha]_D^{20}$ = 48.4° +/-0.92° (c = 1.00; chloroform)

Example	Structure Name	Analytical Data
12.2	6-({7-[2-methyl-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carboxamide (ent-2)	prep. HPLC (method C) analyt. HPLC (method 6): R_t = 3.72 min optical rotation: $[a]_D^{20}$ = -42.5° +/-0.85 0 (c = 1.00; chloroform)

Example 13

4-methyl-5-({2-[2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin -4-yl]-2,6-diazaspiro[3.4]oct-6-yl}methyl)-1H-indole-2-carbonitrile

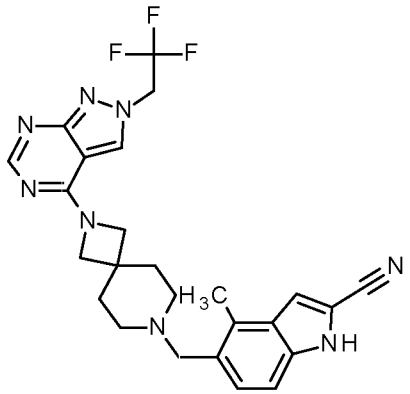
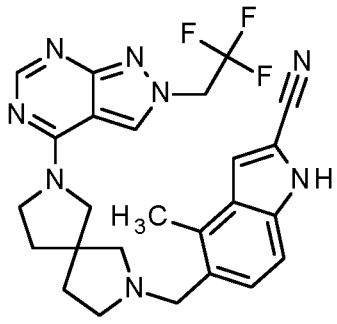


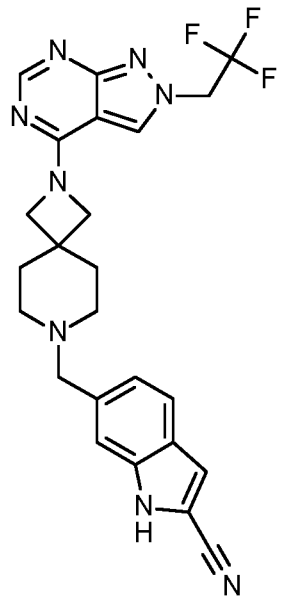
To a suspension of 100 mg (21 1 μηιοI) 4-(2,6-diazaspiro[3.4]oct-2-yl)-2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidine trifluoroacetate (intermediate **132)** in 2.7 mI dichloromethane was added 65 μI triethylamine (460 μηιοI), followed by 38.9 mg (21 1 μηιοI) 5-formyl-4-methyl-1 H-indole-2-carbonitrile (CAS[1 857296-22-0) and 82.8 mg (391 μηιοI) sodium triacetoxyborohydride (CAS[56553-60-7]) and the mixture was stirred for 17 h at RT. The reaction mixture was concentrated in vacuo and the residue was purified by preparative HPLC to yield 47.1 mg (44%) of the desired product.

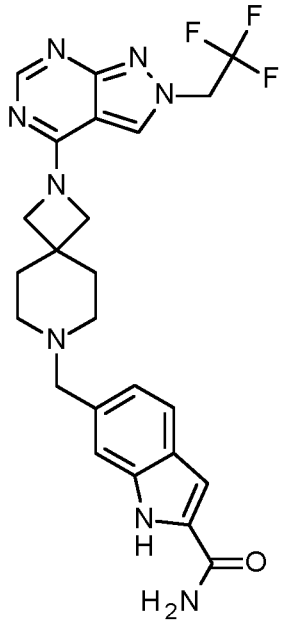
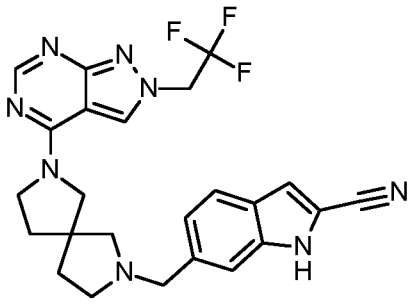
LC-MS (method 2): Rt = 0.51 min; MS (ESIpos): m/z = 481 $[M+H]^+$

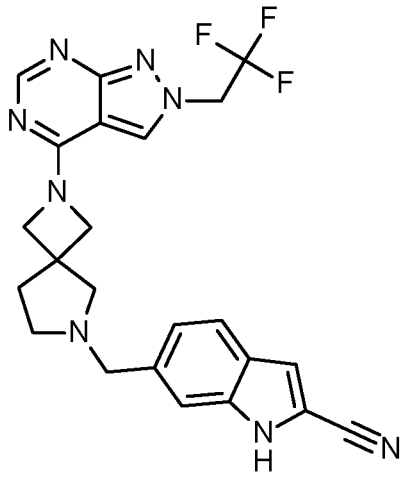
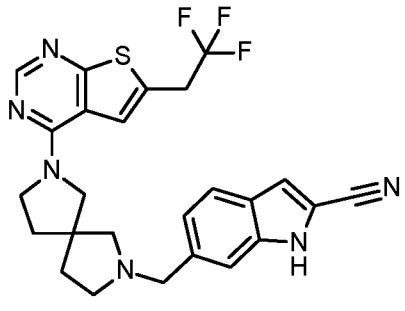
^{1}H-NMR (500 MHz, DMSO-d6) δ [ppm]: 2.095 (1.01), 2.108 (1.91), 2.1 19 (2.00), 2.132 (1.02), 2.358 (0.48), 2.361 (0.64), 2.365 (0.47), 2.515 (3.59), 2.518 (2.94), 2.522 (2.32), 2.540 (0.65), 2.590 (0.89), 2.603 (0.72), 2.632 (0.58), 2.635 (0.75), 2.639 (0.51), 2.690 (0.79), 2.707 (1.21), 2.815 (1.23), 2.834 (0.76), 3.662 (9.52), 4.108 (2.35), 4.319 (3.14), 5.320 (1.25), 5.338 (3.52), 5.356 (3.27), 5.373 (0.99), 7.218 (2.25), 7.235 (4.1 1), 7.271 (5.69), 7.288 (2.99), 7.445 (6.72), 7.446 (6.45), 8.192 (16.00), 8.583 (10.39), 12.254 (1.86).

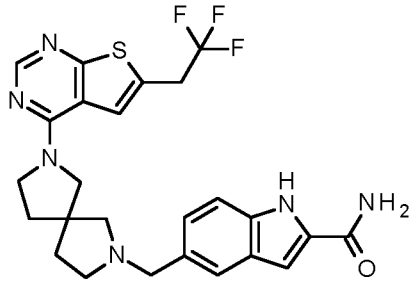
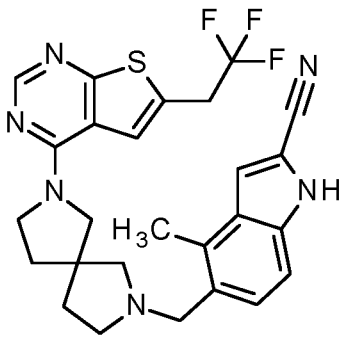
The following examples were prepared analogous to the preparation of example **13** starting from the corresponding intermediates **I28, 131 , I28, I32, I30, I26** or **I35** by reacting with the corresponding aldehydes.

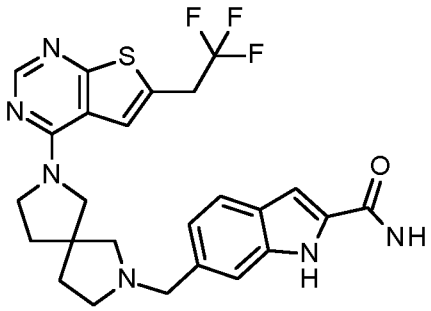
Example	Structure Name	Analytical Data
14	 4-methyl-5-({2-[2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1H-indole-2-carbonitrile	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.777 (3.13), 2.280 (0.71), 2.323 (1.30), 2.327 (1.61), 2.331 (1.26), 2.337 (0.87), 2.417 (0.77), 2.518 (4.35), 2.523 (3.05), 2.540 (0.96), 2.660 (0.43), 2.665 (0.87), 2.669 (1.16), 2.673 (0.83), 3.492 (8.78), 3.891 (5.25), 4.124 (5.04), 5.327 (1.26), 5.349 (3.60), 5.371 (3.37), 5.394 (1.04), 7.214 (0.98), 7.235 (7.05), 7.241 (9.35), 7.262 (1.26), 7.447 (8.68), 8.202 (16.00), 8.645 (6.71), 12.271 (1.54). LC-MS (method 2): R_t = 0.53 min; m/z = 495 $(M+H)^+$
15	 4-methyl-5-({7-[2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carbonitrile	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.774 (2.40), 1.792 (5.01), 1.810 (3.10), 1.823 (1.87), 1.838 (2.66), 1.852 (2.96), 1.868 (1.57), 1.885 (0.61), 1.910 (0.70), 1.922 (1.44), 1.940 (3.40), 1.950 (2.79), 1.966 (1.79), 2.029 (0.74), 2.041 (1.22), 2.060 (2.66), 2.078 (2.70), 2.095 (1.40), 2.109 (0.65), 2.323 (1.79), 2.327 (2.53), 2.331 (1.87), 2.337 (1.00), 2.423 (4.23), 2.444 (6.02), 2.518 (10.86), 2.523 (10.07), 2.539 (7.19), 2.561 (4.62), 2.572 (4.62), 2.580 (2.35), 2.594 (3.14), 2.613 (1.48), 2.625 (2.92), 2.646 (2.70), 2.665 (2.70), 2.669 (3.27), 2.673 (2.18), 3.531 (2.49), 3.561 (4.01), 3.585 (1.48), 3.597 (1.44), 3.616 (2.88), 3.636 (7.06), 3.650 (15.56), 3.666 (8.59), 3.697 (2.79), 3.711 (1.92), 3.728 (5.01), 3.742 (2.09), 3.753 (3.44), 3.775 (1.61), 3.789 (1.83), 3.806 (1.26), 3.832 (0.44), 5.306 (1.53), 5.328 (4.75), 5.355 (5.89), 5.378 (4.62), 5.401

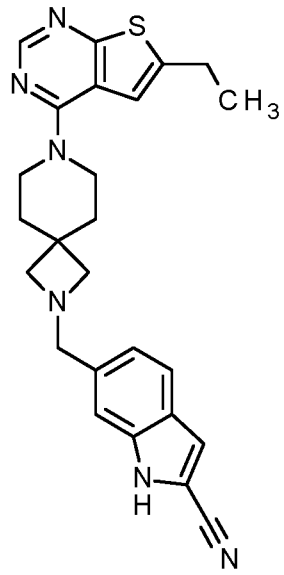
Example	Structure Name	Analytical Data
		(1.31), 7.184 (3.01), 7.205 (5.58), 7.221 (4.97), 7.260 (6.84), 7.266 (6.84), 7.281 (4.01), 7.287 (3.57), 7.417 (8.81), 7.436 (8.33), 8.192 (15.08), 8.201 (16.00), 8.693 (9.63), 8.753 (10.29), 12.244 (3.79). LC-MS (method 2): Rt = 0.51 min; m/z = 495 (M+H)+
15.1	4-methyl-5-({7-[2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carbonitrile (ent-1)	separation of example **15** by chiral chromatography afforded **15.1** and its enantiomer **15.2**. prep. HPLC (method F) analyt. HPLC (method 9): R_t = 5.77 min optical rotation: $[\alpha]_D^{20}$ = 38.3° +/-0.08° (c = 1.00; DMSO)
15.2	4-methyl-5-({7-[2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carbonitrile (ent-2)	prep. HPLC (method F) analyt. HPLC (method 9): R_t = 5.48 min optical rotation: $[\alpha]_D^{20}$ = -29.1° +/-0.59° (c = 1.00; DMSO)
16	 6-({2-[2-(2,2,2-trifluoroethyl)-2H-	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.817 (3.75), 2.289 (0.75), 2.318 (0.94), 2.323 (1.33), 2.327 (1.65), 2.331 (1.27), 2.518 (4.42), 2.523 (3.19), 2.540 (1.69), 2.660 (0.43), 2.665 (0.88), 2.669 (1.18), 2.673 (0.84), 3.563 (9.26), 3.892 (5.90), 4.116 (5.77), 5.321 (1.33), 5.344 (3.82), 5.366 (3.60), 5.389 (1.11), 7.103 (2.89), 7.105 (2.87), 7.124 (3.00), 7.126 (3.11), 7.314 (7.51), 7.316 (8.06), 7.361 (5.28), 7.595 (4.63), 7.616 (4.16), 8.201 (16.00), 8.570 (0.43), 8.632 (8.81). LC-MS (method 2): Rt = 0.54 min; m/z = 481 (M+H)+

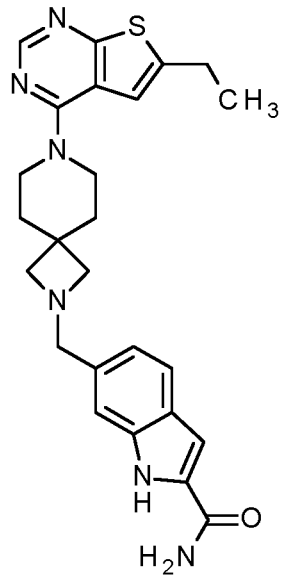
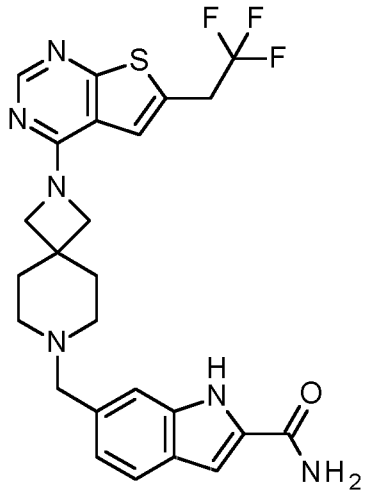
Example	Structure Name	Analytical Data
	pyrazolo[3,4-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1H-indole-2-carbonitrile	
17	 6-({2-[2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1H-indole-2-carboxamide	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.810 (2.54), 2.268 (0.52), 2.318 (0.69), 2.323 (1.12), 2.327 (1.40), 2.332 (1.08), 2.336 (0.60), 2.518 (3.94), 2.523 (2.91), 2.540 (3.75), 2.665 (0.82), 2.669 (1.12), 2.673 (0.75), 3.517 (6.12), 3.890 (4.22), 4.115 (4.18), 5.319 (0.97), 5.342 (2.73), 5.364 (2.56), 5.386 (0.80), 6.979 (2.33), 6.982 (2.20), 7.000 (2.33), 7.003 (2.33), 7.078 (3.38), 7.082 (3.34), 7.326 (4.87), 7.516 (3.29), 7.537 (2.93), 7.927 (1.10), 8.199 (16.00), 8.633 (6.63), 11.472 (2.50), 11.476 (2.43). LC-MS (method 2): Rt = 0.38 min; m/z = 499.2 (M+H)+
18	 6-({7-[2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carbonitrile	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.798 (2.03), 1.817 (4.09), 1.833 (3.16), 1.850 (2.10), 1.869 (2.17), 1.886 (1.13), 1.903 (0.73), 1.919 (0.86), 1.932 (1.06), 1.950 (2.25), 1.969 (2.32), 1.986 (1.08), 1.999 (0.55), 2.051 (0.53), 2.064 (0.95), 2.081 (2.28), 2.099 (2.23), 2.115 (1.06), 2.129 (0.49), 2.323 (0.93), 2.327 (1.28), 2.331 (0.95), 2.449 (2.32), 2.472 (4.35), 2.518 (4.55), 2.523 (3.31), 2.540 (6.34), 2.562 (2.65), 2.575 (2.14), 2.597 (4.93), 2.620 (2.65), 2.632 (0.95), 2.650 (1.86), 2.665 (3.43), 2.669 (3.16), 2.686 (1.44), 2.704 (0.46), 3.566 (1.83), 3.596 (3.12),

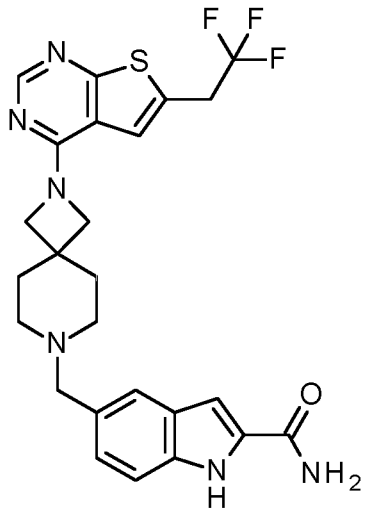
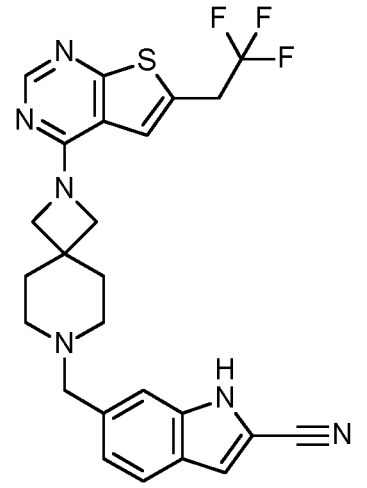
Example	Structure Name	Analytical Data
		3.620 (0.88), 3.634 (1.15), 3.651 (1.90), 3.666 (5.90), 3.696 (16.00), 3.708 (5.66), 3.736 (3.58), 3.761 (2.54), 3.780 (1.90), 3.799 (1.75), 3.819 (0.93), 5.311 (1.19), 5.333 (4.42), 5.356 (6.32), 5.378 (4.00), 5.401 (0.99), 7.136 (4.13), 7.156 (4.42), 7.313 (13.13), 7.363 (4.55), 7.385 (4.49), 7.578 (3.91), 7.590 (4.02), 7.599 (3.62), 7.610 (3.49), 8.205 (14.48), 8.206 (14.98), 8.699 (7.27), 8.771 (7.47), 12.291 (2.06). LC-MS (method 2): Rt = 0.51 min; m/z = 481 (M+H)+
19	 6-({2-[2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,6-diazaspiro[3.4]oct-6-yl}methyl)-1H-indole-2-carbonitrile	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 2.119 (1.20), 2.137 (2.36), 2.145 (2.34), 2.331 (0.79), 2.518 (4.08), 2.522 (2.88), 2.539 (1.20), 2.548 (0.89), 2.565 (1.35), 2.580 (1.26), 2.595 (1.39), 2.611 (0.83), 2.673 (0.81), 2.746 (0.66), 2.767 (1.80), 2.814 (1.80), 2.837 (0.62), 3.701 (4.00), 3.709 (3.92), 4.136 (3.57), 4.348 (3.50), 5.320 (1.37), 5.342 (3.98), 5.364 (3.73), 5.387 (1.14), 7.131 (3.00), 7.134 (2.96), 7.151 (3.19), 7.155 (3.19), 7.325 (7.88), 7.327 (8.29), 7.376 (5.20), 7.602 (4.60), 7.623 (4.19), 8.199 (16.00), 8.591 (10.49), 12.300 (1.00). LC-MS (method 2): Rt = 0.52 min; m/z = 467 (M+H)+
20	 6-({7-[6-(2,2,2-	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.801 (0.91), 1.820 (1.50), 1.836 (1.60), 1.854 (0.76), 1.995 (0.67), 2.322 (0.51), 2.327 (0.74), 2.332 (0.54), 2.457 (1.83), 2.480 (3.27), 2.518 (2.63), 2.523 (1.88), 2.539 (4.27), 2.559 (1.91), 2.575 (1.26), 2.582 (1.50), 2.591 (1.26), 2.611 (0.56), 2.629 (0.50), 2.647 (0.98), 2.665 (1.24), 2.669 (1.35), 2.673 (0.88), 3.656 (0.85), 3.689 (3.15),

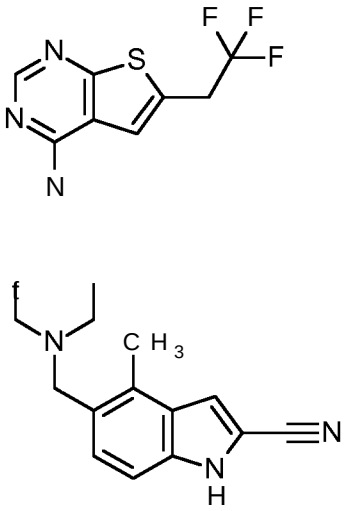
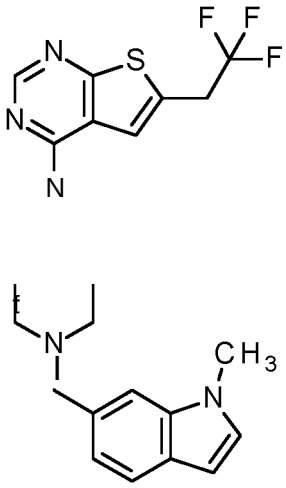
Example	Structure Name	Analytical Data
	trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carbonitrile	3.699 (3.59), 3.733 (1.26), 4.015 (0.56), 4.043 (1.51), 4.070 (1.45), 4.098 (0.51), 7.128 (2.27), 7.131 (2.26), 7.149 (2.39), 7.152 (2.45), 7.312 (5.96), 7.314 (6.31), 7.373 (3.12), 7.582 (3.16), 7.603 (2.80), 7.684 (3.45), 8.308 (16.00), 12.279 (1.29). LC-MS (method 2): Rt = 0.85 min; m/z = 497 (M+H)+
21	 5-({7-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carboxamide	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.786 (0.88), 1.804 (1.44), 1.821 (1.49), 1.839 (0.74), 1.980 (0.74), 2.323 (0.74), 2.327 (1.04), 2.331 (0.77), 2.430 (1.36), 2.452 (1.99), 2.523 (5.05), 2.540 (16.00), 2.607 (0.59), 2.626 (1.11), 2.641 (0.84), 2.665 (1.04), 2.669 (1.19), 2.673 (0.84), 3.590 (0.81), 3.623 (2.80), 3.637 (3.03), 3.669 (1.17), 3.725 (0.68), 4.016 (0.56), 4.044 (1.45), 4.072 (1.42), 4.098 (0.54), 7.049 (2.84), 7.053 (2.91), 7.143 (1.58), 7.146 (1.60), 7.164 (1.90), 7.167 (1.94), 7.324 (3.12), 7.346 (2.17), 7.478 (3.39), 7.685 (3.20), 7.905 (0.99), 8.304 (9.07), 8.318 (0.50), 11.455 (2.15). LC-MS (method 2): Rt = 0.64 min; m/z = 515.2 (M+H)+
22	 4-methyl-5-({7-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.782 (0.84), 1.798 (1.43), 1.816 (1.54), 1.833 (0.69), 1.971 (0.69), 2.414 (1.56), 2.437 (2.20), 2.518 (3.59), 2.523 (3.35), 2.539 (4.48), 2.545 (1.46), 2.549 (1.44), 2.554 (1.31), 2.577 (0.49), 2.601 (0.59), 2.620 (1.12), 2.635 (0.85), 2.660 (0.46), 3.359 (0.46), 3.613 (0.77), 3.645 (3.92), 3.651 (4.02), 3.684 (0.95), 3.734 (0.67), 4.011 (0.56), 4.038 (1.46), 4.066 (1.43), 4.093 (0.49), 7.191 (1.54), 7.212 (2.79), 7.259 (3.89), 7.280 (2.07),

Example	Structure Name	Analytical Data
	diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carbonitrile	7.424 (3.59), 7.672 (4.35), 8.298 (16.00), 12.236 (2.08). LC-MS (method 2): Rt = 0.86 min; m/z = 511 (M+H)+
22.1	4-methyl-5-({7-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carbonitrile (ent-1)	separation of example 22 by chiral chromatography afforded 22.1 and its enantiomer 22.2. prep. HPLC (method A) analyt. HPLC (method 4): R_t = 3.26 min optical rotation: $[a]_D^{20}$ = 47.5° +/-0.49 0 (c = 1.00; chloroform)
22.2	4-methyl-5-({7-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carbonitrile (ent-2)	prep. HPLC (method A) analyt. HPLC (method 4): R_t = 2.74 min optical rotation: $[a]_D^{20}$ = -48.3° +/-0.48 0 (c = 1.00; chloroform)
23	 6-({7-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carboxamide	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.793 (0.77), 1.809 (1.32), 1.828 (1.38), 1.845 (0.64), 1.989 (0.56), 2.323 (0.50), 2.327 (0.71), 2.332 (0.49), 2.451 (1.55), 2.475 (3.09), 2.518 (2.40), 2.523 (1.77), 2.540 (16.00), 2.546 (1.60), 2.569 (1.49), 2.585 (0.94), 2.606 (0.49), 2.614 (0.53), 2.634 (0.93), 2.649 (0.67), 2.660 (0.47), 2.665 (0.64), 2.669 (0.89), 2.673 (0.64), 3.608 (0.67), 3.641 (2.24), 3.656 (2.57), 3.689 (1.05), 4.015 (0.47), 4.043 (1.22), 4.070 (1.18), 4.098 (0.41), 6.995 (1.84), 6.998 (1.77), 7.015 (1.90), 7.019 (1.87), 7.061 (2.79), 7.065 (2.78), 7.067 (2.51), 7.306 (0.91), 7.337 (2.56), 7.494 (2.40), 7.514 (2.13), 7.686 (2.76), 7.908 (0.88), 8.305 (14.49), 11.445 (1.95), 11.449 (1.90).

Example	Structure Name	Analytical Data
		LC-MS (method 2): Rt = 0.71 min; m/z = 515 (M+H)+
23.1	6-({7-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carboxamide (ent-1)	separation of example **23** by chiral chromatography afforded example **23.1** and its enantiomer example **23.2**. prep. HPLC (method B) analyt. HPLC (method 5): R_t = 3.27 min optical rotation: $[\alpha]_D^{20}$ = 54.2° +/-0.56° (c = 1.00; chloroform)
23.2	6-({7-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carboxamide (ent-2)	prep. HPLC (method B) analyt. HPLC (method 5): R_t = 2.24 min optical rotation: $[\alpha]_D^{20}$ = -52.8° +/-0.54° (c = 1.00; chloroform)
24	 6-{[7-(6-ethylthieno[2,3-d]pyrimidin-4-yl)-2,7-diazaspiro[3.5]non-2-yl]methyl}-1H-indole-2-carbonitrile	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.261 (7.44), 1.279 (15.73), 1.298 (7.76), 1.780 (2.82), 1.794 (3.47), 1.807 (2.88), 2.332 (0.46), 2.518 (2.14), 2.523 (1.55), 2.872 (1.04), 2.874 (1.09), 2.890 (3.17), 2.893 (3.25), 2.909 (3.16), 2.912 (3.19), 2.928 (1.00), 2.930 (0.98), 3.027 (16.00), 3.705 (6.61), 3.727 (2.96), 3.741 (3.51), 3.754 (2.82), 7.076 (2.02), 7.079 (1.98), 7.097 (2.11), 7.100 (2.17), 7.247 (4.78), 7.249 (2.54), 7.317 (5.77), 7.319 (6.03), 7.354 (3.19), 7.584 (2.93), 7.606 (2.64), 8.315 (12.56), 12.285 (0.57). LC-MS (method 1): Rt = 0.97 min; m/z = 443 (M+H)+

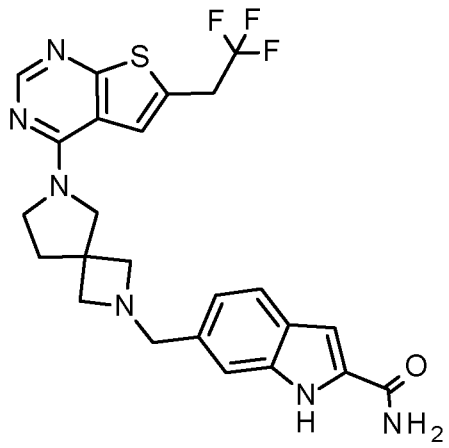
Example	Structure Name	Analytical Data
25	 6-{[7-(6-ethylthieno[2,3-d]pyrimidin-4-yl)-2,7-diazaspiro[3.5]non-2-yl]methyl}-1H-indole-2-carboxamide	^{1}H-NMR (400 MHz, DMS0-d6) δ [ppm]: 1.259 (7.79), 1.278 (16.00), 1.297 (8.01), 1.774 (2.79), 1.787 (3.49), 1.800 (2.86), 2.518 (2.01), 2.523 (1.49), 2.539 (3.00), 2.871 (1.08), 2.873 (1.13), 2.890 (3.27), 2.892 (3.32), 2.909 (3.15), 2.910 (3.23), 2.927 (1.03), 2.929 (1.02), 3.006 (14.39), 3.656 (6.11), 3.723 (2.87), 3.737 (3.51), 3.750 (2.79), 6.950 (1.95), 6.954 (1.97), 6.971 (2.07), 6.974 (2.06), 7.064 (2.91), 7.066 (2.86), 7.244 (2.56), 7.246 (5.04), 7.249 (2.62), 7.320 (3.79), 7.497 (2.82), 7.518 (2.60), 7.910 (0.86), 8.313 (13.56), 11.446 (1.98). LC-MS (method 1): Rt = 0.79 min; m/z = 461 (M+H)+
26	 6-({2-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1H-indole-2-carboxamide	1H-NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 1.115 (0.72), 1.213 (0.72), 1.228 (0.74), 1.694 (5.95), 1.883 (4.76), 1.897 (9.67), 1.910 (5.68), 2.182 (0.41), 2.417 (1.19), 2.435 (1.50), 2.454 (1.53), 2.629 (0.63), 3.593 (1.75), 3.620 (16.00), 3.643 (4.90), 3.668 (1.60), 4.091 (3.81), 5.308 (2.03), 6.897 (4.53), 6.900 (4.56), 7.138 (9.62), 7.158 (3.26), 7.160 (3.24), 7.404 (5.48), 7.605 (4.08), 7.626 (3.71), 8.426 (13.33), 8.433 (0.81), 9.270 (2.40). LC-MS (method 2): Rt = 0.66 min; m/z = 515 (M+H)+

Example	Structure Name	Analytical Data
27	 5-({2-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1H-indole-2-carboxamide	^{1}H-NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 1.260 (0.92), 1.896 (6.59), 1.909 (13.19), 1.922 (7.62), 2.108 (11.19), 2.182 (1.64), 2.238 (2.94), 2.475 (1.78), 2.924 (0.43), 3.591 (2.20), 3.617 (6.99), 3.629 (16.00), 3.642 (7.08), 3.667 (2.17), 4.090 (4.88), 5.881 (0.41), 6.882 (6.26), 7.133 (8.85), 7.302 (3.11), 7.306 (3.19), 7.324 (4.59), 7.327 (4.70), 7.402 (6.12), 7.423 (4.00), 7.590 (6.98), 8.425 (9.95), 8.441 (0.78), 9.255 (2.89). LC-MS (method 2): Rt = 0.63 min; m/z = 515 (M+H)+
28	 6-({2-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1H-indole-2-carbonitrile	^{1}H-NMR (600 MHz, DMSO-d6) δ [ppm]: -0.006 (0.49), 0.000 (15.93), 0.005 (0.49), 1.806 (4.62), 2.387 (1.09), 2.389 (1.27), 2.393 (1.10), 2.520 (1.68), 2.524 (1.71), 2.527 (1.40), 2.545 (0.92), 2.614 (0.54), 2.618 (0.74), 2.621 (0.55), 3.562 (12.68), 3.900 (0.61), 4.027 (1.61), 4.045 (4.15), 4.064 (3.94), 4.082 (1.41), 4.191 (0.62), 7.123 (3.79), 7.125 (3.71), 7.137 (3.89), 7.139 (3.92), 7.328 (9.52), 7.368 (6.84), 7.474 (7.13), 7.607 (5.84), 7.620 (5.30), 8.313 (16.00), 8.318 (1.14), 12.295 (4.11). LC-MS (method 2): Rt = 0.77 min; m/z = 497.2 (M+H)+

Example	Structure Name	Analytical Data
29	 4-methyl-5-({2-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1H-indole-2-carbonitrile	^{1}H-NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 1.603 (6.75), 1.870 (2.75), 2.449 (1.04), 2.572 (10.20), 2.604 (0.59), 2.630 (0.68), 2.637 (2.72), 2.816 (0.41), 3.573 (1.58), 3.597 (2.22), 3.623 (4.94), 3.648 (4.72), 3.673 (1.59), 4.105 (3.11), 4.182 (0.48), 4.768 (0.41), 7.006 (0.41), 7.140 (4.78), 7.213 (1.08), 7.234 (1.47), 7.245 (4.35), 7.250 (4.37), 7.349 (0.67), 8.435 (16.00), 8.683 (0.64). LC-MS (method 2): Rt = 0.78 min; m/z = 511.2 (M+H)+
30	 4-{7-[(1-methyl-1 H-indol-6-yl)methyl]-2,7-diazaspiro[3.5]non-2-yl}-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidine	^{1}H-NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 1.642 (0.46), 1.901 (1.59), 2.507 (0.45), 3.593 (0.65), 3.618 (1.89), 3.644 (1.92), 3.668 (0.63), 3.819 (16.00), 3.827 (1.62), 4.084 (1.16), 4.114 (0.51), 6.663 (1.49), 6.669 (1.50), 7.075 (1.81), 7.083 (1.82), 7.091 (0.73), 7.109 (0.87), 7.136 (2.41), 7.189 (0.84), 7.209 (1.43), 7.227 (1.05), 7.290 (0.70), 8.420 (5.88). LC-MS (method 2): Rt = 0.78 min; m/z = 486.2 (M+H)+

Example 31

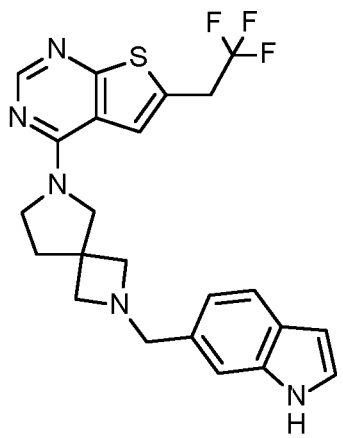
6-({6-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl] -2,6-diazaspiro[3.4]oct-2-yl}methyl)-1 H-indole-2-carboxamide

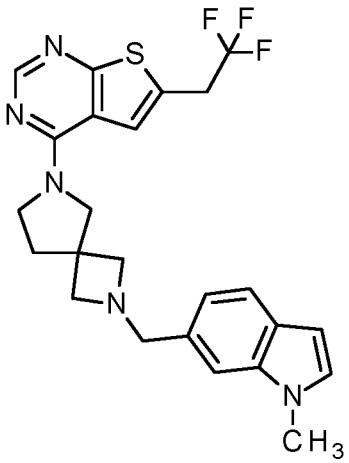
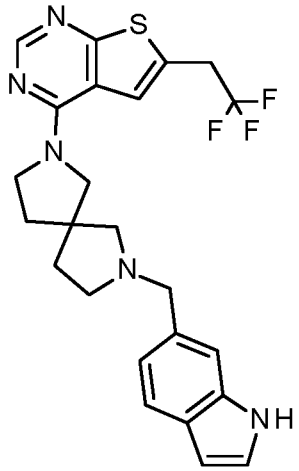


49 mg (134 μmol) 4-(2,6-diazaspiro[3.4]oct-6-yl)-6-(2 ,2,2-trifluoroethyl)thieno[2,3-d]pyrimidine hydrochloride (intermediate **122)** was solved in 1 ml NMP, 34 mg (180 μmol) 6-formyl-1 H-indole-2-carboxamide dissolved in 0.32 ml NMP was added, then 26 mg triethylamine (255 μmol) in 0.5 ml NMP, followed by the addition of 59 mg (278 μmol) sodium triacetoxyborohydride dissolved in 1 ml NMP. The mixture was shaken for 2 days at RT. To the reaction mixture was added 0.14 ml sodium hydroxide solution (2M). After filtration the filtrate was purified by preparative HPLC to yield 15 mg (20%) of the desired product.

LC-MS (method 3): Rt = 1.05 min; MS (ESIpos): m/z = 501 $[M+H]^+$

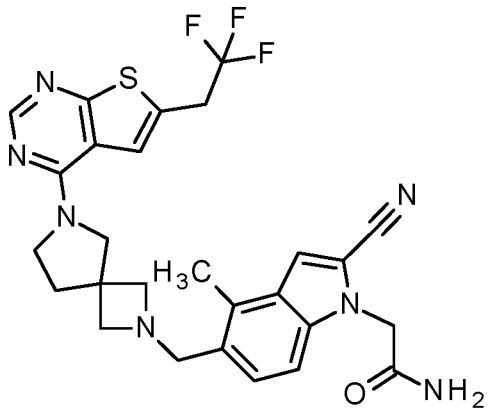
According to the preparation of example **31** the following examples **32-34** were prepared starting from the intermediate **I22** or intermediate **I30** by reacting with the corresponding aldehydes.

Example	Structure Name	Analytical Data
32		LC-MS (method 3): R_t = 1.22 min; m/z = 458 $(M+H)^+$

Example	Structure Name	Analytical Data
	4-[2-(1H-indol-6-ylmethyl)-2,6-diazaspiro[3.4]oct-6-yl]-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidine	
33	 4-{2-[(1-methyl-1H-indol-6-yl)methyl]-2,6-diazaspiro[3.4]oct-6-yl}-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidine	LC-MS (method 3): R_t = 1.32 min; m/z = 472 $(M+H)^+$
34	 4-[7-(1H-indol-6-ylmethyl)-2,7-diazaspiro[4.4]non-2-yl]-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidine	LC-MS (method 3): R_t = 1.30 min; m/z = 472 $(M+H)^+$

Example 35

2-[2-cyano-4-methyl-5-({6-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4^]-2,6-diazaspiro[3.4]oct-2-yl}methyl)-1 H-indol-1 -yl]acetamide



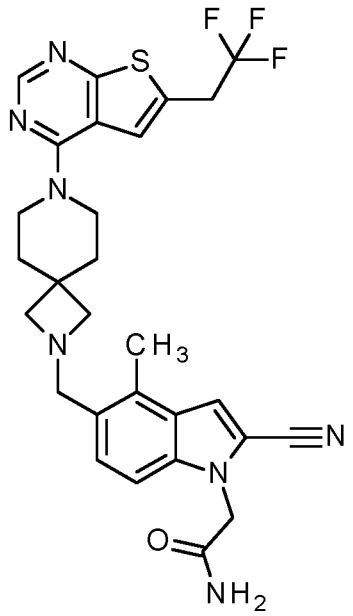
To a stirred solution of 40 mg (77 μηιοΙ) 4-methyl-5-({6-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,6-diazaspiro[3.4]oct-2-yl}methyl)-1 H-indole-2-carbonitrile (example **5)** in 2 ml DMF was added 100 mg cesium carbonate (306 μηηοΙ). After stirring for 5 min 11.6 mg 2-bromoacetamide (84 μηηοΙ) was added and the reaction mixture stirred for 2.5h at RT. The reaction mixture was filtered and purified by preparative HPLC. The product rich fractions were pooled and the solvent was removed under reduced pressure and freeze dried to yield the desired product as an white solid (15 mg, 33 %).

LC-MS (method 2): Rt = 0.72 min; m/z = 554 (M+H)+

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.232 (0.73), 2.152 (1.50), 2.332 (1.93), 2.336 (0.77), 2.518 (9.93), 2.523 (7.19), 2.673 (1.80), 2.679 (0.77), 3.176 (1.75), 3.192 (1 1.59), 3.679 (8.56), 3.746 (0.90), 3.880 (1.1 1), 4.026 (0.98), 4.053 (2.61), 4.081 (2.52), 4.1 08 (0.81), 4.899 (10.27), 7.272 (1.84), 7.294 (4.36), 7.318 (5.73), 7.340 (2.31), 7.364 (2.35), 7.523 (8.21), 7.525 (8.00), 7.702 (3.04), 7.755 (2.35), 8.312 (16.00), 8.484 (0.43).

Example 36

2-[2-cyano-4-methyl-5-({7-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}methyl)-1 H-indol-1 -yl]acetamide



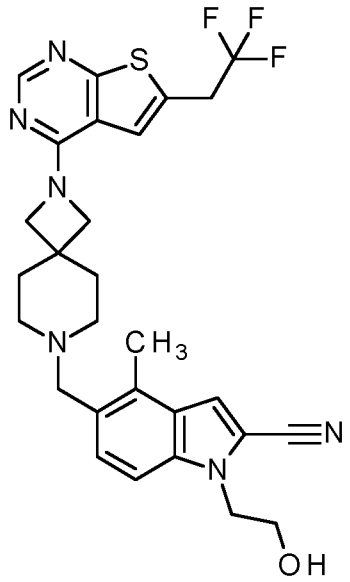
To a stirred solution of 40 mg (74 μηιοΙ) 4-methyl-5-({7-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}methyl)-1 H-indole-2-carbonitrile (example **6)** in 2 ml DMF was added 97 mg cesium carbonate (298 μηηοΙ). After stirring for 5 min 11.3 mg 2-bromoacetamide (82 μηηοΙ) was added and the reaction mixture stirred for 2.5h at RT. The reaction mixture was filtered and purified by preparative HPLC. The product rich fractions were pooled and the solvent was removed under reduced pressure and freeze dried to yield the desired product as an off white solid (11 mg, 25 %).

LC-MS (method 2): Rt = 0.76 min; m/z = 568 (M+H)+

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.785 (3.75), 1.798 (4.73), 1.811 (3.71), 2.075 (0.49), 2.322 (1.73), 2.327 (2.31), 2.332 (1.82), 2.518 (11.27), 2.522 (6.88), 2.665 (1.47), 2.669 (2.02), 2.673 (1.47), 3.009 (16.00), 3.680 (7.27), 3.755 (3.85), 3.768 (4.76), 3.781 (3.65), 4.043 (1.04), 4.071 (2.90), 4.098 (2.77), 4.126 (0.88), 4.901 (8.70), 7.273 (1.47), 7.294 (3.88), 7.315 (4.89), 7.336 (1.79), 7.369 (2.12), 7.524 (6.65), 7.608 (5.15), 7.766 (2.09), 8.363 (10.43), 8.557 (1.69).

Example 37

1-(2-hydroxyethyl)-4-methyl-5-({2-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carbonitrile



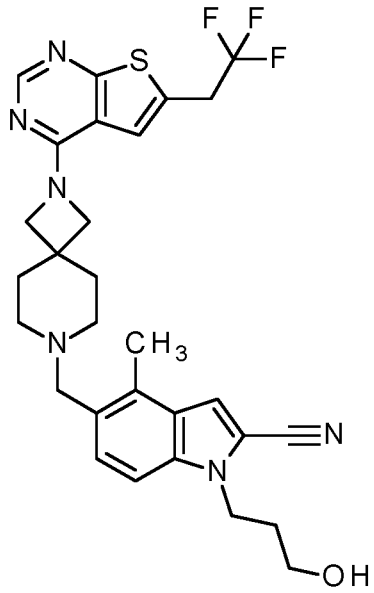
To a solution of 125 mg (0.196 mmol) 4-methyl-1-[2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-5-({2-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1H-indole-2-carbonitrile (intermediate **I72)** in methanol (3.0 ml) was added cone. HCl (49 µl, 0.587 mmol) and the reaction mixture stirred at RT for one hour. The reaction mixture was concentrated to dryness under reduced pressure, dissolved in DMSO, filtered and purified by preparative HPLC. The product rich fractions were pooled and the solvent was removed under reduced pressure and freeze dried to yield the desired product as an white solid (4 mg, 4 % yield).

LC-MS (method 2): Rt = 0.76 min; m/z = 555 (M+H)+

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.769 (3.60), 2.073 (0.44), 2.083 (10.30), 2.322 (1.77), 2.326 (2.16), 2.331 (1.77), 2.518 (6.37), 2.522 (4.10), 2.529 (2.10), 2.539 (16.00), 2.664 (1.11), 2.668 (1.38), 2.673 (1.05), 3.238 (0.78), 3.383 (0.50), 3.511 (1.88), 3.680 (1.72), 3.693 (4.32), 3.706 (4.26), 3.719 (1.66), 4.019 (1.61), 4.047 (3.76), 4.075 (3.54), 4.102 (1.44), 4.315 (2.71), 4.328 (4.76), 4.341 (2.55), 4.959 (2.21), 4.972 (5.31), 4.986 (2.16), 7.275 (1.77), 7.296 (2.49), 7.377 (2.21), 7.399 (1.49), 7.457 (0.44), 7.479 (4.98), 7.489 (6.15), 7.507 (0.50), 7.578 (0.50), 8.313 (15.17).

Example 38

1-(3-hydroxypropyl)-4-methyl-5-({2-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1H-indole-2-carbonitrile



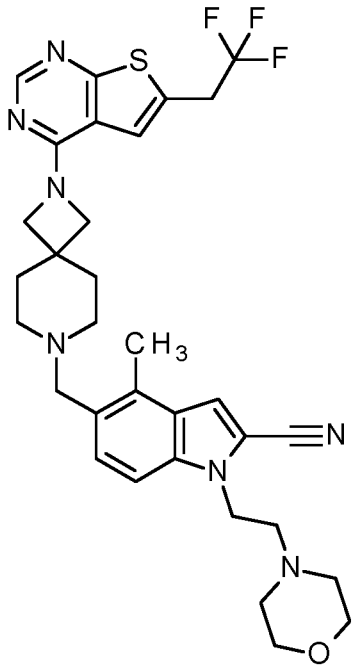
According to the preparation of example **37,** example **38** was prepared starting from intermediate **173** (127 mg, 195 μηηοl). After purification by preparative HPLC the desired product was obtained as a white solid (10 mg, 9 % yield).

LC-MS (method 2): Rt = 0.79 min; m/z = 569 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.763 (1.56), 1.874 (0.99), 1.890 (1.51), 1.907 (1.04), 2.083 (3.18), 2.323 (0.49), 2.327 (0.57), 2.331 (0.54), 2.366 (0.47), 2.518 (0.95), 2.523 (0.69), 2.539 (16.00), 3.374 (2.53), 3.387 (2.04), 3.402 (0.82), 3.501 (1.22), 4.016 (0.62), 4.044 (1.44), 4.072 (1.37), 4.099 (0.57), 4.330 (0.99), 4.348 (1.82), 4.365 (0.95), 4.662 (0.99), 4.674 (2.29), 4.686 (0.97), 7.292 (0.89), 7.313 (1.32), 7.381 (1.17), 7.402 (0.75), 7.479 (1.99), 7.516 (2.85), 8.312 (5.79).

