(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 March 2014 (06.03.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/033170 A1

(51) International Patent Classification:
C07D 309/14 (2006.01) *A61K 31/4453* (2006.01)
C07D 231/14 (2006.01) *A61K 31/381* (2006.01)
C07D 333/46 (2006.01) *A61P 31/20* (2006.01)
C07C 311/37 (2006.01) *A61P 1/18* (2006.01)
C07D 295/26 (2006.01) *A61K 31/337* (2006.01)
A61K 31/18 (2006.01) *A61K 31/341* (2006.01)
A61K 31/277 (2006.01) *A61K 31/4164* (2006.01)
A61K 31/351 (2006.01)

(21) International Application Number:
PCT/EP2013/067821

(22) International Filing Date:
28 August 2013 (28.08.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

12182076.5	28 August 2012 (28.08.2012)	EP
12185055.6	19 September 2012 (19.09.2012)	EP
12190837.0	31 October 2012 (31.10.2012)	EP
13157230.7	28 February 2013 (28.02.2013)	EP
13169574.4	28 May 2013 (28.05.2013)	EP

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

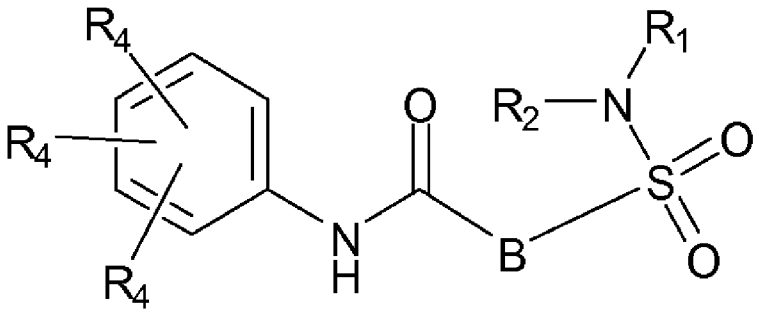
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

(54) Title: SULFAMOYL-ARYLAMIDES AND THE USE THEREOF AS MEDICAMENTS FOR THE TREATMENT OF HEPATITIS B



(Ia)

(57) Abstract: Inhibitors of HBV replication of Formula (I) including stereochemically isomeric forms, and salts, hydrates, solvates thereof, wherein B, R_1, R_2 and R_4 have the meaning as defined herein. The present invention also relates to pharmaceutical compositions containing these inhibitors and to their use, alone or in combination with other HBV inhibitors, in HBV therapy.

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SULFAMOYL-ARYLAMIDES AND THE USE THEREOF AS MEDICAMENTS FOR THE TREATMENT OF HEPATITIS B.

Background Art

The Hepatitis B virus (HBV) is an enveloped, partially double-stranded DNA (dsDNA) virus of the Hepadnavirus family (*Hepadnaviridae*). Its genome contains 4 overlapping reading frames: the precore/core gene; the polymerase gene; the L, M, and S genes, which encode for the 3 envelope proteins; and the X gene.

Upon infection, the partially double-stranded DNA genome (the relaxed circular DNA; rcDNA) is converted to a covalently closed circular DNA (cccDNA) in the nucleus of the host cell and the viral mRNAs are transcribed. Once encapsidated, the pregenomic RNA (pgRNA), which also codes for core protein and Pol, serves as the template for reverse transcription, which regenerates the partially dsDNA genome (rcDNA) in the nucleocapsid.

HBV has caused epidemics in parts of Asia and Africa, and it is endemic in China. HBV has infected approximately 2 billion people worldwide of which approximately 350 million people have developed chronic infections. The virus causes the disease hepatitis B and chronic infection is correlated with a strongly increased risk for the development cirrhosis and hepatocellular carcinoma.

Transmission of hepatitis B virus results from exposure to infectious blood or body fluids, while viral DNA has been detected in the saliva, tears, and urine of chronic carriers with high titer DNA in serum.

An effective and well-tolerated vaccine exists, but direct treatment options are currently limited to interferon and the following antivirals; tenofovir, lamivudine, adefovir, entecavir and telbivudine.

In addition, heteroaryldihydropyrimidines (HAPs) were identified as a class of HBV inhibitors in tissue culture and animal models (Weber et al., Antiviral Res. 54: 69–78).

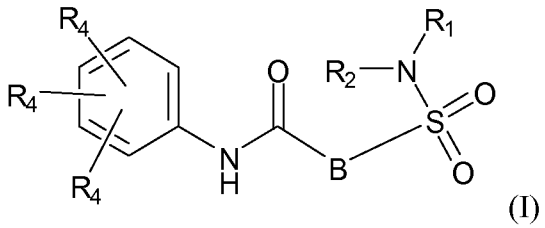
WO2013/006394, published on January 10, 2013, and WO2013/096744, published on June 27, 2013 relate to subclasses of Sulphamoyl-arylamides active against HBV.

Amongst the problems which HBV direct antivirals may encounter are toxicity, mutagenicity, lack of selectivity, poor efficacy, poor bioavailability and difficulty of synthesis.

There is a need for additional HBV inhibitors that may overcome at least one of these disadvantages or that have additional advantages such as increased potency or an increased safety window.

Description of the Invention

The present invention relates to compounds of Formula (I)



(I)

or a stereoisomer or tautomeric form thereof, wherein:

B represents a monocyclic 5 to 6 membered aromatic ring, optionally containing one or more heteroatoms each independently selected from the group consisting of O, S and N, such 5 to 6 membered aromatic ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halogen, C_1-C_3alkyl, CN, CFH_2, CF_2H and CF_3;

R_1 represents hydrogen or C_1-C_3alkyl;

R_2 represents C_1-C_6alkyl, C_1-C_6alkenyl, C_1-C_6alkyl-R_5, C(=O)-R_5, CFH_2, CF_2H, CF_3, a dihydro-indenyl or tetrahydronaphtalenyl moiety optionally substituted with OH, or a 3-7 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O, S and N, such 3-7 membered saturated ring, C_1-C_6alkyl-R_5 or C_1-C_6alkyl optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halogen, C_1-C_4alkyloxy, C_1-C_4alkyloxycarbonyl, oxo, C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3;

Or R_1 and R_2 together with the Nitrogen to which they are attached form a 6-10 membered bicyclic or bridged ring or a 5-7 membered saturated ring, such bicyclic, bridged or saturated ring moiety optionally containing one or more additional heteroatoms each independently selected from the group consisting of O, S and N, such 5-7 membered saturated ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halogen, C_1-C_4alkyloxy, C_1-C_4alkyloxycarbonyl, oxo, C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3;

Each R_4 is independently selected from hydrogen, halogen, C_1-C_4alkyloxy, C_1-C_4alkyl, C_1-C_4alkenyl, OH, CN, CFH_2, CF_2H, CF_3 , HC≡C or a 3-5 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O and N, such C_1-C_4alkyl optionally substituted with OH;

R_5 represents C_1-C_6alkyl, CFH_2, CF_2H, CF_3, phenyl, pyridyl or a 3-7 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O, S and N, such 3-7 membered saturated ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halogen, C_1-C_4alkyloxy, C_1-C_4alkyloxycarbonyl, oxo, C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3;

or a pharmaceutically acceptable salt or a solvate thereof.

The invention further relates to a pharmaceutical composition comprising a compound of Formula (I), and a pharmaceutically acceptable carrier.

The invention also relates to the compounds of Formula (I) for use as a medicament, preferably for use in the prevention or treatment of an HBV infection in a mammal.

In a further aspect, the invention relates to a combination of a compound of Formula (I), and another HBV inhibitor.

Definitions

The term "C_{1-3}alkyl" or "C_1-C_3alkyl" as a group or part of a group refers to a hydrocarbyl radical of Formula C_nH_{2n+1} wherein n is a number ranging from 1 to 3. In case C_{1-3}alkyl is coupled to a further radical, it refers to a Formula C_nH_{2n}.. C_{1-3}alkyl groups comprise from 1 to 3 carbon atoms, more preferably 1 to 2 carbon atoms. C_{1-3}alkyl includes all linear, or branched alkyl groups with between 1 and 3 carbon atoms, and thus includes such as for example methyl, ethyl, *n*-propyl, and *i*-propyl.

C_{1-4}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as the group defined for C_{1-3}alkyl and butyl and the like.

C_{1-6}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as the groups defined for C_{1-4}alkyl and pentyl, hexyl, 2-methylbutyl and the like.

C_{1-4}alkenyl as a group or part of a group defines straight or branched chain hydrocarbon radicals having from 1 to 4 carbon atoms with at least one double bond at any possible position. Examples of such alkenyls are ethenyl, propenyl, 1-butenyl, 2-butenyl. C_{1-6}alkenyl as a group or part of a group defines straight or branched chain hydrocarbon radicals having from 1 to 6 carbon atoms with at least one double bond.

The term "C_{1-3}alkyloxy" as a group or part of a group refers to a radical having the Formula --OR^c wherein R^c is C_{1-3}alkyl. Non-limiting examples of suitable C_{1-3}alkyloxy include methyloxy (also methoxy), ethyloxy (also ethoxy), propyloxy and isopropyloxy.

The term oxo, C(=O), or carbonyl refers to a group composed of a carbon atom double bonded to an oxygen atom.

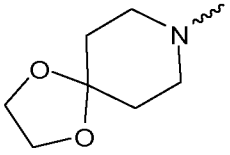
As used herein, the term "3-7 membered saturated ring" means saturated cyclic hydrocarbon with 3, 4, 5, 6 or 7 carbon atoms and is generic to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.
Such saturated ring optionally contains one or more heteroatoms, such that at least one carbon atom is replaced by a heteroatom selected from N, O and S, in particular from N and O. Examples include oxetane, azetidine, tetrahydro-2H-pyranyl, piperidinyl, tetrahydrofuranyl, morpholinyl and pyrrolidinyl. Preferred are saturated cyclic hydrocarbon with 3 or 4 carbon atoms and 1 oxygen atom. Examples include oxetane and tetrahydrofuranyl.

As used herein, the term monocyclic 5 to 6 membered aromatic ring ("aryl"), means an aromatic cyclic hydrocarbon with 5 or 6 carbon atoms. A preferred example of an aryl group is phenyl.
Such saturated ring optionally contains one or more heteroatoms each independently selected from the group consisting of O, S and N("heteroaryl") For the purposes of the invention, a heteroaryl group need only have some degree of aromatic character. Illustrative examples of heteroaryl groups include, but are not limited to, pyridinyl, pyridazinyl, pyrimidyl, pyrazyl, triazinyl, pyrrolyl, pyrazolyl, imidazolyl, (1,2,3,)- and (1,2,4)-triazolyl, pyrazinyl, pyrimidinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, isoxazolyl, and oxazolyl. A heteroaryl group can be unsubstituted or substituted with one or more suitable substituents.

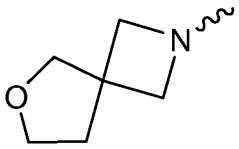
As used herein, the term 6-10 membered bicyclic ring indicates a saturated bi-cyclic ring with 6-7-8-9 or 10 atoms. Such saturated bi-cyclic ring optionally contains one or

more heteroatoms, such that at least one carbon atom is replaced by a heteroatom selected from N, O and S, in particular from N and O.

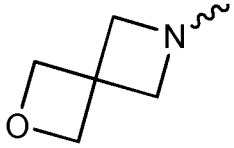
Examples of such 6-10 membered bicyclic ring as used herein arean1,4-dioxa-8-azaspiro[4.5] decyl moiety indicating a group with structural formula



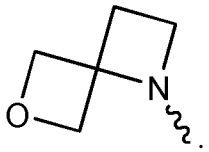
, a 6-Oxa-2-azaspiro[3.4]octane moiety indicating a group with structural formula



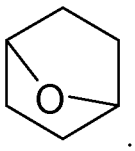
a 2-oxa-6-azaspiro[3.3]heptyl moiety indicating a group with structural formula



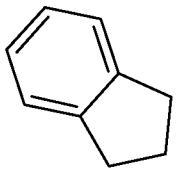
or a 6-oxa-1-azaspiro[3.3]heptyl moiety with structural formula

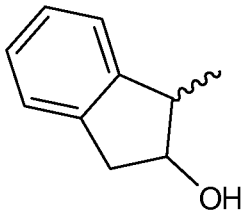


As used herein, the term 6-10 membered bridged ring indicates a saturated bridged ring with 6-7-8-9 or 10 atoms. Such saturated bi-cyclic ring optionally contains one or more heteroatoms, such that at least one carbon atom is replaced by a heteroatom selected from N, O and S, in particular from N and O. An example of such 6-10 membered bridged ring as used herein is -oxabicyclo[2.2.1]heptan represented by structure



As used herein, a dihydroindenyl moiety represents a group with structural formula

 . Such dihydroindenyl moiety can be optionally substituted with OH. One example as used herein, a 2-hydroxy-2,3-dihydro-1H-indenyl moiety, indicates a group with structural formula



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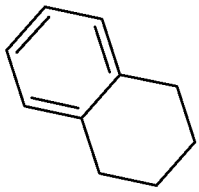
As used herein, a tetrahydronaphtalenyl moiety represents a group with structural formula


.

If not indicated, for any of the moieties above, the attachment to the main structure may be anywhere on such moiety as long as it is chemically stable.

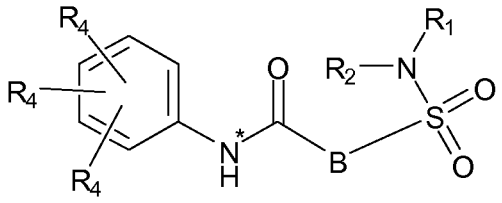
It should be noted that different isomers of the various heterocycles may exist within the definitions as used throughout the specification. For example, pyrrolyl may be 1H-pyrrolyl or 2H-pyrrolyl.

The term halo and halogen are generic to fluoro, chloro, bromo or iodo. Preferred halogens are fluoro and Chloro.

It should also be noted that the radical positions on any molecular moiety used in the definitions may be anywhere on such moiety as long as it is chemically stable. For instance pyridyl includes 2-pyridyl, 3-pyridyl and 4-pyridyl; pentyl includes 1-pentyl, 2-pentyl and 3-pentyl.

Positions indicated on phenyl (e.g. *ortho, meta* and/or *para*) are indicated relative to the bond connecting the phenyl to the main structure. An example with regard to the

position of R_4, any location is indicated relative to the nitrogen (*) connected to the main structure:



(Formula (I*)

When any variable (*e.g.* halogen or C_{1-4}alkyl) occurs more than one time in any constituent, each definition is independent.

For therapeutic use, the salts of the compounds of formula (I) are those wherein the counter ion is pharmaceutically or physiologically acceptable. However, salts having a pharmaceutically unacceptable counter ion may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound of formula (I). All salts, whether pharmaceutically acceptable or not are included within the ambit of the present invention.

The pharmaceutically acceptable or physiologically tolerable addition salt forms which the compounds of the present invention are able to form can conveniently be prepared using the appropriate acids, such as, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid; sulfuric; hemisulphuric, nitric; phosphoric and the like acids; or organic acids such as, for example, acetic, aspartic, dodecylsulphuric, heptanoic, hexanoic, nicotinic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like acids.

Conversely said acid addition salt forms can be converted by treatment with an appropriate base into the free base form.

The term "salts" also comprises the hydrates and the solvent addition forms that the compounds of the present invention are able to form. Examples of such forms are *e.g.* hydrates, alcoholates and the like.

The present compounds may also exist in their tautomeric forms for example, tautomeric forms of amide (-C(=O)-NH-) groups are iminoalcohols (-C(OH)=N-). Tautomeric forms, although not explicitly indicated in the structural formulae

represented herein, are intended to be included within the scope of the present invention.

The term stereochemically isomeric forms of compounds of the present invention, as used hereinbefore, defines all possible compounds made up of the same atoms bonded by the same sequence of bonds but having different three-dimensional structures which are not interchangeable, which the compounds of the present invention may possess. Unless otherwise mentioned or indicated, the chemical designation of a compound encompasses the mixture of all possible stereochemically isomeric forms which said compound may possess. Said mixture may contain all diastereomers and/or enantiomers of the basic molecular structure of said compound. All stereochemically isomeric forms of the compounds of the present invention both in pure form or in admixture with each other are intended to be embraced within the scope of the present invention.

Pure stereoisomeric forms of the compounds and intermediates as mentioned herein are defined as isomers substantially free of other enantiomeric or diastereomeric forms of the same basic molecular structure of said compounds or intermediates. In particular, the term 'stereoisomerically pure' concerns compounds or intermediates having a stereoisomeric excess of at least 80% (i. e. minimum 90% of one isomer and maximum 10% of the other possible isomers) up to a stereoisomeric excess of 100% (i.e. 100% of one isomer and none of the other), more in particular, compounds or intermediates having a stereoisomeric excess of 90% up to 100%, even more in particular having a stereoisomeric excess of 94% up to 100% and most in particular having a stereoisomeric excess of 97% up to 100%. The terms 'enantiomerically pure' and 'diastereomerically pure' should be understood in a similar way, but then having regard to the enantiomeric excess, respectively the diastereomeric excess of the mixture in question.