Example 39

4-methyl-1-[2-(morpholin-4-yl)ethyl]-5-({2-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyri midin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carbonitrile



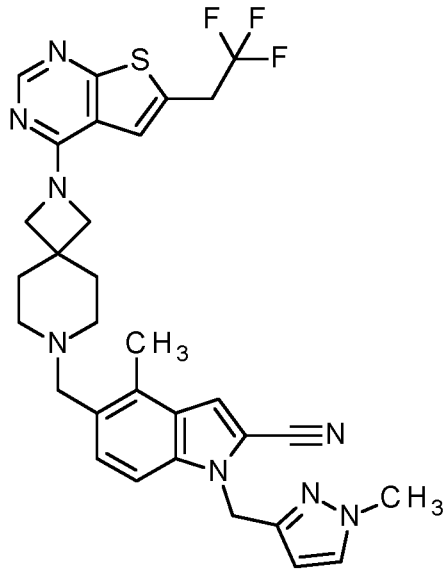
To a stirred solution of 4-methyl-5-({2-[6-(2 ,2,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carbonitrile (example **29)** (100 mg, 196 μηηοI) in DMF (2.0 ml) was added 4-(2-chloroethyl)morpholine hydrochloride (77 mg, 411 μηηοI) followed by potassium carbonate (100 mg, 725 μηηοI). The reaction mixture was heated in a microwave for 3h at 95°C. The reaction mixture was filtered and purified by preparative HPLC. The desired product was obtained as a white solid (48 mg, 39 % yield).

LC-MS (method 2): Rt = 0.68 min; m/z = 624 $(M+H)^+$

1H-NMR (400 MHz, DMSO-d6) delta [ppm]: 1.765 (0.77), 2.076 (0.20), 2.084 (16.00), 2.091 (0.18), 2.318 (0.31), 2.323 (0.49), 2.327 (0.63), 2.331 (0.52), 2.337 (0.38), 2.380 (1.29), 2.518 (1.65), 2.523 (1.12), 2.598 (0.48), 2.612 (0.95), 2.627 (0.48), 2.665 (0.34), 2.669 (0.46), 2.674 (0.32), 3.502 (2.17), 3.516 (1.52), 3.528 (1.06), 4.020 (0.28), 4.048 (0.66), 4.075 (0.65), 4.103 (0.26), 4.359 (0.43), 4.374 (0.83), 4.389 (0.42), 7.284 (0.65), 7.306 (0.91), 7.393 (0.69), 7.415 (0.46), 7.484 (1.12), 7.488 (1.92), 8.313 (3.50).

Example 40

4-methyl-1 -[(1 -methyl-1 H-pyrazol-3-yl)methyl]-5-({2-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carbonitrile



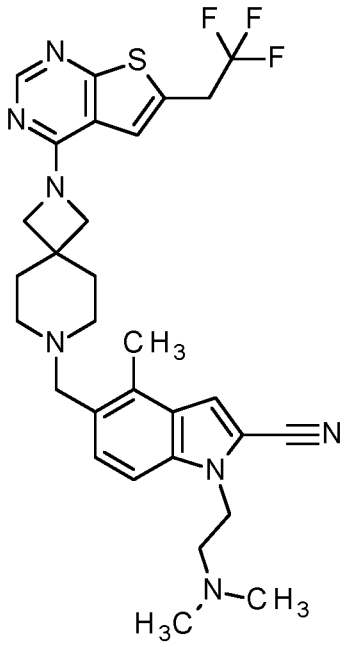
To a stirred solution of 4-methyl-5-({2-[6-(2 ,2,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carbonitrile (example **29)** (100 mg, 196 μηηοl) in DMF (2.0 ml) was added 3-(chloromethyl)-1-methyl-1 H-pyrazole (32 μl, 290 μιτιοl) followed by caesium carbonate (191 mg, 588 μηηοl). The reaction mixture was stirred for 16 h at RT. The reaction mixture was filtered and purified by preparative HPLC. The desired product was obtained as a solid (16 mg, 13 %).

LC-MS ((method 8): Rt = 1.42 min; m/z = 605 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.755 (1.90), 2.323 (1.33), 2.327 (1.71), 2.331 (1.36), 2.336 (0.90), 2.518 (5.22), 2.523 (3.61), 2.660 (0.42), 2.665 (0.88), 2.669 (1.23), 2.673 (0.88), 3.489 (3.61), 3.740 (0.58), 3.749 (16.00), 3.849 (0.42), 4.020 (0.67), 4.047 (1.58), 4.075 (1.52), 4.102 (0.61), 5.408 (4.48), 6.088 (2.82), 6.094 (2.94), 7.276 (1.63), 7.298 (1.98), 7.427 (1.59), 7.448 (1.19), 7.483 (2.40), 7.533 (3.48), 7.581 (2.46), 7.587 (2.40), 8.312 (6.51).

Example 41

1-[2-(dimethylamino)ethyl]-4-methyl-5-({2-[6-(2,2,2-trifluoroethyl)thieno^^,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1H-indole-2-carbonitrile



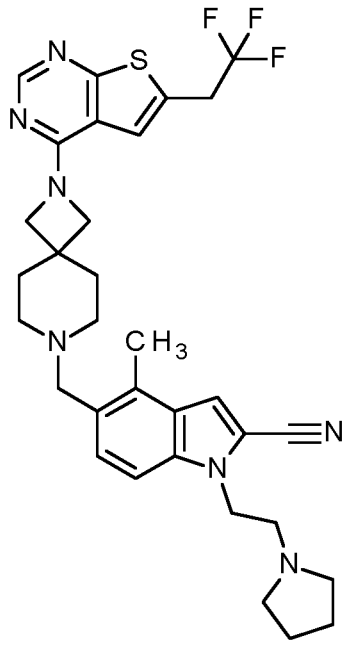
To a stirred solution of 4-methyl-5-({2-[6-(2 ,2,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carbonitrile (example **29)** (100 mg, 196 μηηοI) in DMF (2.0 ml) was added 2-chloro-N,N-dimethylethanamine hydrochloride (59 mg, 411 μηηοI) followed by potassium carbonate (100 mg, 725 μηηοI). The reaction mixture was stirred for 16 h at RT. The reaction mixture was filtered and purified by preparative HPLC. The desired product was obtained as a pale yellow solid (47 mg, 41 %).

LC-MS (method 2): Rt = 0.58 min; m/z = 582 $(M+H)^+$

1H-NMR (400 MHz, DMSO-d6) delta [ppm]: 1.765 (1.03), 2.162 (16.00), 2.318 (0.34), 2.323 (0.55), 2.327 (0.71), 2.331 (0.56), 2.336 (0.41), 2.518 (1.60), 2.523 (1.12), 2.567 (0.71), 2.582 (1.56), 2.598 (0.72), 2.665 (0.33), 2.669 (0.46), 3.500 (2.11), 4.021 (0.37), 4.048 (0.88), 4.076 (0.84), 4.104 (0.34), 4.334 (0.61), 4.350 (1.26), 4.366 (0.59), 7.284 (0.84), 7.305 (1.22), 7.386 (0.93), 7.408 (0.61), 7.487 (2.99), 8.314 (4.46).

Example 42

4-methyl-1-[2-(pyrrolidin-1-yl)ethyl]-5-({2-[6-(2,2,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1H-indole-2-carbonitrile



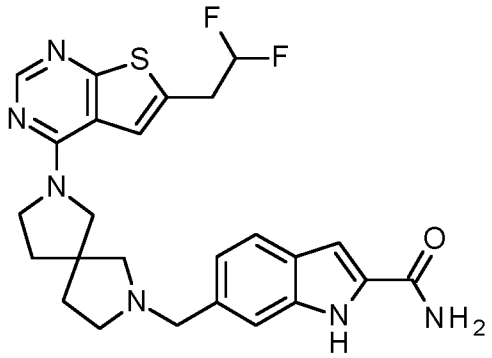
To a stirred solution of 4-methyl-5-({2-[6-(2 ,2,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carbonitrile (example **29)** (100 mg, 196 μηηοl) in DMF (2.0 ml) was added 1-(2-bromoethyl)pyrrolidine hydrobromide (76 mg, 294 μηηοl) followed by caesium carbonate (191 mg, 588 μηηοl). The reaction mixture was stirred for 16 h at RT. The reaction mixture was filtered and purified by preparative HPLC. The desired product was obtained as a pale yellow solid (6 mg, 5 %).

LC-MS (method 2): Rt = 0.60 min; m/z = 608 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.640 (12.60), 1.764 (6.17), 2.084 (2.29), 2.323 (3.35), 2.327 (4.47), 2.331 (3.88), 2.461 (11.91), 2.477 (6.59), 2.523 (10.21), 2.665 (2.29), 2.669 (3.46), 2.673 (2.76), 2.743 (3.56), 2.759 (7.65), 2.774 (3.72), 3.502 (11.32), 4.021 (2.13), 4.049 (4.84), 4.077 (4.68), 4.104 (11.91), 4.355 (3.19), 4.371 (6.43), 4.387 (3.24), 4.411 (0.48), 7.285 (4.09), 7.306 (6.01), 7.383 (4.94), 7.404 (3.19), 7.485 (7.65), 7.491 (12.97), 7.517 (0.74), 7.579 (0.85), 8.314 (16.00), 8.553 (0.74).

Example 43

6-({7-[6-(2,2-difluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carboxamide



To a mixture of 39.5 mg (210 μηηοl) 6-formyl-1 H-indole-2-carboxamide and (intermediate **11)** 82 mg (388 μηηοl) sodium triacetoxyborohydride was added a solution of 78 mg (210 μηηοl) 4-[2,7-diazaspiro[4.4]non-2-yl]-6-(2,2-difluoroethyl)thieno[2,3-d]pyrimidine hydrochloride (intermediate **I94)** and 64 μl triethylamine (460 μηηοl) in 2 ml dichloromethane. The mixture was stirred for 21 h at RT. After removal of the solvent the residue was purified by preparative HPLC to yield 52 mg (48%) of the desired product a white solid.

LC-MS (method 13): Rt = 1.04 min; m/z = 497 (M+H)+

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.775 (0.42), 1.787 (1.07), 1.805 (1.96), 1.823 (2.07), 1.840 (1.00), 1.856 (0.43), 1.981 (0.87), 2.322 (0.56), 2.326 (0.78), 2.332 (0.56), 2.450 (1.98), 2.473 (3.23), 2.518 (3.62), 2.522 (2.54), 2.534 (2.07), 2.539 (1.69), 2.557 (1.40), 2.572 (1.20), 2.589 (1.38), 2.609 (1.21), 2.628 (1.36), 2.645 (0.96), 2.664 (0.80), 2.668 (1.05), 2.673 (0.67), 3.467 (0.85), 3.475 (0.92), 3.51 1 (1.69), 3.520 (1.72), 3.556 (0.94), 3.565 (0.92), 3.606 (1.03), 3.639 (3.44), 3.655 (3.81), 3.687 (1.58), 3.727 (0.89), 6.181 (0.74), 6.31 1 (0.72), 6.321 (1.47), 6.332 (0.72), 6.462 (0.67), 6.994 (2.50), 6.997 (2.45), 7.015 (2.63), 7.018 (2.68), 7.061 (3.88), 7.064 (3.82), 7.306 (1.25), 7.338 (4.06), 7.495 (3.61), 7.516 (3.23), 7.577 (4.15), 7.910 (1.21), 8.281 (16.00), 11.447 (2.74).

30 mg of 6-({7-[6-(2,2-difluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carboxamide (example **43)** were separated by using chiral prep. HPLC (method D) into its enantiomers.

Example 43.1 : 6-({7-[6-(2,2-difluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carboxamide (ent-1)

13.5 mg, HPLC (Methode 7): Rt = 3.6 min

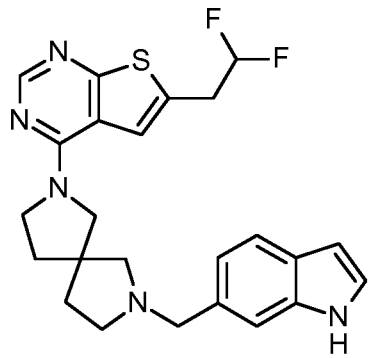
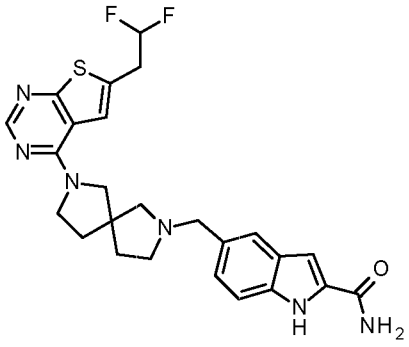
Optical rotation: [a]D20 = 36.8° +/-1 .99° (c = 1.00; DMSO)

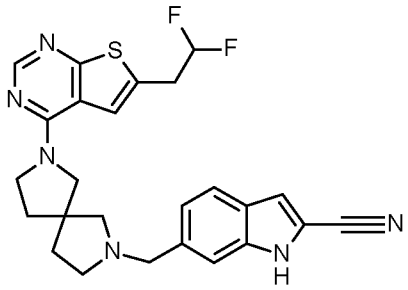
Example 43.2: 6-({7-[6-(2,2-difluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carboxamide (ent-2)

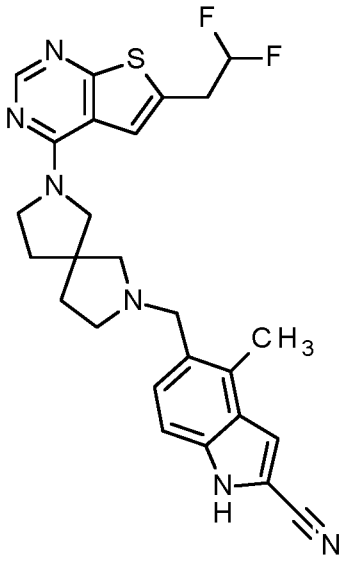
13.1 mg, HPLC (Methode 7): Rt = 4.61 min

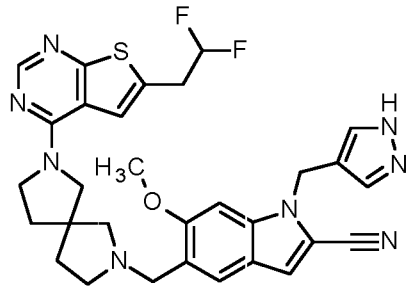
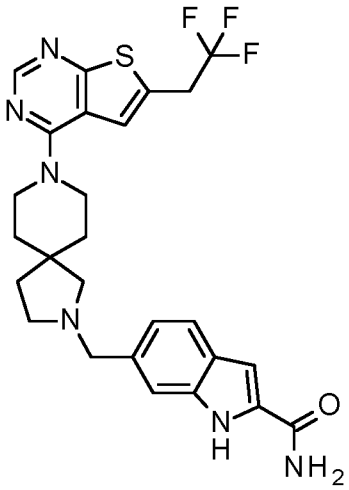
Optical rotation: [a]D20 = -31.4° +7-1.00° (c = 1.00; DMSO)

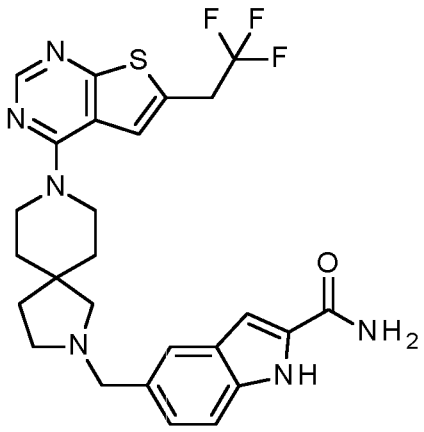
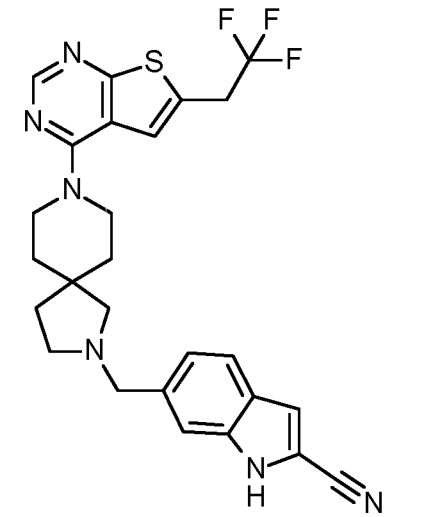
According to the preparation of example **43** the following examples **44-77** were prepared starting from the intermediate **11,1100, 1101, 1102, 1103, 1105, 1107, 1108** by reacting with the corresponding aldehydes.

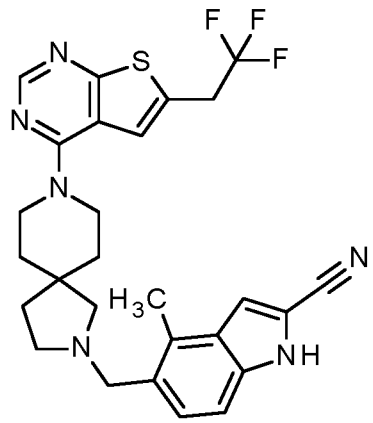
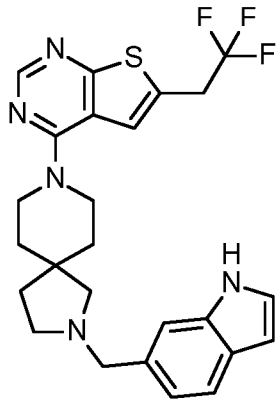
Example	Structure Name	Analytical Data
44	 6-(2,2-difluoroethyl)-4-[7-(1H-indol-6-ylmethyl)-2,7-diazaspiro[4.4]non-2-yl]thieno[2,3-d]pyrimidine	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.754 (0.44), 1.786 (1.96), 1.803 (3.70), 1.820 (3.94), 1.837 (1.89), 1.870 (0.51), 1.982 (1.79), 2.327 (1.14), 2.449 (3.70), 2.472 (6.89), 2.540 (4.77), 2.564 (4.08), 2.585 (2.82), 2.606 (1.56), 2.614 (1.51), 2.634 (2.49), 2.649 (1.86), 2.669 (1.77), 3.292 (0.51), 3.382 (0.42), 3.474 (1.75), 3.510 (3.19), 3.519 (3.31), 3.556 (1.84), 3.615 (1.91), 3.647 (7.03), 3.660 (7.59), 3.693 (2.77), 6.171 (0.63), 6.180 (1.23), 6.311 (1.26), 6.321 (2.42), 6.331 (1.30), 6.359 (5.43), 6.461 (1.14), 6.945 (4.01), 6.965 (4.36), 7.271 (4.24), 7.278 (6.43), 7.285 (4.33), 7.307 (6.92), 7.428 (5.68), 7.449 (5.24), 7.577 (7.31), 8.282 (16.00), 10.972 (3.98). LC-MS (method 13): Rt = 1.21 min; MS (ESIpos): m/z = 454 [M+H]+
45	 5-({7-[6-(2,2-difluoroethyl)thieno[2,3-	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.752 (0.40), 1.769 (0.45), 1.782 (1.12), 1.800 (1.88), 1.817 (2.01), 1.835 (0.98), 1.850 (0.45), 1.973 (0.98), 2.074 (0.58), 2.336 (0.40), 2.431 (2.10), 2.454 (2.99), 2.518 (5.23), 2.523 (4.34), 2.540 (1.61), 2.551 (1.56), 2.574 (1.25), 2.602 (0.85), 2.622 (1.47), 2.638 (1.03), 3.467 (0.89), 3.476 (0.94), 3.511 (1.74), 3.520 (1.74), 3.556 (0.98), 3.564 (0.98), 3.589 (1.16), 3.621 (3.71), 3.637

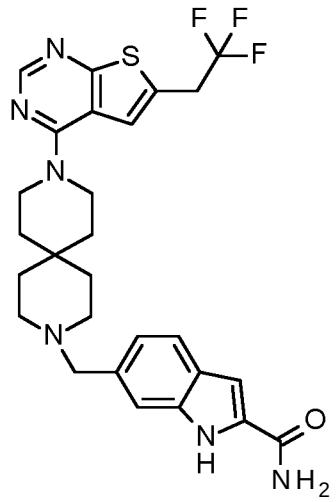
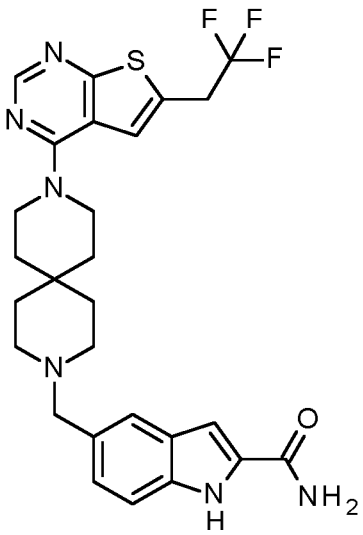
Example	Structure Name	Analytical Data
	d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carboxamide	(3.84), 3.669 (1.52), 3.737 (0.89), 6.181 (0.76), 6.311 (0.72), 6.321 (1.47), 6.331 (0.76), 6.462 (0.67), 7.050 (3.84), 7.054 (3.75), 7.143 (2.23), 7.146 (2.28), 7.164 (2.59), 7.167 (2.73), 7.314 (1.30), 7.327 (4.25), 7.348 (3.04), 7.479 (4.42), 7.576 (4.42), 7.911 (1.21), 8.280 (16.00), 11.464 (2.68). LC-MS (method 13): Rt = 1.03 min; MS (ESIpos): m/z = 497 [M+H]+
46	 6-({7-[6-(2,2-difluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carbonitrile	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.784 (0.52), 1.797 (1.34), 1.815 (2.43), 1.832 (2.63), 1.849 (1.31), 1.865 (0.58), 1.990 (1.19), 2.322 (0.61), 2.326 (0.87), 2.331 (0.67), 2.458 (2.37), 2.481 (4.57), 2.522 (5.13), 2.539 (1.64), 2.549 (3.18), 2.572 (2.55), 2.596 (1.84), 2.616 (1.00), 2.625 (0.90), 2.644 (1.57), 2.664 (1.66), 2.668 (1.60), 2.673 (1.04), 3.467 (1.18), 3.476 (1.28), 3.512 (2.24), 3.521 (2.34), 3.556 (1.27), 3.566 (1.24), 3.654 (1.43), 3.687 (5.06), 3.699 (5.61), 3.732 (1.99), 6.172 (0.46), 6.182 (0.93), 6.192 (0.46), 6.312 (0.88), 6.322 (1.84), 6.333 (0.93), 6.454 (0.40), 6.463 (0.84), 6.473 (0.45), 7.126 (2.96), 7.129 (3.21), 7.147 (3.21), 7.150 (3.52), 7.310 (8.13), 7.312 (9.40), 7.373 (5.01), 7.575 (5.55), 7.583 (5.55), 7.604 (4.34), 8.283 (16.00). LC-MS (method 13): Rt = 1.23 min; MS (ESIpos): m/z = 479 [M+H]+

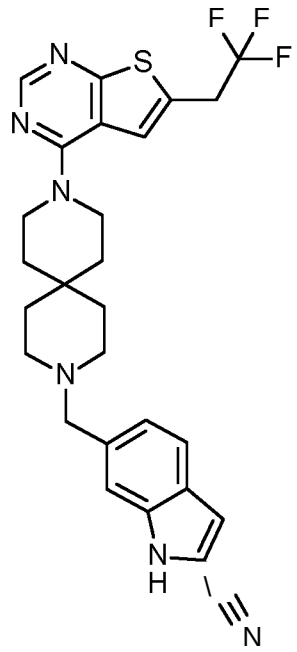
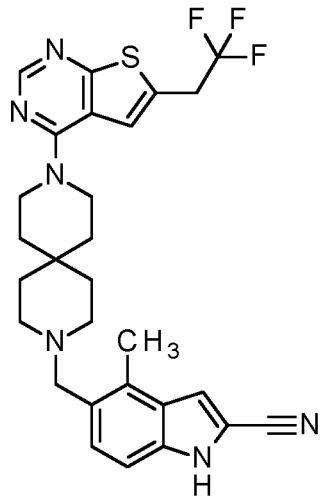
Example	Structure Name	Analytical Data
47	 5-({7-[6-(2,2-difluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-4-methyl-1 H-indole-2-carbonitrile	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.777 (1.07), 1.795 (1.85), 1.812 (2.00), 1.829 (0.97), 1.844 (0.42), 1.964 (0.92), 2.421 (2.17), 2.443 (3.10), 2.518 (5.10), 2.523 (3.23), 2.537 (1.62), 2.549 (1.38), 2.567 (1.50), 2.587 (0.77), 2.596 (0.80), 2.616 (1.42), 2.631 (1.03), 2.654 (0.43), 2.674 (0.68), 3.462 (0.93), 3.471 (1.00), 3.507 (1.83), 3.516 (1.87), 3.552 (1.05), 3.560 (1.02), 3.614 (0.95), 3.646 (5.47), 3.651 (5.48), 3.683 (1.20), 6.169 (0.42), 6.180 (0.83), 6.309 (0.78), 6.319 (1.63), 6.329 (0.78), 6.460 (0.73), 7.194 (2.10), 7.215 (3.85), 7.259 (5.15), 7.280 (2.70), 7.425 (6.83), 7.427 (6.63), 7.566 (5.37), 8.275 (16.00), 12.240 (0.47). LC-MS (method 13): Rt = 1.31 min; MS (ESIpos): m/z = 493 [M+H]+
47.1	5-({7-[6-(2,2-difluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-4-methyl-1 H-indole-2-carbonitrile (ent-1)	separation of example 47 by chiral chromatography afforded **47.1** and its enantiomer 47.2. prep. HPLC (method E) analyt. HPLC (method 8): R_t = 6.21 min optical rotation: $[a]_D^{20}$ = -33.7° +/-1.01 ° (c = 1.00; DMSO)
47.2	5-({7-[6-(2,2-difluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-4-methyl-1 H-indole-2-carbonitrile (ent-2)	prep. HPLC (method E) analyt. HPLC (method 8): R_t = 6.97 min optical rotation: $[a]_D^{20}$ = 28.7° +/-1.64° (c = 1.00; DMSO)

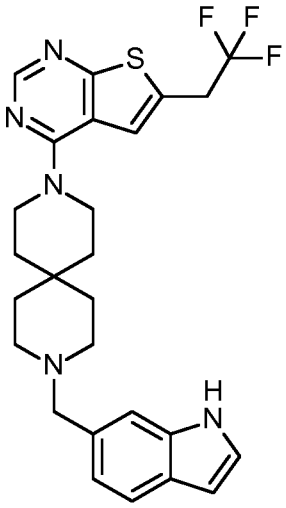
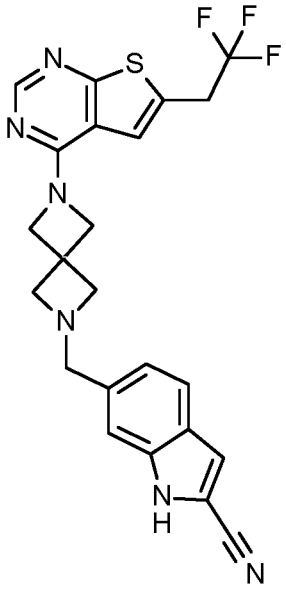
Example	Structure Name	Analytical Data
48	 5-({7-[6-(2,2-difluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-6-methoxy-1-(1 H-pyrazol-4-ylmethyl)-1 H-indole-2-carbonitrile	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.402 (0.48), 1.784 (1.00), 1.800 (1.67), 1.818 (1.75), 1.835 (0.85), 1.986 (0.84), 2.323 (0.79), 2.327 (1.03), 2.332 (0.82), 2.522 (4.01), 2.565 (0.64), 2.591 (2.39), 2.604 (1.51), 2.615 (1.59), 2.651 (0.70), 2.669 (2.08), 2.684 (0.91), 3.469 (0.90), 3.478 (0.94), 3.514 (1.69), 3.523 (1.69), 3.559 (0.97), 3.604 (0.60), 3.641 (6.01), 3.679 (0.82), 3.752 (0.90), 3.821 (0.73), 3.890 (16.00), 5.376 (6.82), 6.184 (0.66), 6.314 (0.66), 6.325 (1.30), 6.335 (0.64), 6.464 (0.60), 7.271 (4.79), 7.290 (2.23), 7.466 (0.87), 7.556 (4.20), 7.587 (3.54), 7.754 (0.85), 8.285 (8.42), 12.814 (1.06). LC-MS (method 8): Rt = 1.25 min; MS (ESIpos): m/z = 589 [M+H]+
49	 6-({8-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,8-diazaspiro[4.5]dec-2-yl}methyl)-1H-indole-2-carboxamide	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.603 (0.45), 1.641 (3.71), 1.653 (3.84), 1.672 (3.65), 1.689 (1.90), 2.423 (6.82), 2.518 (5.49), 2.523 (3.53), 2.539 (0.57), 2.551 (1.67), 2.569 (3.08), 2.585 (1.55), 3.628 (6.47), 3.719 (0.59), 3.736 (0.90), 3.752 (1.35), 3.770 (1.51), 3.781 (0.98), 3.826 (0.98), 3.836 (1.63), 3.852 (1.29), 3.872 (0.98), 3.886 (0.57), 4.036 (0.92), 4.064 (2.63), 4.091 (2.49), 4.1 19 (0.80), 6.995 (2.18), 6.998 (2.10), 7.016 (2.24), 7.019 (2.35), 7.067 (3.18), 7.071 (3.22), 7.308 (1.00), 7.345 (3.78), 7.506 (3.12), 7.526 (2.86), 7.61 1 (5.02), 7.912 (0.98), 8.359 (16.00), 11.446 (2.22), 11.450 (2.22). LC-MS (method 8): Rt = 1.22 min; MS (ESIpos): m/z = 529 [M+H]+

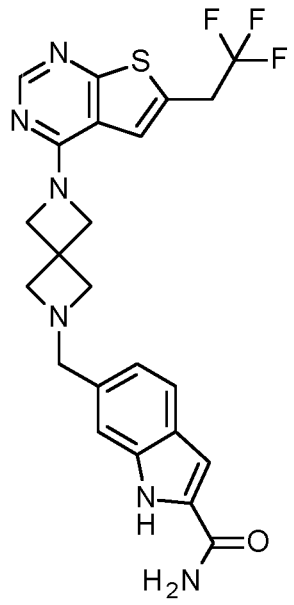
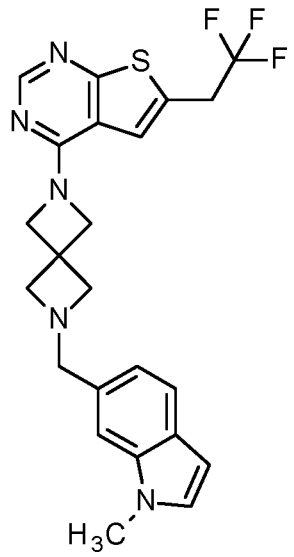
Example	Structure Name	Analytical Data
50	 5-({8-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,8-diazaspiro[4.5]dec-2-yl}methyl)-1H-indole-2-carboxamide	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.559 (0.52), 1.576 (0.58), 1.586 (1.09), 1.600 (0.90), 1.632 (5.83), 1.646 (5.25), 1.664 (4.80), 1.681 (2.54), 2.336 (0.61), 2.411 (9.05), 2.518 (7.31), 2.523 (5.12), 2.537 (2.64), 2.555 (4.28), 2.572 (2.16), 2.619 (1.09), 2.821 (0.42), 3.608 (8.66), 3.707 (0.84), 3.723 (1.35), 3.739 (1.84), 3.758 (2.03), 3.770 (1.32), 3.812 (0.45), 3.842 (2.29), 3.857 (1.77), 3.877 (1.55), 3.891 (0.90), 4.035 (1.26), 4.063 (3.57), 4.091 (3.44), 4.118 (1.09), 7.060 (4.19), 7.063 (4.19), 7.146 (2.54), 7.150 (2.51), 7.167 (2.93), 7.170 (3.06), 7.318 (1.38), 7.335 (4.54), 7.356 (3.35), 7.481 (4.83), 7.612 (6.60), 7.625 (0.68), 7.913 (1.35), 8.357 (16.00), 8.370 (1.22), 11.461 (2.90). LC-MS (method 8): Rt = 1.22 min; MS (ESIpos): m/z = 529 [M+H]+
51	 6-({8-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,8-diazaspiro[4.5]dec-2-yl}methyl)-1H-indole-2-carbonitrile	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.606 (0.59), 1.644 (5.65), 1.653 (4.34), 1.663 (4.77), 1.681 (5.13), 1.698 (2.61), 2.332 (1.21), 2.336 (0.56), 2.435 (10.29), 2.518 (7.87), 2.522 (4.80), 2.563 (2.45), 2.581 (4.47), 2.597 (2.29), 3.384 (0.49), 3.675 (9.67), 3.715 (0.88), 3.731 (1.34), 3.748 (1.86), 3.767 (2.09), 3.777 (1.34), 3.836 (1.40), 3.847 (2.25), 3.862 (1.73), 3.883 (1.47), 3.896 (0.85), 4.036 (1.24), 4.064 (3.56), 4.092 (3.40), 4.120 (1.08), 7.129 (2.87), 7.132 (2.84), 7.150 (3.04), 7.153 (3.13), 7.321 (7.48), 7.322 (7.80), 7.376 (4.96), 7.594 (4.44), 7.614 (8.07), 8.361 (16.00), 12.275 (0.88). LC-MS (method 8): Rt = 1.43 min; MS (ESIpos): m/z = 511 [M+H]+

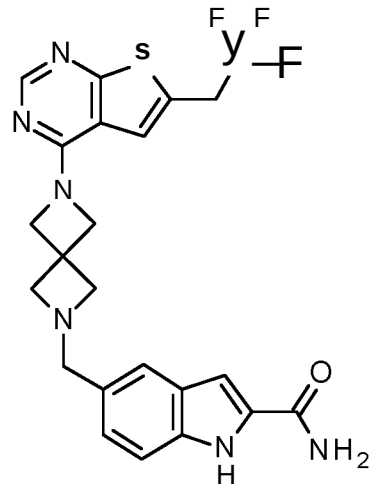
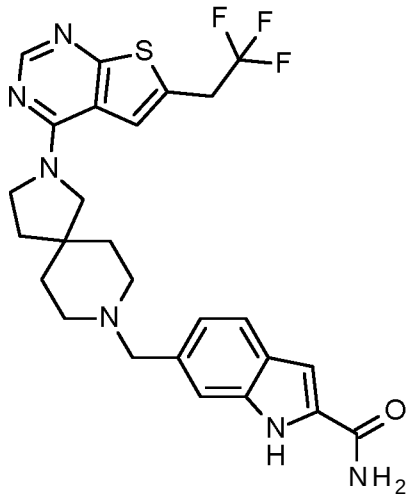
Example	Structure Name	Analytical Data
52	 4-methyl-5-({8-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,8-diazaspiro[4.5]dec-2-yl}methyl)-1H-indole-2-carbonitrile	^{1}H-NMR (400 MHz, DMS0-d6) δ [ppm]: 1.583 (0.44), 1.607 (3.1 1), 1.619 (5.41), 1.631 (4.91), 1.649 (4.47), 1.666 (2.27), 2.404 (8.82), 2.470 (0.55), 2.518 (4.53), 2.522 (3.95), 2.539 (4.09), 2.555 (1.95), 3.622 (8.80), 3.678 (0.82), 3.694 (1.36), 3.71 1 (1.62), 3.730 (1.74), 3.741 (1.08), 3.843 (1.10), 3.854 (1.92), 3.869 (1.42), 3.876 (1.13), 3.889 (1.54), 3.903 (0.79), 4.031 (1.11), 4.059 (3.20), 4.086 (3.02), 4.1 14 (0.95), 7.207 (2.09), 7.229 (4.10), 7.266 (5.72), 7.287 (2.82), 7.437 (8.1 1), 7.439 (8.04), 7.610 (6.07), 8.354 (16.00), 12.237 (0.84). LC-MS (method 8): Rt = 1.51 min; MS (ESIpos): m/z = 525 [M+H]+
53	 2-(1 H-indol-6-ylmethyl)-8-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,8-diazaspiro[4.5]decane	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.145 (0.44), 1.602 (0.57), 1.641 (5.45), 1.652 (5.36), 1.670 (5.14), 1.688 (2.62), 2.336 (0.87), 2.428 (10.33), 2.518 (9.98), 2.523 (6.98), 2.540 (0.74), 2.551 (2.44), 2.568 (4.53), 2.585 (2.22), 3.635 (10.07), 3.712 (0.87), 3.729 (1.26), 3.745 (1.79), 3.764 (1.96), 3.775 (1.31), 3.835 (1.35), 3.846 (2.18), 3.861 (1.61), 3.882 (1.44), 3.896 (0.83), 4.035 (1.26), 4.063 (3.49), 4.091 (3.31), 4.1 18 (1.05), 6.361 (2.35), 6.366 (3.62), 6.371 (2.35), 6.946 (2.75), 6.949 (2.79), 6.966 (2.92), 6.969 (2.96), 7.275 (3.44), 7.282 (4.40), 7.289 (3.23), 7.31 1 (4.93), 7.438 (4.05), 7.458 (3.75), 7.612 (6.37), 8.359 (16.00), 10.972 (2.31). LC-MS (method 8): Rt = 1.42 min; MS (ESIpos): m/z = 486 [M+H]+

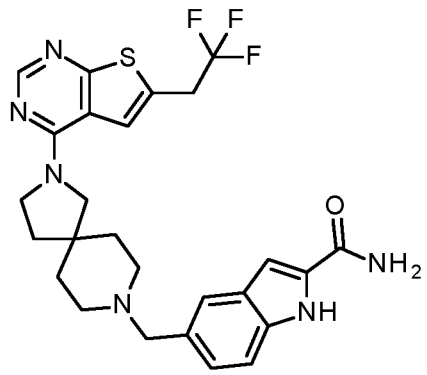
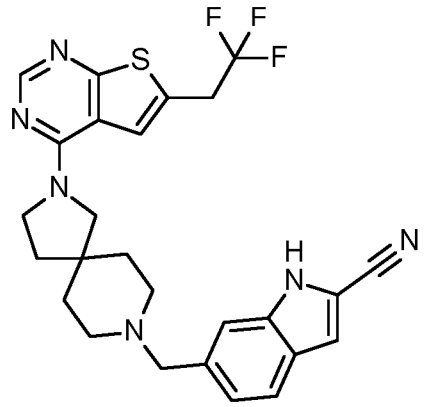
Example	Structure Name	Analytical Data
54	 6-({9-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-3,9-diazaspiro[5.5]undec-3-yl}methyl)-1 H-indole-2-carboxamide	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.537 (6.16), 1.564 (3.47), 2.318 (0.47), 2.322 (0.94), 2.327 (1.31), 2.332 (1.05), 2.336 (0.66), 2.373 (3.84), 2.518 (4.68), 2.523 (3.10), 2.539 (0.53), 2.664 (0.82), 2.669 (1.19), 2.673 (0.86), 3.530 (6.74), 3.810 (3.31), 3.825 (4.17), 3.838 (3.31), 4.027 (0.99), 4.055 (2.81), 4.083 (2.65), 4.1 11 (0.84), 6.973 (2.44), 6.976 (2.32), 6.994 (2.49), 6.997 (2.57), 7.073 (3.61), 7.077 (3.55), 7.322 (5.01), 7.504 (3.51), 7.525 (3.16), 7.637 (5.46), 7.919 (1.13), 8.352 (16.00), 11.454 (2.65), 11.458 (2.61). LC-MS (method 8): Rt = 1.23 min; MS (ESIpos): m/z = 543 [M+H]+
55	 5-({9-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-3,9-diazaspiro[5.5]undec-3-yl}methyl)-1 H-indole-2-carboxamide	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.415 (1.01), 1.530 (7.90), 2.323 (1.68), 2.327 (2.34), 2.331 (1.96), 2.367 (4.82), 2.518 (7.90), 2.523 (5.21), 2.539 (0.73), 2.650 (0.80), 2.665 (2.38), 2.669 (2.79), 2.674 (1.99), 3.518 (8.14), 3.826 (5.94), 4.027 (1.26), 4.054 (3.53), 4.082 (3.39), 4.1 10 (1.08), 7.062 (4.26), 7.066 (4.26), 7.124 (2.48), 7.127 (2.59), 7.144 (2.93), 7.148 (3.00), 7.320 (1.43), 7.335 (4.61), 7.356 (3.42), 7.461 (4.96), 7.635 (6.60), 7.919 (1.36), 8.350 (16.00), 8.354 (2.52), 11.472 (3.04). LC-MS (method 8): Rt = 1.23 min; MS (ESIpos): m/z = 543 [M+H]+

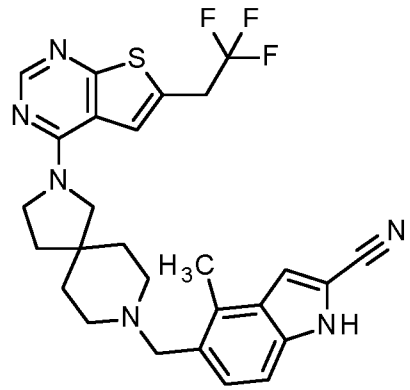
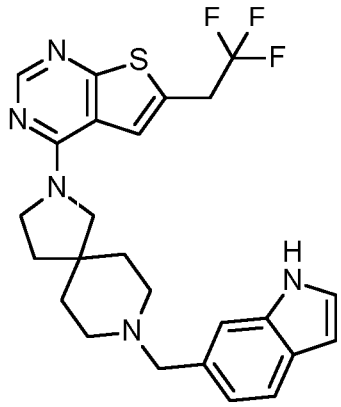
Example	Structure Name	Analytical Data
56	 6-({9-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-3,9-diazaspiro[5.5]undec-3-yl}methyl)-1 H-indole-2-carbonitrile	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.538 (9.55), 1.549 (9.43), 1.567 (4.99), 2.387 (5.53), 2.518 (9.20), 2.523 (6.03), 3.580 (9.78), 3.812 (4.64), 3.827 (5.84), 3.839 (4.64), 4.029 (1.31), 4.056 (3.75), 4.084 (3.56), 4.1 12 (1.16), 7.1 10 (3.05), 7.1 12 (3.01), 7.131 (3.25), 7.133 (3.29), 7.326 (7.96), 7.360 (5.53), 7.594 (4.83), 7.614 (4.37), 7.636 (6.96), 8.353 (16.00), 12.274 (0.85). LC-MS (method 8): Rt = 1.44 min; MS (ESIpos): m/z = 525 [M+H]+
57	 4-methyl-5-({9-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-3,9-diazaspiro[5.5]undec-3-	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.496 (6.09), 1.543 (4.43), 1.557 (5.80), 1.569 (4.55), 2.323 (1.46), 2.327 (1.95), 2.331 (1.63), 2.375 (5.80), 2.518 (6.99), 2.523 (4.58), 2.665 (1.25), 2.669 (1.72), 2.673 (1.22), 3.514 (9.91), 3.81 1 (4.69), 3.826 (5.89), 3.839 (4.63), 4.030 (1.31), 4.059 (3.79), 4.086 (3.61), 4.1 14 (1.14), 7.204 (1.87), 7.225 (5.95), 7.241 (7.78), 7.262 (2.24), 7.436 (8.68), 7.637 (7.1 1), 8.354 (16.00), 12.250 (1.81). LC-MS (method 8): Rt = 1.52 min; MS (ESIpos): m/z = 539 [M+H]+

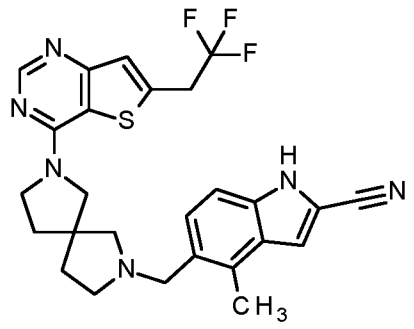
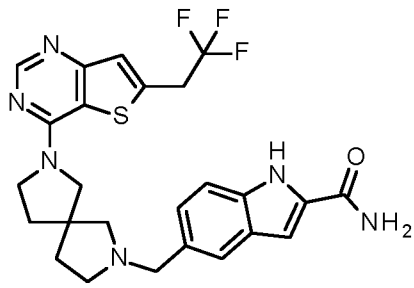
Example	Structure Name	Analytical Data
	yl}methyl)-1 H-indole-2-carbonitrile	
58	 3-(1 H-indol-6-ylmethyl)-9-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-3,9-diazaspiro[5.5]undecane	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.532 (6.55), 1.541 (6.64), 1.561 (3.69), 2.332 (0.85), 2.336 (0.49), 2.379 (3.94), 2.518 (4.92), 2.523 (3.28), 2.539 (0.56), 2.673 (0.78), 3.542 (7.96), 3.809 (3.46), 3.824 (4.33), 3.837 (3.51), 4.026 (1.00), 4.053 (2.88), 4.081 (2.73), 4.109 (0.87), 6.363 (1.75), 6.365 (2.06), 6.368 (2.14), 6.370 (3.20), 6.373 (2.27), 6.376 (2.03), 6.378 (1.77), 6.921 (2.47), 6.924 (2.47), 6.941 (2.58), 6.944 (2.68), 7.282 (3.30), 7.290 (5.07), 7.296 (6.96), 7.436 (3.58), 7.456 (3.27), 7.636 (5.39), 8.351 (16.00), 10.970 (2.14). LC-MS (method 8): Rt = 1.43 min; MS (ESIpos): m/z = 500 [M+H]+
59	 6-({6-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,6-diazaspiro[3.3]hept-2-yl}methyl)-1H-indole-2-carbonitrile	1H-NMR (400 MHz, CHLOROFORM-d) delta [ppm]: 2.264 (8.28), 3.389 (0.83), 3.392 (1.16), 3.397 (0.83), 3.401 (0.46), 3.477 (16.00), 3.576 (1.35), 3.601 (3.94), 3.627 (3.85), 3.652 (1.33), 3.722 (9.43), 4.470 (4.16), 7.045 (2.32), 7.048 (2.45), 7.066 (2.52), 7.069 (2.65), 7.100 (5.81), 7.110 (6.23), 7.112 (6.83), 7.301 (4.21), 7.575 (3.72), 7.596 (3.44), 8.359 (10.06). LC-MS (method 1): Rt = 0.82 min; MS (ESIpos): m/z = 469 [M+H]+

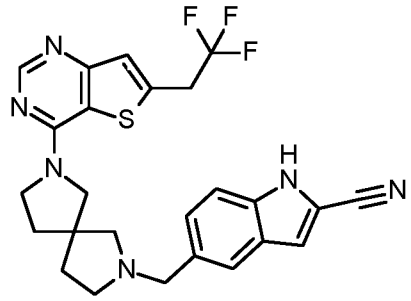
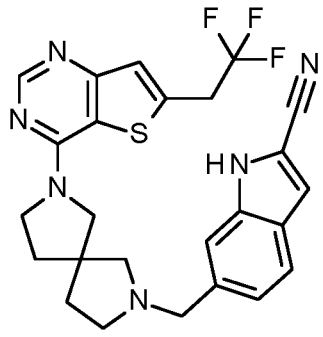
Example	Structure Name	Analytical Data
60	 6-({6-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,6-diazaspiro[3.3]hept-2-yl}methyl)-1H-indole-2-carboxamide	1H-NMR (400 MHz, CHLOROFORM-d) delta [ppm]: 1.636 (15.39), 3.481 (16.00), 3.584 (1.15), 3.609 (3.34), 3.635 (3.28), 3.660 (1.12), 3.731 (8.39), 4.491 (4.83), 6.887 (3.18), 6.890 (3.19), 7.006 (0.43), 7.077 (2.10), 7.080 (2.07), 7.102 (6.63), 7.359 (3.74), 7.613 (2.81), 7.634 (2.59), 8.430 (10.68), 9.208 (1.38). LC-MS (method 1): Rt = 0.69 min; MS (ESIpos): m/z = 487 [M+H]+
61	 4-{6-[(1-methyl-1H-indol-6-yl)methyl]-2,6-diazaspiro[3.3]hept-2-yl}-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidine	1H-NMR (400 MHz, CHLOROFORM-d) delta [ppm]: 1.671 (1.95), 3.511 (10.39), 3.581 (0.62), 3.605 (1.81), 3.630 (1.78), 3.656 (0.59), 3.814 (16.00), 3.922 (5.38), 4.479 (2.18), 6.581 (1.91), 6.583 (1.80), 6.589 (1.79), 6.591 (1.95), 7.050 (1.08), 7.051 (1.12), 7.067 (1.37), 7.069 (1.34), 7.083 (2.50), 7.091 (2.48), 7.101 (2.54), 7.194 (0.99), 7.212 (0.84), 7.215 (1.77), 7.233 (1.50), 7.287 (0.89), 8.425 (6.30). LC-MS (method 1): Rt = 0.85 min; MS (ESIpos): m/z = 458 [M+H]+