Pure stereoisomeric forms of the compounds and intermediates of this invention may be obtained by the application of art-known procedures. For instance, enantiomers may be separated from each other by the selective crystallization of their diastereomeric salts with optically active acids or bases. Examples thereof are tartaric acid, dibenzoyltartaric acid, ditoluoyltartaric acid and camphosulfonic acid. Alternatively, enantiomers may be separated by chromatographic techniques using chiral stationary phases. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably, if a specific

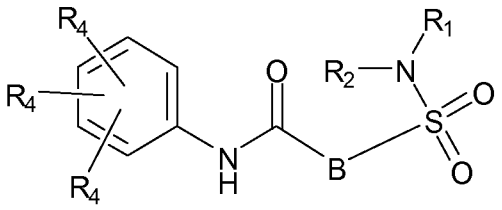
stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

The diastereomeric racemates of formula (I) can be obtained separately by conventional methods. Appropriate physical separation methods that may advantageously be employed are, for example, selective crystallization and chromatography, e.g. column chromatography.

The present invention is also intended to include all isotopes of atoms occurring on the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

Detailed description of the invention

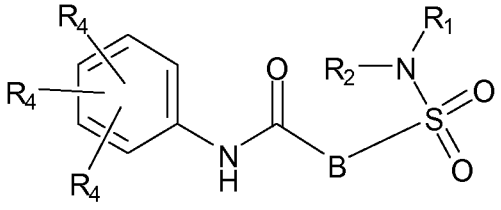
Whenever used hereinafter, the term "compounds of formula (I)",



or "the present compounds" or similar term is meant to include the compounds of general formula (I),(I*), (Ia) ,(Ib),(Ic) and (Id), salts, stereoisomeric forms and racemic mixtures or any subgroups thereof.

Compounds for use in the prevention or treatment of an HBV infection in a mammal are disclosed as compounds per se and not limited to this use unless restricted by the claims.

The present invention relates to compounds of Formula (I)



(I)

or a stereoisomer or tautomeric form thereof, wherein:

B represents a monocyclic 5 to 6 membered aromatic ring, optionally containing one or more heteroatoms each independently selected from the group consisting of O, S and N, such 5 to 6 membered aromatic ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halogen, C_1-C_3alkyl, CN, CFH_2, CF_2H and CF_3;

R_1 represents hydrogen or C_1-C_3alkyl;

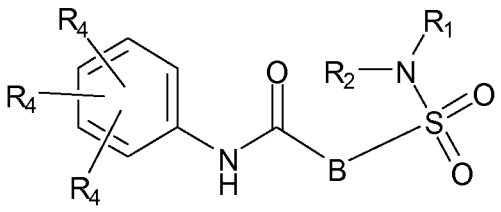
R_2 represents C_1-C_6alkyl, C_1-C_6alkenyl, C_1-C_6alkyl-R_5, C(=O)-R_5, CFH_2, CF_2H, CF_3, a dihydro-indenyl or tetrahydronaphtalenyl moiety optionally substituted with OH, or a 3-7 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O, S and N, such 3-7 membered saturated ring, C_1-C_6alkyl-R_5 or C_1-C_6alkyl optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halogen, C_1-C_4alkyloxy, C_1-C_4alkyloxycarbonyl, oxo, C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3;
Or R_1 and R_2 together with the Nitrogen to which they are attached form a 6-10 membered bicyclic or bridged ring or a 5-7 membered saturated ring, such bicyclic, bridged or saturated ring moiety optionally containing one or more additional heteroatoms each independently selected from the group consisting of O, S and N, such 5-7 membered saturated ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halogen, C_1-C_4alkyloxy, C_1-C_4alkyloxycarbonyl, oxo, C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3;

Each R_4 is independently selected from hydrogen, halogen, C_1-C_4alkyloxy, C_1-C_4alkyl, C_1-C_4alkenyl, OH, CN, CFH_2, CF_2H, CF_3, HC≡C or a 3-5 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O and N, such C_1-C_4alkyl optionally substituted with OH;

R_5 represents C_1-C_6alkyl, CFH_2, CF_2H, CF_3, phenyl, pyridyl or a 3-7 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O, S and N, such 3-7 membered saturated ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halogen, C_1-C_4alkyloxy, C_1-C_4alkyloxycarbonyl, oxo, C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3;

or a pharmaceutically acceptable salt or a solvate thereof.

In a first aspect, the invention further provides compound of Formula (I)



(I)

or a stereoisomer or tautomeric form thereof, wherein:

B represents a monocyclic 5 to 6 membered aromatic ring, optionally containing one or more heteroatoms each independently selected from the group consisting of O, S and N, such 5 to 6 membered aromatic ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halo, C_1-C_3alkyl, CN, CFH_2, CF_2H and CF_3;

R_1 represents hydrogen or C_1-C_3alkyl;

R_2 represents C_1-C_6alkyl, C_1-C_6alkenyl, C_1-C_6alkyl-R_5, C(=O)-R_5, CFH_2, CF_2H, CF_3, a 2-hydroxy-2,3-dihydro-1H-indenyl moiety or a 3-7 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O, S and N, such 3-7 membered saturated ring, C_1-C_6alkyl-R_5 or C_1-C_6alkyl optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halogen, C_1-C_4alkyl-oxy, C_1-C_4alkyloxycarbonyl, oxo, C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3;

Or R_1 and R_2 together with the Nitrogen to which they are attached form a 1,4-dioxa-8-azaspiro[4.5]decyl moiety, a 2-oxa-6-azaspiro[3.3]heptyl moiety or a 5-7 membered saturated ring optionally containing one or more additional heteroatoms each independently selected from the group consisting of O, S and N, such 5-7 membered saturated ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halogen, C_1-C_4alkyloxy, C_1-C_4alkyloxycarbonyl, oxo, C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3;

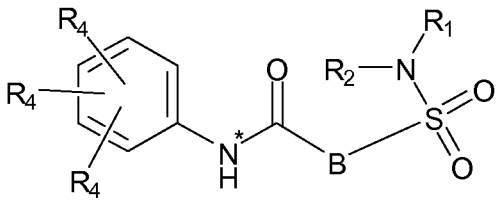
Each R_4 is independently selected from hydrogen, halogen, C_1-C_4alkyloxy, C_1-C_4alkyl, C_1-C_4alkenyl, OH, CN, CFH_2, CF_2H, CF_3, HC≡C or a 3-5 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O and N, such C_1-C_4alkyl optionally substituted with OH;

R_5 represents C_1-C_6alkyl, CFH_2, CF_2H, CF_3, phenyl, pyridyl or a 3-7 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O, S and N, such 3-7 membered saturated ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halogen, C_1-C_4alkyloxy, C_1-C_4alkyloxycarbonyl, oxo, C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3;

or a pharmaceutically acceptable salt or a solvate thereof.

In one embodiment, at least one R_4 represents Fluor, and one other R_4 is selected from the group consisting of C_1-C_3alkyl, C_1-C_3alkenyl, CHF_2 or cyclopropyl.

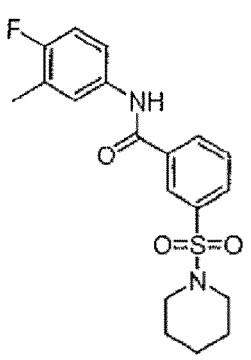
In a sub-embodiment, one R_4 represents Fluor and one other R_4 is selected from the group consisting of methyl or CHF_2, preferably methyl, and wherein the location of said Fluor is on the *para* position and the location of said methyl or CHF_2 is on the *meta* position related to the Nitrogen(*) as indicated In Formula (I*) below.



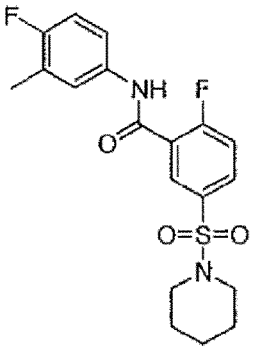
(I*)

In yet another embodiment, the invention provides compound of Formula (I) wherein at least one R_4 represents Fluor, and one other R_4 is selected from the group consisting of C_1-C_3alkyl, C_1-C_3alkenyl, CHF_2 or cyclopropyl; more preferably, one R_4 represents Fluor and one other R_4 is selected from the group consisting of methyl or CHF_2 and wherein the location of said Fluor is on the *para* position and the location of said methyl or CHF_2 is on the *meta* position related to the Nitrogen (*) and R_2 represents a 4-7 membered saturated ring containing carbon and one or more oxygen atoms, such 4-7 membered saturated ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halo, C_1-C_4alkyl-oxy, C_1-C_4alkyloxycarbonyl, C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3.