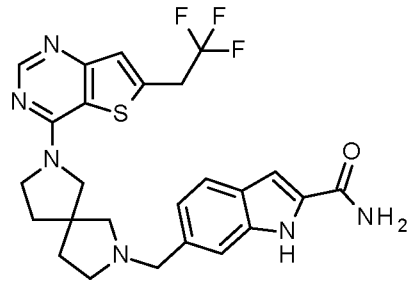
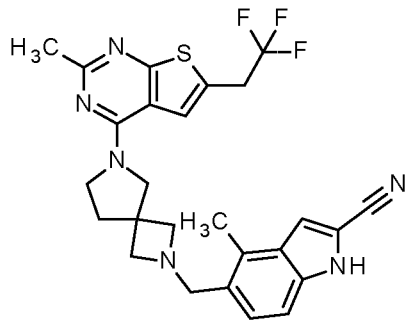
Example	Structure Name	Analytical Data
62	 5-({6-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,6-diazaspiro[3.3]hept-2-yl}methyl)-1H-indole-2-carboxamide	1H-NMR (400 MHz, DMS0-d6) delta [ppm]: 0.852 (0.55), 1.233 (0.75), 2.318 (0.59), 2.322 (1.40), 2.327 (1.99), 2.332 (1.40), 2.336 (0.62), 2.518 (6.68), 2.523 (4.43), 2.539 (0.68), 2.660 (0.59), 2.664 (1.34), 2.669 (1.89), 2.673 (1.37), 2.678 (0.55), 3.253 (0.72), 3.573 (7.23), 4.014 (1.01), 4.042 (2.90), 4.070 (2.74), 4.097 (0.91), 4.423 (0.85), 7.063 (3.58), 7.066 (3.55), 7.083 (2.28), 7.087 (2.25), 7.104 (2.61), 7.108 (2.67), 7.329 (4.37), 7.350 (3.00), 7.435 (5.80), 7.456 (4.01), 7.918 (1.11), 8.316 (16.00), 8.323 (0.55), 11.468 (2.44). LC-MS (method 2): Rt = 0.58 min; MS (ESIpos): m/z = 487 [M+H]+
63	 6-({2-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,8-diazaspiro[4.5]dec-8-yl}methyl)-1H-indole-2-carboxamide	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.144 (0.41), 1.533 (1.16), 1.545 (1.31), 1.583 (6.15), 1.595 (6.38), 1.629 (1.08), 1.892 (2.42), 2.327 (3.17), 2.331 (2.76), 2.368 (2.05), 2.436 (2.65), 2.522 (7.72), 2.669 (2.28), 2.775 (0.41), 3.542 (12.27), 3.588 (2.20), 3.834 (1.27), 4.023 (1.38), 4.051 (3.58), 4.078 (3.43), 4.106 (1.23), 6.988 (3.88), 7.008 (4.14), 7.072 (6.19), 7.076 (6.15), 7.313 (2.31), 7.332 (8.06), 7.507 (5.52), 7.528 (5.03), 7.705 (6.04), 7.918 (2.20), 8.312 (16.00), 11.462 (4.81). LC-MS (method 8): Rt = 1.15 min; MS (ESIpos): m/z = 529 [M+H]+

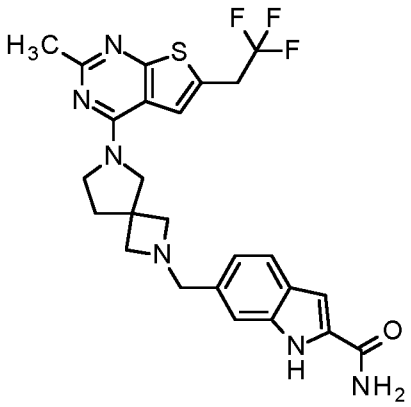
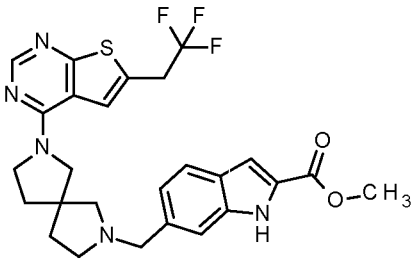
Example	Structure Name	Analytical Data
64	 5-({2-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,8-diazaspiro[4.5]dec-8-yl}methyl)-1H-indole-2-carboxamide	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.144 (0.43), 1.512 (1.19), 1.525 (1.54), 1.539 (1.49), I .576 (6.02), 1.588 (6.14), 1.888 (2.52), 2.327 (3.67), 2.331 (3.1 1), 2.356 (1.92), 2.433 (2.47), 2.522 (9.00), 2.665 (1.96), 2.669 (2.65), 2.673 (1.96), 2.765 (0.73), 3.526 (1 1.48), 3.582 (2.18), 3.835 (1.32), 4.022 (1.49), 4.049 (3.88), 4.077 (3.75), 4.105 (1.32), 7.061 (5.80), 7.065 (5.80), 7.135 (3.33), 7.138 (3.29), 7.159 (4.14), 7.318 (2.09), 7.338 (5.89), 7.359 (4.35), 7.471 (6.87), 7.702 (6.23), 7.723 (0.85), 7.916 (2.05), 8.31 1 (16.00), 8.316 (3.07), 8.438 (0.43), I I .472 (4.39). LC-MS (method 8): Rt = 1.13 min; MS (ESIpos): m/z = 529 [M+H]+
65	 6-({2-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,8-diazaspiro[4.5]dec-8-yl}methyl)-1H-indole-2-carbonitrile	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.589 (6.87), 1.601 (7.20), 1.635 (1.20), 1.890 (2.55), 2.327 (2.12), 2.331 (1.92), 2.379 (2.40), 2.669 (1.55), 3.591 (16.00), 3.832 (1.32), 4.020 (1.45), 4.048 (3.87), 4.075 (3.75), 4.103 (1.30), 7.122 (4.27), 7.143 (4.60), 7.325 (9.55), 7.369 (7.95), 7.596 (6.07), 7.617 (5.55), 7.702 (7.07), 8.312 (15.47), 12.283 (4.92). LC-MS (method 8): Rt = 1.35 min; MS (ESIpos): m/z = 5 1 1 [M+H]+

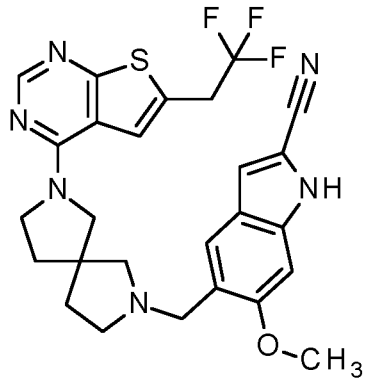
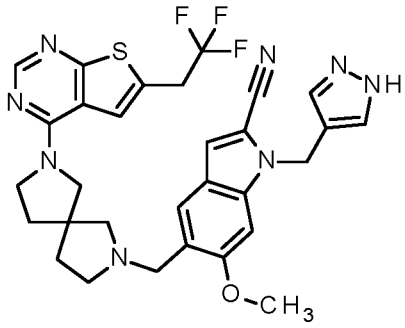
Example	Structure Name	Analytical Data
66	 4-methyl-5-({2-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,8-diazaspiro[4.5]dec-8-yl}methyl)-1H-indole-2-carbonitrile	^{1}H-NMR (400 MHz, DMS0-d6) δ [ppm]: 1.551 (7.11), 1.563 (7.34), 1.598 (1.33), 1.892 (2.75), 2.327 (3.12), 2.331 (2.84), 2.371 (2.57), 2.428 (3.39), 2.669 (2.29), 3.528 (14.21), 3.589 (2.84), 3.828 (1.42), 4.020 (1.51), 4.047 (4.03), 4.075 (3.90), 4.102 (1.38), 7.206 (2.66), 7.228 (7.89), 7.246 (9.08), 7.267 (2.98), 7.438 (10.77), 7.704 (7.01), 8.313 (16.00), 12.255 (3.48). LC-MS (method 8): Rt = 1.42 min; MS (ESIpos): m/z = 525 [M+H]+
67	 8-(1 H-indol-6-ylmethyl)-2-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,8-diazaspiro[4.5]decane	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.544 (0.51), 1.565 (1.68), 1.580 (3.27), 1.593 (3.45), 1.629 (0.54), 1.886 (1.14), 2.318 (0.57), 2.322 (1.08), 2.327 (1.44), 2.332 (1.23), 2.336 (0.87), 2.370 (0.96), 2.440 (1.14), 2.518 (4.56), 2.523 (3.09), 2.664 (0.78), 2.669 (1.11), 2.673 (0.78), 3.550 (8.32), 3.581 (1.08), 3.829 (0.57), 4.021 (0.66), 4.048 (1.80), 4.076 (1.74), 4.104 (0.60), 6.362 (1.80), 6.364 (2.13), 6.366 (2.19), 6.369 (3.30), 6.371 (2.28), 6.374 (2.04), 6.377 (1.77), 6.932 (2.58), 6.936 (2.49), 6.953 (2.70), 6.956 (2.67), 7.282 (3.18), 7.289 (3.90), 7.295 (3.42), 7.304 (4.29), 7.438 (3.66), 7.459 (3.36), 7.701 (3.72), 8.31 1 (16.00), 10.977 (2.13). LC-MS (method 8): Rt = 1.33 min; MS (ESIpos): m/z = 486 [M+H]+

Example	Structure Name	Analytical Data
68	 4-methyl-5-({7-[6-(2,2,2-trifluoroethyl)thieno[3,2-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carbonitrile	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.145 (0.46), 1.780 (1.30), 1.795 (2.21), 1.814 (2.42), 1.830 (1.09), 1.968 (1.51), 1.984 (1.47), 2.323 (1.54), 2.327 (2.14), 2.331 (1.51), 2.391 (1.89), 2.414 (2.38), 2.518 (9.45), 2.523 (6.83), 2.529 (3.43), 2.537 (3.57), 2.560 (2.10), 2.624 (0.70), 2.643 (1.40), 2.660 (1.93), 2.665 (2.45), 2.669 (2.59), 2.674 (1.79), 2.678 (1.12), 3.619 (0.63), 3.651 (9.24), 3.684 (0.91), 3.794 (0.74), 4.121 (1.33), 4.149 (3.71), 4.177 (3.57), 4.205 (1.12), 7.190 (2.45), 7.211 (4.24), 7.262 (5.88), 7.282 (3.26), 7.373 (7.91), 7.421 (6.44), 8.351 (16.00), 12.237 (2.84). LC-MS (method 8): Rt = 1.39 min; MS (ESIpos): m/z = 511 [M+H]+
69	 5-({7-[6-(2,2,2-trifluoroethyl)thieno[3,2-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carboxamide	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.780 (0.91), 1.801 (1.36), 1.817 (1.41), 1.836 (0.72), 1.976 (0.98), 1.990 (0.98), 2.318 (0.45), 2.323 (1.03), 2.327 (1.50), 2.332 (1.05), 2.337 (0.45), 2.413 (1.43), 2.436 (1.93), 2.518 (5.56), 2.523 (4.24), 2.534 (1.43), 2.540 (2.29), 2.565 (1.50), 2.623 (0.45), 2.641 (0.93), 2.660 (1.17), 2.665 (1.57), 2.669 (1.74), 2.673 (1.24), 2.679 (0.74), 3.630 (6.70), 3.791 (0.62), 4.121 (0.93), 4.149 (2.60), 4.176 (2.48), 4.204 (0.76), 7.050 (3.22), 7.053 (3.15), 7.147 (2.10), 7.150 (2.03), 7.168 (2.41), 7.172 (2.48), 7.323 (3.58), 7.345 (2.53), 7.374 (5.72), 7.478 (3.60), 7.904 (0.98), 8.356 (16.00), 11.452 (2.17). LC-MS (method 8): Rt = 1.08 min; MS (ESIpos): m/z = 515 [M+H]+

Example	Structure Name	Analytical Data
70	 5-({7-[6-(2,2,2-trifluoroethyl)thieno[3,2-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carbonitrile	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.775 (0.41), 1.787 (1.07), 1.807 (1.67), 1.823 (1.73), 1.843 (0.88), 1.978 (1.24), 1.993 (1.26), 2.318 (0.41), 2.323 (0.90), 2.327 (1.30), 2.332 (0.96), 2.336 (0.47), 2.402 (1.56), 2.425 (2.05), 2.518 (8.13), 2.523 (5.56), 2.543 (3.12), 2.566 (2.16), 2.634 (0.53), 2.654 (1.13), 2.660 (1.05), 2.665 (1.56), 2.669 (2.25), 2.673 (1.78), 2.691 (0.41), 3.622 (0.47), 3.655 (8.06), 3.689 (0.75), 3.786 (0.71), 4.124 (1.07), 4.152 (3.06), 4.180 (2.91), 4.207 (0.94), 7.289 (5.24), 7.312 (1.93), 7.316 (1.95), 7.334 (3.23), 7.338 (3.40), 7.377 (6.76), 7.383 (4.58), 7.404 (2.14), 7.566 (4.43), 8.355 (16.00), 12.314 (1.95). LC-MS (method 8): Rt = 1.27 min; MS (ESIpos): m/z = 497 [M+H]+
71	 6-({7-[6-(2,2,2-trifluoroethyl)thieno[3,2-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carbonitrile	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.779 (0.45), 1.785 (0.45), 1.797 (1.15), 1.817 (1.83), 1.833 (1.88), 1.852 (0.97), 1.868 (0.45), 1.988 (1.22), 2.004 (1.24), 2.322 (0.85), 2.326 (1.18), 2.331 (0.83), 2.441 (2.31), 2.465 (3.38), 2.518 (4.68), 2.522 (3.20), 2.534 (0.80), 2.539 (1.01), 2.564 (3.09), 2.572 (1.86), 2.587 (2.25), 2.644 (0.76), 2.664 (2.29), 2.668 (2.02), 2.673 (1.34), 2.678 (1.42), 2.701 (0.47), 3.695 (9.40), 3.792 (0.80), 4.121 (1.22), 4.149 (3.42), 4.177 (3.26), 4.205 (1.03), 7.131 (2.80), 7.134 (2.76), 7.151 (2.99), 7.155 (3.03), 7.31 1 (7.17), 7.313 (7.46), 7.376 (1 1.22), 7.580 (4.14), 7.601 (3.75), 8.360 (16.00), 12.281 (2.19). LC-MS (method 8): Rt = 1.32 min; MS (ESIneg): m/z = 497 [M+H]-

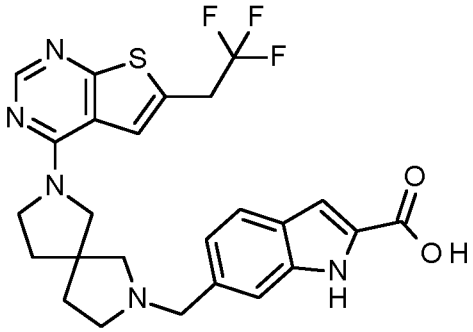
Example	Structure Name	Analytical Data
72	 6-({7-[6-(2,2,2-trifluoroethyl)thieno[3,2-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carboxamide	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.145 (0.43), 1.777 (0.50), 1.790 (1.26), 1.809 (2.02), 1.826 (2.12), 1.845 (1.10), 2.000 (1.26), 2.323 (1.46), 2.327 (2.06), 2.331 (1.43), 2.434 (2.16), 2.457 (3.12), 2.518 (7.83), 2.523 (5.61), 2.540 (2.92), 2.549 (3.95), 2.572 (2.56), 2.632 (0.76), 2.651 (1.53), 2.665 (2.56), 2.669 (3.15), 2.673 (2.32), 2.688 (0.50), 3.650 (9.56), 3.785 (0.90), 4.121 (1.29), 4.148 (3.68), 4.176 (3.55), 4.204 (1.13), 6.998 (2.92), 7.002 (2.89), 7.019 (3.12), 7.022 (3.15), 7.060 (4.48), 7.063 (4.55), 7.304 (1.53), 7.340 (5.28), 7.374 (7.90), 7.492 (4.12), 7.512 (3.75), 7.906 (1.49), 8.357 (16.00), 11.444 (3.32). LC-MS (method 8): Rt = 1.13 min; MS (ESIpos): m/z = 515 [M-H]+
73	 4-methyl-5-({6-[2-methyl-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,6-diazaspiro[3.4]oct-2-yl}methyl)-1H-indole-2-carbonitrile	1H-NMR (400 MHz, DMSO-d6) delta [ppm]: 2.076 (0.20), 2.084 (16.00), 2.155 (0.22), 2.323 (0.16), 2.327 (0.22), 2.332 (0.17), 2.409 (4.73), 2.518 (1.04), 2.523 (0.68), 2.530 (0.23), 2.669 (0.22), 3.207 (0.20), 3.740 (0.24), 3.868 (0.27), 3.979 (0.19), 4.008 (0.50), 4.036 (0.47), 4.063 (0.16), 7.223 (0.20), 7.243 (0.34), 7.292 (0.31), 7.313 (0.19), 7.452 (0.48), 7.623 (0.59), 12.259 (0.17). LC-MS (method 8): Rt = 1.36 min; MS (ESIpos): m/z = 511 [M+H]+

Example	Structure Name	Analytical Data
74	 6-({6-[2-methyl-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,6-diazaspiro[3.4]oct-2-yl}methyl)-1H-indole-2-carboxamide	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.958 (0.60), 1.167 (0.80), 1.902 (0.73), 1.983 (1.57), 2.079 (13.59), 2.091 (0.77), 2.140 (1.69), 2.405 (16.00), 2.518 (1.88), 3.205 (1.85), 3.662 (1.44), 3.739 (0.94), 3.862 (1.19), 3.977 (0.75), 4.005 (2.01), 4.031 (2.07), 4.060 (0.65), 7.060 (2.81), 7.064 (2.78), 7.105 (1.45), 7.125 (1.70), 7.329 (3.14), 7.350 (2.10), 7.480 (2.32), 7.629 (2.47), 7.916 (1.00), 11.468 (1.71). LC-MS (method 8): Rt = 1.10 min; MS (ESIpos): m/z = 515 [M+H]+
75	 methyl 6-({7-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carboxylate	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.822 (0.72), 1.839 (0.72), 1.997 (0.42), 2.323 (0.43), 2.327 (0.62), 2.332 (0.43), 2.518 (2.70), 2.523 (1.89), 2.561 (0.62), 2.580 (0.67), 2.660 (0.53), 2.665 (0.77), 2.669 (0.92), 2.673 (0.68), 3.672 (1.13), 3.859 (16.00), 4.042 (1.03), 4.071 (0.97), 7.058 (0.82), 7.079 (0.89), 7.110 (1.75), 7.114 (1.77), 7.380 (0.93), 7.565 (0.89), 7.586 (0.82), 7.684 (2.01), 8.308 (8.55), 11.844 (0.70). LC-MS (method 8): Rt = 1.36 min; MS (ESIpos): m/z = 530 [M+H]+
75.1	methyl 6-({7-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carboxylate (ent-1)	separation of example **75** by chiral chromatography afforded **75.1** and its enantiomer **75.2**. prep. HPLC (method G) analyt. HPLC (method 10): R_t = 1.92 min
75.2	methyl 6-({7-[6-(2,2,2-trifluoroethyl)thieno[2,3-	prep. HPLC (method G) analyt. HPLC (method 10): R_t = 1.33 min

Example	Structure Name	Analytical Data
	d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carboxylate (ent-2)	
76	 6-methoxy-5-({7-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carbonitrile	^{1}H-NMR (400 MHz, DMS0-d6) δ [ppm]: 1.391 (0.47), 1.797 (0.82), 1.816 (1.24), 1.831 (1.29), 1.850 (0.62), 2.000 (0.55), 2.323 (0.72), 2.327 (1.01), 2.331 (0.71), 2.518 (3.79), 2.523 (2.52), 2.587 (0.84), 2.606 (2.25), 2.628 (1.26), 2.665 (1.09), 2.669 (1.41), 2.674 (0.96), 2.686 (0.97), 2.701 (0.72), 3.586 (0.44), 3.645 (6.23), 3.681 (0.50), 3.776 (0.71), 3.808 (1.80), 3.820 (16.00), 4.022 (0.52), 4.050 (1.39), 4.078 (1.34), 4.106 (0.47), 6.868 (4.70), 7.215 (0.96), 7.221 (0.99), 7.559 (3.16), 7.700 (3.01), 8.313 (10.58), 12.087 (1.34). LC-MS (method 8): Rt = 1.35 min; MS (ESIpos): m/z = 527 [M+H]+
77	 6-methoxy-1-(1 H-pyrazol-4-ylmethyl)-5-({7-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carbonitrile	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.789 (0.79), 1.807 (1.33), 1.824 (1.42), 1.841 (0.67), 1.993 (0.58), 2.322 (0.74), 2.327 (1.06), 2.332 (0.76), 2.518 (4.20), 2.523 (2.85), 2.539 (0.68), 2.582 (0.76), 2.602 (2.04), 2.625 (1.12), 2.660 (0.72), 2.665 (1.03), 2.669 (1.55), 2.673 (1.60), 2.691 (0.74), 3.643 (5.26), 3.679 (0.59), 3.761 (0.58), 3.863 (0.45), 3.889 (16.00), 4.019 (0.58), 4.047 (1.46), 4.074 (1.42), 4.102 (0.50), 5.376 (6.63), 7.272 (5.05), 7.464 (0.95), 7.481 (0.49), 7.555 (3.17), 7.696 (3.05), 7.754 (0.97), 8.310 (13.57), 12.812 (0.68). LC-MS (method 8): Rt = 1.25 min; MS (ESIpos): m/z = 607 [M+H]+

Example 78

6-({7-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carboxylic acid



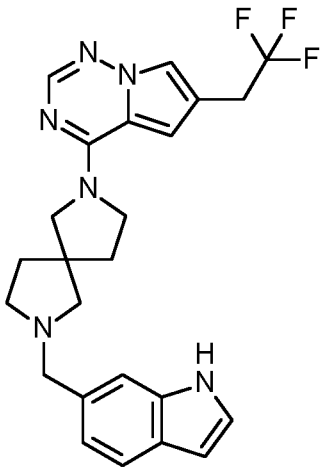
A solution of methyl 6-({7-[6-(2 ,2,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carboxylate (example **75)** (100 mg, 189 μηηοΙ) in 3 ml THF was treated with lithium hydroxide (940 μΙ, 1.0 M, 940 μηηοΙ) and stirred for 2 d at RT. After removal of the solvent by evaporation 1 drop of HCl was added and the residue was purified by prep. HPLC under acidic conditions. The product rich fractions were pooled, the solvent was removed under reduced pressure and freeze dried to yield the desired product as an solid (32 mg, 32 % yield).

LC-MS (method 8): Rt = 0.69 min; MS (ESIpos): m/z = 516 [M-H]+

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.796 (0.52), 1.808 (1.31), 1.825 (2.42), 1.843 (2.51), 1.861 (1.17), 1.907 (0.52), 2.001 (1.02), 2.318 (0.58), 2.323 (1.28), 2.327 (1.81), 2.332 (1.31), 2.336 (0.58), 2.518 (9.76), 2.523 (6.32), 2.540 (1.05), 2.589 (2.42), 2.61 1 (2.39), 2.628 (1.46), 2.660 (1.25), 2.665 (2.04), 2.669 (2.91), 2.673 (2.62), 2.691 (1.02), 3.530 (2.77), 3.657 (1.34), 3.690 (3.67), 3.705 (4.66), 3.736 (1.95), 4.014 (0.82), 4.041 (2.10), 4.069 (2.01), 4.096 (0.73), 7.019 (4.90), 7.022 (4.93), 7.034 (3.23), 7.037 (3.12), 7.055 (3.29), 7.058 (3.35), 7.368 (4.08), 7.542 (4.1 1), 7.563 (3.73), 7.582 (0.50), 7.640 (0.44), 7.684 (4.66), 8.156 (3.18), 8.284 (1.46), 8.298 (1.22), 8.308 (16.00), 11.659 (3.29).

Example 79

4-[7-(1H-indol-6-ylmethyl)-27-diazaspiro[4.4]non-2-yl]-6-(2,2,2-trifluoroethyl)pyrrolo[2,^ -f][1,2,4]triazine



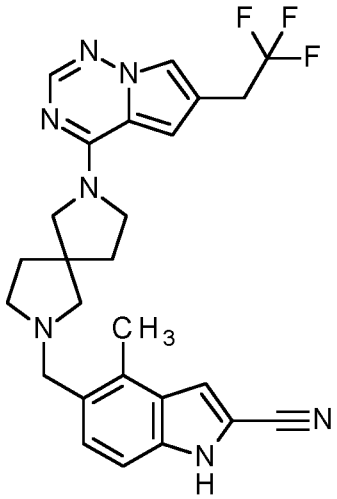
A mixture of 4-(2,7-diazaspiro[4.4]non-2-yl)-6-(2 ,2,2-trifluoroethyl)pyrrolo[2,1-f][1 ,2,4]triazine hydrochloride (intermediate **1106),** 150 mg (0.345 mmol), and 1H-indole-6-carbaldehyde, 41.7 mg (0.288 mmol), in dichloromethane, 1.40 ml, and triethylamine, 132 µl (0.949 mmol), was stirred at RT for 30 minutes. Sodium triacetoxyborohydride, 183 mg (0.863 mmol), was added in portions. The reaction mixture was stirred at RT for 18 hours. The reaction was quenched with water and stirred at RT for 30 minutes. The product was extracted into dichloromethane and the organics were dried over sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel 60 (eluent: ethyl acetate-5% ammonia/methanol 1:0, 9:1) to give the desired product, 130 mg (83% yield).

LC-MS (method 6): Rt = 0.85 min., 96%. MS (ESIpos): m/z = (M+H)+ 454.

1H NMR (400 MHz, MeOD-d3): δ [ppm] = 1.85-2.17 (m, 4H), 2.42-2.86 (m, 4H), 3.36-3.47 (m, 2H), 3.64-4.01 (m, 6H), 6.51 (s, 1H), 6.65 (s, 1H), 7.07 (d, 1H), 7.17 (dd, 1H), 7.35 (d, 1H), 7.50 (s, 1H), 7.56 (d, 1H), 7.81 (s, 1H), 8.31 (br s, 1H).

Example 80

4-methyl-5-({7-[6-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carbonitrile



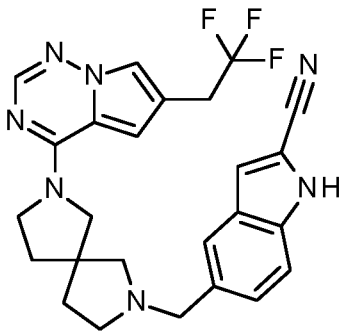
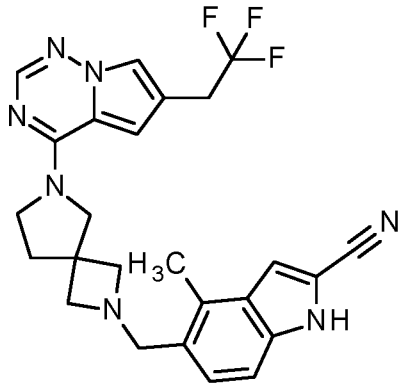
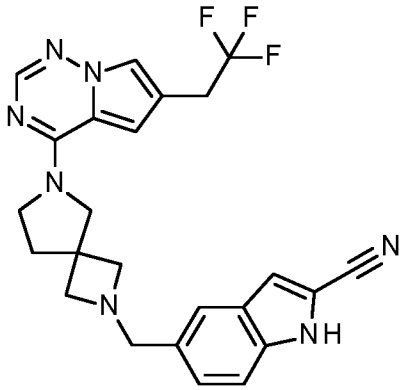
To a mixture of 2-(2,2,2-trifluoroethyl)-2H-pyrazolo[4,3-d]pyrimidin-7-ol (intermediate **178),** 50.0 mg (0.230 mmol), in acetonitrile, 2.30 ml, and triethylamine, 1.30 ml, was added (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate, 132 mg (0.253 mmol), and 5-(2,7-diazaspiro[4.4]non-2-ylmethyl)-4-methyl-1 H-indole-2-carbonitrile hydrochloride (intermediate **I37),** 84.6 mg (0.230 mmol). The mixture was heated to 80 °C for 18 hours. The reaction mixture was concentrated under vacuum. The residue was dissolved in ethyl acetate and washed with aqueous saturated sodium hydrogen carbonate solution. The organics were dried over magnesium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel 60 (eluent: dichloromethane-methanol; 98:2, 96:4, 9:1) to give the desired product, 45 mg (40% yield).

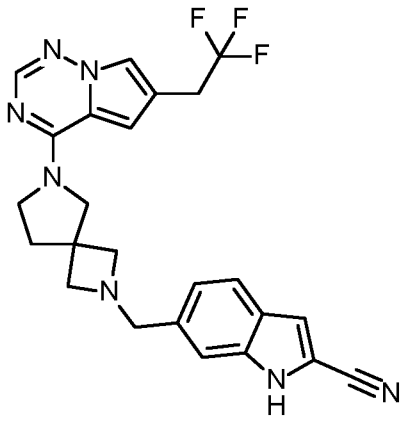
LC-MS (method 7): Rt = 2.81 min., 95%. MS (ESIpos): m/z = (M+H)+ 494.

1H NMR (400 MHz, CDCh3): δ [ppm] = 1.81-2.12 (m, 4H), 2.42-2.81 (m, 8H), 3.34-3.44 (m, 2H), 3.60-4.00 (m, 5H), 6.64 (s, 1H), 7.15 (d, 1H), 7.21 (s, 1H), 7.28-7.34 (m, 1H), 7.50 (s, 1H), 7.81 (s, 1H), 8.81 (d, 1H).

The following examples were prepared analogous to the preparation of example **80** starting from the corresponding intermediate **I78** by reacting with the corresponding spirocyclic amines.

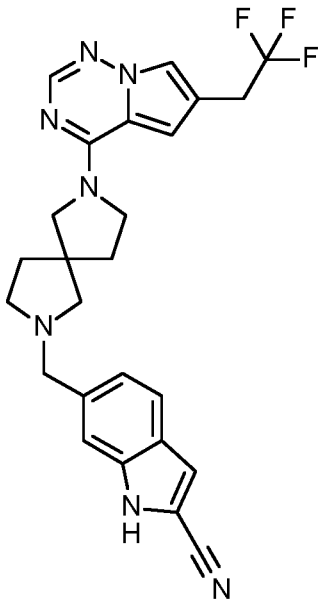
Example	**Structure** **Name**	**Analytical Data**

Example	Structure Name	Analytical Data
81	 5-({7-[6-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carbonitrile	1H NMR (CDCl3, 400 MHz): 8.62 (br s, 1H); 7.81 (s, 1H); 7.58 (s, 1H); 7.5 (s, 1H); 7.39-7.33 (m, 2H); 7.13 (s, 1H); 6.66 (s, 1H); 3.96 (br s, 1H); 3.78 (s, 2H); 3.47-3.36 (m, 3H); 2.61 (s, 1H); 2.05-1.95 (m, 12H). LC-MS (method 6): 2.51 mins, m/z 480.31 [M+H]+, 90.91%
82	 4-methyl-5-({6-[6-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazin-4-yl]-2,6-diazaspiro[3.4]oct-2-yl}methyl)-1H-indole-2-carbonitrile	1H NMR (400 MHz, CDCl3): δ [ppm] = 2.10-2.36 (m, 2H), 2.53 (s, 3H), 2.26-3.45 (m, 6H), 3.73-4.10 (m, 6H), 6.66 (br s, 1H), 7.19 (d, 1H), 7.22-7.23 (m, 1H), 7.32 (d, 1H), 7.51 (s, 1H), 7.82 (s, 1H), 8.55 (br s, 1H). LC-MS (method 6): Rt = 0.86 min., 97%. MS (ESIpos): m/z = (M+H)+ 480
83		1H NMR (400 MHz, CDCl¬3): δ [ppm] = 2.17 (br s, 1H), 2.36 (br s, 1H), 3.33-3.44 (m, 6H), 3.73-3.85 (m, 4H), 3.99 (s, 1H), 4.12 (s, 1H), 6.67 (s, 1H), 7.14 (d, 1H), 7.31 (s, 2H), 7.55 (d, 2H), 7.82 (s, 1H), 9.10 (d, 1H). LC-MS (method 5): Rt = 0.81 min., 100%. MS (ESIpos): m/z = (M+H)+ 466.

Example	Structure Name	Analytical Data
	5-({6-[6-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazin-4-yl]-2,6-diazaspiro[3.4]oct-2-yl}methyl)-1H-indole-2-carbonitrile	
84	 6-({6-[6-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazin-4-yl]-2,6-diazaspiro[3.4]oct-2-yl}methyl)-1H-indole-2-carbonitrile	1H NMR (400 MHz, CDCl¬3): δ [ppm] = 2.17-2.36 (m, 2H), 3.36-3.49 (m, 6H), 3.77-4.13 (m, 6H), 6.68 (s, 1H), 7.12-7.16 (m, 2H), 7.38 (s, 1H), 7.50 (s, 1H), 7.60 (d, 1H), 7.83 (s, 1H), 8.94 (br s, 1H). LC-MS (method 5): Rt = 0.83 min., 99%. MS (ESIpos): m/z = (M+H)+ 466.

Example 85

6-({7-[6-(2,2,2-trifluoroethyl)pyrrolo[2J-f][1,2,4]triazin-4-yl]-27-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carbonitrile



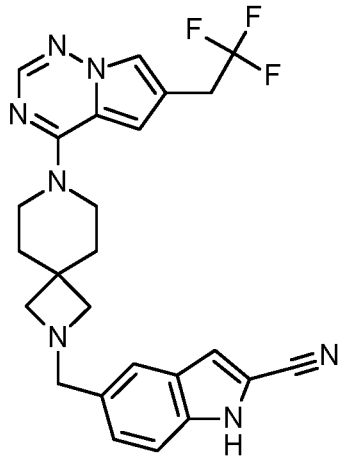
To a solution of tert-butyl 2-cyano-6-({7-[6-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1 ,2,4]triazin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-1-carboxylate (intermediate **I64),** 36.0 mg (0.0621 mmol), in methanol, 1.00 ml, at 0 °C, was added sodium hydroxide (4.0 M aqueous), 388 µl (1.55 mmol), and stirred at room temperature for 1 hour. The reaction was diluted with water and extracted into ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and concentrated to give a residue. The residue was purified by flash chromatography on silica gel 60 (eluent: ethyl acetate to 2-propanol-ethyl acetate/2% triethylamine 1:9) to give the desired product, 9.9 mg (33% yield).

1H NMR (400 MHz, CDCh3): δ [ppm] = 1.67-2.12 (m, 4H), 2.44-2.83 (m, 4H), 3.35-3.42 (m, 2H), 3.64-3.83 (m, 4H), 3.96-4.02 (m, 2H), 6.66 (s, 1H), 7.15 (s, 1H), 7.17 (d, 1H), 7.37 (s, 1H), 7.51 (s, 1H), 7.58 (d, 1H), 7.81 (s, 1H), 9.05-9.15 (d, 1H).

LC-MS (method 5): Rt = 0.88 min., 94%. MS (ESIpos): m/z = (M+H)+ 480.

Example 86

5-({7-[6-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}methyl)-1 H-indole-2-carbonitrile



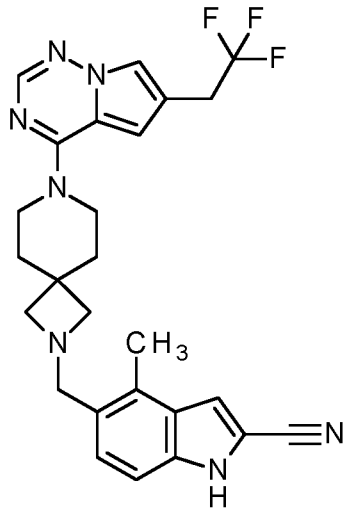
To a stirring solution of tert-butyl 2-cyano-5-({7-[6-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}methyl)-1H-indole-1-carboxylate (intermediate **I54),** ~119 mg (assumed 0.205 mmol), in methanol, 2.80 ml, at -5 °C was added a solution of sodium hydroxide, 161 mg (4.025 mmol), in water, 1.00 ml. Stirring continued for 1.5 hours between -5°C and 0 °C. The mixture was diluted with water and extracted with ethyl acetate. The combined organics were dried over sodium sulphate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel 60 (eluent: heptane-ethyl acetate; 75:25, 0:100) and then purified by flash chromatography on silica gel 60 (eluent: ethyl acetate-13% ammonia/methanol; 99:1, 96:4) to give the desired product, 13.2 mg (13% over 3 steps).

LC-MS (method 10): Rt = 2.68 min., 94%. MS (ESIneg): m/z = (M-H)- 478.

1H NMR (400 MHz, CDCl3): δ [ppm] = 1.87-1.95 (m, 4H), 3.11-3.19 (m, 4H), 3.41 (q, 2H), 3.76 (s, 2H), 3.84-3.91 (m, 4H), 6.60 (s, 1H), 7.16 (s, 1H), 7.32-7.38 (m, 2H), 7.53 (s, 1H), 7.58 (s, 1H), 7.85 (s, 1H), 8.55 (br s, 1H);

Example 87

4-methyl-5-({7-[6-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}methyl)-1H-indole-2-carbonitrile



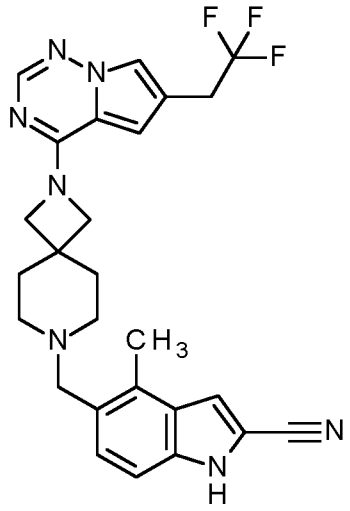
To a mixture of 2-(2,2,2-trifluoroethyl)-2H-pyrazolo[4,3-d]pyrimidin-7-ol (intermediate **178),** 50.0 mg (0.230 mmol), in acetonitrile, 2.30 ml, and triethylamine, 1.30 ml, was added (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate, 132 mg (0.253 mmol), and 5-(2,7-diazaspiro[3.5]non-2-ylmethyl)-4-methyl-1 H-indole-2-carbonitrile hydrochloride (intermediate **I53),** 84.6 mg (0.230 mmol). The mixture was heated to 80 °C for 18 hours. The reaction mixture was concentrated under vacuum. The residue was dissolved in ethyl acetate and washed with aqueous saturated sodium hydrogen carbonate solution. The organics were dried over magnesium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel 60 (eluent: heptane-ethyl acetate; 4:6, 0:1) to give the desired product, 35 mg (30% yield).

1H NMR (400 MHz, CDCh3): δ [ppm] = 1.85-1 .91 (m, 4H), 2.52 (s, 3H), 3.14 (s, 4H), 3.40 (q, 2H), 3.86-3.88 (m, 4H), 6.61 (s, 1H), 7.15 (d, 1H), 7.21 (s, 1H), 7.31 (d, 1H), 7.52 (s, 1H), 7.85 (s, 1H), 8.84 (s, 1H).

LC-MS (method 6): Rt = 0.86 min., 97%. MS (ESIpos): m/z = (M+H)+ 480.

Example 88

4-methyl-5-({2-[6-(2,2,2-trifluoroethyl)pyrrolo[2,1 -n[1,2,4]triazin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carbonitrile



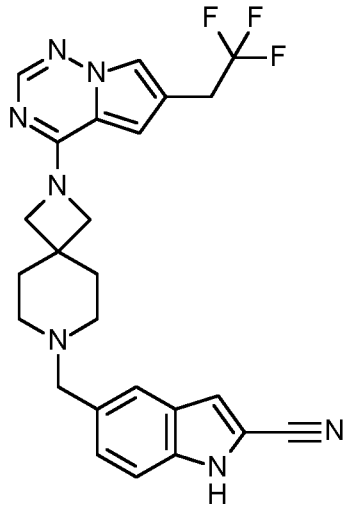
To a mixture of 2-(2,2,2-trifluoroethyl)-2H-pyrazolo[4,3-d]pyrimidin-7-ol (intermediate **178),** 46.1 mg (0.212 mmol), in acetonitrile, 2.12 ml, and triethylamine, 1.20 ml, was added (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate, 121 mg (0.233 mmol), and 5-(2,7-diazaspiro[3.5]non-7-ylmethyl)-4-methyl-1 H-indole-2-carbonitrile dihydrochloride (intermediate **I56),** 78.0 mg (0.212 mmol). The mixture was heated to 80 °C for 18 hours. The reaction mixture was concentrated under vacuum. The residue was dissolved in ethyl acetate and washed with aqueous saturated sodium hydrogen carbonate solution. The organics were dried over magnesium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel 60 (eluent: heptane-ethyl acetate; 4:6, 0:1) to give the desired product, 26 mg (24% yield).

1H NMR (400 MHz, CDCh3): δ [ppm] = 1.79-1 .89 (m, 4H), 2.31-2.54 (m, 4H), 2.54 (s, 3H), 3.49 (q, 2H), 3.56 (s, 2H), 3.98 (s, 2H), 4.23 (s, 2H), 6.49 (s, 1H), 7.18 (d, 1H), 7.22 (s, 1H), 7.30 (d, 1H), 7.49 (s, 1H), 7.83 (s, 1H), 9.03 (s, 1H);

LC-MS (method 7): Rt = 2.67 min., 94%. MS (ESIpos): m/z = (M+H)+ 494.

Example 89

5-({2-[6-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carbonitrile



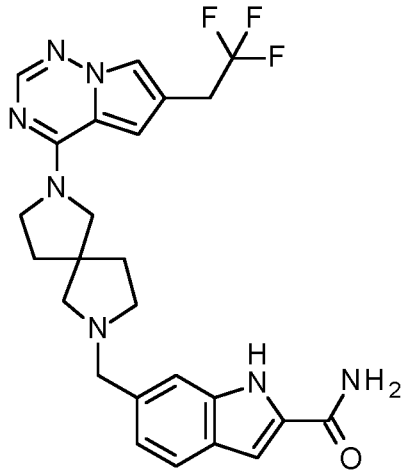
(Benzotriazol-l-yloxy)tripyrrolidinophosphonium hexafluorophosphate, 75.0 mg (0.145 mmol), was added to a solution of 5-(2,7-diazaspiro[3.5]non-7-ylmethyl)-1 H-indole-2-carbonitrile dihydrochloride (intermediate **I62),** 47.0 mg (0.132 mmol), and 6-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1 ,2,4]triazin-4-ol (intermediate **I78),** 29.0 mg (0.132 mmol) in acetonitrile, 2.00 ml, and triethylamine, 1.00 ml, at room temperature under argon. The reaction was heated at 80 °C for 16 hours, and concentrated to give a residue which was washed with saturated sodium hydrogen carbonate solution, and extracted into dichloromethane. The organic layer was dried over sodium sulfate, filtered, and concentrated to give a residue. Purification by flash chromatography on silica gel 60 (eluent: heptane-ethyl acetate; 3:1 , then ethyl acetate-propan-2-ol; 3:1) gave the desired product, 9.1 mg (14% yield).

1H NMR (400 MHz, CDCh3): δ [ppm] = 1.82-1 .99 (m, 5H), 2.47 (br s, 3H), 3.40 (q, 2H), 3.61 (s, 2H), 3.97 (s, 2H), 4.23 (s, 2H), 6.48 (s, 1H), 7.14 (s, 1H), 7.32-7.37 (m, 2H), 7.49 (s, 1H), 7.57 (s, 1H), 7.83 (s, 1H), 9.16 (s, 1H).

LC-MS (method 5): Rt = 0.84 min., 96%. MS (ESIpos): m/z = (M+H)+ 480.

Example 90

6-({7-[6-(2,2,2-trifluoroethyl)pyrrolo[2J-f][1,2,4]triazin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carboxamide



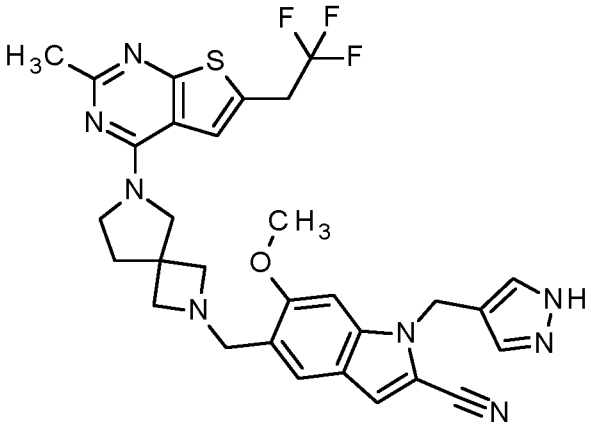
To a 1.13:1 mixture of tert-butyl 2-[(tert-butoxycarbonyl)carbamoyl]-6-({7-[6-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1 ,2,4]triazin-4-yl]-2J-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-1-carboxylate (intermediate **I69)** and tert-butyl 2-[(di-tert-butoxycarbonyl)carbamoyl]-6-({7-[6-(2,2,2-trifluoroethyl)pyrrolo[2 ,1-f][1 ,2,4]triazin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-1 -carboxylate (intermediate **I70),** 32.9 mg (-0.0442 mmol), in dioxane, 1.00 ml, was added hydrochloric acid (4.0 M in dioxane), 1.00 ml (4.00 mmol), and stirred at room temperature for 18 hours. The reaction was concentrated to give a residue which was triturated with diethyl ether. Further purification by flash chromatography on silica gel 60 (eluent: dichloromethane-12% ammonia/methanol 1:0 to 95:5) gave the desired product, 4.7 mg (21%).

1H NMR (400 MHz, CDCh3): δ [ppm] = 1.84-2.20 (m, 4H), 2.42-2.92 (m, 4H), 3.40 (apparent quintet, 2H), 3.51-4.1 1 (m, 6H), 5.43-6.20 (m, 2H), 6.63-6.70 (m, 1H), 6.86 (s, 1H), 7.14 (d, 1H), 7.37-7.44 (m, 1H), 7.51 (s, 1H), 7.59 (d, 1H), 7.81 (s, 1H), 9.13 (br s, 1H).

LC-MS (method 11): Rt = 2.13 min., 98%. MS (ESIpos): m/z = (M+H)+ 498.

Example 91

6-methoxy-5-({6-[2-methyl-6-(2,2,2-triflu^ roethyl)thieno[2,3-d]pyrimidin-4-yl]-2,6-diazaspiro[3.4]oct-2-yl}methyl)-1 -(1 H-pyrazol-4-ylmethyl)-1 H-indole-2-carbonitrile

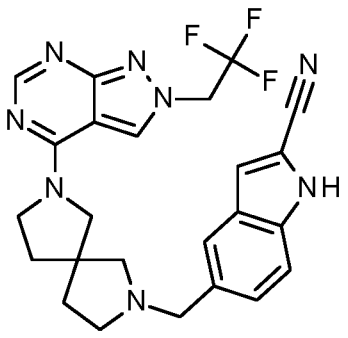


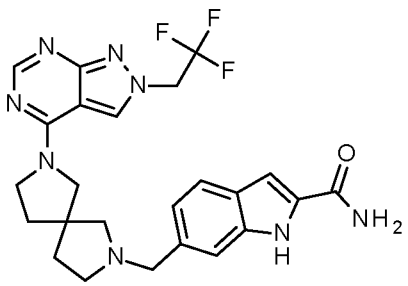
According to the preparation of example **43** 4-(2,6-diazaspiro[3.4]oct-6-yl)-2-methyl-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidine trifluoroacetate (intermediate **107)** (100 mg, 292 μηοl) was reacted with 5-formyl-6-methoxy-1-[(1-trityl-1 H-pyrazol-4-yl)methyl]-1 H-indole-2-carbonitrile (153 mg, 292 μηοl) (for preparation see Journal of Medicinal Chemistry, 2016, 892-913) to yield the desired intermediate 6-methoxy-5-({6-[2-methyl-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,6-diazaspiro[3.4]oct-2-yl}methyl)-1-[(1-trityl-1 H-pyrazol-4-yl)methyl]-1 H-indole-2-carbonitrile which was used without further purification. To a mixture of 250 mg (294 μιοl) 6-methoxy-5-({6-[2-methyl-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,6-diazaspiro[3.4]oct-2-yl}methyl)-1 -[(1 -trityl-1 H-pyrazol-4-yl)methyl]-1 H-indole-2-carbonitrile in acetonitril/water was added 5 ml of a solution of hydrogen chloride in dioxane (4 N). After 1h stirring at RT, the solvent was evaporated and the residue was purified by preparative HPLC to yield 9 mg (5% yield) of the desired product.

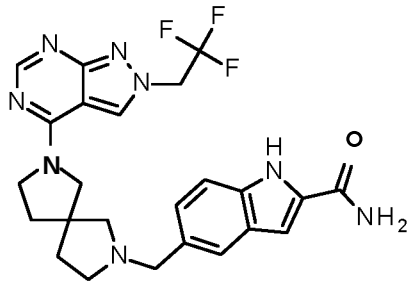
LC-MS (method 12): Rt = 0.88 min; MS (ESIpos): m/z = 607 [M+H]+

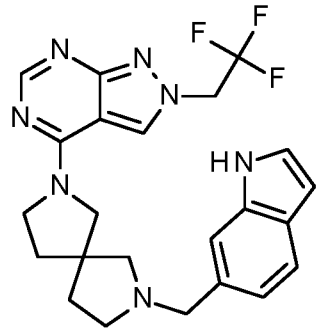
1H-NMR (400 MHz, DMSO-d6) delta [ppm]: 2.182 (0.25), 2.323 (0.41), 2.327 (0.58), 2.331 (0.43), 2.414 (4.45), 2.518 (2.52), 2.523 (1.73), 2.539 (16.00), 2.665 (0.42), 2.669 (0.58), 2.673 (0.42), 3.412 (0.40), 3.769 (0.39), 3.913 (3.88), 3.982 (0.21), 4.010 (0.53), 4.038 (0.50), 4.065 (0.17), 5.390 (1.51), 7.306 (0.80), 7.344 (1.09), 7.554 (0.62), 7.628 (0.77), 8.137 (0.39).

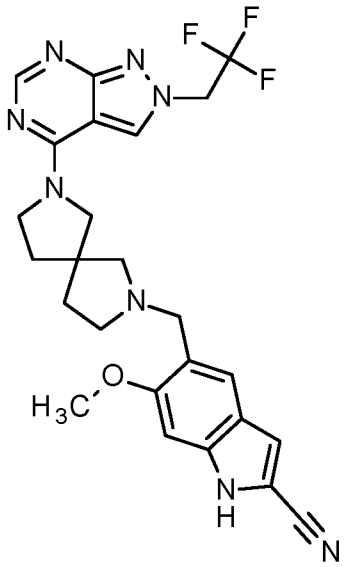
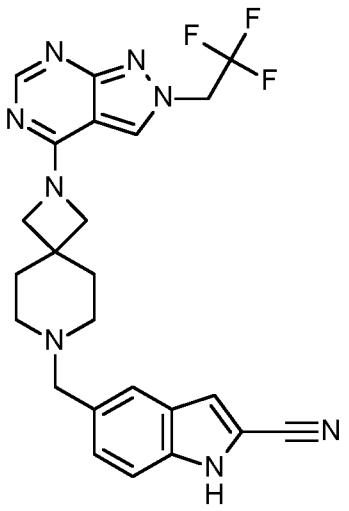
The following examples were prepared analogous to the preparation of example **13** starting from the corresponding intermediates **131, I28** or **1104,** by reacting with the corresponding aldehydes.

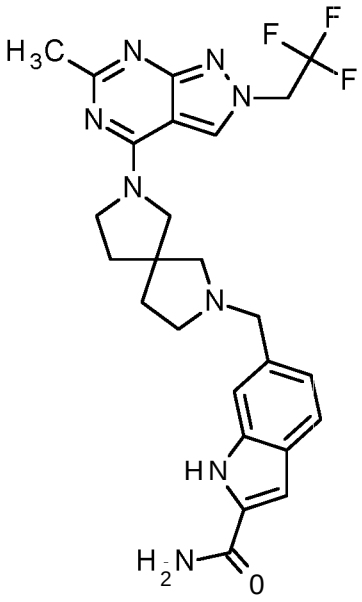
Example	Structure Name	Analytical Data
92	 5-({7-[2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-	¹H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.145 (0.56), 1.786 (1.97), 1.804 (4.16), 1.822 (2.75), 1.845 (2.11), 1.862 (2.26), 1.880 (1.20), 1.896 (0.78), 1.914 (0.85), 1.927 (1.13), 1.944 (2.82), 1.960 (2.47), 1.976 (1.27), 1.989 (0.56), 2.043 (0.63), 2.055 (0.99), 2.074 (2.68), 2.084 (2.19), 2.090 (2.26), 2.106 (1.13), 2.318 (1.13), 2.323 (2.47), 2.327 (3.52), 2.331 (2.54), 2.337 (1.13), 2.379 (0.63), 2.382 (0.56), 2.430 (4.86), 2.453 (6.91), 2.518 (13.74), 2.523 (9.73), 2.532 (3.31), 2.540 (1.55), 2.551 (2.61), 2.572 (2.96), 2.582 (3.59), 2.605 (2.54), 2.619 (0.85), 2.636

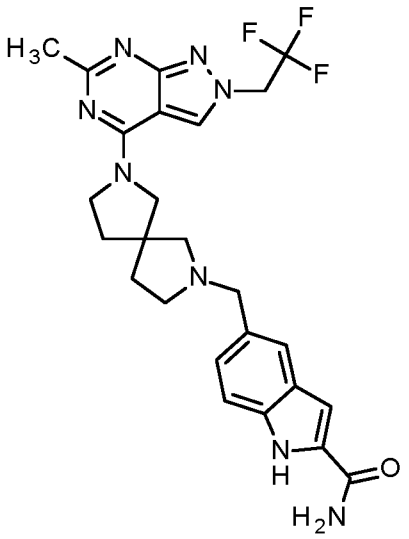
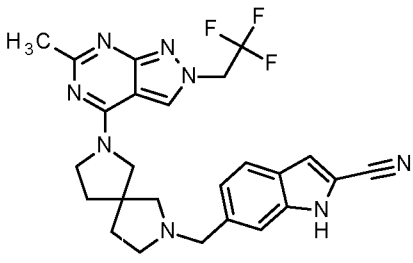
Example	Structure Name	Analytical Data
	carbonitrile	(2.26), 2.654 (2.47), 2.659 (2.82), 2.665 (3.59), 2.669 (4.86), 2.674 (3.67), 3.545 (1.97), 3.575 (3.10), 3.606 (1.06), 3.620 (1.20), 3.636 (2.19), 3.656 (13.74), 3.664 (1 1.98), 3.679 (4.16), 3.688 (3.81), 3.702 (1.41), 3.717 (0.99), 3.736 (3.74), 3.761 (2.61), 3.794 (1.48), 3.812 (0.99), 5.307 (1.27), 5.330 (3.81), 5.352 (4.16), 5.358 (4.58), 5.380 (3.74), 5.403 (1.06), 7.279 (7.54), 7.280 (7.75), 7.306 (8.95), 7.315 (2.33), 7.319 (2.19), 7.327 (3.59), 7.331 (3.88), 7.337 (3.38), 7.341 (3.24), 7.375 (4.65), 7.395 (6.13), 7.416 (2.40), 7.565 (8.60), 8.198 (14.94), 8.201 (16.00), 8.550 (0.56), 8.696 (7.96), 8.772 (8.74), 12.316 (0.42). LC-MS (method 2): Rt = 0.44 min; MS (ESIpos): m/z = 481 [M+H]+
93	 6-({7-[2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carboxamide	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.922 (0.41), 1.752 (0.41), 1.790 (2.10), 1.807 (4.41), 1.824 (3.40), 1.841 (2.37), 1.859 (2.48), 1.876 (1.25), 1.893 (0.65), 1.916 (0.79), 1.928 (1.12), 1.946 (2.26), 1.967 (2.29), 1.984 (1.20), 1.996 (0.65), 2.046 (0.60), 2.059 (1.01), 2.076 (2.12), 2.084 (7.05), 2.096 (2.10), 2.1 14 (1.09), 2.126 (0.54), 2.323 (1.17), 2.327 (1.66), 2.331 (1.17), 2.378 (1.01), 2.381 (0.95), 2.448 (2.12), 2.470 (5.69), 2.518 (7.84), 2.523 (6.01), 2.540 (1.93), 2.544 (2.18), 2.571 (2.48), 2.589 (6.18), 2.61 1 (3.29), 2.623 (1.71), 2.641 (3.43), 2.659 (2.61), 2.664 (3.05), 2.669 (2.31), 2.674 (1.61), 2.678 (1.28), 3.567 (1.90), 3.597 (3.35), 3.618 (1.99), 3.650 (14.53), 3.663 (7.16), 3.687 (6.15), 3.719 (1.06), 3.733 (3.73), 3.758 (2.75), 3.777 (2.12), 3.797 (1.90), 3.815 (1.01), 5.307 (1.25), 5.330 (4.54), 5.353 (6.50), 5.376 (4.22), 5.399 (1.09),

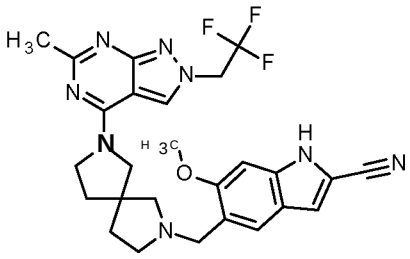
Example	Structure Name	Analytical Data
		7.002 (5.03), 7.023 (5.36), 7.061 (8.33), 7.065 (8.30), 7.310 (2.75), 7.324 (6.18), 7.352 (5.01), 7.490 (4.16), 7.500 (4.08), 7.51 1 (3.86), 7.521 (3.48), 7.909 (2.48), 8.202 (14.64), 8.204 (16.00), 8.698 (7.89), 8.772 (8.57), 11.448 (3.40), 11.458 (3.56). LC-MS (method 2): Rt = 0.36 min; MS (ESIpos): m/z = 499 [M+H]+
94	 5-({7-[2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carboxamide	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.923 (0.54), 1.752 (0.54), 1.783 (1.63), 1.801 (3.39), 1.819 (2.58), 1.839 (1.90), 1.855 (1.97), 1.874 (1.08), 1.889 (0.54), 1.913 (0.61), 1.925 (1.08), 1.942 (2.37), 1.959 (2.31), 1.975 (1.08), 1.988 (0.47), 2.041 (0.47), 2.054 (0.88), 2.072 (2.03), 2.084 (16.00), 2.104 (0.95), 2.1 18 (0.41), 2.318 (1.36), 2.323 (2.98), 2.327 (4.07), 2.331 (2.98), 2.337 (1.36), 2.380 (1.29), 2.382 (1.29), 2.423 (0.47), 2.436 (3.93), 2.459 (5.76), 2.518 (14.24), 2.523 (10.64), 2.540 (2.24), 2.564 (2.31) , 2.590 (3.12), 2.613 (2.37), 2.625 (1.76), 2.648 (1.97), 2.665 (4.20), 2.669 (5.08), 2.673 (3.53), 3.551 (1.69), 3.581 (2.58), 3.598 (0.81), 3.615 (1.15), 3.634 (7.46), 3.645 (6.37), 3.656 (4.95), 3.685 (4.00), 3.703 (1.15), 3.718 (0.88), 3.734 (3.19), 3.759 (2.10), 3.770 (1.56), 3.794 (1.36), 3.81 1 (0.81), 5.306 (1.02), 5.328 (3.19), 5.355 (3.93), 5.378 (3.12), 5.400 (0.88), 7.044 (3.86), 7.050 (5.02), 7.056 (3.53), 7.149 (3.86), 7.170 (4.68), 7.319 (5.56), 7.331 (4.14), 7.340 (3.32) , 7.352 (2.64), 7.482 (8.34), 7.906 (2.31), 8.201 (14.17), 8.550 (0.68), 8.696 (6.44), 8.770 (7.53), 11.456 (4.34). LC-MS (method 2): Rt = 0.34 min; MS (ESIpos): m/z = 499 [M+H]+

Example	Structure Name	Analytical Data
95	 4-[7-(1 H-indol-6-ylmethyl)-2,7-diazaspiro[4.4]non-2-yl]-2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidine	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.788 (2.01), 1.807 (4.06), 1.823 (2.99), 1.840 (2.15), 1.856 (2.29), 1.874 (1.07), 1.891 (0.51), 1.916 (0.65), 1.928 (0.98), 1.946 (2.24), 1.964 (2.29), 1.982 (1.07), 1.995 (0.56), 2.046 (0.51), 2.058 (0.89), 2.076 (2.10), 2.084 (1.35), 2.095 (2.10), 2.1 11 (0.98), 2.124 (0.47), 2.318 (0.89), 2.323 (1.96), 2.327 (2.75), 2.331 (1.91), 2.337 (0.84), 2.442 (2.05), 2.466 (4.43), 2.518 (9.80), 2.523 (7.28), 2.528 (3.87), 2.540 (1.45), 2.551 (2.43), 2.567 (2.19), 2.585 (2.99), 2.594 (3.59), 2.618 (2.33), 2.630 (1.31), 2.649 (2.94), 2.665 (3.73), 2.669 (4.43), 2.673 (2.99), 2.687 (0.70), 3.563 (1.77), 3.592 (2.89), 3.628 (1.26), 3.636 (1.26), 3.659 (16.00), 3.670 (6.67), 3.685 (4.52), 3.702 (1.87), 3.718 (0.89), 3.733 (3.41), 3.757 (2.43), 3.776 (1.77), 3.797 (1.63), 3.816 (0.89), 5.307 (1.17), 5.330 (4.38), 5.352 (6.20), 5.375 (4.01), 5.397 (0.98), 6.358 (5.50), 6.361 (5.55), 6.945 (2.43), 6.949 (2.89), 6.952 (3.03), 6.955 (2.66), 6.965 (2.66), 6.969 (3.17), 6.972 (3.22), 6.975 (2.80), 7.269 (2.75), 7.276 (6.58), 7.282 (6.62), 7.290 (4.85), 7.294 (4.80), 7.320 (4.29), 7.424 (3.83), 7.432 (3.69), 7.444 (3.55), 7.452 (3.31), 8.202 (14.46), 8.204 (15.07), 8.698 (7.32), 8.769 (8.02), 10.973 (4.48). LC-MS (method 2): Rt = 0.50 min; MS (ESIpos): m/z = 456 [M+H]+

Example	Structure Name	Analytical Data
96	 6-methoxy-5-({7-[2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carbonitrile	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.398 (0.65), 1.791 (1.14), 1.809 (2.44), 1.826 (1.87), 1.846 (1.14), 1.865 (1.14), 1.882 (0.65), 1.938 (0.65), 1.955 (1.54), 1.972 (1.54), 1.988 (0.73), 2.071 (0.57), 2.089 (1.06), 2.109 (1.06), 2.126 (0.57), 2.318 (0.49), 2.322 (1.14), 2.327 (1.71), 2.332 (1.22), 2.336 (0.57), 2.518 (8.45), 2.523 (5.28), 2.528 (2.52), 2.539 (2.76), 2.584 (2.11), 2.592 (1.54), 2.608 (2.03), 2.631 (0.65), 2.645 (1.79), 2.669 (3.25), 2.673 (1.79), 2.679 (1.30), 2.683 (1.30), 2.700 (1.30), 2.715 (0.73), 3.298 (0.57), 3.378 (0.57), 3.562 (1.14), 3.591 (1.62), 3.642 (5.28), 3.660 (6.42), 3.686 (2.44), 3.693 (2.52), 3.715 (1.71), 3.727 (0.49), 3.755 (1.87), 3.780 (1.46), 3.792 (1.30), 3.817 (16.00), 3.825 (14.46), 5.316 (0.73), 5.337 (2.19), 5.356 (2.76), 5.377 (2.19), 5.399 (0.65), 6.871 (7.72), 7.185 (4.14), 7.253 (3.65), 7.555 (4.14), 7.575 (3.65), 8.207 (8.37), 8.210 (8.85), 8.713 (4.30), 8.787 (5.04), 12.093 (1.38). LC-MS (method 2): Rt = 0.49 min; MS (ESIpos): m/z = 511 [M+H]+
97	 5-({2-[2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.231 (0.44), 1.751 (1.45), 1.803 (3.42), 2.266 (0.66), 2.318 (0.96), 2.322 (1.53), 2.326 (1.97), 2.331 (1.49), 2.336 (0.88), 2.421 (0.66), 2.518 (6.84), 2.522 (4.78), 2.539 (0.75), 2.659 (0.61), 2.664 (1.23), 2.668 (1.67), 2.673 (1.18), 2.678 (0.57), 3.525 (8.90), 3.883 (5.79), 4.108 (5.70), 5.318 (1.32), 5.340 (3.73), 5.363 (3.51), 5.385 (1.10), 7.299 (2.41), 7.303 (2.45), 7.324 (11.05), 7.409 (4.52), 7.431 (3.02), 7.557 (5.13), 8.197 (16.00), 8.632 (8.42), 12.340 (0.48). LC-MS (method 2): Rt = 0.44 min; MS

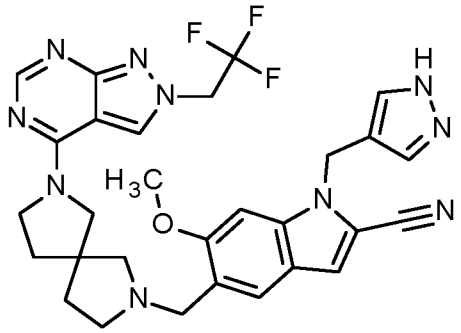
Example	Structure Name	Analytical Data
	2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carbonitrile	(ESIpos): m/z = 481 [M+H]+
98	 6-({7-[6-methyl-2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carboxamide	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.764 (1.14), 1.783 (2.29), 1.800 (1.14), 1.819 (1.14), 1.834 (1.14), 1.850 (1.14), 1.900 (0.00), 1.919 (1.14), 1.936 (1.14), 1.952 (0.00), 2.029 (0.00), 2.047 (1.14), 2.067 (1.14), 2.084 (0.00), 2.323 (12.57), 2.337 (13.71), 2.428 (1.14), 2.435 (1.14), 2.442 (1.14), 2.457 (2.29), 2.466 (2.29), 2.518 (4.57), 2.522 (3.43), 2.539 (1.14), 2.546 (2.29), 2.569 (2.29), 2.601 (1.14), 2.619 (1.14), 2.634 (1.14), 2.660 (1.14), 2.665 (1.14), 2.670 (1.14), 2.674 (1.14), 3.277 (0.00), 3.326 (0.00), 3.336 (0.00), 3.357 (0.00), 3.367 (0.00), 3.374 (0.00), 3.382 (0.00), 3.393 (0.00), 3.416 (1.14), 3.431 (1.14), 3.439 (1.14), 3.452 (1.14), 3.466 (2.29), 3.471 (2.29), 3.482 (2.29), 3.493 (3.43), 3.499 (3.43), 3.513 (4.57), 3.535 (12.57), 3.541 (16.00), 3.623 (13.71), 3.630 (11.43), 3.642 (13.71), 3.673 (3.43), 3.687 (3.43), 3.702 (2.29), 3.712 (2.29), 3.732 (1.14), 3.748 (1.14), 3.757 (1.14), 3.771 (1.14), 3.791 (1.14), 3.799 (1.14), 3.808 (0.00), 3.831 (0.00), 3.844 (0.00), 3.865 (0.00), 5.231 (1.14), 5.253 (2.29), 5.275 (3.43), 5.296 (2.29), 5.318 (0.00), 7.003 (2.29), 7.006 (2.29), 7.024 (3.43), 7.027 (3.43), 7.059 (4.57), 7.287 (1.14), 7.331 (2.29), 7.350 (2.29), 7.480 (2.29), 7.500 (3.43), 7.519 (2.29), 7.928 (1.14), 8.593 (3.43), 8.657 (3.43), 11.397 (3.43). LC-MS (method 2): Rt = 0.37 min; MS (ESIpos): m/z = 513 [M+H]+

Example	Structure Name	Analytical Data
99	 5-({7-[6-methyl-2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carboxamide	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.752 (0.40), 1.795 (1.77), 1.812 (1.68), 1.828 (1.55), 1.846 (1.62), 1.861 (0.78), 1.902 (0.71), 1.921 (1.62), 1.937 (1.55), 1.952 (0.75), 2.035 (0.62), 2.054 (1.27), 2.074 (1.37), 2.084 (0.93), 2.332 (16.00), 2.346 (14.76), 2.422 (1.52), 2.435 (1.49), 2.444 (1.99), 2.458 (2.11), 2.518 (7.24), 2.523 (5.06), 2.539 (1.96), 2.556 (1.80), 2.576 (2.80), 2.600 (1.86), 2.618 (1.15), 2.647 (1.06), 2.665 (1.93), 2.669 (2.27), 2.673 (1.55), 3.542 (1.15), 3.571 (2.05), 3.590 (1.12), 3.606 (1.06), 3.622 (3.98), 3.637 (8.08), 3.650 (2.80), 3.662 (1.80), 3.669 (2.05), 3.686 (0.84), 3.710 (2.05), 3.735 (1.55), 3.745 (1.30), 3.766 (1.15), 3.785 (0.65), 5.262 (0.71), 5.285 (2.33), 5.310 (2.98), 5.333 (2.21), 5.356 (0.65), 7.042 (2.49), 7.046 (2.67), 7.056 (2.64), 7.060 (2.55), 7.146 (1.65), 7.150 (1.68), 7.167 (2.11), 7.172 (2.02), 7.316 (3.98), 7.336 (3.82), 7.355 (1.96), 7.480 (5.69), 7.909 (1.71), 8.612 (4.54), 8.681 (4.66), 11.458 (3.79). LC-MS (method 2): Rt = 0.34 min; MS (ESIpos): m/z = 513 [M+H]+
100	 6-({7-[6-methyl-2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carbonitrile	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.794 (0.99), 1.811 (1.80), 1.827 (1.69), 1.841 (1.49), 1.859 (1.56), 1.875 (0.72), 1.900 (0.44), 1.912 (0.68), 1.930 (1.40), 1.949 (1.42), 1.966 (0.68), 2.045 (0.66), 2.064 (1.32), 2.074 (0.77), 2.084 (2.04), 2.100 (0.70), 2.323 (1.36), 2.328 (2.21), 2.334 (14.55), 2.348 (16.00), 2.458 (1.58), 2.468 (1.82), 2.518 (4.65), 2.523 (3.24), 2.538 (2.28), 2.561 (1.64), 2.573 (1.67), 2.584 (2.52), 2.607 (1.86), 2.631 (0.96), 2.649 (1.97), 2.665 (2.10), 2.669 (2.50), 2.673 (1.88), 2.688 (0.50),

Example	Structure Name	Analytical Data
		3.556 (1.14), 3.585 (2.17), 3.599 (0.61), 3.614 (0.68), 3.638 (2.96), 3.661 (2.83), 3.678 (1.38), 3.701 (5.68), 3.736 (2.30), 3.756 (1.42), 3.773 (1.32), 3.792 (0.66), 5.267 (0.77), 5.290 (2.81), 5.312 (3.92), 5.334 (2.45), 5.356 (0.61), 7.133 (3.62), 7.136 (3.64), 7.154 (3.81), 7.157 (3.95), 7.314 (8.99), 7.360 (2.78), 7.381 (3.02), 7.575 (2.35), 7.593 (3.48), 7.612 (2.30), 8.614 (4.89), 8.681 (4.45), 12.284 (0.55). LC-MS (method 2): Rt = 0.47 min; MS (ESIpos): m/z = 495 [M+H]+
101	 6-methoxy-5-({7-[6-methyl-2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carbonitrile	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.788 (0.94), 1.806 (1.73), 1.821 (1.61), 1.837 (1.38), 1.855 (1.53), 1.872 (0.69), 1.886 (0.43), 1.904 (0.51), 1.916 (0.61), 1.934 (1.51), 1.952 (1.45), 1.968 (0.71), 2.054 (0.59), 2.074 (1.65), 2.084 (2.67), 2.094 (1.12), 2.1 11 (0.65), 2.323 (1.08), 2.327 (1.55), 2.339 (15.57), 2.347 (16.00), 2.518 (4.56), 2.523 (3.56), 2.528 (2.28), 2.540 (0.61), 2.580 (2.34), 2.603 (2.22), 2.632 (1.97), 2.656 (1.63), 2.665 (1.26), 2.669 (1.61), 2.674 (2.04), 2.697 (1.45), 2.713 (0.85), 3.545 (1.20), 3.575 (1.79), 3.609 (0.65), 3.639 (5.35), 3.655 (6.41), 3.662 (4.76), 3.681 (1.26), 3.692 (1.59), 3.712 (0.61), 3.732 (2.02), 3.757 (1.59), 3.765 (1.45), 3.783 (1.32), 3.816 (14.49), 3.827 (14.51), 5.272 (0.75), 5.294 (2.30), 5.312 (2.75), 5.334 (2.18), 5.356 (0.61), 6.871 (8.04), 7.179 (4.36), 7.251 (4.38), 7.552 (4.07), 7.573 (4.03), 8.627 (4.64), 8.700 (4.62), 12.095 (0.39). LC-MS (method 2): Rt = 0.47 min; MS (ESIpos): m/z = 525 [M+H]+

Example 102

6-methoxy-1-(1H-pyrazol-4-ylmethyl)-5-({7-[2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-27-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carbonitrile



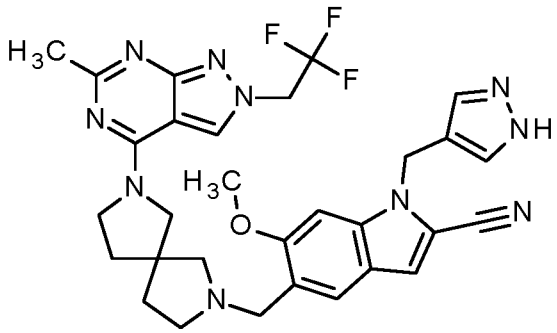
According to the preparation of example **13** 4-[2,7-diazaspiro[4.4]non-2-yl]-2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidine trifluoroacetate (intermediate **31)** (120 mg, 70 % purity, 191 μηηοl) was reacted with 5-formyl-6-methoxy-1-[(1-trityl-1 H-pyrazol-4-yl)methyl]-1 H-indole-2-carbonitrile (99.7 mg, 191 μηηοl, synthesis described in Journal of Medicinal Chemistry, 2016, 892- 913) to yield after removal of all solvents 160 mg 6-methoxy-5-({7-[2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 -[(1 -trityl-1 H-pyrazol-4-yl)methyl]-1 H-indole-2-carbonitrile which was used without further purification in the following reaction. A solution of 6-methoxy-5-({7-[2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1-[(1 -trityl-1 H-pyrazol-4-yl)-methyl]-1 H-indole-2-carbonitrile (160 mg, 192 μηιοl) in methanokethyl acetate (1:1, 2.4 ml) was treated with dioxane in HCl (4M, 192.1 μl, 0.77 mmol) and stirred for 16 h. The solvents were removed under reduced pressure and the residue thus obtained was purified by prep. HPLC The product fractions were pooled and evaporated to give the desired product as an off white solid (37.0 mg, 32 % yield).

LC-MS (method 2): Rt = 0.54 min; MS (ESIpos): m/z = 591 [M+H]+

1H-NMR (400 MHz, DMSO-d6) delta [ppm]: 1.232 (0.31), 1.786 (1.25), 1.804 (2.54), 1.821 (1.84), 1.837 (1.37), 1.854 (1.45), 1.871 (0.74), 1.886 (0.35), 1.905 (0.39), 1.919 (0.39), 1.931 (0.67), 1.949 (1.60), 1.967 (1.56), 1.983 (0.70), 1.996 (0.35), 2.052 (0.35), 2.064 (0.55), 2.084 (1.41), 2.103 (1.10), 2.120 (0.63), 2.134 (0.31), 2.150 (0.16), 2.318 (0.74), 2.323 (1.64), 2.327 (2.31), 2.331 (1.60), 2.337 (0.74), 2.518 (9.39), 2.523 (7.16), 2.540 (3.21), 2.580 (2.46), 2.603 (2.31), 2.643 (1.88), 2.660 (1.53), 2.665 (3.13), 2.669 (3.72), 2.674 (2.70), 2.692 (1.25), 3.559 (1.25), 3.589 (1.80), 3.613 (0.39), 3.642 (4.69), 3.659 (7.04), 3.680 (3.09), 3.687 (2.89), 3.709 (1.80), 3.748 (2.00), 3.773 (1.60), 3.788 (1.45), 3.805 (1.29), 3.821 (0.74), 3.889 (16.00), 3.895 (14.55), 5.314 (0.78), 5.336 (2.31), 5.351 (2.74), 5.358 (2.70), 5.377 (12.99), 7.254 (5.40), 7.275 (5.87), 7.320 (4.62), 7.550 (4.69), 7.571 (4.15), 8.205 (8.37), 8.209 (9.62), 8.229 (1.80), 8.707 (4.58), 8.782 (5.24), 12.805 (0.27).

Example 103

6-methoxy-5-({7-[6-methyl-2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1-(1H-pyrazol-4-ylmethyl)-1H-indole-2-carbonitrile



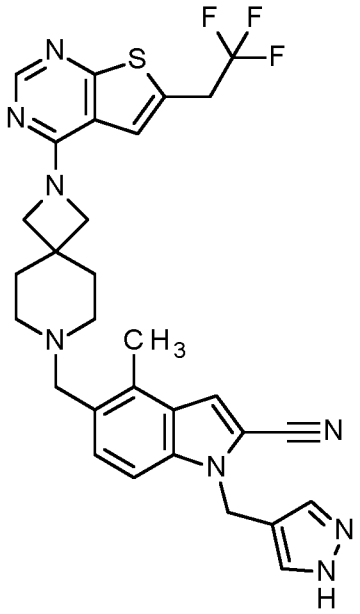
According to the preparation of example **102,** example **103** was prepared starting from 4-[2,7-diazaspiro[4.4]non-2-yl]-6-methyl-2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidine hydrochloride (100 mg, 80 % purity, 212 μηηοΙ) (intermediate **1104)** the intermediate 6-methoxy-5-({7-[6-methyl-2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 -[(1 -trityl-1 H-pyrazol-4-yl)methyl]-1 H-indole-2-carbonitrile was obtained. After deprotection and purification by preparative HPLC the desired product was obtained as a white solid (29 mg, 33 % yield).

LC-MS (method 2): Rt = 0.51 min; MS (ESIpos): m/z = 605 [M+H]+

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.405 (0.72), 1.779 (0.94), 1.798 (1.73), 1.812 (1.59), 1.826 (1.44), 1.844 (1.44), 1.859 (0.72), 1.897 (0.43), 1.910 (0.58), 1.928 (1.44), 1.945 (1.37), 1.962 (0.65), 2.047 (0.58), 2.066 (1.08), 2.083 (4.18), 2.104 (0.65), 2.318 (0.86), 2.322 (1.80), 2.326 (2.67), 2.337 (16.00), 2.345 (15.78), 2.518 (7.64), 2.522 (5.91), 2.539 (0.58), 2.574 (2.23), 2.596 (2.16), 2.630 (1.73), 2.652 (1.51), 2.664 (2.74), 2.668 (3.17), 2.673 (2.09), 2.678 (1.44), 2.684 (1.44), 2.703 (0.79), 3.304 (0.72), 3.542 (1.08), 3.572 (1.73), 3.596 (0.58), 3.610 (0.65), 3.632 (3.82), 3.643 (4.18), 3.653 (6.77), 3.677 (1.44), 3.685 (1.59), 3.706 (0.65), 3.725 (1.87), 3.749 (1.44), 3.761 (1.44), 3.778 (1.30), 3.794 (0.65), 3.887 (13.48), 3.896 (13.48), 5.270 (0.72), 5.292 (2.16), 5.306 (2.38), 5.313 (2.31), 5.328 (2.23), 5.350 (0.72), 5.377 (10.09), 7.250 (4.61), 7.274 (7.86), 7.318 (4.61), 7.471 (0.79), 7.547 (4.04), 7.569 (3.89), 7.752 (0.79), 8.621 (4.40), 8.694 (4.47), 12.815 (1.44).

Example 104

4-methyl-1-(1H^yrazol-4-ylmethyl)-5-({2-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidm -4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1H-indole-2-carbonitrile



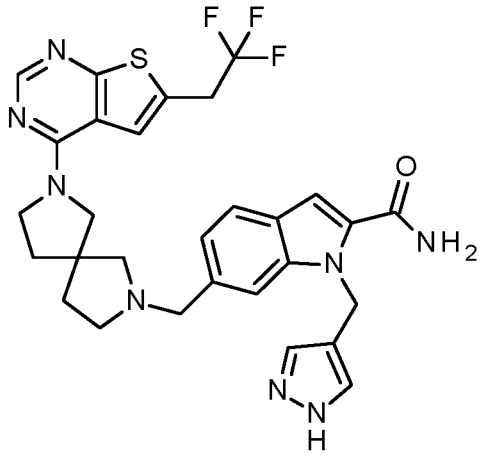
A solution of tert-butyl 4-{[2-cyano-4-methyl-5-({2-[6-(2 ,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indol-1 -yl]methyl}-1 H-pyrazole-1 -carboxylate intermediate 171 (108 mg, 156 μηηοl) in methanol (2 ml) was treated with dioxane in HCl (4M, 200 μl, 0.8 mmol) and stirred for 17 h. Then another 100 μl of a solution 4M HCl in dioxane was added and after stirring for additional 23 h at RT the solvents were removed under reduced pressure and the residue was purified by prep. HPLC The product fractions were pooled and evaporated to give the desired product as an off white solid (24 mg, 26 % yield).

LC-MS (method 8): Rt = 1.34 min; MS (ESIpos): m/z = 591 [M+H]+

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.753 (3.55), 2.327 (1.59), 2.480 (16.00), 2.669 (0.66), 3.490 (5.97), 4.018 (1.19), 4.046 (2.71), 4.074 (2.63), 4.100 (1.13), 5.378 (6.90), 7.294 (2.47), 7.316 (2.82), 7.432 (0.66), 7.482 (4.01), 7.529 (5.93), 7.539 (2.74), 7.560 (2.08), 7.732 (0.69), 8.312 (7.97), 12.820 (1.05).

Example 105

1-(1H^yrazol-4-ylmethyl)-6-({7-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-^ -yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carboxamide



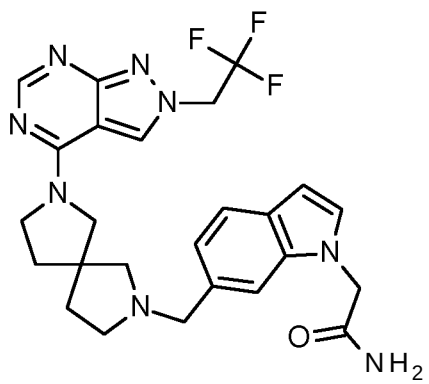
According to the preparation of example **102,** starting from 4-[2,7-diazaspiro[4.4]non-2-yl]-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidine hydrochloride (27.6 mg, 70.6 μηηοl) (intermediate **1105)** by reaction with tert-butyl 4-[(2-carbamoyl-6-formyl-1 H-indol-1-yl)methyl]-1 H-pyrazole-1-carboxylate (26.0 mg, 70.6 μηηοl) (intermediate **1109)** the intermediate tert-butyl 4-{[2-carbamoyl-6-({7-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indol-1-yl]methyl}-1 H-pyrazole-1 -carboxylate was obtained. After deprotection and purification by preparative HPLC the desired product was obtained as a white solid (14 mg, 29 % yield).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.840 (1.69), 1.857 (1.73), 1.907 (0.83), 2.003 (1.26), 2.323 (1.26), 2.327 (1.77), 2.331 (1.26), 2.518 (7.75), 2.523 (5.37), 2.540 (2.34), 2.612 (1.12), 2.665 (2.16), 2.669 (2.63), 2.673 (2.09), 2.686 (1.05), 3.758 (2.20), 3.890 (0.61), 4.008 (1.37), 4.035 (3.71), 4.063 (3.53), 4.090 (1.19), 5.610 (1.51), 5.647 (4.1 1), 5.673 (3.82), 5.71 1 (1.37), 7.058 (2.05), 7.079 (2.49), 7.089 (8.83), 7.310 (0.47), 7.360 (1.73), 7.514 (2.67), 7.535 (2.52), 7.598 (2.56), 7.693 (5.44), 7.953 (1.44), 8.139 (0.61), 8.310 (16.00), 12.622 (0.47).

LC-MS (method 8): Rt = 1.14 min; MS (ESIpos): m/z = 595 [M+H]+

Example 106

2-[6-({7-[2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indol-1-yl]acetamide

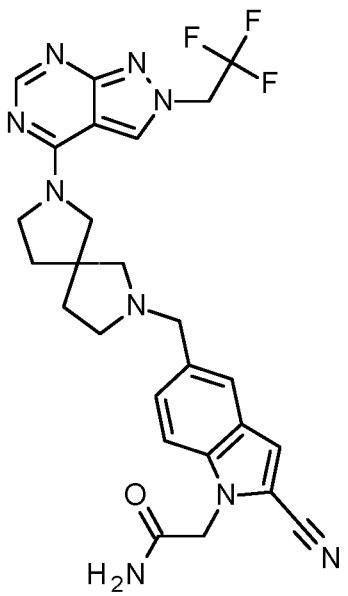


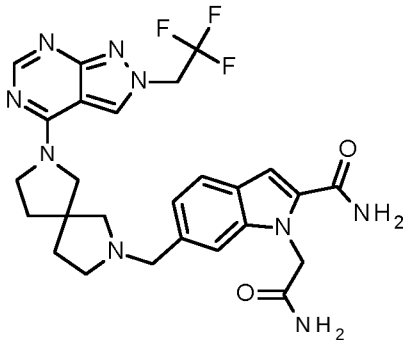
To a stirred solution of 4-[7-(1 H-indol-6-ylmethyl)-2,7-diazaspiro[4.4]non-2-yl]-2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidine (example **95)** (26 mg, 55.1 μηηοI) in DMF (1.6 ml) was added caesium carbonate (72 mg, 0.22 mmol). After 5 min, 2-bromoacetamide (8.4 mg, 60.6 μηηοI) was added and the reaction mixture stirred for 16 h at RT. The reaction mixture was filtered and purified by prep. HPLC. The product rich fractions were pooled, the solvent was removed under reduced pressure and freeze dried to yield the desired product as an off white solid (2.8 mg, 9 % yield).

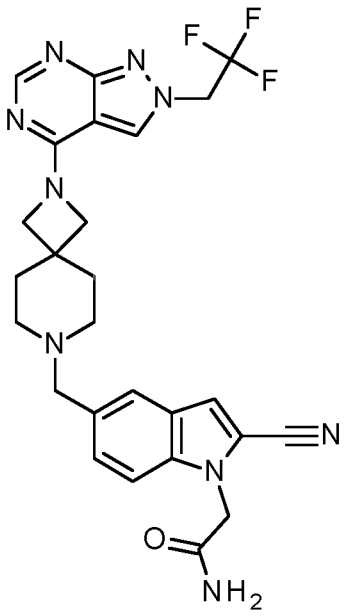
LC-MS (method 2): Rt = 0.42 min; MS (ESIpos): m/z = 513 [M+H]+

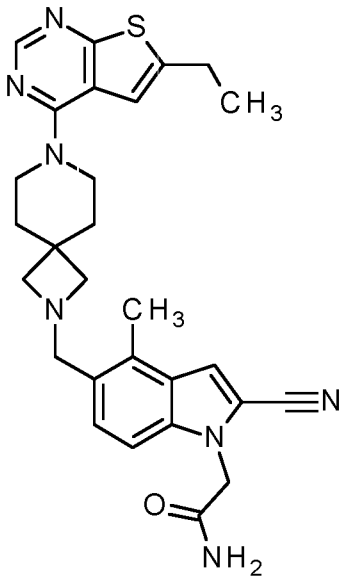
1H-NMR (400 MHz, DMSO-d6) delta [ppm]: 1.208 (0.59), 1.772 (2.46), 1.790 (4.83), 1.807 (3.51), 1.823 (2.46), 1.841 (2.37), 1.860 (1.46), 1.875 (1.00), 1.892 (1.19), 1.905 (1.37), 1.923 (2.51), 1.945 (2.51), 1.963 (1.37), 2.038 (1.19), 2.061 (2.51), 2.076 (2.37), 2.093 (1.28), 2.304 (1.82), 2.343 (0.91), 2.437 (2.05), 2.567 (4.42), 2.591 (4.79), 2.612 (2.23), 2.630 (2.83), 2.647 (4.56), 2.687 (1.28), 3.537 (2.19), 3.566 (3.42), 3.617 (2.19), 3.648 (11.99), 3.656 (12.81), 3.695 (2.28), 3.712 (4.38), 3.737 (2.69), 3.751 (2.10), 3.775 (1.82), 4.243 (0.50), 4.260 (0.50), 4.730 (14.72), 4.735 (14.18), 5.284 (1.32), 5.306 (5.15), 5.328 (7.38), 5.350 (4.79), 5.371 (1.19), 6.352 (7.43), 6.358 (5.61), 6.974 (6.11), 6.994 (6.56), 7.217 (4.83), 7.233 (7.20), 7.240 (12.17), 7.246 (16.00), 7.301 (0.46), 7.415 (5.24), 7.425 (5.06), 7.436 (5.01), 7.445 (4.51), 7.467 (2.92), 7.516 (2.51), 8.164 (0.96), 8.180 (15.59), 8.675 (7.84), 8.748 (8.75).