In yet another embodiment, compounds are disclosed wherein one R_4 on the *para* position represents Fluor and the other one R_4 on the *meta* position represents methyl and such compound is not



or



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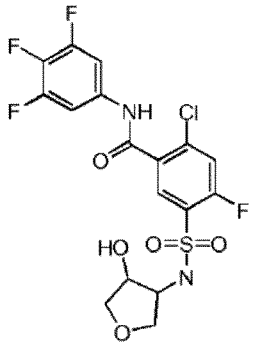
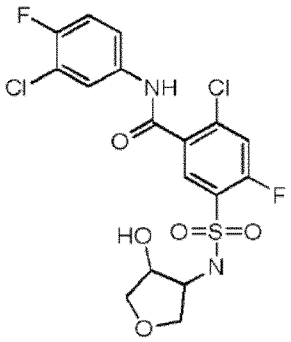
In another embodiment of the present invention, compounds according to Formula (I) are provided wherein R_2 represents a 4-7 membered saturated ring containing carbon and one or more oxygen atoms, such 4-7 membered saturated ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halogen, C_1-C_4alkyloxy, C_1-C_4alkyloxycarbonyl, C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3. A preferred substituent for such a 4-7 membered saturated ring containing carbon and one or more oxygen atoms is C_1-C_4alkyl. In a sub-embodiment, the saturated ring is a 4, 5 or 6 membered ring.

In another embodiment of the present invention, compounds according to Formula (I) are provided wherein R_2 represents a 4-7 membered saturated ring containing carbon and one or more nitrogen atoms, such 4-7 membered saturated ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halogen, C_1-C_4alkyloxy, C_1-C_4alkyloxycarbonyl , C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3.In a further embodiment, R_2 represents a 4-7 membered saturated ring containing carbon and one or more oxygen atoms, such 4-7 membered saturated ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halogen, C_1-C_4alkyloxy, C_1-C_4alkyloxycarbonyl, C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3 wherein such compound is not



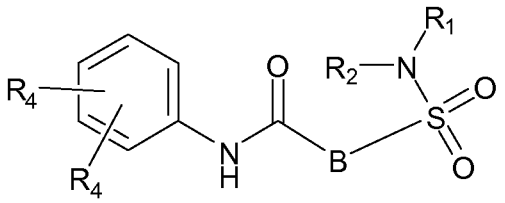
or



Preferably, any optional substituent on such 3-7, 4-7 and 5-7 membered saturated ring, 6-10 membered bicyclic or bridged ring, C_1-C_6alkyl-R_5 or C_1-C_6alkyl is independently selected from the group consisting of hydrogen, Fluoro, OH, C_1-C_3alkyl and CF_3, most preferably from the group consisting of hydrigen C_1-C_3alkyl, Fluoro and CF_3.

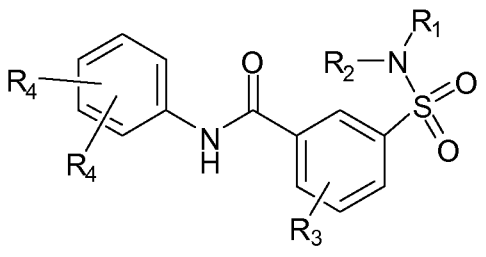
In another embodiment of the present invention, compounds according to Formula (I) are provided wherein B represents phenyl or thiophene, optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halogen, C_1-C_3alkyl, CN, CFH_2, CF_2H and CF_3.

In one sub-embodiment, compounds according to the present invention are represented by Formula (Ia)



(Ia), wherein R_1, R_2 and R_4 are defined as in any one of the embodiments as described.

In a sub-embodiment, such compounds are represented by Formula (Ib)

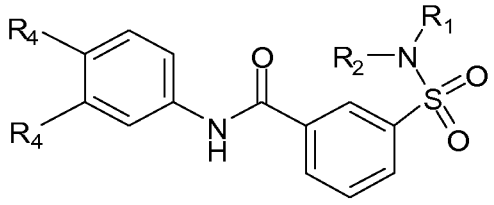


(Ib)

wherein R_1, R_2, R_4 are defined as in any one of the embodiments as described and R_3 is selected from the group comprising hydrogen, halogen, C_1-C_3alkyl, CN, CFH_2, CF_2H,

CF_3. In a preferred embodiment, R_3 represents Fluor or hydrogen, more preferably hydrogen.

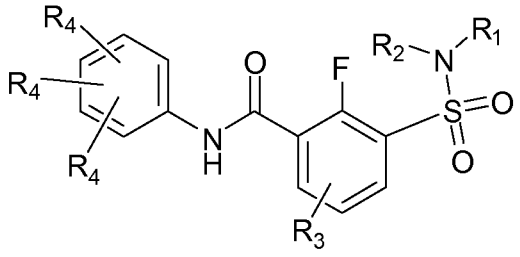
In yet another sub-embodiment, compounds are represented by Formula (Ic):



(Ic)

wherein R_1, R_2 and R_4 are defined as in any one of the embodiments as described.

In one sub-embodiment, compounds according to the present invention are represented by Formula (Id)

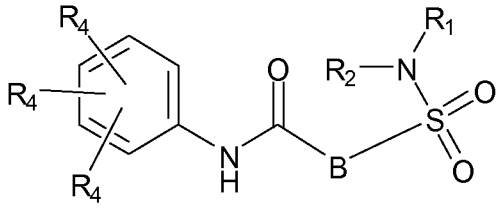


(Id)

wherein R_1, R_2 and R_4 are defined as in any one of the embodiments described and R_3 is selected from the group comprising hydrogen, halogen, C_1-C_3alkyl, CN, CFH_2, CF_2H, CF_3.

In a preferred embodiment, the compounds according to the invention are envisioned for use in the prevention or treatment of an HBV infection in a mammal.

In one further aspect, the present invention provides compounds which can be represented by Formula (I):



(I)

or a stereoisomer or tautomeric form thereof, wherein:

B represents a monocyclic 5 to 6 membered aromatic ring, optionally containing one or more heteroatoms each independently selected from the group consisting of O, S and N, such 5 to 6 membered aromatic ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halo, C_1-C_3alkyl, CN, CFH_2, CF_2H and CF_3;

R_1 represents hydrogen or C_1-C_3alkyl;

R_2 represents C_1-C_6alkyl, C_1-C_3alkyl-R_5, benzyl, C(=O)-R_5, CFH_2, CF_2H, CF_3 or a 3-7 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O, S and N, such 3-7 membered saturated ring or C_1-C_6alkyl optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halo, C_1-C_4alkyloxy, oxo, C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3;

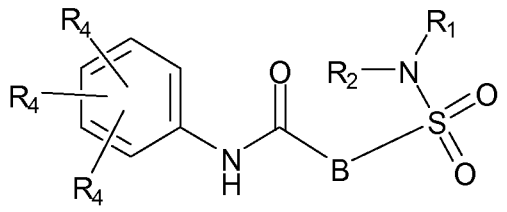
Or R_1 and R_2 together with the Nitrogen to which they are attached form a 1,4-dioxa-8-azaspiro[4.5] moiety or a 5-7 membered saturated ring, optionally containing one or more additional heteroatoms each independently selected from the group consisting of O, S and N, such 5-7 membered saturated ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halo, C_1-C_4alkyloxy, oxo, C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3;

Each R_4 is independently selected from hydrogen, halo, C_1-C_4alkyloxy, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H, CF_3 , HC≡C or a 3-5 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O and N;

R_5 represents C_1-C_6alkyl, CFH_2, CF_2H, CF_3 or a 3-7 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O, S and N, such 3-7 membered saturated ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halo, C_1-C_4alkyloxy, oxo, C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3;

or a pharmaceutically acceptable salt or a solvate thereof. These compounds are especially suited for use in the prevention or treatment of an HBV infection in a mammal.

In yet a further aspect, the invention relates to compounds according to Formula (I)



(I)

or a stereoisomer or tautomeric form thereof, wherein:

B represents a monocyclic 5 to 6 membered aromatic ring, optionally containing one or more heteroatoms each independently selected from the group consisting of O, S and N, such 5 to 6 membered aromatic ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halo, C_1-C_3alkyl, CN, CFH_2, CF_2H and CF_3;

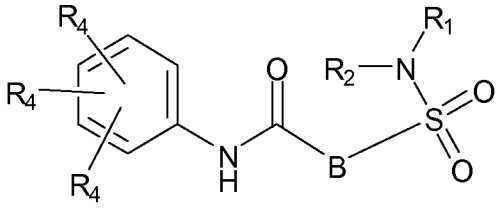
R_1 represents hydrogen or C_1-C_3alkyl;

R_2 represents a 4-7 membered saturated ring consisting of carbon atoms and one or more heteroatoms each independently selected from the group consisting of O or S, such 4-7 membered saturated ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halo, C_1-C_4alkyloxy, oxo, C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3;

Each R_4 is independently selected from hydrogen, halo, C_1-C_4alkyloxy, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H, CF_3, HC≡C or a 3-5 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O and N;

or a pharmaceutically acceptable salt or a solvate thereof.