The following examples were prepared analogous to the preparation of example **106** starting from the corresponding examples **92, 93, 97,** or **1.**

Example	Structure Name	Analytical Data
107		1H-NMR (400 MHz, DMSO-d6) delta [ppm]: 1.232 (1.20), 1.794 (1.58), 1.812 (3.08), 1.829 (2.63), 1.847 (1.88), 1.863 (1.88), 1.882 (0.98), 1.903 (0.75), 1.915 (0.75), 1.943 (2.10), 1.959 (1.88), 1.975 (0.98), 2.076 (1.88), 2.084 (3.08), 2.318 (1.28), 2.322 (2.93), 2.327 (4.21), 2.332 (3.08), 2.336 (1.28), 2.414 (1.50), 2.431 (2.25), 2.437 (2.70), 2.453 (2.55), 2.518 (16.00), 2.523 (11.57), 2.539 (1.80), 2.555 (1.43), 2.571 (1.95), 2.587 (3.83), 2.609 (2.10), 2.660 (2.85), 2.665 (4.43), 2.669 (5.78), 2.673 (4.36), 2.678 (2.78), 3.536 (1.80), 3.566 (2.48), 3.603 (0.98), 3.617 (1.05), 3.634 (1.88), 3.660 (4.06), 3.681

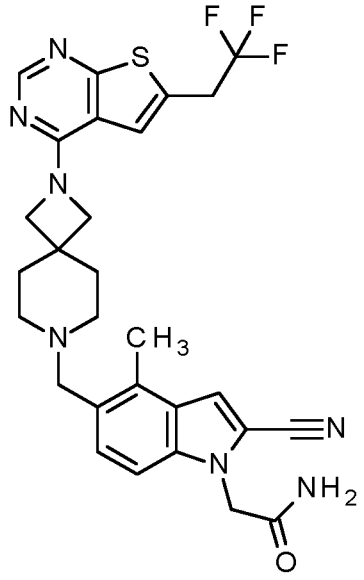
Example	Structure Name	Analytical Data
	2-[2-cyano-5-({7-[2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indol-1-yl]acetamide	(10.89), 3.706 (1.80), 3.724 (3.08), 3.750 (2.03), 3.759 (1.50), 3.777 (1.20), 3.794 (1.20), 4.568 (0.75), 4.759 (13.15), 5.304 (0.90), 5.326 (2.85), 5.349 (3.08), 5.357 (3.23), 5.379 (2.78), 5.402 (0.83), 7.1 15 (0.45), 7.128 (0.45), 7.295 (3.38), 7.316 (4.36), 7.352 (7.06), 7.397 (0.53), 7.414 (0.45), 7.445 (3.00), 7.459 (2.93), 7.467 (2.48), 7.480 (2.18), 7.597 (0.53), 7.629 (7.51), 8.200 (14.57), 8.258 (0.45), 8.318 (0.98), 8.644 (2.40), 8.692 (6.23), 8.770 (6.69). LC-MS (method 2): Rt = 0.32 min; MS (ESIpos): m/z = 538 [M+H]+
108	 1-(2-amino-2-oxoethyl)-6-({7-[2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carboxamide	1H-NMR (500 MHz, DMSO-d6) delta [ppm]: -0.120 (1.27), -0.006 (9.30), 0.006 (8.56), 0.1 17 (1.27), 1.808 (1.04), 1.824 (2.05), 1.838 (1.67), 1.852 (0.97), 1.865 (0.89), 1.879 (0.89), 1.891 (0.74), 1.904 (0.45), 1.909 (1.00), 1.928 (0.56), 1.938 (0.71), 1.953 (1.12), 1.965 (1.04), 1.979 (1.04), 1.991 (0.71), 2.002 (0.45), 2.073 (0.60), 2.087 (6.66), 2.099 (0.74), 2.1 11 (0.86), 2.124 (0.67), 2.358 (0.67), 2.361 (1.49), 2.365 (2.16), 2.368 (1.56), 2.372 (0.71), 2.475 (1.38), 2.518 (6.96), 2.522 (6.66), 2.525 (4.65), 2.537 (1.04), 2.543 (1.49), 2.609 (2.27), 2.617 (1.41), 2.628 (2.16), 2.631 (2.08), 2.635 (2.42), 2.638 (2.60), 2.642 (1.97), 2.645 (1.30), 2.662 (1.04), 2.680 (1.08), 2.696 (0.78), 3.568 (1.27), 3.591 (1.75), 3.636 (0.60), 3.646 (0.78), 3.661 (1.45), 3.673 (1.34), 3.684 (3.27), 3.688 (3.31), 3.699 (6.66), 3.707 (4.50), 3.725 (0.89), 3.734 (0.93), 3.748 (1.97), 3.756 (0.89), 3.768 (1.49), 3.777 (1.08), 3.792 (0.78), 3.806 (0.78), 3.820 (0.60), 5.178 (0.74), 5.206 (4.24), 5.227 (2.16), 5.261 (0.63), 5.31 1 (0.63), 5.328 (1.90), 5.347 (2.05), 5.353

Example	Structure Name	Analytical Data
		(2.08), 5.371 (1.75), 5.389 (0.56), 7.081 (4.58), 7.095 (4.02), 7.129 (5.02), 7.131 (5.43), 7.275 (1.12), 7.320 (4.35), 7.416 (1.34), 7.456 (1.23), 7.526 (2.57), 7.538 (2.46), 7.542 (2.38), 7.554 (2.05), 7.936 (1.23), 8.191 (0.67), 8.203 (2.49), 8.206 (16.00), 8.312 (0.82), 8.315 (1.49), 8.698 (4.17), 8.780 (4.99). LC-MS (method 2): Rt = 0.34 min; MS (ESIpos): m/z = 556 [M+H]+
109	 2-[2-cyano-5-({2-[2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1H-indol-1-yl]acetamide	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.232 (0.91), 1.808 (3.49), 2.084 (1.00), 2.286 (0.72), 2.318 (1.29), 2.322 (2.34), 2.327 (3.15), 2.332 (2.39), 2.336 (1.24), 2.423 (0.67), 2.518 (9.31), 2.523 (5.78), 2.539 (1.24), 2.660 (0.91), 2.665 (1.96), 2.669 (2.82), 2.673 (2.01), 2.678 (0.91), 3.547 (7.36), 3.883 (5.40), 4.1 10 (5.21), 4.584 (0.62), 4.778 (7.83), 5.318 (1.19), 5.341 (3.44), 5.363 (3.25), 5.385 (1.05), 7.147 (0.67), 7.280 (2.39), 7.283 (2.34), 7.301 (2.77), 7.304 (2.77), 7.372 (5.06), 7.476 (3.77), 7.497 (3.01), 7.587 (0.48), 7.620 (4.63), 8.194 (1.96), 8.198 (16.00), 8.285 (0.67), 8.632 (8.17), 8.661 (1.58). LC-MS (method 2): Rt = 0.32 min; MS (ESIpos): m/z = 538 [M+H]+

Example	Structure Name	Analytical Data
110	 2-(2-cyano-5-{[7-(6-ethylthieno[2,3-d]pyrimidin-4-yl)-2,7-diazaspiro[3.5]non-2-yl]methyl}-4-methyl-1H-indol-1-yl)acetamide	1H-NMR (400 MHz, DMSO-d6) delta [ppm]: 1.258 (6.55), 1.277 (14.72), 1.296 (6.69), 1.768 (3.33), 1.782 (4.29), 1.795 (3.45), 2.085 (0.69), 2.323 (0.88), 2.327 (1.25), 2.331 (0.92), 2.518 (4.73), 2.523 (3.14), 2.665 (0.92), 2.669 (1.23), 2.673 (0.88), 2.870 (1.28), 2.888 (3.74), 2.906 (3.66), 2.925 (1.21), 3.001 (16.00), 3.677 (7.19), 3.717 (3.47), 3.731 (4.33), 3.744 (3.37), 4.901 (8.47), 7.240 (4.94), 7.271 (1.36), 7.293 (3.68), 7.313 (4.68), 7.336 (1.67), 7.369 (1.92), 7.523 (6.67), 7.761 (1.92), 8.309 (9.96). LC-MS (method 2): Rt = 0.71 min; MS (ESIpos): m/z = 514 [M+H]+

Example 111

2-[2-cyano-4-methyl-5-({2-[6-(2,2,2-trifluo roethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indol-1 -yl]acetamide

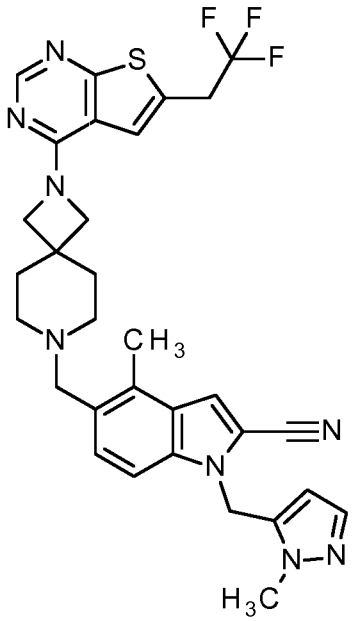


To a stirred solution of 4-methyl-5-({2-[6-(2 ,2,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carbonitrile (example **29)** (443 mg, 868 μηηοl) in DMF (14.8 ml) was added caesium carbonate (848 mg, 2.6 mmol). After 5 min, 2-bromoacetamide (179.6 mg, 1.3 mmol) was added and the reaction mixture stirred for 1 h at RT. The reaction mixture was filtered and purified by prep. HPLC. The product rich fractions were pooled, the solvent was removed under reduced pressure and freeze dried to yield the desired product as an off white solid (424 mg, 84 % yield).

LC-MS (method 2): Rt = 0.69 min; MS (ESIpos): m/z = 568 [M+H]+

1H-NMR (400 MHz, DMSO-d6) delta [ppm]: 1.779 (2.45), 2.074 (0.60), 2.318 (0.97), 2.323 (1.57), 2.327 (2.04), 2.331 (1.60), 2.337 (1.07), 2.358 (0.72), 2.518 (16.00), 2.540 (0.85), 2.660 (0.57), 2.665 (1.16), 2.669 (1.60), 2.674 (1.19), 2.678 (0.57), 3.520 (0.88), 4.019 (1.45), 4.047 (3.43), 4.074 (3.30), 4.102 (1.32), 4.915 (7.76), 7.307 (3.30), 7.377 (2.42), 7.478 (3.36), 7.543 (3.65), 7.770 (2.36), 8.135 (0.66), 8.315 (13.83).

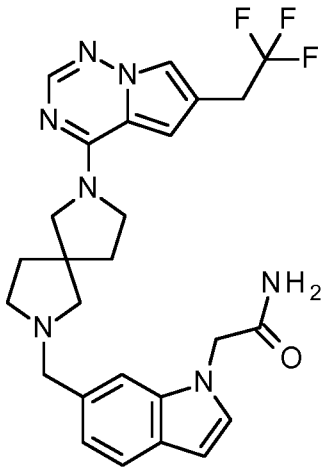
The following example was prepared analogous to the preparation of example **111** starting from the corresponding example **29** by reacting with 5-(chloromethyl)-1-methyl-1 H-pyrazole hydrochloride [CAS 1434128-56-9].

Example	Structure Name	Analytical Data
112	 4-methyl-1-[(1-methyl-1H-pyrazol-5-yl)methyl]-5-({2-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-	¹H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.762 (1.80), 2.323 (0.82), 2.327 (1.02), 2.332 (0.85), 2.514 (12.23), 2.523 (2.11), 2.665 (0.43), 2.669 (0.61), 2.673 (0.43), 3.501 (3.44), 3.848 (16.00), 4.021 (0.68), 4.048 (1.49), 4.076 (1.43), 4.103 (0.57), 5.670 (4.17), 5.756 (2.33), 5.761 (2.30), 7.276 (2.82), 7.281 (2.84), 7.302 (1.49), 7.324 (1.92), 7.435 (1.52), 7.457 (1.11), 7.483 (2.30), 7.644 (3.46), 7.646 (3.45), 8.313 (6.77). LC-MS (method 8): Rt = 1.39 min; MS (ESIpos): m/z = 605 [M+H]+

Example	Structure Name	Analytical Data
	diazaspiro[3.5]non-7-yl}methyl)-1H-indole-2-carbonitrile	

Example 113

2-[6-({7-[6-(2,2,2-trifluoroethyl)pyrrolo^ -f][1,2,4]triazin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indol-1 -yl]acetamide



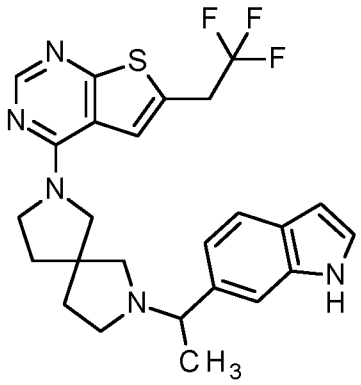
To a stirring solution of 4-[7-(1 H-indol-6-ylmethyl)-2,7-diazaspiro[4.4]non-2-yl]-6-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1 ,2,4]triazine, 57.0 mg (0.125 mmol) example **79,** in N,N-dimethylformamide, 0.500 ml, at 0 °C was added sodium hydride (60% in oil), 6.00 mg (0.150 mmol). After stirring for 30 minutes, ethyl chloroacetate, 16.1 µL (0.150 mmol), was added and the mixture was stirred at 0 °C for 1 hour. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organics were washed with brine, dried over magnesium sulphate and concentrated under vacuum to give the desired intermediate ethyl [6-({7-[6-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1 ,2,4]triazin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indol-1 -yl]acetate , 66.0 mg (97% yield) and was used directly in the next step without purification. A solution of ethyl [6-({7-[6-(2,2,2-trifluoroethyl)pyrrolo[2,1-fl[1 ,2,4]triazin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indol-1 -yl]acetate, 56.0 mg (0.104 mmol), in 15% ammonia/methanol, 1.70 ml, was irradiated in the microwave at 100 °C for 1 hour. The mixture was concentrated under vacuum. The residue was purified by reverse phase chromatography (BIOTAGE ISOLERA, 12 g; SNAP C18 Biotage cartridge) using acetonitrile and water containing 10mM ammonium bicarbonate pH 10 buffer (10:90 to 100:0) to give the desired product, 11.0 mg (20% yield).

LC-MS (method 7): Rt = 2.19 min., 96.13%. MS (ESIpos): m/z = (M+H)+ 512.

1H NMR (400 MHz, MeOD-d3): δ [ppm] = 1.81-2.09 (m, 4H), 2.53-2.82 (m, 4H), 3.46-3.55 (m, 2H), 3.60-3.78 (m, 4H), 3.87-3.99 (m, 2H), 4.82 (s, 2H), 6.46 (d, 1H), 6.86 (s, 1H), 7.06 (dd, 1H), 7.17 (d, 1H), 7.30 (s, 1H), 7.49 (d, 1H), 7.53 (s, 1H), 7.69 (s, 1H);

Example 114

4-{7-[1-(1H-indol-6-yl)ethyl]-2,7-diazaspiro[4.4]non-2-yl}-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidine

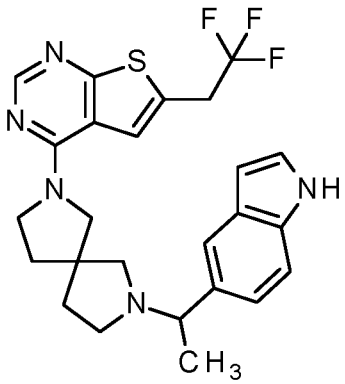


A solution of 4-[2,7-diazaspiro[4.4]non-2-yl]-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidine hydrochloride (100 mg, 264 μmol) (intermediate **11.05**) and 1-(1H-indol-6-yl)ethanone (63.0 mg, 396 μmol) [CAS 81223-73-6], in a mixture of methanol (2 ml), dichloromethane (1 ml) und acetic acid (60 μl) was stirred at 60 °C for 30 min. Then sodium cyanoborohydride (36.5 mg, 581 μmol) was added and the mixture was heated at 60 °C for 16 h. After cooling the solvents were evaporated and the residue was purified by prep. HPLC. The product rich fractions were pooled, the solvent was removed under reduced pressure and freeze dried to yield the desired product as a mixture of stereoisomers as a solid (35 mg, 27 % yield).

LC-MS (method 8): Rt = 1.39 min; MS (ESIpos): m/z = 486 [M+H]+

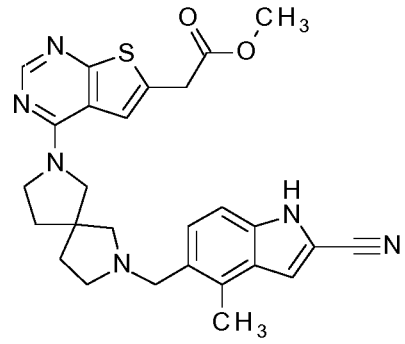
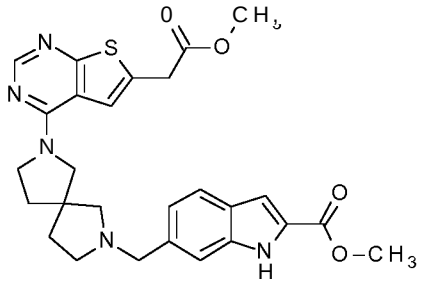
^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.144 (0.55), 1.313 (8.14), 1.323 (9.30), 1.330 (9.47), 1.338 (8.14), 1.763 (2.16), 1.782 (3.32), 1.867 (0.50), 1.969 (1.72), 2.322 (1.94), 2.326 (2.60), 2.331 (1.88), 2.364 (2.16), 2.388 (2.49), 2.418 (1.61), 2.441 (4.32), 2.462 (4.60), 2.522 (16.00), 2.575 (1.94), 2.599 (1.55), 2.630 (0.72), 2.651 (1.27), 2.664 (2.93), 2.668 (3.82), 2.673 (2.71), 2.732 (0.94), 2.749 (0.89), 3.288 (2.55), 3.305 (3.32), 3.703 (1.55), 4.042 (2.82), 4.069 (2.77), 6.333 (3.04), 6.356 (3.21), 6.965 (2.38), 6.968 (2.44), 6.975 (2.71), 6.979 (2.66), 6.986 (2.77), 6.988 (2.77), 6.996 (2.77), 6.999 (2.66), 7.253 (2.82), 7.260 (3.99), 7.267 (3.49), 7.270 (3.60), 7.276 (4.15), 7.283 (3.16), 7.295 (3.49), 7.309 (4.10), 7.396 (1.77), 7.417 (1.72), 7.434 (3.60), 7.454 (3.21), 7.668 (2.88), 7.691 (3.49), 8.297 (7.14), 8.305 (11.13), 10.947 (3.10).

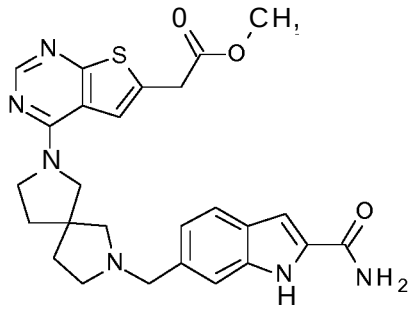
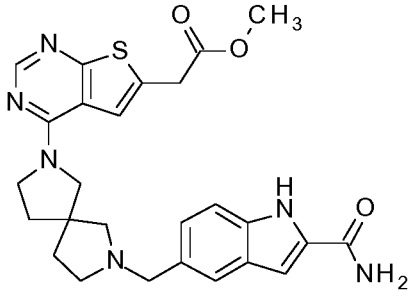
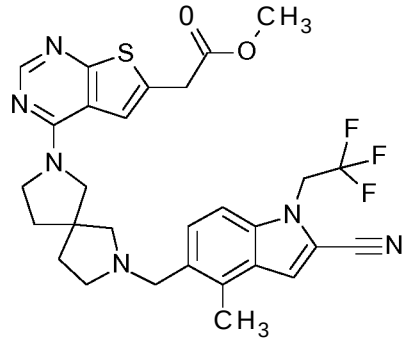
The following example was prepared analogous to the preparation of example **114** starting from intermediate **11.05** and the corresponding 1-(1H-indol-5-yl)ethanone [CAS 53330-94-2].

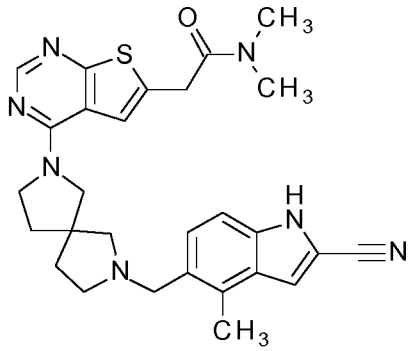
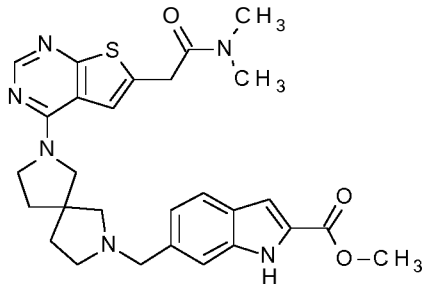
Example	Structure Name	Analytical Data
115	 4-{7-[(1 R)-1 -(1 H-indol-5-yl)ethyl]-2,7-diazaspiro[4.4]non-2-yl}-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidine	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.93 1 (0.62), 0.948 (0.62), 1.145 (0.54), 1.183 (0.45), 1.202 (0.99), 1.221 (0.45), 1.26 1 (0.45), 1.277 (0.50), 1.31 1 (9.80), 1.31 6 (10.46), 1.327 (10.46), 1.333 (9.88), 1.755 (1.61), 1.774 (2.77), 1.798 (2. 11), 1.8 18 (1.16), 1.957 (1.74), 2.31 8 (0.83), 2.323 (1.82), 2.327 (2.69), 2.332 (2.27), 2.337 (2.94), 2.360 (2.56), 2.389 (0.99), 2.41 1 (6.57), 2.440 (1.86), 2.46 1 (1.74), 2.51 8 (10.87), 2.523 (7.77), 2.539 (1.98), 2.570 (1.20), 2.590 (1.24), 2.6 16 (0.66), 2.637 (1.32), 2.660 (1.53), 2.665 (2.07), 2.669 (2.8 1), 2.673 (2.27), 2.736 (0.54), 2.756 (1.07), 2.770 (0.99), 2.79 1 (0.4 1), 3.278 (2.60), 3.284 (2.40), 3.295 (2.73), 3.301 (2.40), 3.7 13 (1.4 1), 4.045 (2.40), 4.072 (2.48), 6.307 (1.32), 6.350 (2.44), 6.355 (3.60), 6.360 (2.36), 7.052 (1.53), 7.072 (3.97), 7.093 (2.65), 7.097 (2.69), 7.255 (3.80), 7.262 (4.63), 7.269 (3.84), 7.280 (3.97), 7.287 (4.75), 7.294 (3.51), 7.302 (4. 18), 7.322 (3.43), 7.41 4 (4.0 1), 7.432 (4.59), 7.677 (2.23), 7.692 (3.89), 8.290 (5. 17), 8.304 (16.00), 10.955 (2.40), 10.982 (2.52). LC-MS (method 8): Rt = 1.38 min; MS (ESIpos): m/z = 486 [M+H]+

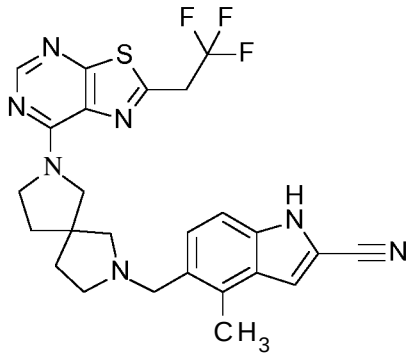
New examples

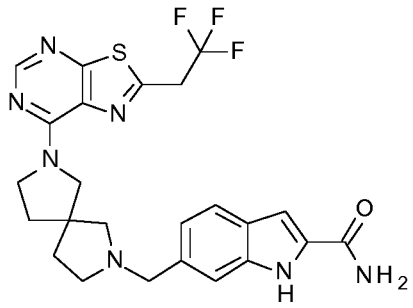
The following examples were prepared analogous to the preparation of example **43** starting from the spirocyclic amines (intermediates **11 29, 11 30, 11 3 1, 11 32,** and **11 33)** reacting with the corresponding aldehydes.

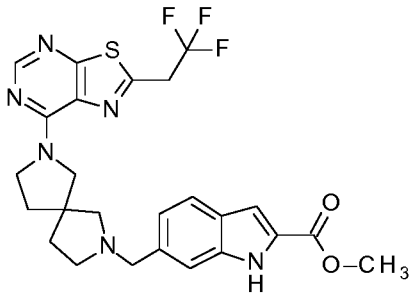
Example	Structure Name	Analytical Data
116	 methyl (4-{7-[(2-cyano-4-methyl-1H-indol-5-yl)methyl]-2,7-diazaspiro[4.4]non-2-yl}thieno[2,3-d]pyrimidin-6-yl)acetate	LC-MS (method 13): Rt = 1.27 min; MS (ESIpos): m/z = 501 $[M+H]^+$ ^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.73 - 1.86 (m, 2H), 1.96 (br s, 2H), 2.43 (d, 1H), 2.52 - 2.66 (m, 3H), 3.48 - 3.90 (m, 10H), 4.03 (s, 2H), 7.17 - 7.23 (m, 1H), 7.24 - 7.29 (m, 1H), 7.42 (s, 1H), 7.51 (s, 1H), 8.26 (s, 1H), 12.23 (br s, 1H).
117	 methyl 6-({7-[6-(2-methoxy-2-oxoethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carboxylate	LC-MS (method 12): Rt = 0.80 min; MS (ESIpos): m/z = 520 $[M+H]^+$ ^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.73 - 1.88 (m, 2H), 1.99 (br s, 2H), 2.55 (s, 3H), 3.54 - 3.83 (m, 8H), 3.86 (s, 4H), 4.04 (s, 2H), 7.06 (dd, 1H), 7.11 (d, 1H), 7.38 (s, 1H), 7.53 (s, 1H), 7.57 (d, 1H), 8.27 (s, 1H), 11.84 (s, 1H).

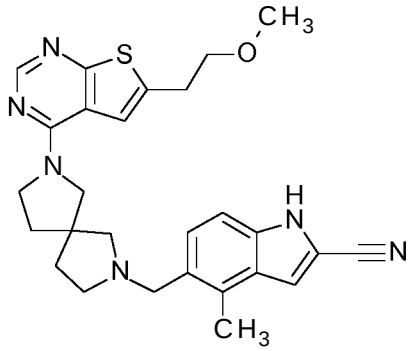
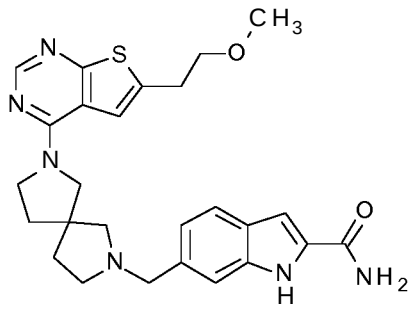
118	 methyl (4-{7-[(2-carbamoyl-1 H-indol-6-yl)methyl]-2,7-diazaspiro[4.4]non-2-yl}thieno[2,3-d]pyrimidin-6-yl)acetate	LC-MS (method 13): Rt = 1.01 min; MS (ESIpos): m/z = 505 [M+H]+ ^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.76 - I .88 (m, 2H), 1.98 (br s, 2H), 2.53 - 2.69 (m, 3H), 3.58 - 3.90 (m, 9H), 4.04 (s, 2H), 7.01 (dd, 1H), 7.06 (d, 1H), 7.27 - 7.36 (m, 2H), 7.48 - 7.55 (m, 2H), 7.91 (br s, 1H), 8.27 (s, 1H), I I .44 (s, 1H).
119	 methyl (4-{7-[(2-carbamoyl-1 H-indol-5-yl)methyl]-2,7-diazaspiro[4.4]non-2-yl}thieno[2,3-d]pyrimidin-6-yl)acetate	LC-MS (method 13): Rt = 1.05 min; MS (ESIpos): m/z = 505 $[M+H]^+$ ^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.75 - 1.87 (m, 2H), 1.97 (br s, 2H), 2.44 (d, 1H), 2.52 - 2.65 (m, 3H), 3.53 - 3.90 (m, 9H), 4.04 (s, 2H), 7.05 (d, 1H), 7.15 (dd, 1H), 7.27 - 7.37 (m, 2H), 7.48 (s, 1H), 7.53 (s, 1H), 7.90 (br s, 1H), 8.27 (s, 1H), 11.45 (s, 1H).
120	 methyl {4-[7-{[2-cyano-4-methyl-1-(2,2,2-trifluoroethyl)-1 H-indol-5-yl]methyl}-2,7-diazaspiro[4.4]non-2-yl]thieno[2,3-d]pyrimidin-6-yl}acetate	LC-MS (method 13): Rt = 1.43 min; MS (ESIpos): m/z = 583 $[M+H]^+$ ^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.73 - 1.87 (m, 2H), 1.87 - 2.06 (m, 2H), 2.45 (d, 1H), 2.52 (br s, 3H), 2.54 - 2.65 (m, 2H), 3.50 - 3.91 (m, 9H), 4.04 (s, 2H), 5.33 (q, 2H), 7.40 (d, 1H), 7.49 - 7.55 (m, 2H), 7.70 - 7.72 (m, 1H), 8.27 (s, 1H).

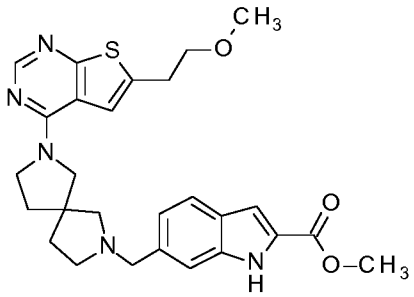
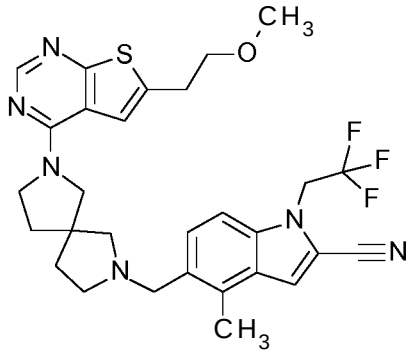
121	 2-(4-{7-[(2-cyano-4-methyl-1 H-indol-5-yl)methyl]-2,7-diazaspiro[4.4]non-2-yl}thieno[2,3-d]pyrimidin-6-yl)-N,N-dimethylacetamide	LC-MS (method 13): Rt = 1.16 min; MS (ESIpos): m/z = 514 $[M+H]^+$ ^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.73 - 1.86 (m, 2H), 1.95 (br d, 2H), 2.43 (d, 1H), 2.54 - 2.66 (m, 2H), 2.85 (s, 3H), 3.06 (s, 3H), 3.56 - 3.87 (m, 6H), 4.02 (s, 2H), 7.18 - 7.23 (m, 1H), 7.24 - 7.29 (m, 1H), 7.43 (d, 2H), 8.24 (s, 1H), 12.23 (br s, 1H).
122	 methyl 6-{[7-{6-[2-(dimethylamino)-2-oxoethyl]thieno[2,3-d]pyrimidin-4-yl}-2,7-diazaspiro[4.4]non-2-yl]methyl}-1 H-indole-2-carboxylate	LC-MS (method 13): Rt = 1.12 min; MS (ESIpos): m/z = 533 $[M+H]^+$ ^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.75 - 1.88 (m, 2H), 1.99 (br s, 2H), 2.48 (br s, 2H), 2.52 - 2.66 (m, 3H), 2.85 (s, 3H), 3.06 (s, 3H), 3.57 - 3.90 (m, 9H), 4.03 (s, 2H), 7.06 (dd, 1H), 7.11 (s, 1H), 7.38 (s, 1H), 7.46 (s, 1H), 7.57 (d, 1H), 8.25 (s, 1H), 11.84 (d, 1H).

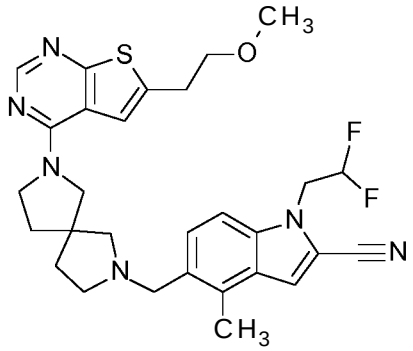
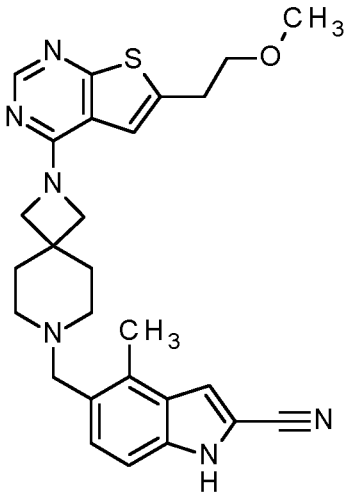
123	 4-methyl-5-({7-[2-(2,2,2-trifluoroethyl)[1 ,3]thiazolo[5,4-d]pyrimidin-7-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carbonitrile	LC-MS (method 13): Rt = 1.45 min; MS (ESIpos): m/z = 512 $[M+H]^+$ ^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.79 (br t, 2H), 1.85 - 2.07 (m, 2H), 2.34 - 2.45 (m, 1H), 2.47 - 2.49 (m, 2H), 2.52 - 2.58 (m, 2H), 2.61 - 2.70 (m, 1H), 3.54 - 3.78 (m, 4H), 3.89 - 4.17 (m, 2H), 4.28 - 4.44 (m, 2H), 7.16 - 7.24 (m, 1H), 7.24 - 7.31 (m, 1H), 7.42 (br d, 1H), 8.36 (s, 1H), 12.23 (s, 1H).
123.1	4-methyl-5-({7-[2-(2,2,2-trifluoroethyl)[1 ,3]thiazolo[5,4-d]pyrimidin-7-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carbonitrile (enantiomer 1)	Separation of example **123** by chiral chromatography afforded **123.1** and its enantiomer **123.2.** preparative HPLC (method H) analyt. HPLC (method 11): R_t = 2.03 min optical rotation: $[a]_D^{20}$ = +34 ° (c = 1.00; DMSO)
123.2	4-methyl-5-({7-[2-(2,2,2-trifluoroethyl)[1 ,3]thiazolo[5,4-d]pyrimidin-7-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carbonitrile (enantiomer 2)	preparative HPLC (method H) analyt. HPLC (method 11): R_t = 3.19 min optical rotation: $[a]_D^{20}$ = -35.2 ° (c = 1.00; DMSO)

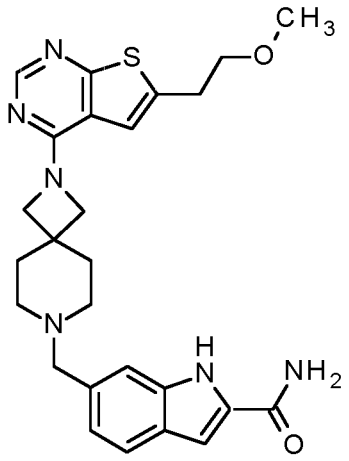
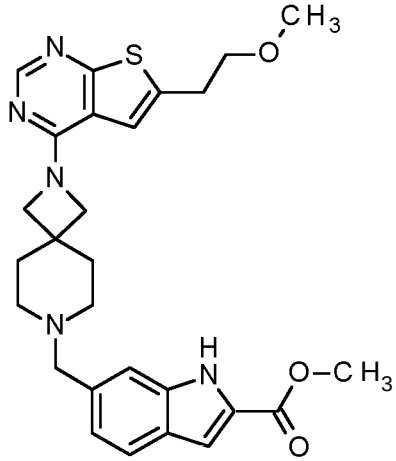
124	 6-({7-[2-(2,2,2-trifluoroethyl)[1 ,3]thiazolo[5,4-d]pyrimidin-7-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carboxamide	LC-MS (method 13): Rt = 1.16 min; MS (ESIpos): m/z = 516 $[M+H]^+$ ^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.80 (br d, 2H), 1.87 - 2.09 (m, 2H), 2.46 (br d, 1H), 2.52 - 2.61 (m, 2H), 2.62 - 2.71 (m, 1H), 3.57 - 3.77 (m, 4H), 3.95 - 4.16 (m, 2H), 4.29 - 4.46 (m, 2H), 7.01 (d, 1H), 7.06 (d, 1H), 7.34 (br d, 2H), 7.50 (dd, 1H), 7.91 (br s, 1H), 8.37 (s, 1H), 11.45 (s, 1H).
124.1	6-({7-[2-(2,2,2-trifluoroethyl)[1 ,3]thiazolo[5,4-d]pyrimidin-7-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carboxamide (enantiomer 1)	separation of example **124** by chiral chromatography afforded **124.1** and its enantiomer **124.2.** preparative HPLC (method I) analyt. HPLC (method 12): R_t = 4.64 min optical rotation: $[a]_D^{20}$ = +33.1 ° (c = 1.00; DMSO)
124.2	6-({7-[2-(2,2,2-trifluoroethyl)[1 ,3]thiazolo[5,4-d]pyrimidin-7-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carboxamide (enantiomer 2)	preparative HPLC (method I) analyt. HPLC (method 12): R_t = 5.53 min optical rotation: $[a]_D^{20}$ = -31 .2 ° (c = 1.00; DMSO)

125	 methyl 6-({7-[2-(2,2,2-trifluoroethyl)[1 ,3]thiazolo[5,4-d]pyrimidin-7-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carboxylate	LC-MS (method 13): Rt = 1.39 min; MS (ESI pos): m/z = 531 $[M+H]^+$ ^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.81 (br s, 2H), 1.88 - 2.11 (m, 2H), 2.45 (br s, 1H), 2.52 - 2.60 (m, 2H), 2.64 - 2.72 (m, 1H), 3.58 - 3.78 (m, 4H), 3.86 (s, 3H), 3.95 - 4.17 (m, 2H), 4.29 - 4.46 (m, 2H), 7.06 (dd, 1H), 7.11 (d, 1H), 7.37 (br d, 1H), 7.56 (br t, 1H), 8.37 (s, 1H), 11.84 (br s, 1H).
125.1	methyl 6-({7-[2-(2,2,2-trifluoroethyl)[1 ,3]thiazolo[5,4-d]pyrimidin-7-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carboxylate (enantiomer 1)	separation of example **125** by chiral chromatography afforded **125.1** and its enantiomer **125.2.** preparative HPLC (method J) analyt. HPLC (method 13): R_t = 3.10 min optical rotation: $[a]_D^{20}$ = +36.4 ° (c = 1.00; DMSO)
125.2	methyl 6-({7-[2-(2,2,2-trifluoroethyl)[1 ,3]thiazolo[5,4-d]pyrimidin-7-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carboxylate (enantiomer 2)	preparative HPLC (method J) analyt. HPLC (method 13): R_t = 3.89 min optical rotation: $[a]_D^{20}$ = -33.1 ° (c = 1.00; DMSO)

126	 5-({7-[6-(2-methoxyethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-4-methyl-1 H-indole-2-carbonitrile	LC-MS (method 13): Rt = 1.32 min; MS (ESIpos): m/z = 487 $[M+H]^+$ ^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.80 (td, 2H), 1.88 - 2.04 (m, 2H), 2.43 (d, 1H), 2.52 - 2.64 (m, 3H), 3.08 (t, 2H), 3.28 (s, 3H), 3.54 - 3.92 (m, 8H), 7.17 - 7.23 (m, 1H), 7.25 - 7.31 (m, 1H), 7.39 (s, 1H), 7.43 (s, 1H), 8.24 (s, 1H), 12.24 (br s, 1H).
127	 6-({7-[6-(2-methoxyethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carboxamide	LC-MS (method 13): Rt = 1.03 min; MS (ESIpos): m/z = 491 $[M+H]^+$ ^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.74 - 1.88 (m, 2H), 1.89 - 2.06 (m, 2H), 2.46 (br s, 1H), 2.52 (br s, 4H), 3.08 (t, 2H), 3.28 (s, 3H), 3.56 - 3.89 (m, 8H), 7.01 (dd, 1H), 7.06 (d, 1H), 7.26 - 7.36 (m, 2H), 7.40 (s, 1H), 7.51 (d, 1H), 7.91 (br s, 1H), 8.24 (s, 1H), 11.45 (s, 1H).

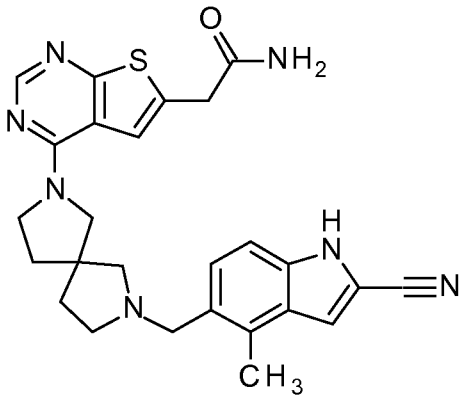
128	 methyl 6-({7-[6-(2-methoxyethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carboxylate	LC-MS (method 13): Rt = 1.26 min; MS (ESIpos): m/z = 506 $[M+H]^+$ ^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.74 - 1.89 (m, 2H), 1.90 - 2.07 (m, 2H), 2.46 (br s, 1H), 2.52 - 2.66 (m, 3H), 3.08 (t, 2H), 3.28 (s, 3H), 3.59 (t, 2H), 3.62 - 3.89 (m, 9H), 7.06 (dd, 1H), 7.11 (d, 1H), 7.38 (s, 1H), 7.40 (s, 1H), 7.57 (d, 1H), 8.25 (s, 1H), 11.84 (s, 1H).
129	 5-({7-[6-(2-methoxyethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-4-methyl-1-(2,2,2-trifluoroethyl)-1H-indole-2-carbonitrile	LC-MS (method 13): Rt = 1.46 min; MS (ESIpos): m/z = 569 $[M+H]^+$ ^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.73 - 1.87 (m, 2H), 1.88 - 2.04 (m, 2H), 2.44 (d, 1H), 2.52 (br s, 3H), 2.54 - 2.65 (m, 2H), 3.08 (t, 2H), 3.28 (s, 3H), 3.54 - 3.88 (m, 8H), 5.33 (q, 2H), 7.37 - 7.42 (m, 2H), 7.53 (d, 1H), 7.71 (s, 1H), 8.24 (s, 1H).

130	 1-(2,2-difluoroethyl)-5-({7-[6-(2-methoxyethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-4-methyl-1 H-indole-2-carbonitrile	LC-MS (method 13): Rt = 1.39 min; MS (ESIpos): m/z = 551 $[M+H]^+$ ^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.73 - 1.87 (m, 2H), 1.87 - 2.05 (m, 2H), 2.44 (d, 1H), 2.53 - 2.65 (m, 3H), 3.08 (t, 2H), 3.28 (s, 3H), 3.50 - 3.92 (m, 9H), 4.74 - 4.85 (m, 2H), 6.29 - 6.60 (m, 1H), 7.33 - 7.37 (m, 1H), 7.39 (s, 1H), 7.41 - 7.46 (m, 1H), 7.62 (s, 1H), 8.24 (s, 1H).
131	 5-({2-[6-(2-methoxyethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-4-methyl-1 H-indole-2-carbonitrile	LC-MS (method 13): Rt = 1.26 min; MS (ESIneg): m/z = 485 $[M-H]^-$ ^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.75 (br s, 4H), 2.24 - 2.46 (m, 3H), 3.08 (t, 2H), 3.28 (s, 3H), 3.51 (br s, 2H), 3.59 (t, 2H), 3.75 - 4.34 (m, 4H), 7.18 - 7.21 (m, 1H), 7.21 - 7.28 (m, 2H), 7.45 (s, 1H), 8.26 (s, 1H), 12.28 (br s, 1H).

132	 6-({2-[6-(2-methoxyethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1H-indole-2-carboxamide	LC-MS (method 13): Rt = 0.97 min; MS (ESIpos): m/z = 491 $[M+H]^+$ ^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.77 (br s, 4H), 2.22 - 2.46 (m, 4H), 3.08 (t, 2H), 3.27 (s, 3H), 3.50 (s, 2H), 3.58 (t, 2H), 3.77 - 4.28 (m, 5H), 6.99 (d, 1H), 7.08 (s, 1H), 7.20 (s, 1H), 7.33 (s, 2H), 7.52 (d, 1H), 7.94 (br s, 1H), 8.25 (s, 1H), 11.48 (s, 1H).
	 methyl 6-({2-[6-(2-methoxyethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1H-indole-2-carboxylate	LC-MS (method 13): Rt = 1.20 min; MS (ESIpos): m/z = 506 $[M+H]^+$ ^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.77 (br s, 4H), 2.35 (br s, 4H), 3.08 (br t, 2H), 3.27 (s, 3H), 3.52 (s, 2H), 3.58 (br t, 2H), 3.75 - 4.28 (m, 7H), 7.05 (br d, 1H), 7.13 (s, 1H), 7.19 (s, 1H), 7.37 (s, 1H), 7.59 (br d, 1H), 8.26 (s, 1H), 11.86 (br s, 1H).

Example 134

2-(4^7-[(2-cyano^-methyl-1 H-indol-5-yl)methyl]-2,7-diazaspiro[4.4]non-2-yl}thieno[2,3-d]pyrimidin-6-yl)acetamide



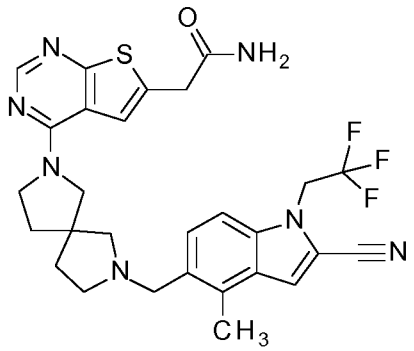
Methyl (4-{7-[(2-cyano-4-methyl-1 H-indol-5-yl)methyl]-2,7-diazaspiro[4.4]non-2-yl}thieno[2,3-d]pyrimidin-6-yl)acetate (48 mg, 90 μmol, example 116) was dissolved in methanol (1 ml). To the solution ammonia (7 M in methanol, 1.3 ml, 9.0 mmol) was added and the resulting mixture was stirred at 40°C for 17 h. The mixture was diluted with DMSO and purified by preparative reversed phase HPLC to give the title compound (18.7 mg, 93 % purity, 40 % yield).

LC-MS (method 13): Rt = 1.05 min; MS (ESIpos): m/z = 486 $[M+H]^+$

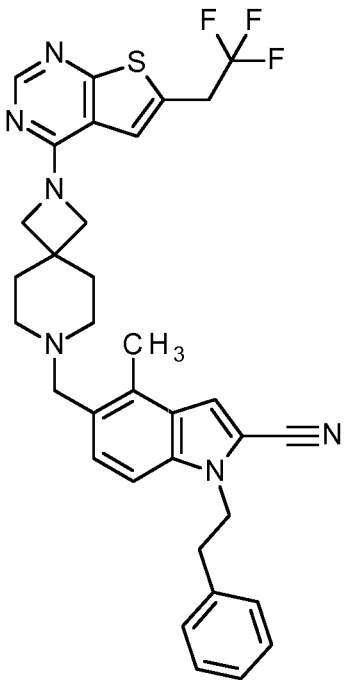
^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.73 - 1.87 (m, 2H), 1.87 - 2.04 (m, 2H), 2.44 (br d, 1H), 2.52 (br s, 3H), 3.56 - 3.87 (m, 9H), 7.08 (br s, 1H), 7.19 - 7.23 (m, 1H), 7.25 - 7.30 (m, 1H), 7.40 (s, 1H), 7.43 (s, 1H), 7.57 (br s, 1H), 8.25 (s, 1H), 12.24 (s, 1H).

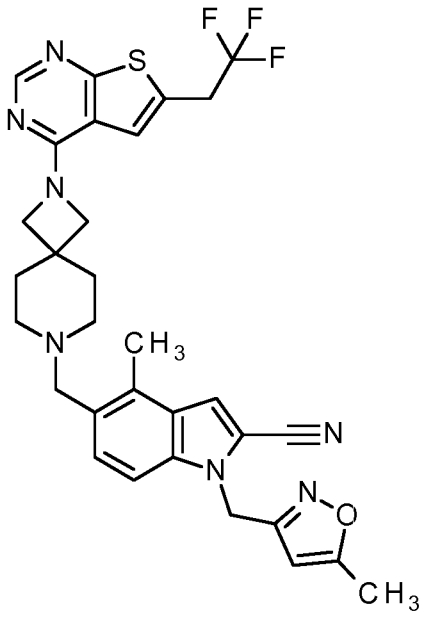
The following example was prepared analogous to the preparation of example **134** starting from the corresponding ester **120** by reacting with ammonia.

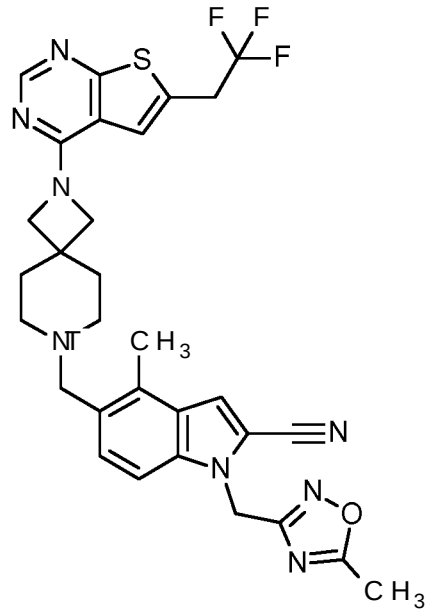
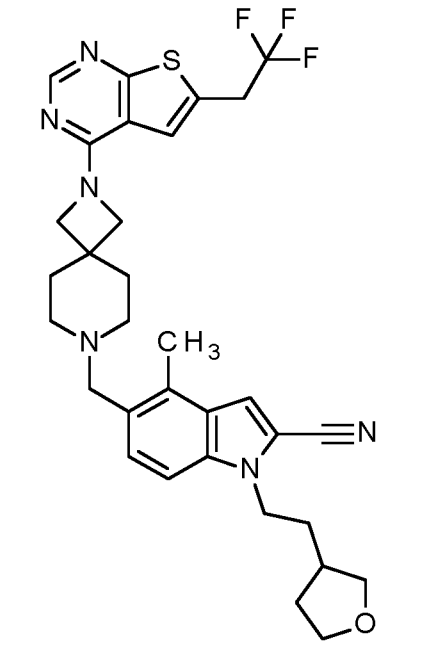
Example	**Structure** **Name**	**Analytical Data**

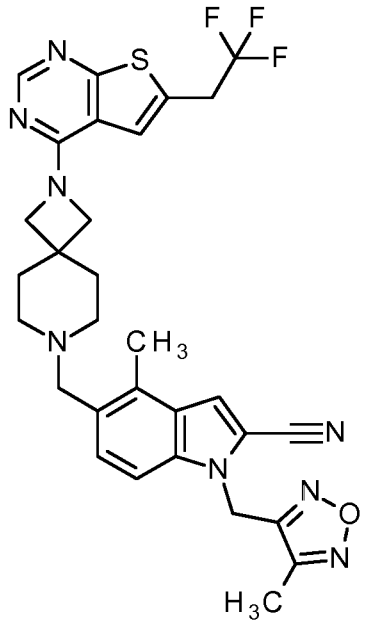
135	 2-{4-[7-{[2-cyano-4-methyl-1 -(2,2,2-trifluoroethyl)-1 H-indol-5-yl]methyl}-2,7-diazaspiro[4.4]non-2-yl]thieno[2,3-d]pyrimidin-6-yl}acetamide	LC-MS (method 13): Rt = 1.20 min; MS (ESIpos): m/z = 568 $[M+H]^+$

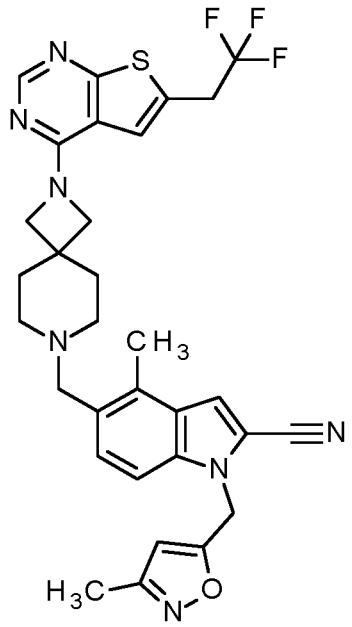
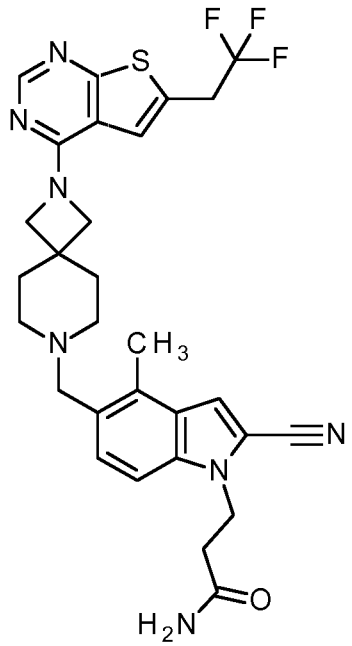
The following examples were prepared analogous to the preparation of example **111** starting from the corresponding example **29** by reacting with the respective alkyl halide.

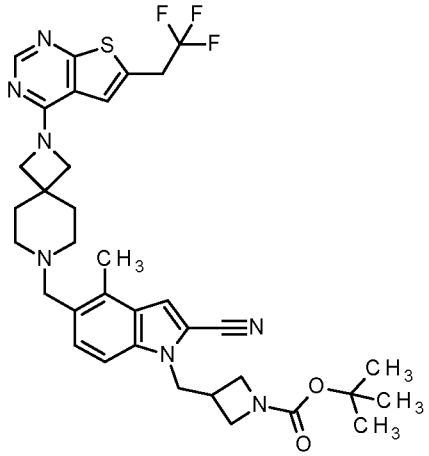
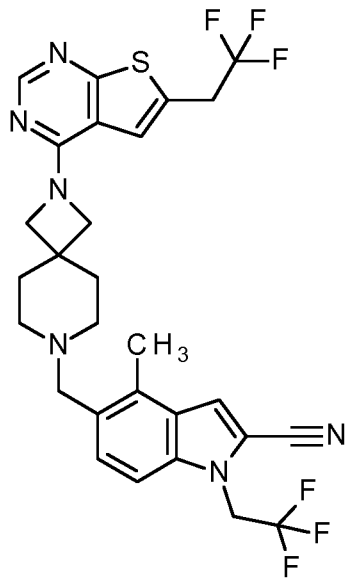
Example	Structure Name	Analytical Data
136	 4-methyl-1-(2-phenylethyl)-5-({2-[6-(2,2,2-	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.351 (2.87), 1.767 (3.22), 2.083 (16.00), 2.180 (0.51), 2.323 (1.33), 2.327 (1.49), 2.331 (1.36), 2.482 (15.84), 2.518 (2.51), 2.523 (1.79), 2.540 (0.92), 2.665 (0.53), 2.669 (0.67), 2.673 (0.48), 3.031 (1.72), 3.049 (3.54), 3.067 (1.79), 3.495 (5.89), 3.932 (0.44), 4.020 (1.10), 4.048 (2.55), 4.076 (2.46), 4.103 (1.01), 4.491 (1.66), 4.509 (3.20), 4.526 (1.61), 7.053 (3.29), 7.069 (3.82), 7.074 (3.38), 7.163 (0.48), 7.167 (0.41), 7.172 (0.41), 7.183 (1.82), 7.189 (1.06), 7.195 (1.93), 7.199 (3.06), 7.207 (4.69), 7.224 (4.02), 7.236 (0.80), 7.241 (1.22), 7.246 (0.97), 7.260 (2.51), 7.282 (3.38), 7.369 (2.62), 7.390 (1.77), 7.448 (5.75), 7.486 (3.82), 8.315 (11.13), 8.358 (0.41).

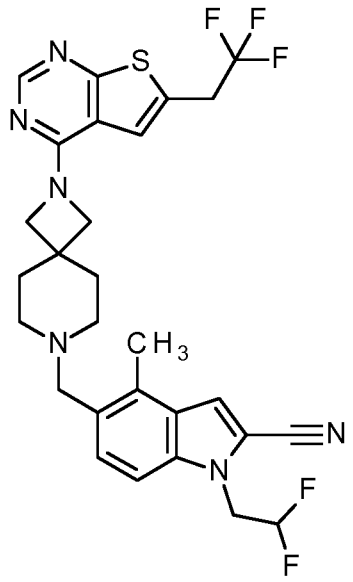
Example	Structure Name	Analytical Data
	trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1H-indole-2-carbonitrile	LC-MS (method 1): Rt = 1.05 min; MS (ESIpos): m/z = 615 [M+H]+
137	 4-methyl-1-[(5-methyl-1,2-oxazol-3-yl)methyl]-5-({2-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1H-indole-2-carbonitrile	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.761 (2.68), 2.084 (0.60), 2.323 (2.51), 2.332 (16.00), 2.518 (7.59), 2.523 (5.08), 2.536 (1.20), 2.665 (1.47), 2.669 (1.97), 2.673 (1.42), 3.499 (4.31), 4.020 (0.93), 4.047 (2.24), 4.075 (2.13), 4.103 (0.87), 5.584 (6.50), 5.632 (0.49), 6.059 (4.26), 6.061 (4.42), 7.310 (1.91), 7.331 (2.57), 7.428 (2.08), 7.450 (1.53), 7.483 (3.22), 7.619 (4.81), 8.313 (9.17). LC-MS (method 1): Rt = 0.93 min; MS (ESIpos): m/z = 606 [M+H]+

Example	Structure Name	Analytical Data
138	 4-methyl-1-[(5-methyl-1 ,2,4-oxadiazol-3-yl)methyl]-5-({2-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1H-indole-2-carbonitrile	^{1}H-NMR (400 MHz, DMS0-d6) δ [ppm]: 1.755 (3.93), 2.082 (3.98), 2.331 (1.36), 2.531 (16.00), 3.493 (5.35), 3.927 (0.54), 4.017 (1.20), 4.044 (2.59), 4.072 (2.55), 4.099 (1.19), 5.695 (6.44), 7.305 (1.77), 7.327 (2.55), 7.405 (2.37), 7.426 (1.60), 7.479 (3.34), 7.622 (4.47), 8.31 1 (5.15). LC-MS (method 2): Rt = 0.80 min; MS (ESIpos): m/z = 606 [M+H]+
139	 4-methyl-1 -{2-[tetrahydrofuran-3-yl]ethyl}-5-({2-[6-(2,2,2-trifluoroethyl)thieno[2,3-	1H-NMR (400 MHz, DMSO-d6) delta [ppm]: 1.422 (0.56), 1.441 (1.19), 1.453 (0.74), 1.460 (1.30), 1.470 (1.46), 1.478 (0.76), 1.489 (1.41), 1.507 (0.65), 1.765 (4.72), 1.802 (2.81), 1.818 (3.22), 1.834 (2.52), 1.851 (1.22), 1.867 (0.50), 1.923 (0.61), 1.936 (0.67), 1.942 (1.13), 1.955 (1.39), 1.961 (1.06), 1.974 (1.61), 1.985 (1.07), 1.991 (0.89), 2.003 (0.98), 2.020 (0.87), 2.037 (1.54), 2.055 (1.67), 2.073 (2.06), 2.083 (12.81), 2.323 (1.69), 2.327 (2.06), 2.332 (1.85), 2.337 (1.61), 2.447 (0.48), 2.452 (0.50), 2.456 (0.67), 2.461 (0.87), 2.466 (1.04), 2.470 (1.00), 2.523 (3.37), 2.532 (1.06), 2.540 (2.85), 2.546 (0.46), 2.665 (0.80), 2.669 (1.07), 2.673 (0.78), 3.202 (2.56), 3.219 (2.87), 3.223 (3.07), 3.240 (2.80), 3.500 (8.78), 3.550 (1.30), 3.568

Example	Structure Name	Analytical Data
	d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1H-indole-2-carbonitrile	(3.02), 3.589 (3.96), 3.608 (1.74), 3.663 (1.67), 3.676 (1.89), 3.685 (4.48), 3.696 (2.98), 3.704 (4.31), 3.716 (1.33), 3.724 (2.37), 3.847 (0.43), 3.925 (0.65), 4.020 (1.57), 4.047 (3.67), 4.075 (3.54), 4.102 (1.48), 4.303 (2.50), 4.321 (4.96), 4.339 (2.44), 7.303 (3.43), 7.325 (4.89), 7.404 (3.91), 7.426 (2.59), 7.483 (5.52), 7.540 (8.63), 8.313 (16.00), 8.402 (0.67). LC-MS (method 2): Rt = 0.85 min; MS (ESIpos): m/z = 609 [M+H]+
140	 4-methyl-1-[(4-methyl-1,2,5-oxadiazol-3-yl)methyl]-5-({2-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1H-indole-2-carbonitrile	1H-NMR (400 MHz, DMSO-d6) delta [ppm]: 1.754 (0.84), 2.081 (16.00), 2.331 (0.41), 2.346 (4.76), 2.514 (3.69), 2.539 (0.82), 2.727 (0.23), 2.885 (0.26), 3.495 (1.34), 4.014 (0.26), 4.042 (0.59), 4.069 (0.57), 4.097 (0.25), 5.841 (1.69), 7.316 (0.47), 7.338 (0.68), 7.415 (0.59), 7.436 (0.39), 7.478 (0.83), 7.671 (1.18), 8.310 (1.61). LC-MS (method 2): Rt = 0.86 min; MS (ESIpos): m/z = 607 [M+H]+

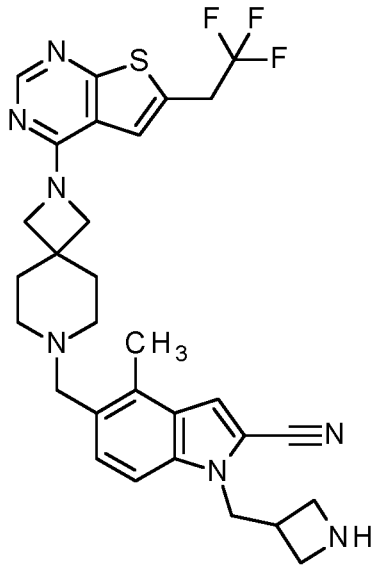
Example	Structure Name	Analytical Data
141	 4-methyl-1-[(3-methyl-1,2-oxazol-5-yl)methyl]-5-({2-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1H-indole-2-carbonitrile	1H-NMR (400 MHz, DMSO-d6) delta [ppm]: 1.757 (3.33), 1.891 (0.56), 2.060 (0.95), 2.073 (0.61), 2.083 (10.85), 2.121 (0.86), 2.166 (16.00), 2.237 (0.56), 2.327 (2.12), 2.332 (1.77), 2.539 (7.09), 2.665 (1.08), 2.669 (1.38), 2.673 (1.04), 3.456 (0.56), 3.500 (4.89), 4.019 (0.95), 4.046 (2.08), 4.073 (2.03), 4.102 (0.99), 5.711 (5.54), 6.300 (4.63), 7.326 (1.95), 7.348 (2.29), 7.481 (3.11), 7.502 (2.08), 7.524 (1.51), 7.637 (4.37), 8.311 (6.27). LC-MS (method 2): Rt = 0.83 min; MS (ESIpos): m/z = 606 [M+H]+
142	 3-[2-cyano-4-methyl-5-({2-[6-(2,2,2-trifluoroethyl)thieno[2,3-	1H-NMR (400 MHz, DMSO-d6) delta [ppm]: 0.905 (0.53), 0.923 (1.06), 0.941 (0.53), 1.232 (0.53), 1.761 (1.59), 2.084 (6.04), 2.332 (3.05), 2.404 (0.73), 2.422 (0.66), 2.518 (16.00), 2.522 (10.89), 2.539 (6.04), 2.572 (1.13), 2.589 (2.26), 2.606 (1.06), 2.673 (2.79), 3.497 (3.19), 4.020 (0.53), 4.048 (1.33), 4.076 (1.26), 4.102 (0.53), 4.473 (0.80), 4.490 (1.66), 4.507 (0.80), 6.900 (0.80), 7.279 (1.13), 7.301 (1.66), 7.391 (1.73), 7.412 (1.06), 7.484 (1.93), 7.510 (2.99), 8.312 (5.71), 8.548 (0.73). LC-MS (method 2): Rt = 0.71 min; MS (ESIpos): m/z = 582 [M+H]+

Example	Structure Name	Analytical Data
	d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1H-indol-1-yl]propanamide	
143	 tert-butyl 3-{[2-cyano-4-methyl-5-({2-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1H-indol-1-yl]methyl}azetidine-1-carboxylate	1H-NMR (400 MHz, DMSO-d6) delta [ppm]: 1.191 (0.45), 1.354 (16.00), 1.762 (0.84), 2.084 (1.71), 2.323 (0.39), 2.327 (0.48), 2.331 (0.43), 2.518 (1.32), 2.523 (1.02), 2.539 (0.19), 2.665 (0.22), 2.669 (0.29), 2.673 (0.21), 3.013 (0.17), 3.027 (0.24), 3.045 (0.18), 3.499 (1.52), 3.678 (0.42), 3.863 (0.49), 4.020 (0.30), 4.048 (0.68), 4.075 (0.66), 4.103 (0.28), 4.529 (0.72), 4.547 (0.70), 7.312 (0.66), 7.334 (0.80), 7.483 (1.07), 7.493 (0.71), 7.516 (0.51), 7.561 (1.59), 8.313 (2.82). LC-MS (method 1): Rt = 1.03 min; MS (ESIpos): m/z = 680 [M+H]+
144	 4-methyl-1-(2,2,2-trifluoroethyl)-5-({2-[6-(2,2,2-trifluoroethyl)thieno[2,3-	1H-NMR (400 MHz, DMSO-d6) delta [ppm]: 1.150 (4.30), 1.168 (8.48), 1.171 (7.22), 1.186 (4.51), 1.224 (0.56), 1.763 (8.05), 1.983 (16.00), 1.986 (13.71), 2.328 (2.98), 2.352 (2.87), 2.668 (0.83), 3.507 (9.67), 3.995 (2.50), 4.013 (5.86), 4.016 (5.82), 4.031 (5.61), 4.047 (5.68), 4.073 (4.82), 4.099 (2.31), 5.313 (1.71), 5.335 (4.42), 5.357 (4.32), 5.378 (1.65), 7.293 (0.48), 7.340 (0.60), 7.363 (3.39), 7.384 (4.19), 7.481 (5.67), 7.539 (3.88), 7.561 (3.14), 7.724 (8.19), 8.271 (0.83), 8.311 (7.78). LC-MS (method 1): Rt = 0.88 min; MS (ESIpos): m/z = 593 [M+H]+

Example	Structure Name	Analytical Data
	d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1H-indole-2-carbonitrile	
145	 1-(2,2-difluoroethyl)-4-methyl-5-({2-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1H-indole-2-carbonitrile	1H-NMR (400 MHz, DMSO-d6) delta [ppm]: 1.154 (3.97), 1.172 (8.45), 1.189 (4.29), 1.762 (2.42), 1.987 (16.00), 2.323 (0.68), 2.327 (0.78), 2.331 (0.74), 2.349 (0.71), 2.522 (0.96), 2.727 (0.41), 2.887 (0.48), 3.506 (4.33), 3.999 (1.48), 4.016 (4.37), 4.034 (4.02), 4.047 (2.10), 4.052 (2.08), 4.075 (1.95), 4.102 (0.79), 4.773 (0.70), 4.808 (1.32), 4.814 (1.36), 4.849 (0.68), 6.319 (0.46), 6.454 (0.95), 6.590 (0.41), 7.322 (1.81), 7.344 (2.43), 7.445 (1.79), 7.466 (1.24), 7.483 (3.06), 7.631 (4.37), 8.314 (7.66). LC-MS (method 1): Rt = 0.84 min; MS (ESIpos): m/z = 575 [M+H]+

Example 146

1-(azetidin-3-ylmethyl)-4-methyl-5-({2-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carbonitrile



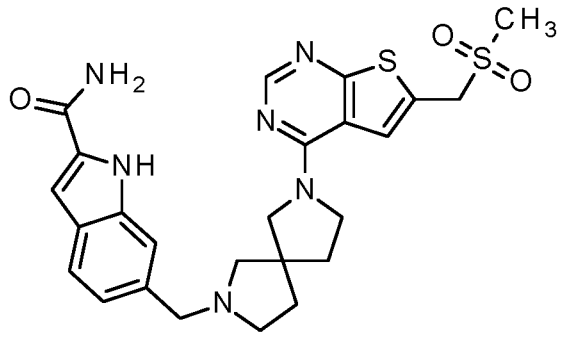
tert-butyl 3-{[2-cyano-4-methyl-5-({2-[6-(2 ,2,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indol-1-yl]methyl}azetidine-1-carboxylate (12.1 mg, 80 % purity, 14.2 μηιοΙ) (example **143)** was treated with 20 μΙ water and then dissolved in 1.0 ml of a solution of 4M hydrochloride in dioxane. The mixture was stirred for 1 h at RT. All solvent was removed by evaporation and the residue was purified by prep. reversed phase HPLC. The product fractions were pooled and evaporated to give the desired product as an off white solid (6.4 mg, 54 % yield).

LC-MS (method 1): Rt = 0.68 min; MS (ESIpos): m/z = 580 [M+H]+

1H-NMR (400 MHz, DMSO-d6) delta [ppm]: 0.917 (0.60), 0.934 (0.60), 1.172 (0.48), 1.190 (1.07), 1.209 (0.60), 1.228 (0.96), 1.254 (1.55), 1.271 (1.55), 1.287 (1.19), 1.303 (1.07), 1.964 (2.51), 2.072 (2.75), 2.082 (16.00), 2.148 (1.67), 2.337 (0.48), 2.410 (1.79), 2.518 (6.69), 2.523 (4.66), 2.529 (2.75), 2.540 (2.63), 2.637 (4.66), 2.674 (1.19), 2.679 (0.60), 3.128 (0.60), 3.223 (0.48), 3.241 (0.72), 3.278 (1.07), 3.313 (1.55), 3.321 (1.91), 3.406 (1.07), 3.763 (1.07), 3.777 (1.07), 3.806 (3.34), 3.972 (0.96), 4.000 (1.43), 4.016 (1.31), 4.044 (1.19), 4.071 (1.19), 4.099 (0.60), 4.397 (1.19), 4.670 (0.48), 4.689 (0.48), 4.707 (1.55), 4.725 (1.43), 7.134 (7.04), 7.261 (7.64), 7.282 (2.27), 7.388 (6.81), 7.594 (0.48), 7.689 (0.84), 7.715 (2.27), 7.792 (0.60), 7.908 (0.72), 7.928 (0.48), 8.342 (5.49).

Example 147

6-{[7-{6-[(methylsulfonyl)methyl]thieno[2,3-^]pyrimidin-4-yl}-2,7-diazaspiro[4.4]non-2-yl]methyl}-1 H-indole-2-carboxamide



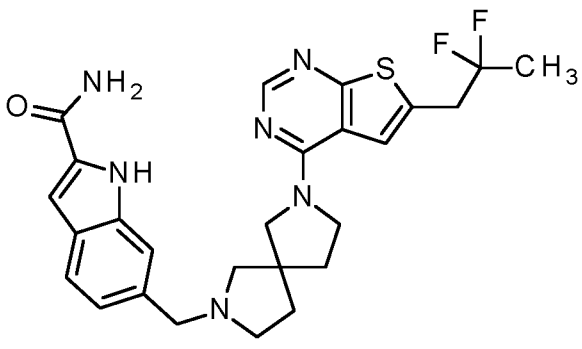
To a suspension of 6-[(methylsulfonyl)methyl]thieno[2,3-d]pyrimidin-4(3H)-one (150 mg, 614 μηηοl) (intermediate **1121)** in 2 ml acetonitrile was given 6-(2,7-diazaspiro[4.4]non-2-ylmethyl)-1H-indole-2-carboxamide hydrochloride (257 mg, 614 μηηοl), triethylamine (170 μl, 1.2 mmol) and PyBOP (383 mg, 737 μηοl) [CAS 128625-52-5]. The mixture was stirred for 4 h at 80°C. The reaction mixture was treated with water, extracted 3x with ethyl acetate. The combined organic phases were evaporated and the residue purified by prep. reversed phase HPLC to yield 20 mg (6 %) of the desired product.

LC-MS (method 1): Rt = 0.51 min; MS (ESIpos): m/z = 525 $[M+H]^+$

1H-NMR (400 MHz, DMSO-d6) delta [ppm]: 1.154 (3.96), 1.172 (7.98), 1.189 (4.04), 1.231 (0.55), 1.809 (0.95), 1.824 (1.74), 1.840 (1.77), 1.907 (1.75), 1.987 (16.00), 2.084 (2.25), 2.326 (0.96), 2.579 (1.32), 2.623 (1.01), 2.669 (1.75), 2.999 (8.86), 3.172 (0.42), 3.680 (2.32), 3.999 (1.24), 4.017 (3.60), 4.035 (3.62), 4.053 (1.25), 4.838 (3.07), 7.002 (1.75), 7.022 (1.88), 7.067 (3.14), 7.315 (1.21), 7.345 (2.72), 7.502 (2.35), 7.523 (2.17), 7.712 (3.59), 7.916 (1.14), 8.314 (7.46), 11.456 (1.99).

Example 148

6-({7-[6-(2,2-difluoropropyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carboxamide



To a suspension of 6-(2,2-difluoropropyl)thieno[2,3-d]pyrimidin-4(3H)-one (100 mg, 434 μηοl) (intermediate **1115)** in 3 ml acetonitrile was given 6-(2,7-diazaspiro[4.4]non-2-ylmethyl)-1 H-

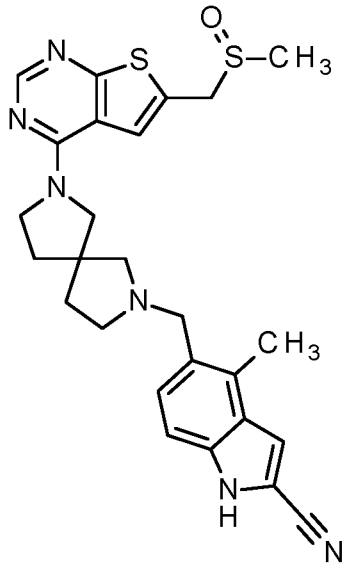
indole-2-carboxamide hydrochloride (175 mg, 521 µmol, intermediate **1137),** triethylamine (240 µl, 1.7 mmol) and PyBOP (249 mg, 478 µmol). The mixture was stirred for 5 h at 80°C. The reaction mixture was evaporated and the residue purified by prep. reversed phase HPLC to yield 60 mg (27 %) of the desired product.

LC-MS (method 1): Rt = 0.63 min; MS (ESIpos): m/z = 511 $[M+H]^+$

1H-NMR (400 MHz, DMSO-d6) delta [ppm]: 1.147 (16.00), 1.270 (0.19), 1.638 (0.62), 1.684 (1.25), 1.731 (0.56), 1.834 (0.21), 1.852 (0.37), 1.870 (0.38), 1.888 (0.20), 2.027 (0.20), 2.504 (0.38), 2.558 (0.67), 2.563 (0.43), 2.580 (0.25), 2.595 (0.39), 2.619 (0.38), 2.642 (0.27), 2.667 (0.17), 2.687 (0.27), 2.704 (0.29), 2.709 (0.29), 3.566 (0.29), 3.607 (0.52), 3.646 (0.32), 3.664 (0.24), 3.696 (0.69), 3.708 (0.78), 3.740 (0.31), 7.038 (0.47), 7.059 (0.50), 7.103 (0.78), 7.106 (0.78), 7.351 (0.27), 7.383 (0.66), 7.538 (0.67), 7.558 (0.61), 7.591 (0.90), 7.955 (0.26), 8.236 (0.23), 8.323 (2.31), 11.502 (0.53).

Example 149

4-methyl-5-{[7-(6-{[methylsulfinyl]methyl}thieno[2,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.4]non-2-yl]methyl}-1H-indole-2-carbonitrile



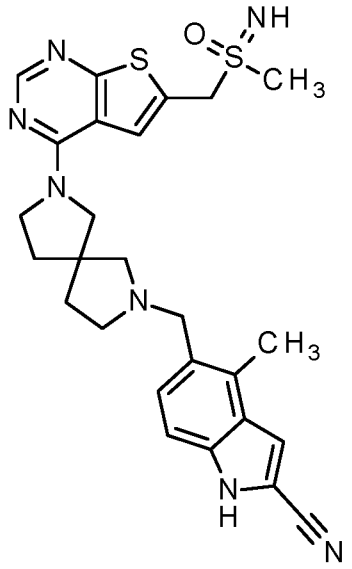
To a solution of scandium(III)triflate (12.1 mg, 24.6 µmol) in 0.5 ml dichloromethane and 70 µl methanol was added hydrogen peroxide (130 µl, 30 % aqueous solution, 1.2 mmol) and stirring continued for 5 min. Then a solution of 4-methyl-5-{[7-{6-[(methylsulfanyl)methyl]-thieno[2,3-d]pyrimidin-4-yl}-2,7-diazaspiro[4.4]non-2-yl]methyl}-1H-indole-2-carbonitrile (60.0 mg, 123 µmol, example **151)** in a mixture of 0.5 ml dichloromethane and 70 µl methanol was added und the reaction mixture was stirred for 2.5 h at RT. The reaction mixture was treated with DMSO and purified by prep. reversed phase HPLC to yield 15 mg (24 %) of the desired product.

LC-MS (method 2): Rt = 0.52 min; MS (ESIpos): m/z = 505 $[M+H]^+$

1H-NMR (400 MHz, DMSO-d6) delta [ppm]: 1.154 (0.49), 1.172 (0.94), 1.190 (0.53), 1.232 (0.64), 1.786 (0.86), 1.801 (1.54), 1.818 (1.58), 1.834 (0.83), 1.875 (1.24), 1.988 (2.37), 2.327 (2.40), 2.332 (1.92), 2.518 (16.00), 2.522 (11.83), 2.530 (15.06), 2.622 (1.09), 2.639 (0.86), 2.669 (2.29), 2.673 (1.73), 3.615 (0.83), 3.653 (3.83), 3.685 (0.90), 4.017 (0.41), 4.242 (0.90), 4.276 (1.20), 4.435 (1.35), 4.470 (0.98), 7.193 (1.28), 7.215 (2.37), 7.259 (2.70), 7.280 (1.46), 7.431 (4.17), 7.591 (3.94), 8.289 (8.38), 12.240 (0.94).

Example 150

4-methyl-5-{[7-{6-[(S-methylsulfonimido yl)methyl]thieno[2,3-d]pyrimidin-4-yl}-2,7-diazaspiro[4.4]non-2-yl]methyl}-1 H-indole-2-carbonitrile



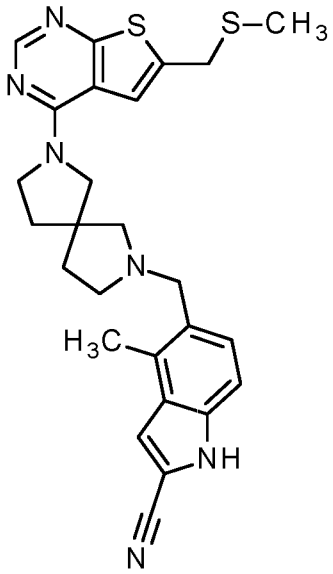
To a solution of 4-methyl-5-{[7-{6-[(methylsulfanyl)methyl]thieno[2,3-d]pyrimidin-4-yl}-2,7-diazaspiro[4.4]non-2-yl]methyl}-1 H-indole-2-carbonitrile (60.0 mg, 123 µmol, example **151)** in 830 µl methanol was added ammonium carbamate (28.8 mg, 368 µmol) and (diacetoxyiodo)benzene (79.1 mg, 246 µmol) and stirring continued for 48 h. The reaction mixture was treated with DMSO and purified by prep. reversed phase HPLC to yield 11 mg (15 %) of the desired product.

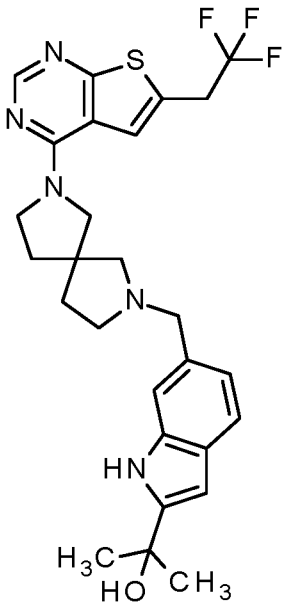
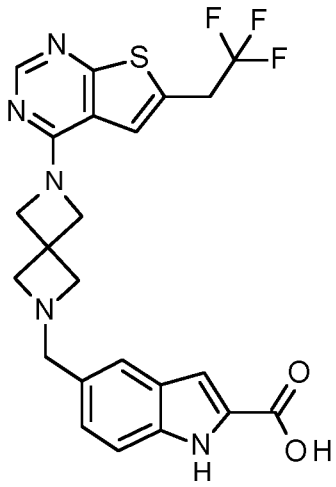
LC-MS (method 2): Rt = 0.50 min; MS (ESIpos): m/z = 520 $[M+H]^+$

1H-NMR (400 MHz, DMSO-d6) delta [ppm]: 1.230 (0.58), 1.774 (7.03), 1.786 (1.36), 1.802 (2.14), 1.818 (2.27), 1.833 (1.23), 1.987 (1.23), 2.014 (2.52), 2.026 (1.41), 2.033 (3.55), 2.074 (0.96), 2.084 (1.23), 2.416 (2.22), 2.439 (3.02), 2.460 (0.76), 2.518 (6.43), 2.523 (5.54), 2.543 (2.44), 2.560 (1.74), 2.579 (0.73), 2.602 (1.21), 2.623 (2.90), 2.629 (2.77), 2.875 (14.34), 3.165 (2.04), 3.615 (1.23), 3.650 (6.35), 3.684 (1.39), 3.807 (1.13), 3.891 (2.47), 3.986 (0.60), 4.008 (1.31), 4.078 (1.31), 4.632 (0.63), 4.667 (2.19), 4.689 (1.97), 4.725 (0.53), 4.856 (0.68), 5.642

(0.48), 7.197 (2.07), 7.218 (4.16), 7.255 (4.59), 7.276 (2.22), 7.371 (0.60), 7.393 (0.60), 7.424 (8.19), 7.426 (7.66), 7.695 (4.81), 8.278 (0.68), 8.290 (16.00).

The following examples were prepared analogous to the preparation of example **13** starting from the corresponding intermediates **131**, **I28** or **1104**, by reacting with the corresponding aldehydes.

Example	Structure Name	Analytical Data
151	 4-methyl-5-{[7-{6-[(methylsulfanyl)methyl]thieno[2,3-d]pyrimidin-4-yl}-2,7-diazaspiro[4.4]non-2-yl]methyl}-1H-indole-2-carbonitrile	1H-NMR (400 MHz, DMSO-d6) delta [ppm]: 1.171 (0.47), 1.777 (0.55), 1.796 (0.87), 1.814 (0.88), 1.832 (0.50), 1.907 (0.42), 1.969 (0.63), 1.987 (1.27), 2.016 (16.00), 2.074 (0.42), 2.326 (0.52), 2.437 (0.57), 2.458 (0.41), 2.462 (0.47), 2.518 (2.48), 2.522 (1.92), 2.539 (0.98), 2.544 (0.73), 2.626 (0.46), 2.660 (0.44), 2.664 (0.55), 2.668 (0.63), 2.673 (0.46), 3.654 (1.71), 4.000 (4.48), 7.195 (1.03), 7.216 (1.90), 7.260 (2.11), 7.281 (1.13), 7.431 (2.22), 7.433 (2.23), 7.495 (3.66), 8.258 (10.25), 12.240 (1.36). LC-MS (method 2): Rt = 0.71 min; MS (ESIpos): m/z = 489 [M+H]+

Example	Structure Name	Analytical Data
152	 2-[6-({7-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indol-2-yl]propan-2-ol	^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.505 (16.00), 1.782 (0.43), 1.799 (0.73), 1.817 (0.79), 2.326 (0.49), 2.427 (0.81), 2.450 (1.16), 2.518 (1.95), 2.522 (1.59), 2.528 (0.94), 2.551 (0.89), 2.568 (0.56), 2.623 (0.50), 2.664 (0.44), 2.668 (0.52), 3.619 (1.44), 3.628 (1.57), 3.660 (0.45), 4.041 (0.66), 4.069 (0.63), 5.141 (4.26), 6.127 (1.64), 6.131 (1.58), 6.874 (1.01), 6.877 (0.98), 6.894 (1.07), 6.897 (1.08), 7.246 (1.33), 7.313 (1.46), 7.333 (1.29), 7.683 (1.66), 8.304 (6.52), 10.764 (1.07), 10.768 (1.07). LC-MS (method 2): Rt = 0.81 min; MS (ESIpos): m/z = 530 [M+H]+
153	 5-({6-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,6-diazaspiro[3.3]hept-2-yl}methyl)-1H-indole-2-carboxylic acid	1H-NMR (400 MHz, DMSO-d6) delta [ppm]: 1.116 (0.16), 1.135 (0.34), 1.153 (0.16), 1.232 (0.23), 1.907 (0.25), 2.332 (0.31), 2.518 (1.62), 2.523 (1.13), 2.539 (16.00), 2.673 (0.33), 3.348 (0.40), 3.691 (1.47), 4.021 (0.36), 4.048 (0.99), 4.076 (0.93), 4.103 (0.31), 4.431 (0.28), 7.024 (1.03), 7.159 (0.61), 7.162 (0.61), 7.180 (0.72), 7.183 (0.74), 7.364 (1.10), 7.386 (0.87), 7.419 (1.82), 7.533 (1.25), 8.169 (0.71), 8.321 (3.62), 11.678 (0.57). LC-MS (method 2): Rt = 0.60 min; MS (ESIpos): m/z = 488 [M+H]+

EXPERIMENTAL SECTION - BIOLOGICAL ASSAYS

Examples were tested in selected biological assays one or more times. When tested more than once, data are reported as either average values or as median values, wherein

- the average value, also referred to as the arithmetic mean value, represents the sum of the values obtained divided by the number of times tested, and
- the median value represents the middle number of the group of values when ranked in ascending or descending order. If the number of values in the data set is odd, the median is the middle value. If the number of values in the data set is even, the median is the arithmetic mean of the two middle values.

Examples were synthesized one or more times. When synthesized more than once, data from biological assays represent average values or median values calculated utilizing data sets obtained from testing of one or more synthetic batch.

The *in vitro* activity of the compounds of the present invention can be demonstrated in the following assays:

In vitro assay 1: **Menin / MLL-1 peptide binding assay**

The ability of the compounds described in the present invention to disrupt the interaction between Menin (full length) and MLL-1 (a.a. 4-15) was used as quantitative measure of their menin-binding affinities.

To this end a TR-FRET assay which detects the binding of a biotinylated MLL-1-derived synthetic peptide (purchased from *e.g.* Biosyntan (Berlin, Germany)) of sequence Btn-PEG2-PEG2-S-Nva-RWRFPARPGTT-Amide to recombinant, full length, N-terminally His-tagged Menin. The protein was produced *in-house* via *E. coli* expression, followed by subsequent Ni-Sepharose affinity- and Superdex S200-size exclusion chromatography purification steps.

Typically, 11 different concentrations of each compound (0.1 nM, 0.33 nM, 1.1 nM, 3.8 nM, 13 nM, 44 nM, 0.15 µM, 0.51 µM, 1.7 µM, 5.9 µM and 20 µM) were tested in duplicate within the same microtiter plate. To this end, 100-fold concentrated compound solutions (in DMSO) were previously prepared with a Precision Pippeting System (BioTek) by serial dilution (1:3.4) of 2 mM stocks in clear, low-volume 384-well microtiter source plates (Greiner Bio-One). Subsequently, 50 nl of compounds were transferred into black, low-volume test plates from the same supplier using a Hummingbird capillary based liquid handling instrument (Digilab). Tests were started by the addition of 2 µl of 2.5-fold concentrated Menin solution (5 nM = 2 nM final concentration in the 5 µl assay volume) in aqueous assay buffer [50 mM Tris/HCl pH 7.5, 50

mM sodium chloride (NaCl), 0.1% bovine serum albumin (BSA) and 1 mM dithiothreitol (DTT)] to the compounds in the test plate with a Multidrop dispenser (Thermo-Fisher). Test plates were then incubated 10' at 22°C, in order to allow pre-equilibration of putative compound-Menin complexes. Subsequently, 3 µl of a 1.67-fold concentrated solution containing MLL-1 peptide (83.5 nM = 50 nM final concentration) and TR-FRET detection reagents [83.5 nM Streptavidin XL-665 = 50 nM final concentration and 3.33 nM anti-6XHis-Tb cryptate = 2 nM final concentration (both from Cisbio), were dispensed into the plates.

The mixture was further incubated in the dark for 0.5-4 hours at 22°C. Finally the inhibition of the formation of menin / MLL-1 complexes was assessed by measurement of the resonance energy transfer from the anti-6XHis-Tb cryptate to the Streptavidin XL-665 present in the reaction. To this end, the fluorescence emissions at 622 nm and 665 nm after excitation at 337 nm were measured in a TR-FRET reader, e.g. a Rubystar or Pherastar (both from BMG Lab Technologies) or a Viewlux (Perkin-Elmer) and the ratio of the emissions at 665 nm and at 622 nm was taken as indicator for the amount of complexes in equilibrium.

The data were normalised using two sets of control wells (16 each). The first accounted for 100% menin / MLL-1 binding (0 % inhibition), and contained all reaction components but DMSO instead of inhibitors. The second represented 0% menin / MLL-1 binding (100% inhibition), and included all assay components except Menin. IC_{50} values were calculated by fitting the normalized inhibition data to a 4-parameter logistic equation using the Screener analysis software (Genedata).

The suitability of the compounds of the present invention for the treatment of different cancer forms can be demonstrated in the following cell line *in vitro* models:

Leukemia models:

In vitro assay 2: MV4-1 1 cell proliferation assay

In accordance with the invention, the ability of the substances to inhibit cell proliferation was determined. Cell viability was determined by means of the alamarBlue® reagent (Invitrogen) in a Victor X3 Multilabel Reader (Perkin Elmer). The excitation wavelength was 530 nm and the emission wavelength 590 nm. The MV4-1 1 cells (American Type Culture Collection ATCC, Catalogue No.: CRL-9591) were sown at a concentration of 6000 cells/well in 100 µl of growth medium (Iscove's Modified Dulbecco's Medium +10% FCS) on 96-well microtiter plates. After overnight incubation at 37°C, the fluorescence values were determined (CO values). Then the plates were treated with various substance dilutions (e.g. 1E-5 M, 3E-6 M, 1E-6 M, 3E-7 M, 1E-7 M, 3E-8 M, 1E-8 M, 3E-9 M) and incubated at 37 °C over 96 hours. Subsequently, the fluorescence values were determined (CI values). For the data analysis, the CO values were

subtracted from the CI values and the results were compared between cells which had been treated with various dilutions of the substance or only with buffer solution. The IC50 values (substance concentration needed for 50% inhibition of cell proliferation) were calculated therefrom.

In vitro assay 3: MOLM-13 cell proliferation assay

In accordance with the invention, the ability of the substances to inhibit cell proliferation was determined. Cell viability was determined by means of the alamarBlue® reagent (Invitrogen) in a Victor X3 Multilabel Reader (Perkin Elmer). The excitation wavelength was 530 nm and the emission wavelength 590 nm. The MOLM-13 cells (The Leibniz Institute DSMZ - German Collection of Microorganisms and Cell Cultures, Catalogue No.: ACC 554) were sown at a concentration of 4000 cells/well in 100 µl of growth medium (RPMI 1640 Medium with stable Glutamine + 10% FCS) on 96-well microtiter plates. After overnight incubation at 37°C, the fluorescence values were determined (CO values). Then the plates were treated with various substance dilutions (e.g. 1E-5 M, 3E-6 M, 1E-6 M, 3E-7 M, 1E-7 M, 3E-8 M, 1E-8 M, 3E-9 M) and incubated at 37 °C over 96 hours. Subsequently, the fluorescence values were determined (CI values). For the data analysis, the CO values were subtracted from the CI values and the results were compared between cells which had been treated with various dilutions of the substance or only with buffer solution. The IC50 values (substance concentration needed for 50% inhibition of cell proliferation) were calculated therefrom.

Prostate cancer models:

In vitro assay 4: LAPC-4 cell proliferation assay

In accordance with the invention, the ability of the substances to inhibit cell proliferation was determined. Cell viability was determined by CellTiter-Glo® staining (Promega) in a Victor X3 Multilabel Reader (Perkin Elmer) by measurement of luminescence. The LAPC-4 cells (American Type Culture Collection ATCC, Catalogue No.: CRL-13009) were sown at a concentration of 1000 cells/well in 30 µl of growth medium (RPMI 1640 without phenol red, 2 mM L-glutamine, 10% FCS, 1 nM R1881) on 384-well microtiter plates and incubated overnight at 37 °C. Then the cells were treated with inhibitor substance at various concentrations(e.g. 1E-5 M, 3E-6 M, 1E-6 M, 3E-7 M, 1E-7 M, 3E-8 M, 1E-8 M, 3E-9 M). Following incubation at 37 °C for 168 hours, cell number was determined. CI value was defined as the signal measured at day 7 for cells treated only with 0.1 % DMSO. CO value was defined as the signal measured at day 0. For the data analysis, the CO values were subtracted from the CI values and the results were compared between cells which had been treated with various dilutions of the substance or only with buffer solution. The IC50 values (substance concentration needed for 50% inhibition of cell proliferation) were calculated therefrom.

In vitro assay 5: LNCaP cell proliferation assay

In accordance with the invention, the ability of the substances to inhibit cell proliferation was determined. Cell viability was determined by CellTiter-Glo® staining (Promega) in a Victor X3 Multilabel Reader (Perkin Elmer) by measurement of luminescence. The LNCaP cells (American Type Culture Collection ATCC, Catalogue No.: CRL-1740) were sown at a concentration of 1000 cells/well in 30 µl of growth medium (RPMI 160 medium with stable glutamine and Pen/Strep + 10% FCS) in 384-well microtiter plates and incubated overnight at 37 °C.Then the plates were treated at day 0 with various inhibitor substance dilutions (e.g. 1E-5 M, 3E-6 M, 1E-6 M, 3E-7 M, 1E-7 M, 3E-8 M, 1E-8 M, 3E-9 M) and incubated at 37 °C over 144 hours. Subsequently, the luminescence values were determined. CI value was defined as the signal measured at day 6 for cells treated only with 0.1% DMSO. CO was defined as the signal measured at day 0. For the data analysis, the CO values were subtracted from the CI values and the results were compared between cells which had been treated with various dilutions of the substance or only with buffer solution. The IC50 values (substance concentration needed for 50% inhibition of cell proliferation) were calculated therefrom.

Breast cancer models:

In vitro assay 6: MCF7 cell proliferation assay

In accordance with the invention, the ability of the substances to inhibit cell proliferation was determined. Cell viability was determined by CellTiter-Glo® staining (Promega) in a Victor X3 Multilabel Reader (Perkin Elmer) by measurement of luminescence. The MCF7 cells (American Type Culture Collection ATCC, Catalogue No.: HTB-22) were sown at a concentration of 120 cells/well in 30 µl of growth medium (RPMI 1640 medium with stable glutamine + 10% FCS + 10 pM E2) in 384-well microtiter plates and incubated overnight at 37 °C. Then the plates were treated at day 0 with various inhibitor substance dilutions (e.g. 1E-5 M, 3E-6 M, 1E-6 M, 3E-7 M, 1E-7 M, 3E-8 M, 1E-8 M, 3E-9 M) and incubated at 37 °C for 96 hours. Cell number was determined at day 0 and day 4. CI was defined as the signal measured at day 4 for cells treated only with 0.1% DMSO. CO was defined as the signal measured at day 0. For the data analysis, the CO values were subtracted from the CI values and the results were compared between cells which had been treated with various dilutions of the substance or only with buffer solution. The IC50 values (substance concentration needed for 50% inhibition of cell proliferation) were calculated therefrom.

In vitro assay 7: MDA-MB-468 cell proliferation assay

In accordance with the invention, the ability of the substances to inhibit cell proliferation was determined. Cell viability was determined by CellTiter-Glo® staining (Promega) in a Victor X3 Multilabel Reader (Perkin Elmer) by measurement of luminescence. The MDA-MB-468 cells (American Type Culture Collection ATCC, Catalogue No.: HTB-132) were sown at a

concentration of 500 cells/well in 30 µl of growth medium (RPMI 1640 medium with stable glutamine + 10% FCS) in 384-well microtiter plates and incubated overnight at 37 °C. Then the plates were treated at day 0 with various inhibitor substance dilutions (e.g. 1E-5 M, 3E-6 M, 1E-6 M, 3E-7 M, 1E-7 M, 3E-8 M, 1E-8 M, 3E-9 M) and incubated at 37 °C for 96 hours. Cell number was determined at day 0 and day 4. CI was defined as the signal measured at day 4 for cells treated only with 0.1% DMSO. CO was defined as the signal measured at day 0. For the data analysis, the CO values were subtracted from the CI values and the results were compared between cells which had been treated with various dilutions of the substance or only with buffer solution. The IC50 values (substance concentration needed for 50% inhibition of cell proliferation) were calculated therefrom.