The present invention additionally relates to compound of Formula (I)



(I)

or a stereoisomer or tautomeric form thereof, or a pharmaceutically acceptable salt or a solvate thereof

wherein:

B represents a monocyclic 5 to 6 membered aromatic ring, optionally containing one or more heteroatoms each independently selected from the group consisting of O, S and N, such 5 to 6 membered aromatic ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halo, C_1-C_3alkyl, CN, CFH_2, CF_2H and CF_3;

R_1 represents hydrogen or C_1-C_3alkyl;

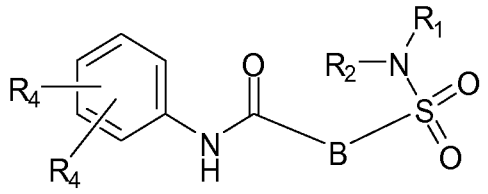
R_2 represents C_1-C_6alkyl, C_1-C_3alkyl-R_5, benzyl, C(=O)-R_5, CFH_2, CF_2H, CF_3 or a 3-7 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O, S and N, such 3-7 membered saturated ring or C_1-C_6alkyl optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halo, C_1-C_4alkyloxy, oxo, C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3;

Or R_1 and R_2 together with the Nitrogen to which they are attached form a 1,4-dioxa-8-azaspiro[4.5] moiety or a 5-7 membered saturated ring, optionally containing one or more additional heteroatoms each independently selected from the group consisting of O, S and N, such 5-7 membered saturated ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halo, C_1-C_4alkyloxy, oxo, C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3;

Each R_4 is independently selected from hydrogen, halo, C_1-C_4alkyloxy, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H, CF_3, HC≡C or a 3-5 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O and N;

R_5 represents C_1-C_6alkyl, CFH_2, CF_2H, CF_3 or a 3-7 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O, S and N, such 3-7 membered saturated ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halo, C_1-C_4alkyloxy, oxo, C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3;

One sub-embodiment of the invention provides compounds which can be represented by formula (Ia)



(Ia)

wherein R_1, R_2, B are defined as above and each R_4 is independently selected from hydrogen, halo, C_1-C_4alkyloxy, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H, CF_3 or a 3-5 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O and N.

In one embodiment, R_2 represents a 3-7 membered saturated ring, containing one or more heteroatoms each independently selected from the group consisting of O, S and N, such 3-7 membered saturated ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halo, C_1-C_4alkyloxy, oxo, C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3.

In yet another embodiment, R_2 represents a 4-7 membered saturated ring containing carbon and one or more oxygen atoms, such 4-7 membered saturated ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halo, C_1-C_4alkyloxy, C(=O)- C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3.

In another embodiment, R_1 and R_2 together with the Nitrogen to which they are attached form a 5-7 membered saturated ring, optionally containing one or more additional heteroatoms each independently selected from the group consisting of O, S and N, such 5-7 membered saturated ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halo, C_1-C_4alkyloxy, oxo, C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3.

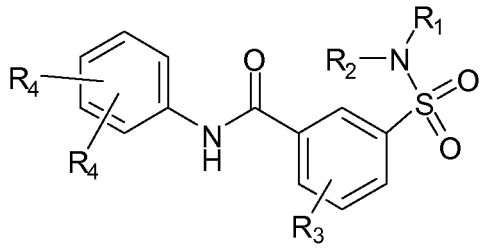
In a preferred embodiment of the invention, B represents phenyl or thiophene, optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halogen, C_1-C_3alkyl, CN, CFH_2, CF_2H and CF_3.

In a selection of compounds according to the invention, or compounds for use in the prevention or treatment of an HBV infection in a mammal at least one R_4 represents Fluor, C_1-C_3alkyl, CHF_2 or cyclopropyl.

Preferably, at least one R_4 represents methyl, *i*-propyl or cyclopropyl. In another embodiment, one R_4 represents methyl, *i*-propyl or cyclopropyl and the other R_4 represents Fluor, or hydrogen. The position of R_4 preferably is *meta* and/or *para* (position indicated from –N~).

One specific embodiment is a compound of Formula (I) wherein one R_4 on the *para* position represents Fluor and the other one R_4 on the *meta* position represents Fluor or methyl (position indicated from –N~).

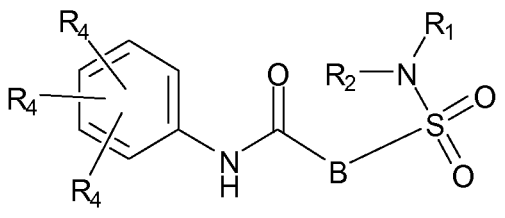
One sub-embodiment of the invention provides compounds which can be represented by formula (Ib)



(Ib)

wherein R_1, R_2, R_4 are defined as above and R_3 is selected from the group comprising hydrogen, halo, C_1-C_3alkyl, CN, CFH_2, CF_2H, CF_3. In a preferred embodiment, R_3 represents Fluor or hydrogen.

The invention further relates to compounds according to Formula (I)



(I)

or a stereoisomer or tautomeric form thereof, wherein:

B represents a monocyclic 5 to 6 membered aromatic ring, optionally containing one or more heteroatoms each independently selected from the group consisting of O, S and N, such 5 to 6 membered aromatic ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halo, C_1-C_3alkyl, CN, CFH_2, CF_2H and CF_3;

R_1 represents hydrogen or C_1-C_3alkyl;

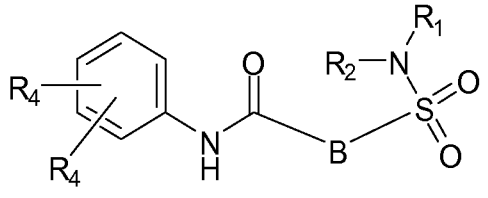
R_2 represents C_1-C_3alkyl-R_6 or a 4-7 membered saturated ring consisting of carbon atoms and one or more heteroatoms each independently selected from the group consisting of O or S, such 4-7 membered saturated ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halo, C_1-C_4alkyloxy, oxo, C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3;

Each R_4 is independently selected from hydrogen, halo, C_1-C_4alkyloxy, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H, CF_3, HC≡C or a 3-5 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O and N;

R_6 represents a 4-7 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O or S, such 4-7 membered saturated ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halo, C_1-C_4alkyloxy, oxo, C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3;

or a pharmaceutically acceptable salt or a solvate thereof.

One sub-embodiment of the invention provides compounds which can be represented by formula (Ia)



(Ia)

wherein R_1, R_2, B are defined as above and each R_4 is independently selected from hydrogen, halo, C_1-C_4alkyloxy, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H, CF_3 or a 3-5 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O and N.

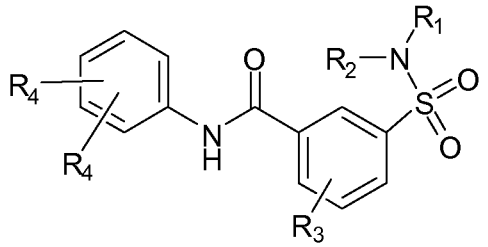
In one embodiment, R_2 represents C_1-C_3alkyl-R_6 or a 4-7 membered saturated ring consisting of carbon atoms and one or more heteroatoms each independently selected from the group consisting of O or S, such 4-7 membered saturated ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halo, C_1-C_4alkyloxy, oxo, C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3.

In a preferred embodiment for the compounds of the invention, B represents phenyl or thiophene, optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halogen, C_1-C_3alkyl, CN, CFH_2, CF_2H and CF_3.

In a selection of compounds according to the invention at least one R_4 represents Fluor, C_1-C_3alkyl ,CHF_2 or cyclopropyl. Preferably, at least one R_4 represents methyl, *i*-propyl or cyclopropyl. In another embodiment, one R_4 represents methyl, *i*-propyl or cyclopropyl and the other R_4 represents Fluor, or hydrogen. The position of R_4 preferably is *meta* and/or *para*.

One specific embodiment is a compound of Formula (I) wherein one R_4 on the *para* position represents Fluor and the other one R_4 on the *meta* position represents Fluor or methyl.