Results:

Binding assay

Table 2 shows the results of the inhibition in the menin/MLL-1 HTRF assay

Table 2:

Example	IC_{50} [menin/MLL-1)] (mol/l)
1.0	8.19 E-7
2.0	8.37 E-8
3.0	9.24 E-8
4.0	1.73 E-7
5.0	2.61 E-7
6.0	2.07 E-7
7.0	2.30 E-7
8.0	7.15 E-8
9.0	6.64 E-7
10.0	1.49 E-6
11.0	3.25 E-6
12.0	1.43 E-8
12.1	1.11 E-8
12.2	2.74 E-7
13.0	4.20 E-7
14.0	2.65 E-7
15.0	2.18 E-7

Example	ICso [menin/MLL-1)] (mol/l)
15.1	1.98 E-7
15.2	3.22 E-7
16.0	4.32 E-7
17.0	1.78 E-6
18.0	6.09 E-7
19.0	3.00 E-6
20.0	1.98 E-8
2 1.0	2.59 E-8
22.0	1.07 E-8
22.1	6.02 E-9
22.2	2.70 E-8
23.0	7.49 E-9
23.1	5.92 E-9
23.2	1.84 E-8
24.0	9.57 E-7
25.0	5.01 E-6
26.0	6.99 E-8
27.0	> 2.00 E-5
28.0	4.93 E-8
29.0	2.19 E-8
30.0	1.41 E-6
3 1.0	3.38 E-7
32.0	5.81 E-7
33.0	3.35 E-6
34.0	2.44 E-8
35.0	1.37 E-7
36.0	1.83 E-7
37.0	6.86 E-9
38.0	1.03 E-8
39.0	7.72 E-9
40.0	7.96 E-9
4 1.0	1.04 E-8
42.0	2.03 E-8
43.0	7.19 E-9
43.1	6.93 E-9
43.2	2.02 E-8

Example	ICso [menin/MLL-1)] (mol/l)
44.0	1.98 E-8
45.0	3.27 E-8
46.0	1.63 E-8
47.0	9.49 E-8
47.1	1.88 E-8
47.2	1.08 E-8
48.0	1.68 E-7
49.0	2.61 E-8
50.0	2.38 E-7
51.0	1.63 E-7
52.0	5.59 E-8
53.0	1.65 E-7
54.0	8.36 E-7
55.0	1.67 E-6
56.0	6.04 E-7
57.0	6.23 E-7
58.0	1.32 E-6
59.0	3.77 E-7
60.0	1.41 E-6
61.0	1.73 E-6
62.0	1.28 E-6
63.0	2.80 E-7
64.0	8.65 E-7
65.0	8.88 E-7
66.0	6.23 E-7
67.0	9.14 E-7
68.0	4.15 E-8
69.0	8.84 E-8
70.0	9.53 E-8
71.0	5.56 E-8
72.0	2.17 E-8
73.0	6.83 E-7
74.0	2.21 E-6
75.0	3.68 E-9
75.1	4.29 E-9
75.2	7.27 E-9

Example	ICso [menin/MLL-1)] (mol/l)
76.0	4.32 E-8
77.0	2.00 E-7
78.0	4.59 E-7
79.0	4.41 E-7
80.0	2.01 E-7
81.0	9.94 E-7
82.0	6.90 E-6
83.0	9.79 E-6
84.0	2.75 E-6
85.0	3.12 E-7
86.0	8.94 E-6
87.0	4.97 E-6
88.0	2.87 E-7
89.0	1.03 E-6
90.0	9.62 E-8
91.0	2.04 E-6
92.0	4.48 E-7
93.0	3.10 E-7
94.0	1.10 E-6
95.0	9.03 E-7
96.0	8.83 E-7
97.0	1.03 E-6
98.0	8.82 E-7
99.0	6.64 E-6
100.0	1.09 E-6
101 .0	9.22 E-6
102.0	>1.70 E-5
103.0	7.40 E-6
104.0	2.96 E-9
105.0	1.47 E-7
106.0	1.69 E-5
107.0	8.13 E-8
108.0	3.58 E-6
109.0	7.14 E-6
110.0	5.61 E-7
111.0	6.52 E-9

Example	ICso [menin/MLL-1)] (mol/l)
112.0	2.1 1 E-8
113.0	5.49 E-6
114.0	1.84 E-7
115.0	6.75 E-7
116.0	4.85 E-8
117.0	2.90 E-8
118.0	1.26 E-7
119.0	4.37 E-7
120.0	7.07 E-8
121 .0	6.13 E-6
122.0	4.41 E-6
123.0	1.01 E-7
123.1	4.54 E-8
123.2	1.35 E-7
124.0	7.54 E-8
124.1	3.13 E-8
124.2	1.44 E-7
125.0	5.37 E-8
125.1	2.51 E-8
125.2	1.05 E-7
126.0	1.57 E-7
127.0	1.71 E-7
128.0	9.13 E-8
129.0	9.79 E-8
130.0	1.28 E-7
131 .0	2.80 E-7
132.0	1.85 E-6
133.0	2.98 E-6
134.0	3.10 E-7
135.0	1.67 E-7
136.0	2.61 E-8
137.0	3.00 E-8
138.0	2.99 E-8
139.0	2.74 E-8
140.0	6.56 E-8
141 .0	2.63 E-8

Example	ICso [menin/MLL-1)] (mol/l)
142.0	2.18 E-7
143.0	2.59 E-7
144.0	4.16 E-8
145.0	3.34 E-8
146.0	3.10 E-9
147.0	4.70 E-8
148.0	2.43 E-8
149.0	4.50 E-7
150.0	3.66 E-7
151 .0	2.55 E-8
152.0	6.39 E-9
153.0	8.39 E-6

4.2 Proliferation assays

Table 3 shows the results of the inhibition in proliferation assays performed in leukemia cell lines

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Table 3:

Example	IC_{50} [MV4-11] (mol/l)	IC_{50} [MOLM-13] (mol/l)
2.0	2.44 E-7	1.98 E-6
3.0	7.83 E-8	9.09 E-7
4.0	>3.00 E-6	>9.00 E-6
5.0	6.39 E-7	3.50 E-6
6.0	3.96 E-7	2.30 E-6
7.0	1.47 E-7	1.09 E-6
8.0	4.57 E-7	1.83 E-6
9.0	2.87 E-6	3.03 E-6
12.0	2.96 E-7	
12.1	9.11 E-8	6.96 E-7
13.0	1.72 E-6	1.13 E-5
14.0	9.53 E-7	8.97 E-6
15.0	2.91 E-7	4.01 E-6
15.1	> 2.80 E-6	8.45 E-6
15.2	> 3.00 E-6	> 9.00 E-6
16.0	1.68 E-6	1.34 E-5
17.0	> 5.00 E-6	
18.0	5.94 E-7	8.08 E-6
19.0	2.77 E-6	1.56 E-5
20.0	1.71 E-7	6.62 E-7
21.0	2.00 E-7	
22.0	8.56 E-8	4.70 E-7
22.1	4.54 E-8	6.88 E-7
22.2	7.82 E-8	1.07 E-6
23.0	5.02 E-8	4.54 E-7
23.1	1.78E-08	1.97 E-7
23.2	3.68 E-8	3.22 E-7
24.0	1.48 E-6	4.07 E-6
25.0	5.16 E-6	4.34 E-6

Example	ICso [MV4-1 1] (mol/l)	ICso [MOLM-1 3] (mol/l)
26.0	4.44 E-7	
28.0	2.15 E-7	5.26 E-7
29.0	4.02 E-8	3.15 E-7
34.0	2.01 E-6	
35.0	1.34 E-6	
36.0	1.55 E-6	
37.0	7.77 E-8	2.55 E-7
38.0	1.66 E-7	2.04 E-7
39.0	1.80 E-7	4.21 E-7
40.0	1.14 E-7	3.52 E-7
41.0	1.03 E-6	1.23 E-6
42.0	5.28 E-7	1.23 E-6
43.0	6.42 E-8	1.03 E-6
43.1	1.18 E-7	6.91 E-7
43.2	3.37 E-7	> 5.06 E-6
44.0	4.72 E-8	8.28 E-7
45.0	2.83 E-7	
46.0	8.24 E-8	1.01 E-6
47.0	4.20 E-8	5.80 E-7
47.1	5.99 E-7	2.62 E-6
47.2	2.25 E-7	1.10 E-6
48.0	> 3.00 E-6	8.92 E-6
49.0	4.24 E-8	6.05 E-7
50.0	1.60 E-6	> 9.00 E-6
51.0	> 2.70 E-6	1.09 E-6
52.0	1.48 E-7	1.13 E-6
53.0	5.41 E-7	
54.0	> 3.00 E-6	7.72 E-6
56.0	2.63 E-6	2.17 E-6
57.0	1.48 E-6	1.16 E-6
59.0	1.81 E-6	5.24 E-6
62.0	> 1.25 E-6	
63.0	> 3.00 E-6	5.44 E-6
64.0	> 3.00 E-6	9.00 E-6
65.0	> 3.00 E-6	2.85 E-6
66.0	> 3.00 E-6	3.01 E-6

Example	ICso [MV4-1 1] (mol/l)	ICso [MOLM-1 3] (mol/l)
67.0	> 3.00 E-6	3.50 E-6
68.0	5.89 E-7	3.09 E-6
69.0	> 1.70 E-6	7.81 E-6
70.0	2.09 E-6	4.62 E-6
71.0	1.37 E-6	2.94 E-6
72.0	6.16 E-7	2.14 E-6
73.0	> 3.00 E-6	3.60 E-6
75.0	7.52 E-8	2.81 E-7
75.1	3.92 E-8	5.34 E-7
75.2	9.11 E-8	1.05 E-6
76.0	1.69 E-7	
77.0	2.77 E-6	3.37 E-6
78.0	> 3.00 E-6	> 9.00 E-6
79.0	> 3.00 E-6	8.31 E-6
80.0	1.44 E-6	
81.0	> 3.00 E-6	> 9.00 E-6
85.0	> 3.00 E-6	6.40 E-6
87.0	> 5.00 E-6	
88.0	1.14 E-6	
89.0	> 5.00 E-6	
90.0	2.00 E-6	3.46 E-6
92.0	> 3.00 E-6	> 9.00 E-6
93.0	> 3.00 E-6	> 9.00 E-6
95.0	> 3.00 E-6	> 9.00 E-6
96.0	> 3.00 E-6	> 9.00 E-6
97.0	2.23 E-6	
98.0	> 3.00 E-6	> 9.00 E-6
102.0	> 1.25 E-6	> 5.00 E-6
104.0	8.38 E-8	2.05 E-7
105.0	> 3.00 E-6	6.70 E-6
107.0	> 1.60 E-6	> 5.00 E-6
110.0	2.83 E-6	4.76 E-6
111.0	1.88 E-8	3.99 E-7
112.0	3.38 E-7	1.57 E-6
114.0	> 3.00 E-6	6.18 E-6
115.0	> 3.00 E-6	3.77 E-6

Example	ICso [MV4-11] (mol/l)	ICso [MOLM-13] (mol/l)
116.0	> 3.00 E-6	8.75E-6
117.0	> 3.00 E-6	> 9.00 E-6
124.0	2.86 E-7	4.23 E-6
125.0	2.43 E-7	1.15 E-6
136.0	1.79 E-7	5.38 E-7
137.0	6.72 E-8	2.01 E-7
138.0	5.71 E-8	8.82 E-7
139.0	7.79 E-8	2.62 E-7
140.0	1.58 E-7	3.85 E-7
141 .0	3.86 E-8	1.39 E-7
147.0	8.52 E-7	5.81 E-6
151 .0	8.26 E-8	9.95 E-7

Table 4 shows the results of the inhibition in proliferation assays performed in prostate and breast cancer cell lines (IC50 is the concentration for 50% of maximal inhibition of cell proliferation)

Table 4:

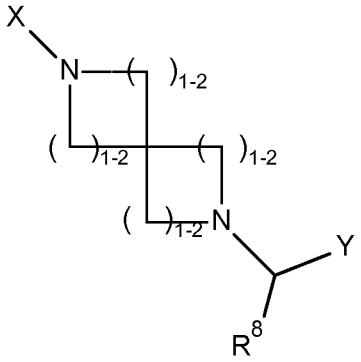
Example	IC_{50} [LAPC-4] (mol/l)	IC_{50} [LNCaP] (mol/l)	IC_{50} [MCF7] (mol/l)	IC_{50} [MDA-MB-468] (mol/l)
2.0	4.12 E-6	2.84 E-6	4.47 E-6	3.27 E-6
3.0	> 1.00 E-5	>6.50 E-6		>6.30 E-6
5.0	6.88 E-6	3.02 E-6	4.76 E-6	4.56 E-6
6.0	3.19 E-6	1.99 E-6	2.72 E-6	1.34 E-6
7.0	> 1.00 E-5	6.11 E-6		
12.0	> 1.00 E-5	7.82 E-6		5.53 E-6
12.1	> 1.00 E-5	8.60 E-6	3.87 E-6	> 1.00 E-5
13.0	> 1.00 E-5	> 1.00 E-5		> 1.00 E-5
14.0	> 1.00 E-5	> 1.00 E-5	> 1.00 E-5	> 1.00 E-5
15.0	> 1.00 E-5	> 6.50 E-6		6.05 E-6
16.0	> 1.00 E-5	> 1.00 E-5		> 1.00 E-5
20.0	7.80 E-6	2.71 E-6		2.53 E-6
21.0	> 1.00 E-5	> 1.00 E-5		> 6.50 E-6
22.0	9.89 E-6	3.01 E-6		2.89 E-6

Example	ICso [LAPC-4] (mol/l)	ICso [LNCaP] (mol/l)	ICso [MCF7] (mol/l)	ICso [MDA-MB-468] (mol/l)
22.1	6.1 1 E-6	3.10 E-6	6.66 E-6	4.57 E-6
22.2	4.94 E-6	3.67 E-6	2.41 E-6	4.32 E-6
23.0	> 1.00 E-5	> 6.30 E-6		6.61 E-6
23.1	> 1.00 E-5	4.75 E-6	6.99 E-6	> 6.50 E-6
23.2	> 1.00 E-5	9.58 E-6	2.50 E-6	5.60 E-6
26.0	> 1.00 E-5	8.55 E-6		> 1.00 E-5
28	7.22 E-6	3.94 E-6	3.53 E-6	5.27 E-6
29	> 1.00 E-5	2.59 E-6	3.82 E-6	5.26 E-6
34	9.73 E-6	5.1 1 E-6	3.40 E-6	3.99 E-6
37.0	> 6.50 E-6	> 6.00 E-6	> 1.00 E-5	6.20 E-6
38.0	6.94 E-6	5.1 1 E-6	> 1.00 E-5	4.1 1 E-6
39.0	> 1.00 E-5	> 1.00 E-5	> 1.00 E-5	> 1.00 E-5
40.0	1.87 E-6	8.19 E-7		1.41 E-6
4 1.0	> 7.00 E-6	> 6.20 E-5	> 1.00 E-5	> 1.00 E-5
42.0	> 1.00 E-5	> 7.50 E-6		> 1.00 E-5
43.0	> 1.00 E-5	> 8.00 E-6		> 7.00 E-6
43.1	> 6.40 E-6	> 6.10 E-6		> 7.35 E-6
43.2	> 1.00 E-5	> 6.35 E-6	> 1.00 E-5	8.18 E-6
44.0	> 7.50 E-6	3.36 E-6		4.91 E-6
45.0	> 1.00 E-5	> 1.00 E-5		> 1.00 E-5
46.0	6.14 E-6	1.69 E-6		3.38 E-6
47.0	> 6.50 E-6	2.49 E-6		3.89 E-6
47.1	> 1.00 E-5	> 5.50 E-6	> 1.00 E-5	6.10 E-6
47.2	> 1.00 E-5	> 6.50 E-6		> 1.00 E-5
49.0	6.67 E-6	6.64 E-6	> 7.30 E-6	4.73 E-6
52.0	4.41 E-6	5.77 E-6	4.70 E-6	3.79 E-6
72.0	> 6.50 E-5	7.13 E-6	5.14 E-6	> 1.00 E-5
75.0	3.10 E-6	1.49 E-6	> 1.00 E-5	2.01 E-6
75.1	> 1.00 E-5	8.71 E-6	> 1.00 E-5	> 1.00 E-5
75.2	3.35 E-6	1.81 E-6	1.68 E-6	2.83 E-6
76.0	5.14 E-6	3.39 E-6		3.77 E-6
104.0	2.73 E-6	8.61 E-7	3.78 E-6	1.86 E-6
107.0	> 1.00 E-5	> 1.00 E-5		> 1.00 E-5
111.0	> 1.00 E-5	> 4.00 E-6	> 1.00 E-5	> 5.50 E-6
112.0	6.08 E-6	3.32 E-6	4.20 E-6	4.39 E-6

Example	ICso [LAPC-4] (mol/l)	ICso [LNCaP] (mol/l)	ICso [MCF7] (mol/l)	ICso [MDA-MB-468] (mol/l)
136	> 1.00 E-5	6.99 E-6		
137	> 1.00 E-5	> 1.00 E-5		
152	5.49 E-6	3.71 E-6		

CLAIMS

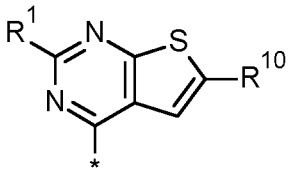
1. A compound of general formula (I):



(I)

in which:

X represents a group selected from: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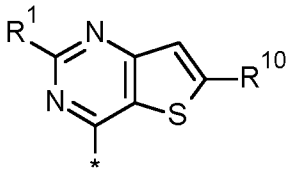
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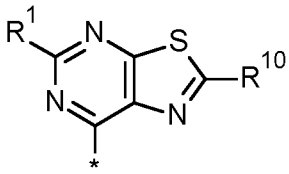
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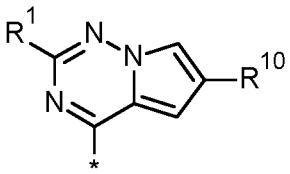
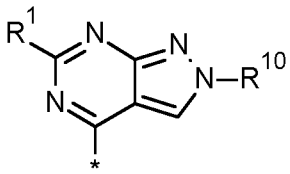
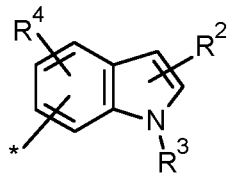


or
,

wherein * indicates the point of attachment of said group with the rest of the molecule;

Y represents a group


,

wherein * indicates the point of attachment of said group with the rest of the molecule;

R^1 represents hydrogen or methyl;

R^2 represents hydrogen, Ci-C_4-hydroxyalkyl, -CN, -$CONH_2$ or -CO2R ^{9};

R^3 represents hydrogen, Ci-C_4-alkyl, Ci-C_4-haloalkyl, C2-C_4-hydroxyalkyl, -C2-C_4-alkylen-NR^6R^7, -CO2R ^{9} or -Ci-C_2-alkylen-R ^{5};

R^4 represents hydrogen, hydroxy, halogen, methyl or methoxy;

R^5 represents -CO2R ^{9}, -CONR ^{6}R^7, 4- to 6-membered heterocycloalkyl optionally substituted with -CO2R ^{9}, phenyl or 5-membered heteroaryl,
wherein said phenyl group is optionally substituted, one or more times, independently from each other, with hydroxy, halogen, cyano, Ci-**C3** -alkyl, Ci-**C3** -haloalkyl, Ci-**C3** -alkoxy or Ci-**C3** -haloalkoxy and said 5-membered heteroaryl is optionally substituted with Ci-**C4** -alkyl;

R^6 and R^7 are the same or different and represent, independently from each other, hydrogen, Ci-**C4** -alkyl, **C 3**-C6 -cycloalkyl, Ci-**C4** -haloalkyl or
together with the nitrogen atom to which they are attached form a 4- to 6-membered nitrogen containing heterocyclic ring, said ring optionally containing one additional heteroatom selected from O, S, NH, NR^a in which R^a represents a **C1-C4-**alkyl or Ci-**C4** -haloalkyl group;

R^8 represents hydrogen or Ci-**C4** -alkyl;

R^9 represents hydrogen or Ci-**C4** -alkyl;

R^{10} represents Ci-**C4** -alkyl, Ci-**C4** -haloalkyl, methoxy-Ci-**C3** -alkyl, methylsulfanylmethyl, methylsulfinylmethyl, methylsulfonylmethyl, S-methylsulfonimidoyl-methyl, -CH2-CO2R ^{11} or -CH$_2$-CONR ^{12}R^{13};

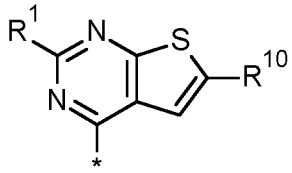
R^{11} represents hydrogen or Ci-**C4** -alkyl;

R^{12}, R^{13} represent, independently from each other, hydrogen, Ci-**C4** -alkyl, **C 3**-C6 -cycloalkyl, Ci-C $_4$-haloalkyl, C$_2$-C$_3$-hydroxyalkyl, tert-butyl-O-C(O)-, -(CO)-Ci-C $_3$-alkyl, -(S0 $_2$)-Ci-C $_3$-alkyl, -(S0 $_2$)-phenyl,
wherein said phenyl group is optionally substituted, one or more times, independently from each other, with hydroxy, halogen, cyano, Ci-**C3** -alkyl, Ci-**C3** -haloalkyl, Ci-**C3** -alkoxy or Ci-**C3** -haloalkoxy, or
together with the nitrogen atom to which they are attached form a 4- to 6-membered nitrogen containing heterocyclic ring, said ring optionally containing one additional heteroatom selected from O, S, NH, NR^a in which R^a represents a **C1-C4-**alkyl or Ci-**C4** -haloalkyl group and optionally substituted with an oxo group;

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

2. The compound according to claim 1, wherein:

X represents a group selected from: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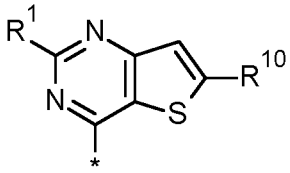
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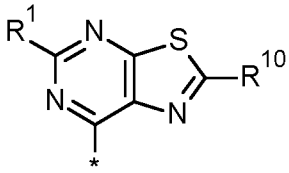
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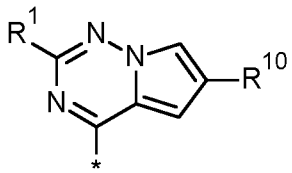
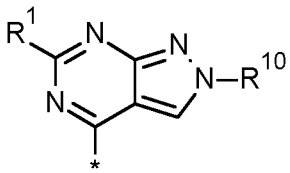
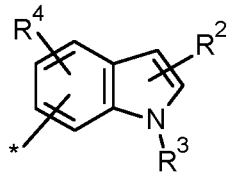


or
,

wherein * indicates the point of attachment of said group with the rest of the molecule;

Y represents a group


,

wherein * indicates the point of attachment of said group with the rest of the molecule;

R^1 represents hydrogen or methyl;

R^2 represents hydrogen, Ci-C_3-hydroxyalkyl, -CN, -$CONH_2$ or -$CO2R^9$;

R^3 represents hydrogen, methyl, Ci-C_3-haloalkyl, C_2-C_3-hydroxyalkyl, -CH_2-CH_2-NR^6R^7, -CO_2R^9 or -Ci-C_2-alkylen-R^5;

R^4 represents hydrogen, methyl or methoxy;

R^5 represents -CO_2R^9, -$CONH_2$, phenyl, pyrazolyl, methylpyrazolyl or 4- to 6-membered heterocycloalkyl;

R^6 and R^7 are the same or different and represent, independently from each other, hydrogen, Ci-C4-alkyl or
together with the nitrogen atom to which they are attached form a
4- to 6-membered nitrogen containing heterocyclic ring, said ring optionally containing one additional heteroatom selected from O, S, NH, NR^a in which R^a represents a C1-C4-alkyl or Ci-C4-haloalkyl group;

R^8 represents hydrogen or methyl;

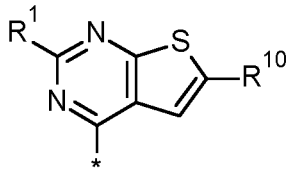
R^9 represents hydrogen or methyl;

R^{10} represents ethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2,2-difluoropropyl, methoxyethyl, methylsulfanylmethyl, methylsulfinylmethyl, methylsulfonylmethyl, S-methylsulfonimidoyl-methyl, -CH2-CO2CH3 or $-CH_2-CONH_2$;

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

3. The compound according to claim 1 or 2, wherein:

X represents a group selected from: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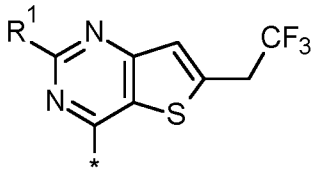
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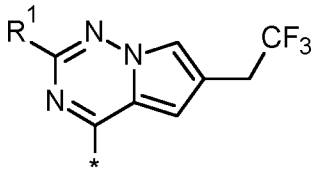
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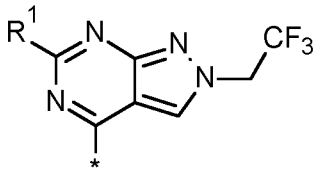
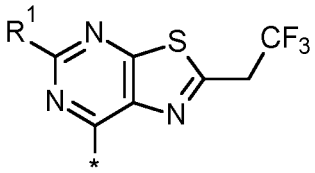
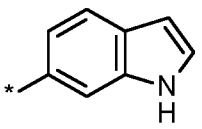


or ,

wherein * indicates the point of attachment of said group with the rest of the molecule;

Y represents a group selected from: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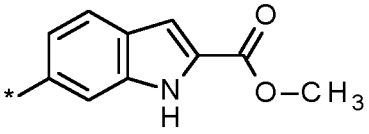
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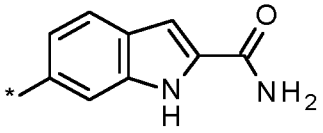
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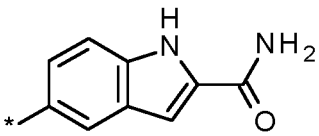
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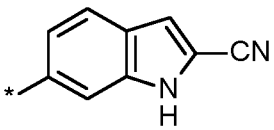
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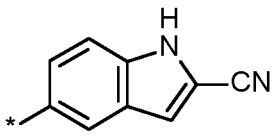
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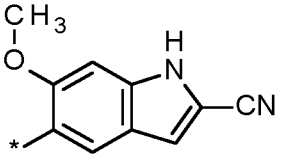
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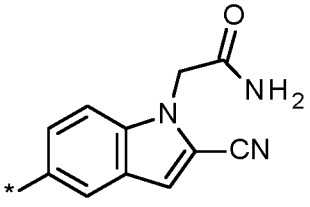
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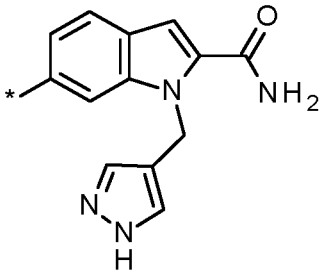
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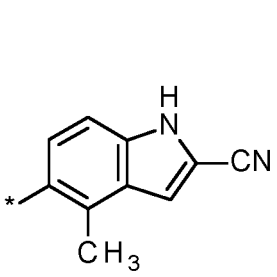
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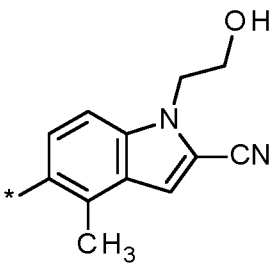
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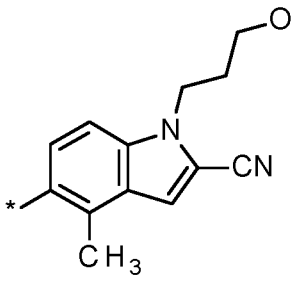
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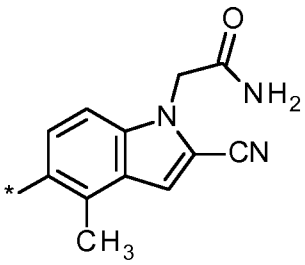
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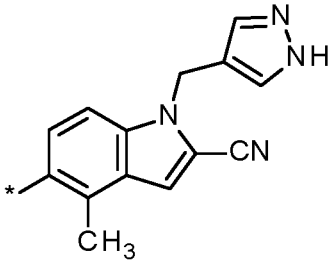
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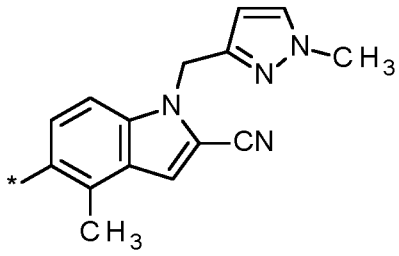
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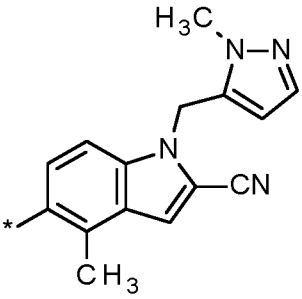
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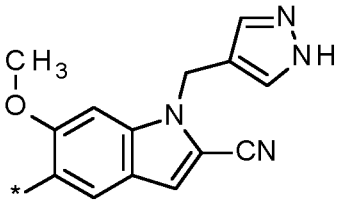
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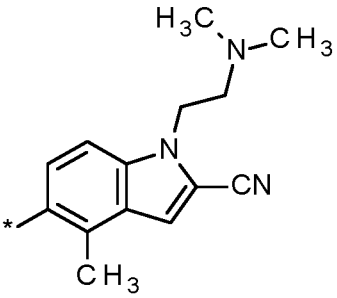
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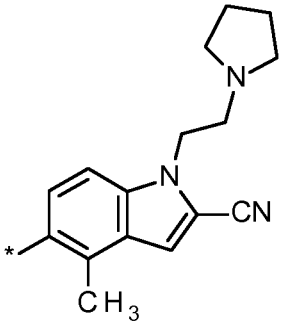
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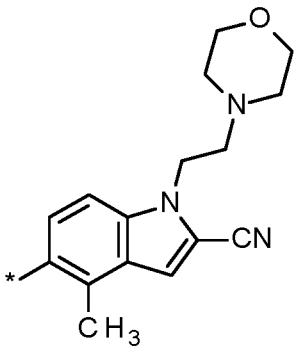
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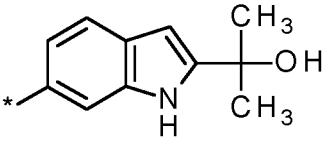
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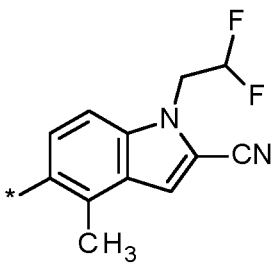
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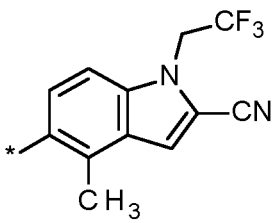
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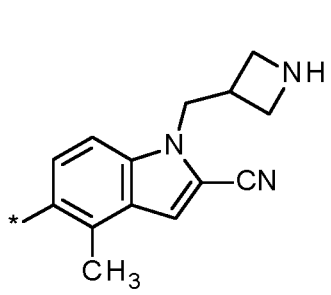
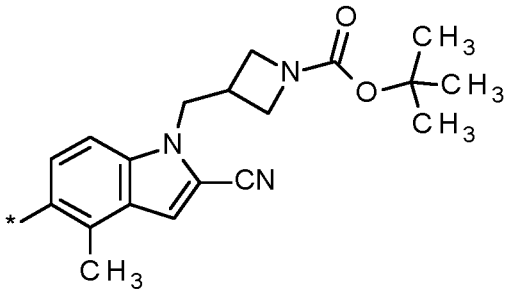
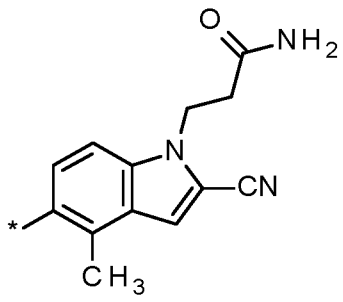
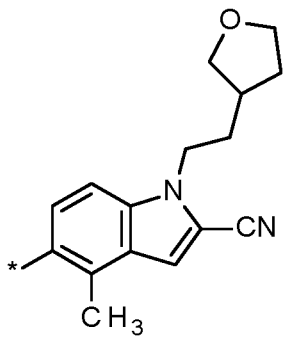
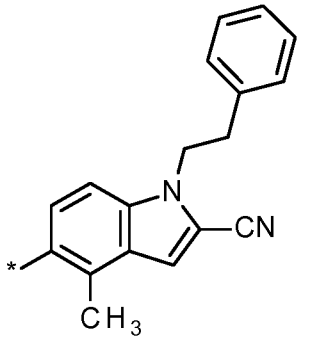
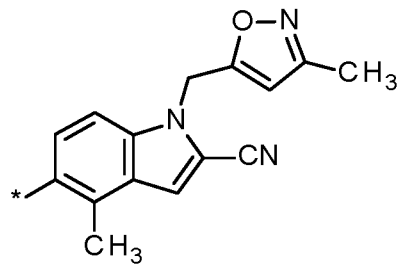
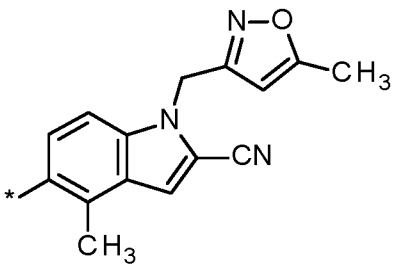
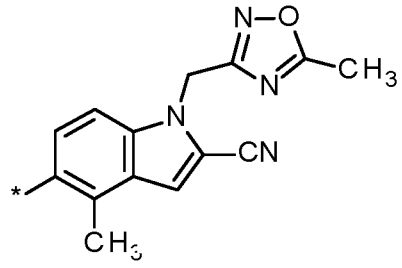
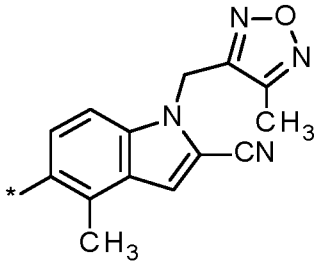










or ,

wherein: * indicates the point of attachment of said group with the rest of the molecule;

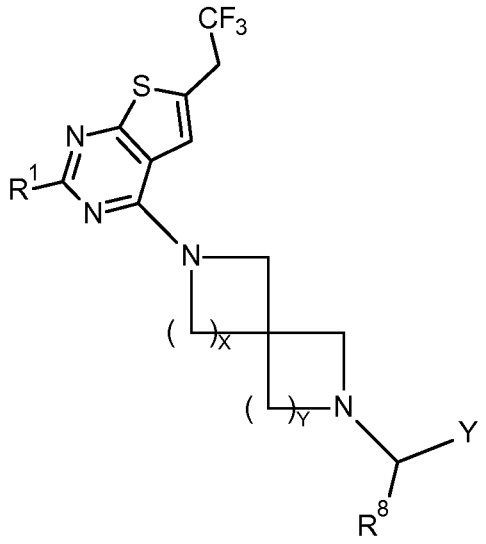
R^1 represents hydrogen or methyl;

R^8 represents hydrogen;

R^{10} represents ethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2,2-difluoropropyl, methoxyethyl, methylsulfanylmethyl, methylsulfinylmethyl, methylsulfonylmethyl, S-methylsulfonimidoyl-methyl, -CH2-CO2CH3 or $-CH_2-CONH_2$;

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

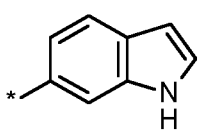
4. The compound according to claim 1, 2 or 3 of general formula (Ia):



(Ia)

in which:

Y represents a group selected from: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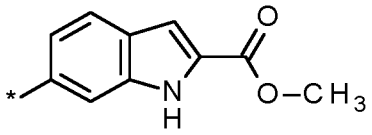
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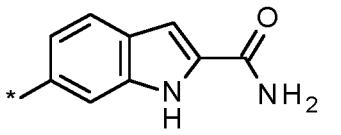
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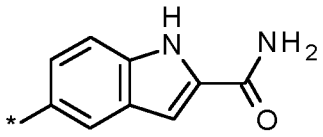
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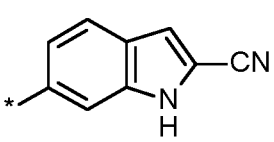
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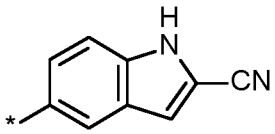
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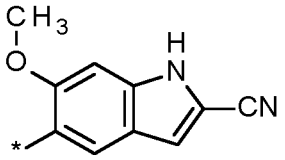
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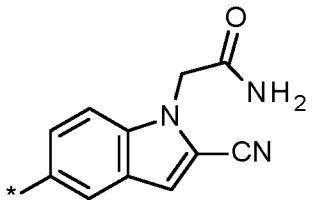
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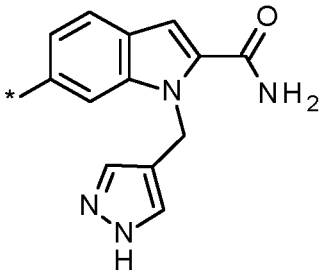
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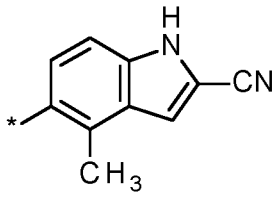
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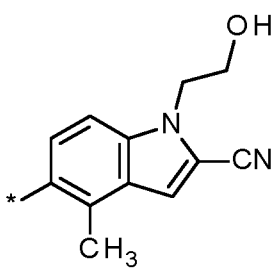
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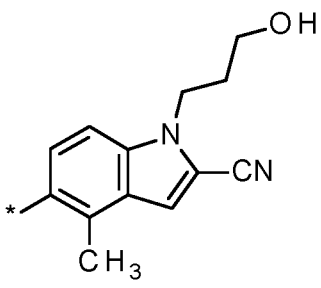
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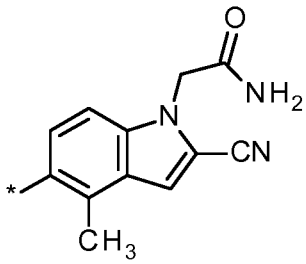
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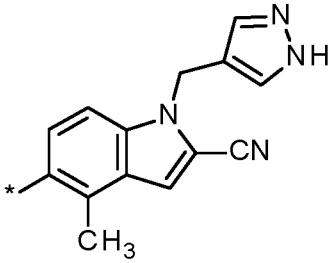
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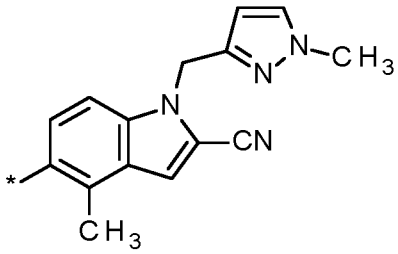
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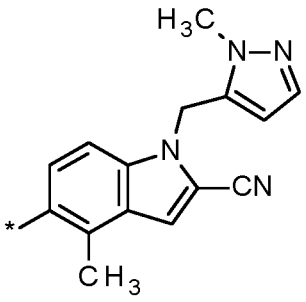
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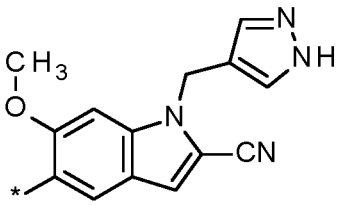
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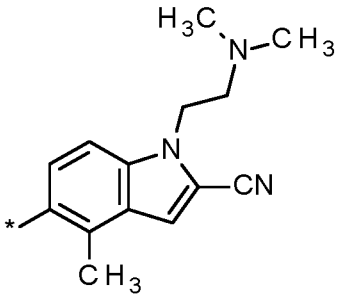
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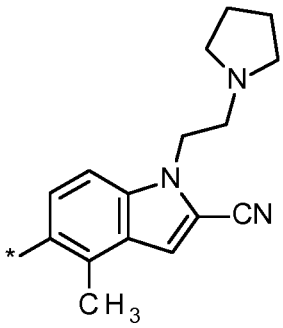
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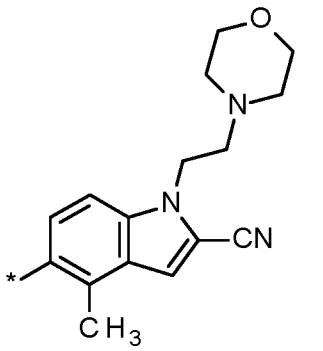
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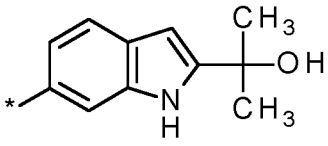
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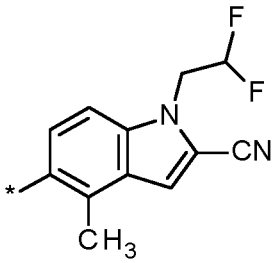
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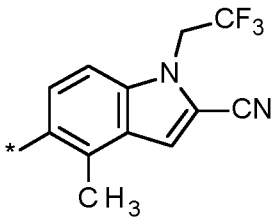
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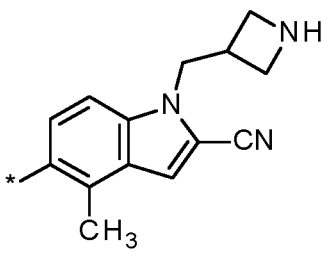
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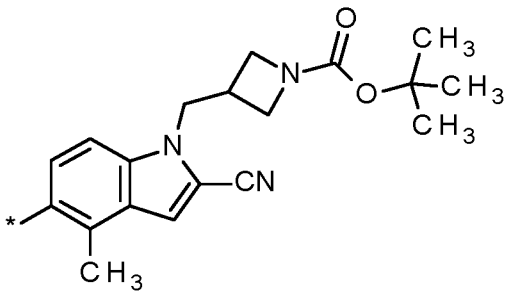
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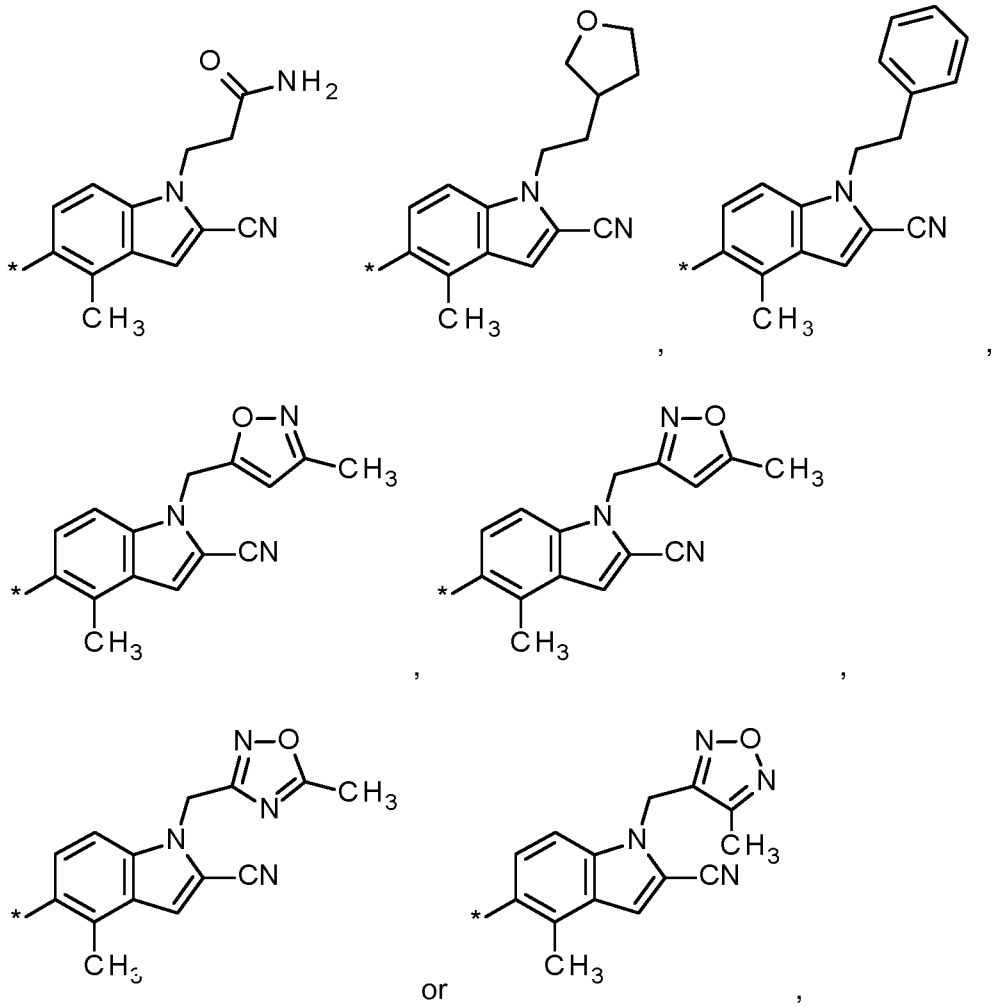


wherein: * indicates the point of attachment of said group with the rest of the molecule;

R^1 represents hydrogen or methyl;

R^8 represents hydrogen or methyl;

x represents 1 or 2;

y represents 1 or 2,

wherein at least one of x and y represent 2;

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

5. The compound according to claim 1, 2, 3 or 4 which is selected from the group consisting of:

5-{[7-(6-ethylthieno[2,3-d]pyrimidin-4-yl)-2,7-diazaspiro[3.5]non-2-yl]methyl}-4-methyl-1 H-indole-2-carbonitrile;

6-({6-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,6-diazaspiro[3.4]oct-2-yl}methyl)-1 H-indole-2-carbonitrile;

4-methyl-5-({2-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,6-diazaspiro[3.4]oct-6-yl}methyl)-1H-indole-2-carbonitrile;

4-methyl-5-({6-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,6-diazaspiro[3.3]hept-2-yl}methyl)-1H-indole-2-carbonitrile;

4-methyl-5-({6-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,6-diazaspiro[3.4]oct-2-yl}methyl)-1H-indole-2-carbonitrile;

4-methyl-5-({7-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}methyl)-1H-indole-2-carbonitrile;

6-({2-[6-(2,2,2-trifluoroethyl)thieno[2>d]pyrimM n-4-yl]-2,6-diazaspiro[3.4]oct-6-yl}methyl)-1H-indole-2-carbonitrile;