One sub-embodiment of the compounds of the invention relates to compounds according Formula (Ib)



(Ib)

wherein R_1 represents hydrogen or C_1-C_3alkyl;

R_2 represents C_1-C_3alkyl-R_6 or a 4-7 membered saturated ring consisting of carbon atoms and one or more heteroatoms each independently selected from the group consisting of O or S, such 4-7 membered saturated ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halo, C_1-C_4alkyloxy, oxo, C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3;

Each R_4 is independently selected from hydrogen, halo, C_1-C_4alkyloxy, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H, CF_3 or a 3-5 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O and N;

R_6 represents a 4-7 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O or S, such 4-7 membered saturated ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halo, C_1-C_4alkyloxy, oxo, C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3;

R_3 is selected from the group comprising hydrogen, halo, C_1-C_3alkyl, CN, CFH_2, CF_2H, CF_3. In a preferred embodiment, R_3 represents Fluor or hydrogen.

In one embodiment, R_6 represents a 4-7 membered saturated ring consisting of carbon atoms and one or more heteroatoms each independently selected from the group consisting of O or S, such 4-7 membered saturated ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halo, C_1-C_4alkyloxy, oxo, C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3.

Further combinations of any of the sub- or preferred embodiments are also envisioned to be in the scope of the present invention.

Preferred compounds according to the invention are compounds or a stereoisomer or tautomeric form thereof with a formula or reference to a formula selected from the following tables 1 and 2:

Table 2.

Co. no.	Co. no.	Co. no.	Co. no.	Co. no.	Co. no.	Co. no.	Co. no.
1	64	94	120	146	172	196	222
2	65	95	121	147	173	197	223
3	66	96	122	148	174	198	224
4	67	97	123	149	175	199	225
5	68	98	124	150	176	200	226
6	69	99	125	151	177	201	227
7	70	100	126	152	178	202	228
8	71	101	127	153	179	203	229
9	72	102	128	154	180	204	230
10	73	103	129	155	181	205	231
11	74	104	130	156	182	206	232
12	76	105	131	157	183	207	233
14	77	106	132	158	184	208	234
16	79	107	133	159	184a	209	235
17	81	108	134	160	184b	210	236
18	82	109	135	161	185	211	237
19	83	110	136	162	186	212	238
38	84	111	137	163	187	213	239
39	85	112	138	164	188	214	240
42	86	113	139	165	189	215	241
43	87	114	140	166	190	216	242
45	89	115	141	167	191	217	243
46	90	116	142	168	192	218	
48	91	117	143	169	193	219	
56	92	118	144	170	194	220	
63	93	119	145	171	195	221	

or a pharmaceutically acceptable salt or a solvate thereof

In a further aspect, the present invention concerns a pharmaceutical composition comprising a therapeutically or prophylactically effective amount of a compound of Formula (I) as specified herein, and a pharmaceutically acceptable carrier. A prophylactically effective amount in this context is an amount sufficient to prevent HBV infection in subjects being at risk of being infected. A therapeutically effective amount in this context is an amount sufficient to stabilize HBV infection, to reduce HBV infection, or to eradicate HBV infection, in infected subjects. In still a further aspect, this invention relates to a process of preparing a pharmaceutical composition as specified herein, which comprises intimately mixing a pharmaceutically acceptable

carrier with a therapeutically or prophylactically effective amount of a compound of Formula (I), as specified herein.

Therefore, the compounds of the present invention or any subgroup thereof may be formulated into various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, optionally in addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, particularly, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules, and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid pharmaceutical carriers are employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations intended to be converted, shortly before use, to liquid form preparations. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin. The compounds of the present invention may also be administered via oral inhalation or insufflation in the form of a solution, a suspension or a dry powder using any art-known delivery system.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated

to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, suppositories, powder packets, wafers, injectable solutions or suspensions and the like, and segregated multiples thereof.

The compounds of Formula (I) are active as inhibitors of the HBV replication cycle and can be used in the treatment and prophylaxis of HBV infection or diseases associated with HBV. The latter include progressive liver fibrosis, inflammation and necrosis leading to cirrhosis, end-stage liver disease, and hepatocellular carcinoma.

Due to their antiviral properties, particularly their anti-HBV properties, the compounds of Formula (I) or any subgroup thereof, are useful in the inhibition of the HBV replication cycle, in particular in the treatment of warm-blooded animals, in particular humans, infected with HBV, and for the prophylaxis of HBV infections. The present invention furthermore relates to a method of treating a warm-blooded animal, in particular human, infected by HBV, or being at risk of infection by HBV, said method comprising the administration of a therapeutically effective amount of a compound of Formula (I).

The compounds of Formula (I), as specified herein, may therefore be used as a medicine, in particular as medicine to treat or prevent HBV infection. Said use as a medicine or method of treatment comprises the systemic administration to HBV infected subjects or to subjects susceptible to HBV infection of an amount effective to combat the conditions associated with HBV infection or an amount effective to prevent HBV infection.

The present invention also relates to the use of the present compounds in the manufacture of a medicament for the treatment or the prevention of HBV infection. In general it is contemplated that an antiviral effective daily amount would be from about 0.01 to about 50 mg/kg, or about 0.01 to about 30 mg/kg body weight. It may be appropriate to administer the required dose as two, three, four or more sub-doses at appropriate intervals throughout the day. Said sub-doses may be formulated as unit dosage forms, for example, containing about 1 to about 500 mg, or about 1 to about 300 mg, or about 1 to about 100 mg, or about 2 to about 50 mg of active ingredient per unit dosage form.

The present invention also concerns combinations of a compound of Formula (I) or any subgroup thereof, as specified herein with other anti-HBV agents. The term

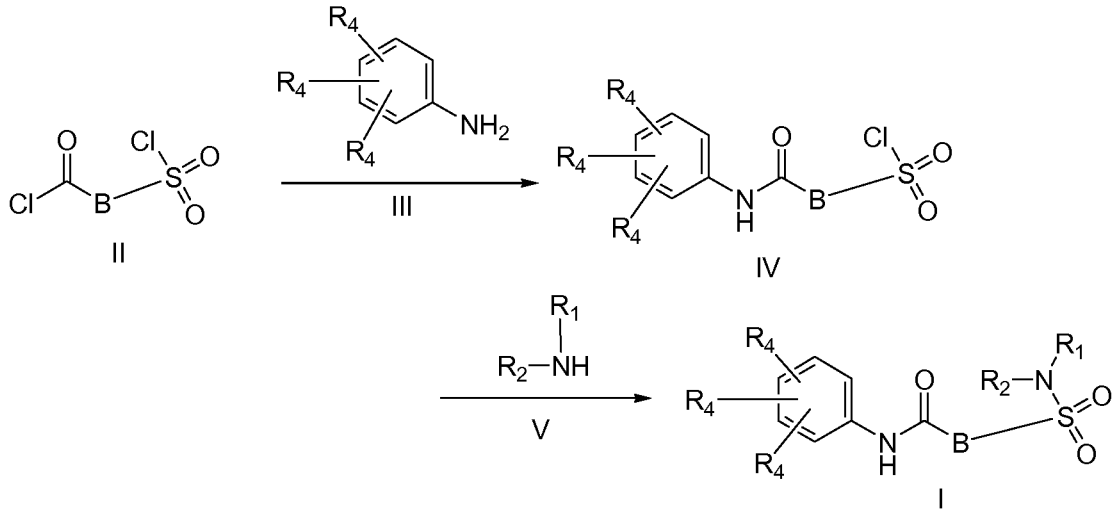
"combination" may relate to a product or kit containing (a) a compound of Formula (I), as specified above, and (b) at least one other compound capable of treating HBV infection (herein designated as anti-HBV agent), as a combined preparation for simultaneous, separate or sequential use in treatment of HBV infections. In an embodiment, the invention concerns combination of a compound of Formula (I) or any subgroup thereof with at least one anti-HBV agent. In a particular embodiment, the invention concerns combination of a compound of formula (I) or any subgroup thereof with at least two anti-HBV agents. In a particular embodiment, the invention concerns combination of a compound of formula (I) or any subgroup thereof with at least three anti-HBV agents. In a particular embodiment, the invention concerns combination of a compound of formula (I) or any subgroup thereof with at least four anti-HBV agents.

The combination of previously known anti-HBV agents, such as interferon-α (IFN-α), pegylated interferon-α, 3TC, adefovir or a combination thereof, and, a compound of formula (I) or any subgroup thereof can be used as a medicine in a combination therapy.

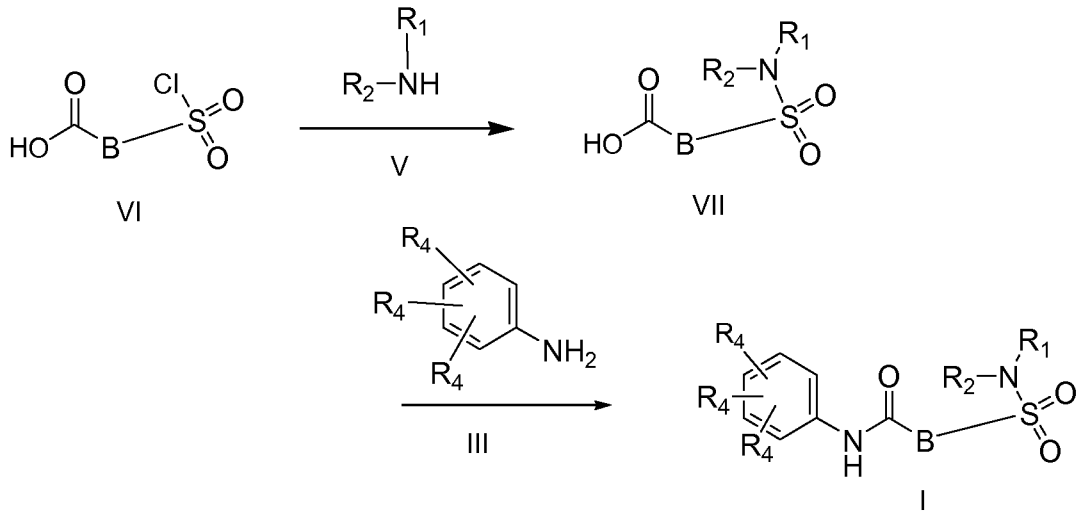
Generic synthesis:

Compound according to Formula (I) can be synthesized as described in general schemes 1 to 7.

A carboxylic acid chloride of general Formula II can be selectively reacted with an aniline of general formula III, for example in an organic solvent like CH_2Cl_2 in the presence of an organic base like triethylamine or DIPEA (N,N-diisopropylethylamine), or, as another example, by addition of the aniline III to a refluxing toluene solution of compound II, resulting in compound IV. The remaining sulfonic acid chloride functionality in compound IV is further reacted with an amine of general formula V, resulting in a compound of general Formula (I). Alternatively a compound of general Formula (I) might be obtained as described in scheme 2. This time the sulfonic acid chloride VI is reacted with an amine of general formula V, for example in an organic solvent like CH_2Cl_2 in the presence of an organic base like triethylamine or DIPEA or or, as another example, in the presence of Na_2CO_3 in a mixture of H_2O/THF. The formed compound VII is coupled with aniline of general formula III in the presence of an activating reagent like for example HATU and an organic base like triethylamine or DIPEA.

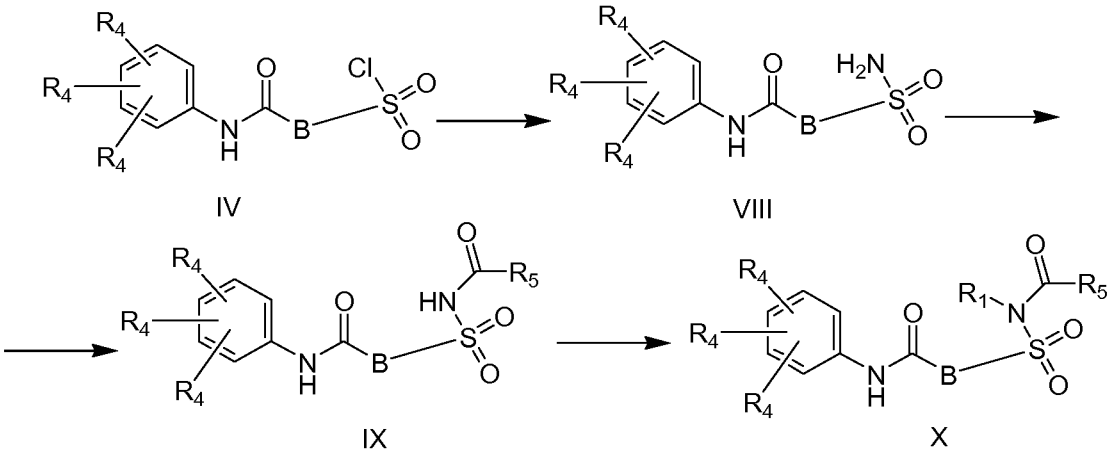


Scheme 1



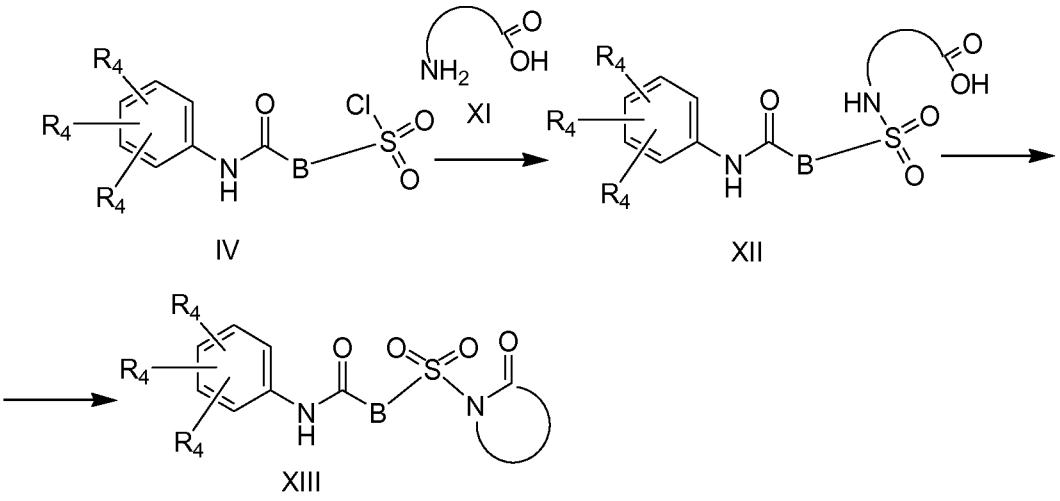
Scheme 2

A general synthesis of compounds of formula IX and X is described in scheme 3. Intermediate IV is reacted with ammonia, resulting in a compound of formula VIII. This intermediate can be further transformed to a compound of formula IX by reacting with a carbonyl chloride, for example cyclohexane carbonyl chloride in the presence of SiO_2 and H_2SO_4 at reflux in $CHCl_3$. The compound of general formula IX can be further transformed to a compound of formula X. In case R_1 equals Me, this can be done by reacting IX with $TMSCHN_2$ in $MeOH/CH_2Cl_2$

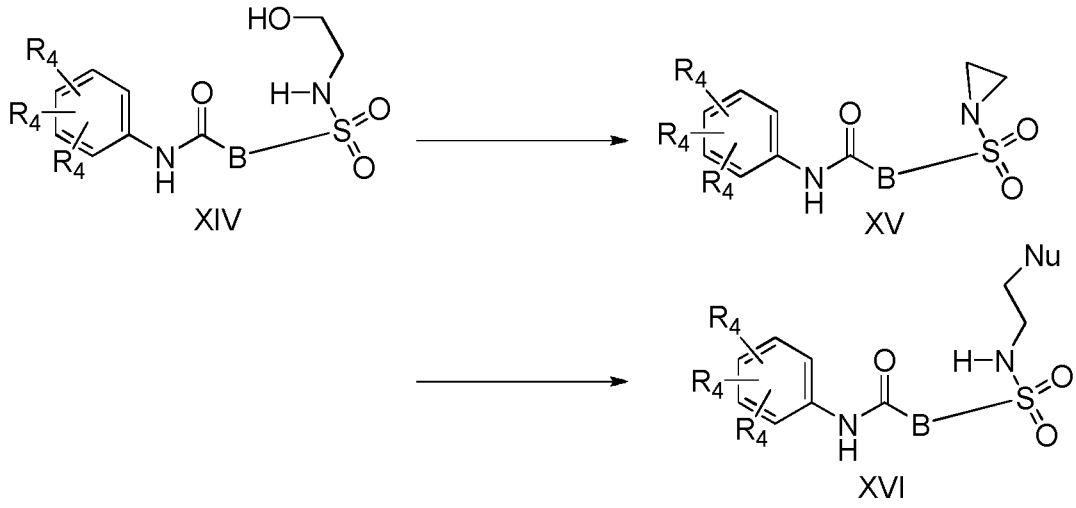


Scheme 3

In another example, compound IV can be reacted with an amino acid XI, in the presence of a base like NaOH, resulting in compound XII as described in scheme 4. This intermediate XII can then optionally be cyclised to compound XIII for example by heating with acetic anhydride and KOAc in toluene, or converting the carboxylic acid to an acid chloride followed by cyclisation in the presence of a base like triethylamine. Suitable examples of amino acids of structure XI are derivatives of 5-aminopentanoic acid or 4-aminobutanoic acid