6-({2-[6-(2,2,2-trifluoroethyl)thieno[2>d]pyrimM n-4-yl]-2,6-diazaspiro[3.4]oct-6-yl}methyl)-1H-indole-2-carboxamide;

5-{[6-(6-ethylthieno[2,3-d]pyrimidin-4-yl)-2,6-diazaspiro[34]oct-2-yl]methyl}-4-methyl-1 H-indole-2-carbonitrile;

6-({6-[2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,6-diazaspiro[3.4]oct-2-yl}methyl)-1H-indole-2-carbonitrile;

4-methyl-5-({6-[2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,6-diazaspiro[3.4]oct-2-yl}methyl)-1H-indole-2-carbonitrile;

6-({7-[2-methyl-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carboxamide;

6-({(5S)-7-[2-methyl-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2J-diazaspiro[44]non-^ -yl}methyl)-1H-indole-2-carboxamide;

6-({(5R)-7-[2-methyl-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2J-diazaspiro[44]non-2-yl}methyl)-1H-indole-2-carboxamide;

4-methyl-5-({2-[2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,6-diazaspiro[3.4]oct-6-yl}methyl)-1H-indole-2-carbonitrile;

4-methyl-5-({2-[2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2J-diazaspiro[3.5]non-7-yl}methyl)-1H-indole-2-carbonitrile;

4-methyl-5-({7-[2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2J-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carbonitrile;

6-({2-[2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1H-indole-2-carbonitrile;

6-({2-[2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1H-indole-2-carboxamide;

6-({7-[2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carbonitrile;

6-({2-[2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,6-diazaspiro[3.4]oct-6-yl}methyl)-1H-indole-2-carbonitrile;

6-({7-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyri midin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carbonitrile;

5-({7-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrim idin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carboxamide;

4-methyl-5-({7-[6-(2,2 ,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carbonitrile;

4-methyW-({(5S)-7-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carbonitrile;

4-methyW-({(5R)-7-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carbonitrile;

6-({7-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin^-yl]-2J<liazaspiro[44]non-2-yl}methyl)-1 H-indole-2-carboxamide;

6-({(5S)-7-[6-(2 ,2,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carboxamide;

6-({(5R)-7-[6-(2 ,2,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carboxamide;

6-{[7-(6-ethylthieno[2,3-d]pyrimidin-4-yl)-2J-diazaspiro[3.5]non-2-yl]methyl}-1 H-indole-2-carbonitrile;

6-{[7-(6-ethylthieno[2,3-d]pyrimidin-4-yl)-2J-diazaspiro[3.5]non-2-yl]methyl}-1 H-indole-2-carboxamide;

6-({2-[6-(2 ,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2J-diazaspiro[3.5]non-7-yl}methyl> 1H-indole-2-carboxamide;

5-({2-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimi din-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1H-indole-2-carboxamide;

6-({2-[6-(2,2 ,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2J-diazaspiro[3.5]non-7-yl}methyl> 1H-indole-2-carbonitrile;

4-methyl-5-({2-[6-(2,2 ,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carbonitrile;

4-{7-[(1-methyl-1 H-indol-6-yl)methyl]-2 ,7-diazaspiro[3.5]non-2-yl}-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidine;

6-({6-[6-(2,2,2-trifluoroethyl)thieno[2>d]pyrimM n-4-yl]-2,6-diazaspiro[3.4]oct-2-yl}methyl)-1H-indole-2-carboxamide;

4-[2-(1 H-indol-6-ylmethyl)-2,6-diazaspiro[3.4]oct-6-yl]-6-(2 ,2,2-trifluoroethyl)thieno[2,3-d]pyrimidine;

4-{2-[(1 -methyl-1 H-indol-6-yl)methyl]-2 ,6-diazaspiro[3.4]oct-6-yl}-6-(2 ,2,2-trifluoroethyl)thieno[2,3-d]pyrimidine;

4-[7-(1 H-indol-6-ylmethyl)-2,7-diazaspiro[4.4]non-2-yl]-6-(2 ,2,2-trifluoroethyl)thieno[2,3-d]pyrimidine;

2-[2-cyano-4-methyl-5-({6-[6-(2,2 ,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,6-diazaspiro[3.4]oct-2-yl}methyl)-1 H-indol-1 -yl]acetamide;

2-[2-cyano-4-methyl-5-({7-[6-(2 ,2,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}methyl)-1 H-indol-1 -yl]acetamide;

4-methyl^-({7-[2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin^-yl]-2J-diazaspiro[44]non-2-yl}methyl)-1 H-indole-2-carbonitrile

4-methyl-5-({(5S)-7-[2-(2,2 ,2-trifluoroethyl)-2H-pyrazolo[3 ,4-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carbonitrile

4-methyl-5-({(5R)-7-[2-(2,2 ,2-trifluoroethyl)-2H-pyrazolo[3 ,4-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carbonitrile

4-methyl^-({7-[2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carbonitrile

1-(2-hydroxyethyl)-4-methyl-5-({2-[6-(2 ,2,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carbonitrile

1-(3-hydroxypropyl)-4-methyl-5-({2-[6-(2 ,2,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carbonitrile

4-methyl-1-[2-(morpholin-4-yl)ethyl]-5-({2-[6-(2,2 ,2-trifluoroethyl)thieno[2,3-d]pyrimidin -4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carbonitrile

4-methyl-1 -[(1 -methyl-1 H-pyrazol-3-yl)methyl]-5-({2-[6-(2 ,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carbonitrile

1-[2-(dimethylamino)ethyl]-4-methyl-5-({2-[6-(2,2 ,2-trifluoroethyl)thieno[2,3-d]pyrimi din-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carbonitrile

4-methyl-1-[2-(pyrrolidin-1-yl)ethyl]-5-({2-[6-(2,2 ,2-trifluoroethyl)thieno[2,3-d]pyrimidin -4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carbonitrile

6-({(5S)-7-[6-(2,2-difluoroethyl)thieno[2,3-d]pyrimidin^-yl]-2J-diazaspiro[44]non-2-yl}methyl)-1H-indole-2-carboxamide

6-({7-[6-(2,2-difluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2J-diazaspiro[44]non-2-yl}methyl)-1 H-indole-2-carboxamide

6-({(5S)-7-[6-(2,2-difluoroethyl)thieno[2,3-d]pyrimidin^-yl]-2J-diazaspiro[44]non-2-yl}methyl)-1H-indole-2-carboxamide

6-({(5R)-7-[6-(2,2-difluoroethyl)thieno[2,3-d]pyrimidin^-yl]-2J-diazaspiro[44]non-2-yl}methyl)-1H-indole-2-carboxamide

6-({7-[6-(2,2-difluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2J-diazaspiro[44]non-2-yl}methyl)-1 H-indole-2-carboxamide

6-(2,2-difluoroethyl)-4-[7-(1 H-indol-6-ylmethyl)-2 ,7-diazaspiro[4.4]non-2-yl]thieno[2,3-d]pyrimidine

5-({7-[6-(2,2-difluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2J-diazaspiro[44]non-2-yl}methyl)-1 H-indole-2-carboxamide

6-({7-[6-(2,2-difluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2J-diazaspiro[44]non-2-yl}m ethyl)-1H-indole-2-carbonitrile

5-({7-[6-(2,2-difluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2J-diazaspiro[44]non-2-yl}methyl)-4-methyl-1 H-indole-2-carbonitrile

5-({(5S)-7-[6-(2,2-difluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2J-diazaspiro[44]non-2-yl}methyl> 4-methyl-1 H-indole-2-carbonitrile

5-({(5R)-7-[6-(2,2-difluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2J-diazaspiro[44]non-2-yl}methyl)-4-methyl-1 H-indole-2-carbonitrile

5-({7-[6-(2,2-difluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2J-diazaspiro[44]non-2-yl}methyl)-4-methyl-1 H-indole-2-carbonitrile

5-({7-[6-(2,2-difluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2J-diazaspiro[44]non-2-yl}methyl)-4-methyl-1 H-indole-2-carbonitrile

5-({7-[6-(2,2-difluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2J-diazaspiro[44]non-2-yl}methyl)-6-methoxy-1-(1 H-pyrazol-4-ylmethyl)-1 H-indole-2-carbonitrile

6-({8-[6-(2,2 ,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,8-diazaspiro[4.5]dec-2-yl}methyl)- 1H-indole-2-carboxamide

5-({8-[6-(2,2,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,8-diazaspiro[4.5]dec-2-yl}methyl)- 1H-indole-2-carboxamide

6-({8-[6-(2,2,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,8-diazaspiro[4.5]dec-2-yl}methyl)- 1H-indole-2-carbonitrile

4-methyl-5-({8-[6-(2,2 ,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,8-diazaspiro[4.5]dec-2-yl}methyl)-1 H-indole-2-carbonitrile

2-(1H-indol-6-ylmethyl)-8-[6-(2 ,2,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,8-diazaspiro[4.5]decane

6-({9-[6-(2,2,2-trifluoroethyl)thieno[2>d]pyrim^ din-4-yl]-3,9-diazaspiro[5.5]undec-3-yl}methyl)-1H-indole-2-carboxamide

5-({9-[6-(2,2,2-trifluoroethyl)thieno[2>d]pyrim^ din-4-yl]-3,9-diazaspiro[5.5]undec-3-yl}methyl)-1H-indole-2-carboxamide

6-({9-[6-(2,2,2-trifluoroethyl)thieno[2>d]pyrim^ din-4-yl]-3,9-diazaspiro[5.5]undec-3-yl}methyl)-1H-indole-2-carbonitrile

4-methyl-5-({9-[6-(2,2 ,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-3,9-diazaspiro[5.5]undec-3-yl}methyl)-1 H-indole-2-carbonitrile

3-(1H-indol-6-ylmethyl)-9-[6-(2 ,2,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-3,9-diazaspiro[5.5]undecane

6-({6-[6-(2,2 ,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,6-diazaspiro[3.3]hept-2-yl}methy0 - 1H-indole-2-carbonitrile

6-({6-[6-(2,2 ,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,6-diazaspiro[3.3]hept-2-yl}methy0 - 1H-indole-2-carboxamide

4-{6-[(1-methyl-1 H-indol-6-yl)methyl]-2,6-diazaspiro[3.3]hept-2-yl}-6-(2 ,2,2-trifluoroethyl)thieno[2,3-d]pyrimidine

5-({6-[6-(2,2,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,6-diazaspiro[3.3]hept-2-yl}methy0 - 1H-indole-2-carboxamide

6-({2-[6-(2,2,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,8-diazaspiro[4.5]dec-8-yl}methyl)- 1H-indole-2-carboxamide

5-({2-[6-(2,2,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,8-diazaspiro[4.5]dec-8-yl}methyl)- 1H-indole-2-carboxamide

6-({2-[6-(2,2,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,8-diazaspiro[4.5]dec-8-yl}methyl)- 1H-indole-2-carbonitrile

4-methyl-5-({2-[6-(2,2 ,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,8-diazaspiro[4.5]dec-8-yl}methyl)-1 H-indole-2-carbonitrile

8-(1 H-indol-6-ylmethyl)-2-[6-(2 ,2,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,8-diazaspiro[4.5]decane

4-methyl-5-({7-[6-(2,2 ,2-trifluoroethyl)thieno[3 ,2-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carbonitrile

5-({7-[6-(2,2,2-trifluoroethyl)thieno[3,2-d]pyrim idin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carboxamide

5-({7-[6-(2,2,2-trifluoroethyl)thieno[3,2-d]pyrimidin-4-yl]-2J-diazaspiro[44]non-2-yl}methyl)-1 H-indole-2-carbonitrile

6-({7-[6-(2,2,2-trifluoroethyl)thieno[3,2-d]pyrimidin-4-yl]-2J-diazaspiro[44]non-2-yl}methyl)-1 H-indole-2-carbonitrile

6-({7-[6-(2,2,2-trifluoroethyl)thieno[3,2-d]pyrimidin-4-yl]-2J-diazaspiro[44]non-2-yl}methyl)-1 H-indole-2-carboxamide

4-methyl-5-({6-[2-methyl-6-(2 ,2,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,6-diazaspiro[3.4]oct-2-yl}methyl)-1 H-indole-2-carbonitrile

6-({6-[2-methyl-6-(2,2 ,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,6-diazaspiro[3.4]oct-2-yl}methyl)-1 H-indole-2-carboxamide

methyl 6-({7-[6-(2,2,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carboxylate

methyl 6-({(5S)-7-[6-(2,2 ,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carboxylate

methyl 6-({(5R)-7-[6-(2,2 ,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carboxylate

methyl 6-({7-[6-(2,2,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carboxylate

methyl 6-({(5R)-7-[6-(2,2 ,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carboxylate

6-methoxy-5-({7-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin^-yl]-2J-diazaspiro[44]non-2-yl}methyl)-1 H-indole-2-carbonitrile

6-methoxy-1-(1 H-pyrazol-4-ylmethyl)-5-({7-[6-(2,2 ,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yO -2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carbonitrile

6-({7-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin^-yl]-2J<liazaspiro[44]non-2-yl}methyl)-1 H-indole-2-carboxylic acid

4-[7-(1 H-indol-6-ylmethyl)-2,7-diazaspiro[4.4]non-2-yl]-6-(2 ,2,2-trifluoroethyl)pyrrolo[2,1-f][1 ,2,4]triazine

4-methyl-5-({7-[6-(2 ,2,2-trifluoroethyl)pyrrolo[2J-^[1 ,2,4]triazin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carbonitrile

5-({7-[6-(2 ,2,2-trifluoroethyl)pyrrolo[2J-^[1 ,2,4]triazin-4-yl]-2J-diazaspiro[44]non-2-yl}methyl)-1H-indole-2-carbonitrile

4-methyl-5-({6-[6-(2 ,2,2-trifluoroethyl)pyrrolo[2J-^[1 ,2,4]triazin-4-yl]-2,6-diazaspiro[3.4]oct-2-yl}methyl)-1 H-indole-2-carbonitrile

5-({6-[6-(2 ,2,2-trifluoroethyl)pyrrolo[2J-^[1 ,2,4]triazin-4-yl]-2,6-diazaspiro[34]oct-2-yl}methyl)-1H-indole-2-carbonitrile

6-({6-[6-(2,2 ,2-trifluoroethyl)pyrrolo[2J-^[1 ,2,4]triazin-4-yl]-2,6-diazaspiro[34]oct-2-yl}methyl)-1H-indole-2-carbonitrile

6-({7-[6-(2 ,2,2-trifluoroethyl)pyrrolo[2J-^[1 ,2,4]triazin-4-yl]-2J-diazaspiro[44]non-2-yl}methyl)-1H-indole-2-carbonitrile

5-({7-[6-(2,2 ,2-trifluoroethyl)pyrrolo[2J-^[1 ,2,4]triazin-4-yl]-2J-diazaspiro[3.5]non-2-yl}methyl)-1H-indole-2-carbonitrile

4-methyl-5-({7-[6-(2 ,2,2-trifluoroethyl)pyrrolo[2J-^[1 ,2,4]triazin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}methyl)-1 H-indole-2-carbonitrile

4-methyl-5-({2-[6-(2 ,2,2-trifluoroethyl)pyrrolo[2J-^[1 ,2,4]triazin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carbonitrile

5-({2-[6-(2,2 ,2-trifluoroethyl)pyrrolo[2J-^[1 ,2,4]triazin-4-yl]-2J-diazaspiro[3.5]non-7-yl}methyl)-1H-indole-2-carbonitrile

6-({(5R)-7-[6-(2 ,2,2-trifluoroethyl)pyrrolo[2 ,1-f][1 ,2,4]triazin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carboxamide

6-methoxy-5-({6-[2-methyl-6-(2 ,2,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,6-diazaspiro[3.4]oct-2-yl}methyl)-1 -(1 H-pyrazol-4-ylmethyl)-1 H-indole-2-carbonitrile

5-({7-[2-(2 ,2,2-trifluoroethyl)-2H-pyrazolo[3 ,4-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carbonitrile

6-({7-[2-(2 ,2,2-trifluoroethyl)-2H-pyrazolo[3 ,4-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carboxamide

5-({7-[2-(2 ,2,2-trifluoroethyl)-2H-pyrazolo[3 ,4-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carboxamide

4-[7-(1 H-indol-6-ylmethyl)-2J-diazaspiro^ 4.4]non-2-yl]-2-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidine

6-methoxy-5-({7-[2-(2 ,2,2-trifluoroethyl)-2H-pyrazolo[3 ,4-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carbonitrile

5-({2-[2-(2 ,2,2-trifluoroethyl)-2H-pyrazolo[3 ,4-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carbonitrile

6-({7-[6-methyl-2-(2,2 ,2-trifluoroethyl)-2H-pyrazolo[3 ,4-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carboxamide

5-({7-[6-methyl-2-(2,2 ,2-trifluoroethyl)-2H-pyrazolo[3 ,4-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carboxamide

6-({7-[6-methyl-2-(2,2 ,2-trifluoroethyl)-2H-pyrazolo[3 ,4-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carbonitrile

6-methoxy-5-({7-[6-methyl-2-(2 ,2,2-trifluoroethyl)-2H-pyrazolo[3 ,4-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carbonitrile

6-methoxy-1 -(1 H-pyrazol-4-ylmethyl)-5-({7-[2-(2 ,2,2-trifluoroethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carbonitrile

6-methoxy-5-({7-[6-methyl-2-(2 ,2,2-trifluoroethyl)-2H-pyrazolo[3 ,4-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 -(1 H-pyrazol-4-ylmethyl)-1 H-indole-2-carbonitrile

4-methyl-1-(1 H-pyrazol-4-ylmethyl)-5-({2-[6-(2,2 ,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yO -2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carbonitrile

1-(1H-pyrazol-4-ylmethyl)-6-({7-[6-(2 ,2,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carboxamide

2-[6-({7-[2-(2 ,2,2-trifluoroethyl)-2H-pyrazolo[3 ,4-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indol-1 -yl]acetamide

2-[2-cyano-5-({7-[2-(2,2 ,2-trifluoroethyl)-2H-pyrazolo[3 ,4-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indol-1 -yl]acetamide

1-(2-amino-2-oxoethyl)-6-({7-[2-(2,2 ,2-trifluoroethyl)-2H-pyrazolo[3 ,4-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carboxamide

2-[2-cyano-5-({2-[2-(2,2 ,2-trifluoroethyl)-2H-pyrazolo[3 ,4-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indol-1 -yl]acetamide

2-(2-cyano-5-{[7-(6-ethylthieno[2,3-d]pyrimidin-4-yl)-2J-diazaspiro[3.5]non-2-yl]methyl}-4-methyl-1 H-indol-1 -yl)acetamide

2-[2-cyano-4-methyl-5-({2-[6-(2,2 ,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indol-1 -yl]acetamide

2-[6-({7-[6-(2 ,2,2-trifluoroethyl)pyrrolo[2 ,1-f][1 ,2,4]triazin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indol-1 -yl]acetamide

4-methyl-1 -[(1 -methyl-1 H-pyrazol-5-yl)methyl]-5-({2-[6-(2 ,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carbonitrile

4-{7-[(1 R)-1-(1 H-indol-6-yl)ethyl]-2J-diazaspiro[44]non-2-yl}-6-(2 ,2,2-trifluoroethyl)thieno[2,3-d]pyrimidine

4-{7-[(1 R)-1-(1 H-indol-5-yl)ethyl]-2J-diazaspiro[44]non-2-yl}-6-(2 ,2,2-trifluoroethyl)thieno[2,3-d]pyrimidine

tert-butyl 4-{[2-cyano-4-methyl-5-({2-[6-(2 ,2,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indol-1 -yl]methyl}-1 H-pyrazole-1 -carboxylate

4-methyl-1-[3-(tetrahydro-2H-pyran-2-yloxy)propyl]-5-({2-[6-(2 ,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carbonitrile

4-methyl-1-[2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-5-({2-[6-(2 ,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carbonitrile

methyl (4-{7-[(2-cyano-4-methyl-1 H-indol-5-yl)methyl]-2,7-diazaspiro[4.4]non-2-yl}thieno[2,3-d]pyrimidin-6-yl)acetate

methyl (4-{(5R)-7-[(2-cyano-4-methyl-1 H-indol-5-yl)methyl]-2,7-diazaspiro[4.4]non-2-yl}thieno[2,3-d]pyrimidin-6-yl)acetate

methyl (4-{(5S)-7-[(2-cyano-4-methyl-1 H-indol-5-yl)methyl]-2,7-diazaspiro[4.4]non-2-yl}thieno[2,3-d]pyrimidin-6-yl)acetate

methyl 6-({7-[6-(2-methoxy-2-oxoethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carboxylate

methyl 6-({(5R)-7-[6-(2-methoxy-2-oxoethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carboxylate

methyl 6-({(5S)-7-[6-(2-methoxy-2-oxoethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carboxylate

methyl (4-{7-[(2-carbamoyl-1 H-indol-6-yl)methyl]-2,7-diazaspiro[4.4]non-2-yl}thieno[2,3-d]pyrimidin-6-yl)acetate

methyl (4-{(5R)-7-[(2-carbamoyl-1 H-indol-6-yl)methyl]-2,7-diazaspiro[4.4]non-2-yl}thieno[2,3-d]pyrimidin-6-yl)acetate

methyl (4-{(5S)-7-[(2-carbamoyl-1 H-indol-6-yl)methyl]-2,7-diazaspiro[4.4]non-2-yl}thieno[2,3-d]pyrimidin-6-yl)acetate

methyl (4-{7-[(2-carbamoyl-1 H-indol-5-yl)methyl]-2,7-diazaspiro[4.4]non-2-yl}thieno[2,3-d]pyrimidin-6-yl)acetate

methyl (4-{(5R)-7-[(2-carbamoyl-1 H-indol-5-yl)methyl]-2,7-diazaspiro[4.4]non-2-yl}thieno[2,3-d]pyrimidin-6-yl)acetate

methyl (4-{(5S)-7-[(2-carbamoyl-1 H-indol-5-yl)methyl]-2,7-diazaspiro[4.4]non-2-yl}thieno[2,3-d]pyrimidin-6-yl)acetate

methyl {4-[7-{[2-cyano-4-methyl-1 -(2,2,2-trifluoroethyl)-1 H-indol-5-yl]methyl}-2,7-diazaspiro[4.4]non-2-yl]thieno[2,3-d]pyrimidin-6-yl}acetate

methyl {4-[(5R)-7-{[2-cyano-4-methyl-1 -(2,2,2-trifluoroethyl)-1 H-indol-5-yl]methyl}-2,7-diazaspiro[4.4]non-2-yl]thieno[2,3-d]pyrimidin-6-yl}acetate

methyl {4-[(5S)-7-{[2-cyano-4-methyl-1 -(2,2,2-trifluoroethyl)-1 H-indol-5-yl]methyl}-2,7-diazaspiro[4.4]non-2-yl]thieno[2,3-d]pyrimidin-6-yl}acetate

2-(4-{7-[(2-cyano-4-methyl-1 H-indol-5-yl)methyl]-2,7-diazaspiro[4.4]non-2-yl}thieno[2,3-d]pyrimidin-6-yl)-N,N-dimethylacetamide

2-(4-{(5R)-7-[(2-cyano-4-methyl-1 H-indol-5-yl)methyl]-2,7-diazaspiro[4.4]non-2-yl}thieno[2,3-d]pyrimidin-6-yl)-N,N-dimethylacetamide

2-(4-{(5S)-7-[(2-cyano-4-methyl-1 H-indol-5-yl)methyl]-2,7-diazaspiro[4.4]non-2-yl}thieno[2,3-d]pyrimidin-6-yl)-N,N-dimethylacetamide

methyl 6-{[7-{6-[2-(dimethylamino)-2-oxoethyl]thieno[2,3-d]pyrimidin-4-yl}-2,7-diazaspiro[4.4]non-2-yl]methyl}-1 H-indole-2-carboxylate

methyl 6-{[(5R)-7-{6-[2-(dimethylamino)-2-oxoethyl]thieno[2,3-d]pyrimidin-4-yl}-2,7-diazaspiro[4.4]non-2-yl]methyl}-1 H-indole-2-carboxylate

methyl 6-{[(5S)-7-{6-[2-(dimethylamino)-2-oxoethyl]thieno[2,3-d]pyrimidin-4-yl}-2,7-diazaspiro[4.4]non-2-yl]methyl}-1 H-indole-2-carboxylate

4-methyl-5-({7-[2-(2,2 ,2-trifluoroethyl)[1 ,3]thiazolo[5,4-d]pyrimidin-7-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carbonitrile

4-methyl-5-({(5R)-7-[2-(2,2 ,2-trifluoroethyl)[1 ,3]thiazolo[5,4-d]pyrimidin-7-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carbonitrile

4-methyl-5-({(5S)-7-[2-(2 ,2,2-trifluoroethyl)[1 ,3]thiazolo[5,4-d]pyrimidin-7-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carbonitrile

6-({7-[2-(2,2 ,2-trifluoroethyl)[1 ,3]thiazolo[5,4-d]pyrimidin-7-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carboxamide

6-({(5R)-7-[2-(2,2 ,2-trifluoroethyl)[1 ,3]thiazolo[5,4-d]pyrimidin-7-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carboxamide

6-({(5S)-7-[2-(2 ,2,2-trifluoroethyl)[1 ,3]thiazolo[5,4-d]pyrimidin-7-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carboxamidemethyl 6-({7-[2-(2,2,2-trifluoroethyl)[1 ,3]thiazolo[5,4-d]pyrimidin-7-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carboxylate

methyl 6-({(5R)-7-[2-(2,2 ,2-trifluoroethyl)[1 ,3]thiazolo[5,4-d]pyrimidin-7-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carboxylate

methyl 6-({(5S)-7-[2-(2,2,2-trifluoroethyl)[1 ,3]thiazolo[5,4-d]pyrimidin-7-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carboxylate

5-({7-[6-(2-methoxyethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-4-methyl-1 H-indole-2-carbonitrile

5-({(5R)-7-[6-(2-methoxyethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-4-methyl-1 H-indole-2-carbonitrile

5-({(5S)-7-[6-(2-methoxyethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-4-methyl-1 H-indole-2-carbonitrile

6-({7-[6-(2-methoxyethyl)thieno[2,3-d]pyrim idin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carboxamide

6-({(5R)-7-[6-(2-methoxyethyl)thieno[2,3-d]pyrimidin-4-yl]-2J-diazaspiro[44]non-2-yl}methyl)-1H-indole-2-carboxamide

6-({(5S)-7-[6-(2-methoxyethyl)thieno[2,3-d]pyrimidin-4-yl]-2J-diazaspiro[44]non-2-yl}methyl)-1H-indole-2-carboxamide

methyl 6-({7-[6-(2-methoxyethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carboxylate

methyl 6-({(5R)-7-[6-(2-methoxyethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carboxylate

methyl 6-({(5S)-7-[6-(2-methoxyethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1 H-indole-2-carboxylate

5-({7-[6-(2-methoxyethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-4-methyl-1 -(2,2,2-trifluoroethyl)-1 H-indole-2-carbonitrile

5-({(5R)-7-[6-(2-methoxyethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-4-methyl-1 -(2,2,2-trifluoroethyl)-1 H-indole-2-carbonitrile

5-({(5S)-7-[6-(2-methoxyethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-4-methyl-1 -(2,2,2-trifluoroethyl)-1 H-indole-2-carbonitrile

1-(2,2-difluoroethyl)-5-({7-[6-(2-methoxyethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-4-methyl-1 H-indole-2-carbonitrile

1-(2,2-difluoroethyl)-5-({(5R)-7-[6-(2-methoxyethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-4-methyl-1 H-indole-2-carbonitrile

1-(2,2-difluoroethyl)-5-({(5S)-7-[6-(2-methoxyethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-4-methyl-1 H-indole-2-carbonitrile

5-({2-[6-(2-methoxyethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-4-methyl-1 H-indole-2-carbonitrile

6-({2-[6-(2-methoxyethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carboxamide

methyl 6-({2-[6-(2-methoxyethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carboxylate

2-(4-{7-[(2-cyano-4-methyl-1 H-indol-5-yl)methyl]-2,7-diazaspiro[4.4]non-2-yl}thieno[2,3-d]pyrimidin-6-yl)acetamide

2-(4-{(5R)-7-[(2-cyano-4-methyl-1 H-indol-5-yl)methyl]-2,7-diazaspiro[4.4]non-2-yl}thieno[2,3-d]pyrimidin-6-yl)acetamide

2-(4-{(5S)-7-[(2-cyano-4-methyl-1 H-indol-5-yl)methyl]-2,7-diazaspiro[4.4]non-2-yl}thieno[2,3-d]pyrimidin-6-yl)acetamide

2-{4-[7-{[2-cyano-4-methyl-1-(2,2 ,2-trifluoroethyl)-1 H-indol-5-yl]methyl}-2,7-diazaspiro[4.4]non-2-yl]thieno[2,3-d]pyrimidin-6-yl}acetamide

2-{4-[(5R)-7-{[2-cyano-4-methyl-1-(2 ,2,2-trifluoroethyl)-1 H-indol-5-yl]methyl}-2,7-diazaspiro[4.4]non-2-yl]thieno[2,3-d]pyrimidin-6-yl}acetamide

2-{4-[(5S)-7-{[2-cyano-4-methyl-1-(2 ,2,2-trifluoroethyl)-1 H-indol-5-yl]methyl}-2,7-diazaspiro[4.4]non-2-yl]thieno[2,3-d]pyrimidin-6-yl}acetamide

4-methyl-1-(2-phenylethyl)-5-({2-[6-(2 ,2,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carbonitrile

4-methyl-1-[(5-methyl-1 ,2-oxazol-3-yl)methyl]-5-({2-[6-(2 ,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carbonitrile

4-methyl-1-[(5-methyl-1 ,2,4-oxadiazol-3-yl)methyl]-5-({2-[6-(2 ,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carbonitrile

4-methyl-1-{2-[tetrahydrofuran-3-yl]ethyl}-5-({2-[6-(2,2 ,2-trifluoroethyl)thieno[2,3-d]pyrimidi n-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carbonitrile

4-methyl-1-{2-[(3R)-tetrahydrofuran-3-yl]ethyl}-5-({2-[6-(2 ,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carbonitrile

4-methyl-1-{2-[(3S)-tetrahydrofuran-3-yl]ethyl}-5-({2-[6-(2 ,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carbonitrile

4-methyl-1-[(4-methyl-1 ,2,5-oxadiazol-3-yl)methyl]-5-({2-[6-(2 ,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carbonitrile

4-methyl-1-[(3-methyl-1 ,2-oxazol-5-yl)methyl]-5-({2-[6-(2 ,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carbonitrile

3-[2-cyano-4-methyl-5-({2-[6-(2 ,2,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indol-1 -yl]propanamide

tert-butyl 3-{[2-cyano-4-methyl-5-({2-[6-(2 ,2,2-trifluoroethyl)thieno[2 ,3-d]pyrimidin-4-yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indol-1 -yl]methyl}azetidine-1 -carboxylate

4-methyl-1-(2 ,2,2-trifluoroethyl)-5-({2-[6-(2 ,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-^ l]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carbonitrile

1-(2,2-difluoroethyl)-4-methyl-5-({2-[6-(2 ,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2 ,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carbonitrile

1-(azetidin-3-ylmethyl)-4-methyl-5-({2-[6-(2,2 ,2-trifluoroethyl)thieno[2,3-d]pyrimidin-^ -yl]-2,7-diazaspiro[3.5]non-7-yl}methyl)-1 H-indole-2-carbonitrile

6-{[7-{6-[(methylsulfonyl)methyl]thieno[2,3-d]pyrimidin-4-yl}-2 ,7-diazaspiro[4.4]non-2-yl]methyl}-1 H-indole-2-carboxamide

6-{[(5R)-7-{6-[(methylsulfonyl)methyl]thieno[2,3-d]pyrimidin-4-yl}-2J-diazaspiro[4.4]non-2-yl]methyl}-1 H-indole-2-carboxamide

6-{[(5S)-7-{6-[(methylsulfonyl)methyl]thieno[2,3-d]pyrimidin-4-yl}-2,7-diazaspiro[4.4]non-2-yl]methyl}-1 H-indole-2-carboxamide

6-({7-[6-(2,2-difluoropropyl)thieno[2,3-d]pyrimidin-4-yl]-2J-diazaspiro[44]non-2-yl}methyl)-1 H-indole-2-carboxamide

6-({(5R)-7-[6-(2,2-difluoropropyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carboxamide

6-({(5S)-7-[6-(2,2-difluoropropyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indole-2-carboxamide

4-methyl-5-{[7-(6-{[methylsulfinyl]methyl}thieno[2,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.4]non-2-yl]methyl}-1H-indole-2-carbonitrile

4-methyl-5-{[7-{6-[methylsulfonimidoyl)methyl]thieno[2,3-d]pyrimidin-4-yl}-2,7-diazaspiro[4.4]non-2-yl]methyl}-1H-indole-2-carbonitrile

4-methyl-5-{[7-{6-[(methylsulfanyl)methyl]thieno[2,3-d]pyrimidin-4-yl}-2,7-diazaspiro[4.4]non-2-yl]methyl}-1H-indole-2-carbonitrile

4-methyl-5-{[(5R)-7-{6-[(methylsulfanyl)methyl]thieno[2,3-d]pyrimidin-4-yl}-2J-diazaspiro[4.4]non-2-yl]methyl}-1H-indole-2-carbonitrile

4-methyl-5-{[(5S)-7-{6-[(methylsulfanyl)methyl]thieno[2,3-d]pyrimidin-4-yl}-2,7-diazaspiro[4.4]non-2-yl]methyl}-1H-indole-2-carbonitrile

2-[6-({7-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]non-2-yl}methyl)-1H-indol-2-yl]propan-2-ol

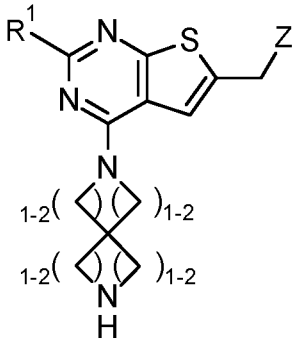
2-[6-({(5R)-7-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2J-diazaspiro[44]non-2-yl}methyl)-1H-indol-2-yl]propan-2-ol

2-[6-({(5S)-7-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2J-diazaspiro[44]non-2-yl}methyl)-1H-indol-2-yl]propan-2-ol

5-({6-[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]-2,6-diazaspiro[3.3]hept-2-yl}methyl)-1H-indole-2-carboxylic acid

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

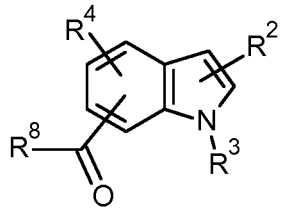
6. A method of preparing a compound of general formula (Ib) according to any one of claims 1 to 5, said method comprising the step of allowing an intermediate compound of general formula (V):



(V),

in which R^1 is as defined for the compound of general formula (I) according to any one of claims 1 to 5, and Z is methyl, difluoromethyl or trifluoromethyl,

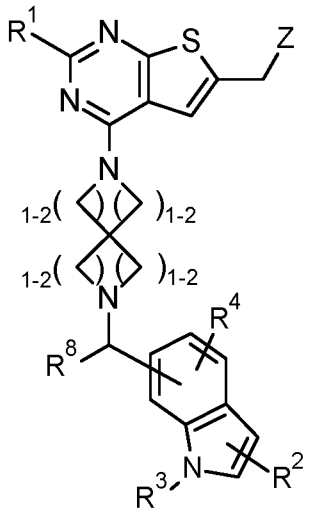
to react with a compound of general formula (VI):



(VI),

in which R^2, R^3, R^4 and R^8 are as defined for the compound of general formula (I) according to any one of claims 1 to 5,

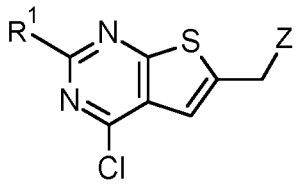
thereby giving a compound of general formula (Ib):



(Ib),

in which R^1, R^2, R^3, R^4 and R^8 are as defined for the compound of general formula (I) according to any one of claims 1 to 5 and Z is methyl, difluoromethyl or trifluoromethyl.

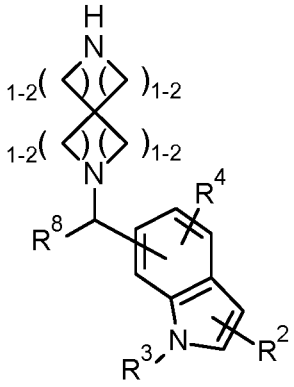
7. A method of preparing a compound of general formula (Ib) according to any one of claims 1 to 5, said method comprising the step of allowing an intermediate compound of general formula (II):



(II).

in which R^1 is as defined for the compound of general formula (I) according to any one of claims 1 to 5, and Z is methyl, difluoromethyl or trifluoromethyl,

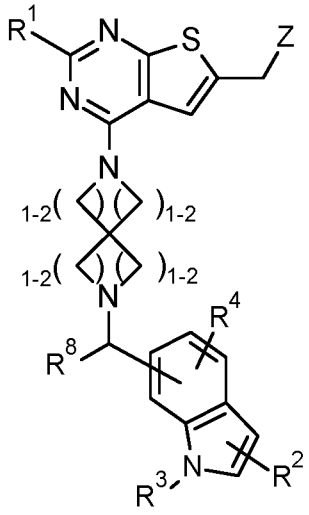
to react with a compound of general formula (VIII):



(VIII),

in which R^2, R^3, R^4 and R^8 are as defined for the compound of general formula (I) according to any one of claims 1 to 5,

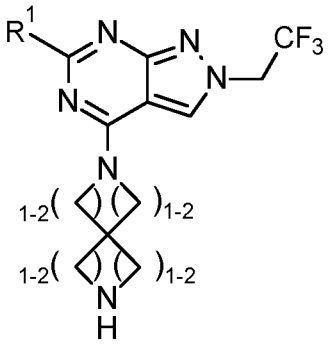
thereby giving a compound of general formula (Ib):



(Ib),

in which R^1, R^2, R^3, R^4 and R^8 are as defined for the compound of general formula (I) according to any one of claims 1 to 5 and Z is methyl, difluoromethyl or trifluoromethyl.

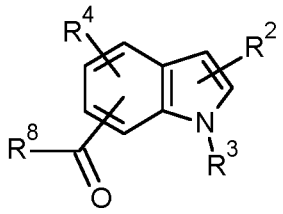
8. A method of preparing a compound of general formula (Ic) according to any one of claims 1 to 5, said method comprising the step of allowing an intermediate compound of general formula (XIII):



(XIII),

in which R^1 is as defined for the compound of general formula (I) according to any one of claims 1 to 5,

to react with a compound of general formula (VI):

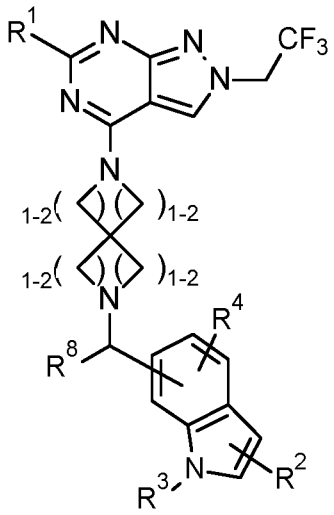


(VI)

(VI),

in which R^2, R^3, R^4 and R^8 are as defined for the compound of general formula (I) according to any one of claims 1 to 5,

thereby giving a compound of general formula (Ic):



(Ic),

in which R^1, R^2, R^3, R^4 and R^8 are as defined for the compound of general formula (I) according to any one of claims 1 to 5.

9. A compound of general formula (I) according to any one of claims 1 to 5 for use in the treatment or prophylaxis of a disease.

10. A pharmaceutical composition comprising a compound of general formula (I) according to any one of claims 1 to 5 and one or more pharmaceutically acceptable excipients.

11. A pharmaceutical combination comprising:

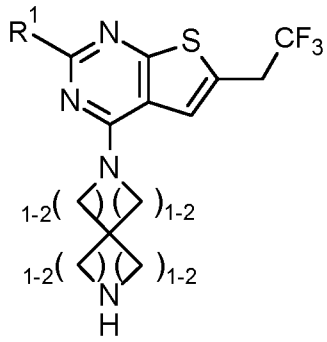
- one or more first active ingredients, in particular compounds of general formula (I) according to any one of claims 1 to 5, and
- one or more further active ingredients, in particular cancer agents.

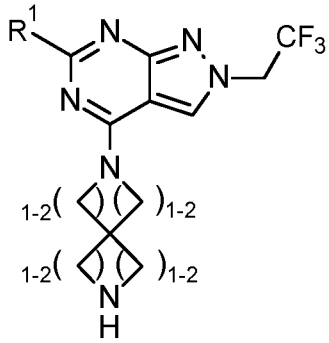
12. Use of a compound of general formula (I) according to any one of claims 1 to 5 for the treatment or prophylaxis of a disease.

13. Use of a compound of general formula (I) according to any one of claims 1 to 5 for the preparation of a medicament for the treatment or prophylaxis of a disease.

14. Use according to claim 9, 12 or 13, wherein the disease is cancer, such as a acute myeloid leukemia, prostate carcinoma, breast carcinoma, hepatocellular carcinoma, for example.

15. A compound of general formula (V) or (XIII):

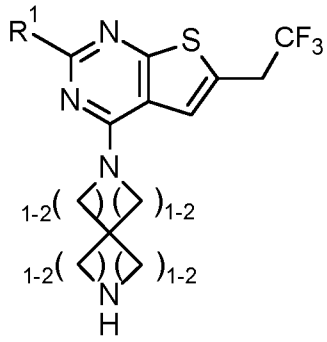


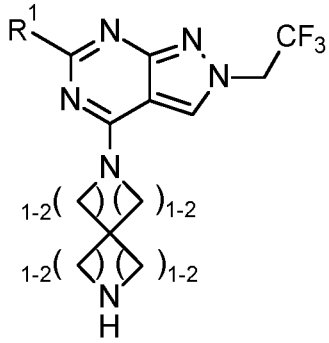


(V) (XIII),

in which R^1 is as defined for the compound of general formula (I) according to any one of claims 1 to 5.

16. Use of a compound of general formula (V) or (XIII):



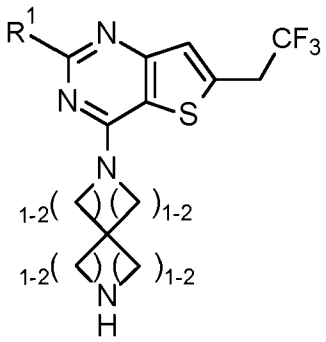


(V) (XIII),

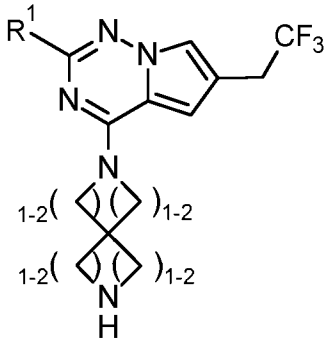
in which R^1 is as defined for the compound of general formula (I) according to any one of claims 1 to 5,

for the preparation of a compound of general formula (I) according to any one of claims 1 to 5.

17. A compound of general formula (XIX) or (XXIII):



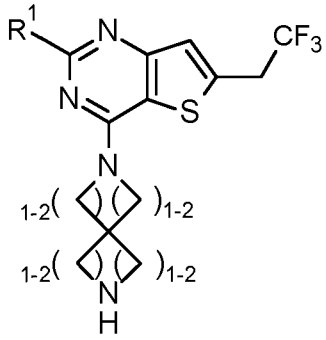
(XIX)



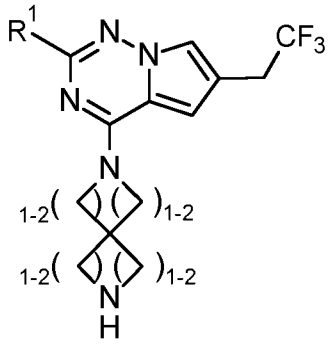
(XXIII),

in which R^1 is as defined for the compound of general formula (I) according to any one of claims 1 to 5.

18. Use of a compound of general formula (XIX) or (XXIII):



(XIX)

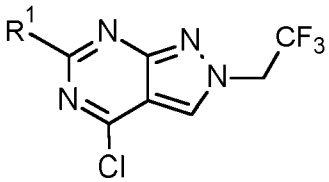


(XXIII),

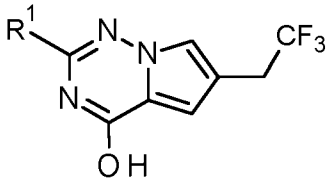
in which R^1 is as defined for the compound of general formula (I) according to any one of claims 1 to 5,

for the preparation of a compound of general formula (I) according to any one of claims 1 to 5.

19. A compound of general formula (X) or (XXI):



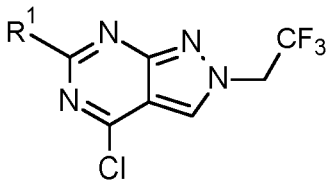
(X)



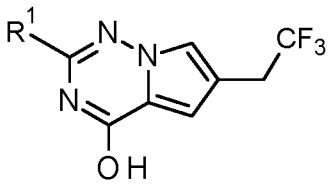
(XXI),

in which R^1 is as defined for the compound of general formula (I) according to any one of claims 1 to 5.

20. Use of a compound of general formula (X) or (XXI):



(X)



(XXI),

in which R^1 is as defined for the compound of general formula (I) according to any one of claims 1 to 5,

for the preparation of a compound of general formula (I) according to any one of claims 1 to 5.

21. A compound according to claim 1, wherein:

R^3 represents -CH2-R^5;

R^5 represents pyrazolyl substituted with -CO2-ferf.-but.yl;

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

22. Use of a compound according to claim 1, wherein:

R^3 represents -CH2-R^5;

R^5 represents pyrazolyl substituted with -CO2-ferf.-but.yl;

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same for the preparation of a compound of general formula (I) according to any one of claims 1 to 5.

23. The compound according to claim 21:

tert-butyl 2-cyano-5-({7-[6-(2,2,2-trifluoroethyl)pyrrolo[2, 1-f][1 ,2,4]triazin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}methyl)-1 H-indole-1 -carboxylate

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/062540

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/10 C07D495/04 C07D513/06 A61P35/02 A61K31/519
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal , WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2014/275070 Al (GREMBECKA JOLANTA [US] ET AL) 18 September 2014 (2014-09-18) cited in the application the whole document	1-23
A	WO 2008/033447 Al (SCHERING CORP [US] ; MCKITTRICK BRIAN [US] ; SMITH ELIZABETH M [US] ; BEN) 20 March 2008 (2008-03-20) cited in the application the whole document	1-23
A	WO 2008/033456 Al (SCHERING CORP [US] ; MCKITTRICK BRIAN [US] ; SMITH ELIZABETH M [US] ; BEN) 20 March 2008 (2008-03-20) cited in the application the whole document	1-23

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" documentwhich may throw doubts on priority claim(s) orwhich is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 June 2017	07/07/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Panday, Narendra

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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