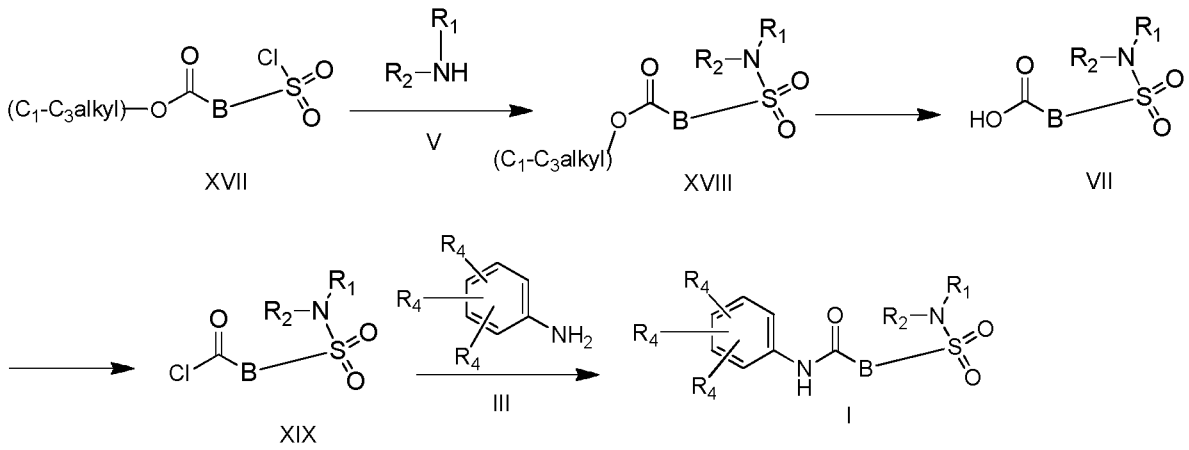


Scheme 4



Scheme 5

A synthetic route to compounds of general formula XVI is described in Scheme 5. A aminoethanol derivative XIV, prepared as described in scheme 1 for the compounds of general Formula (I), is transformed in a aziridine derivative XV by treatement with Diethyl diazene-1,2-dicarboxylate and PPh_3 in THF. The aziridine of general formula XV is reacted with a nucleophile Nu, resulting in a compound of general formula XVI. Examples of such nucleophiles (Nu) are, but are not limited to, morpholine and 1-methylpiperazine. Examples of a compound synthesized according to the route described in scheme 5, are compounds **116** and **117**.

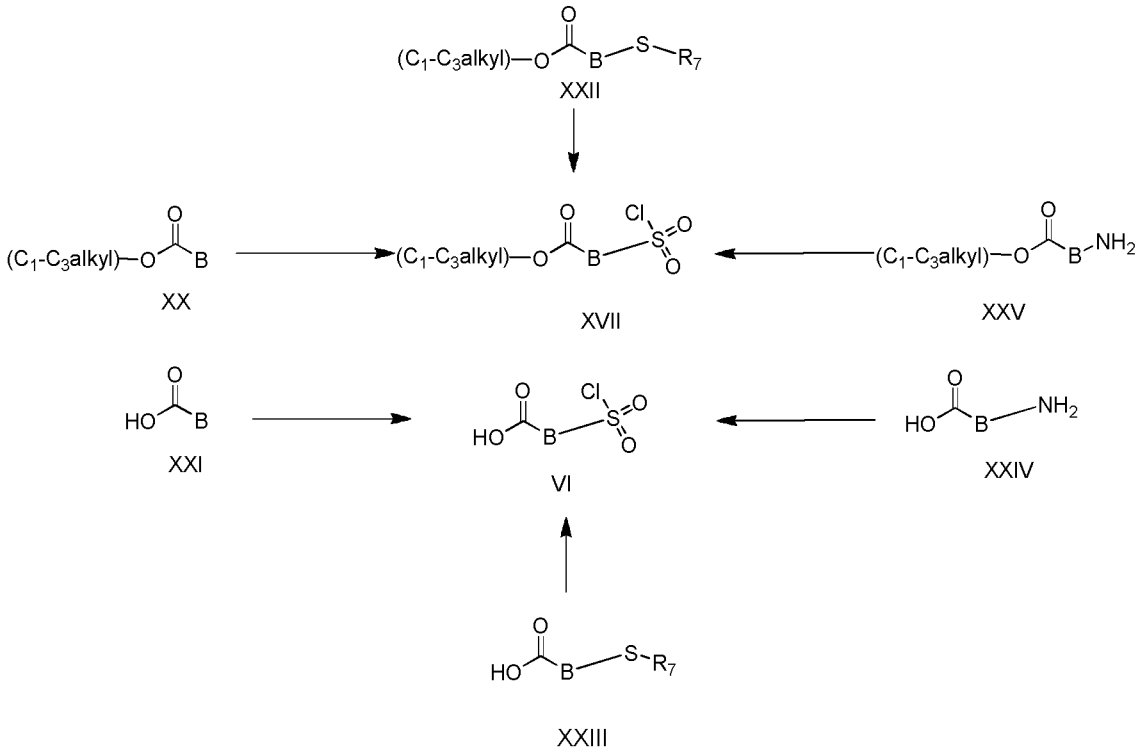


Scheme 6

An alternative method for the synthesis of compounds of general formula VII, is via ester XVII as described in scheme 6. Reaction of XVII with amine V, for example in an organic solvent like CH_2Cl_2 or THF in the presence of an organic base like for example

triethylamine or DIPEA, followed by hydrolysis of the ester, for example with LiOH in THF/H_2O, followed by acidification, results in a compound of general formula VII. A compound of general formula VII, obtained via the route in scheme 2 or scheme 6, can be transformed to and acid chloride of formula XIX, for example by treatement with oxalyl chloride or thionyl chloride. A compound of general formula XIX can then be transformed to a compound of general Formula (I) by reaction with an aniline of general formula III.

A compound of general formula VI can be converted to a compound of general formula II, for example by treatement with oxalyl chloride in CH_2Cl_2.



Scheme 7

Possible synthetic routes, for compounds of general formula XVII or VI are described in scheme 7, and further exemplified in the experimental section. Chlorosulfonation of carboxylic acids XXI or carboxylic esters XX, can results in compounds of general formula VI or XVII respectively, for example by treatement with chlorosulfonic acid (for example as reviewed in Phosphorus, Sulfur, and Silicon and the Related Elements Vol. 56, Iss. 1-4, 1991). Alternatively, compounds of general formula XXV or XXIV, may be converted to compound of general formula XVII and VI respectively, by conversion to the corresponding diazonium salts (for example by $NaNO_2/HCl$), followed by conversion of the diazonium salt to a sulfonyl chloride (for example by

SO_2/CuCl)(for example as described in *Organic Process Research & Development*, 13(5), 875-879; 2009). Alternatively, compounds of general formula XXII and XXIII (with R_7 equaling H, benzyl or methyl) may be converted to compound of general formula XVII and VI respectively, for example by treatement with Cl_2 or N-Chlorosuccinimide in AcOH/H_2O.

The subsitutents represented by R_4 in this general synthesis section are meant to include any substituent or reactive species that is suitable for transformation into any R_4 subsitutent according to the present invention without undue burden for the person skilled in the art.
Compounds not specifically described in the synthesis of compounds section below can be sysnthesized according to the Schemes 1-7 above and were commercially acquired.

Synthesis of compounds:
LC-MS methods:
Method A: mobile phase A : H_2O (0.1%TFA; B:CH_3CN (0.05% TFA) Stop Time : 10 min; gradient time(min) [%A/%B] 0.0 [100/0] to 1 [100/0] to 5 [40/60] to 7.5 [40/60] to 8.0 [100/0]; flow: 0.8 mL/min; column temp.: 50°C, YMC-PACK ODS-AQ, 50×2.0mm 5μm

Method B: mobile phase A : H_2O (0.1%TFA; B:CH_3CN (0.05% TFA) Stop Time : 10 min; gradient time(min) [%A/%B] 0.0 [90/10] to 0.8 [90/10] to 4.5 [20/80] to 7.5 [20/80] to 8.0 [90/10]; flow: 0.8 mL/min; column temp.: 50°C, YMC-PACK ODS-AQ, 50×2.0mm 5μm

Method C: mobile phase A : H_2O (0.1 % TFA); B:CH_3CN (0.05 % TFA) Stop Time : 10 min; gradient time(min) [%A/%B] 0.0 [90/10] to 0.8 [90/10] to 4.5 [20/80] to 7.5 [20/80]; 9.5 [90/10] flow: 0.8 mL/min; column temp.: 50°C; Agilent TC-C18, 50×2.1mm, 5μm

Method D: mobile phase A : H_2O (0.05 % $NH_3.H_2O$); B: CH_3CN Stop Time : 10 min; gradient time(min) [%A/%B] 0.0 [100/0] to 1 [100/0] to 5 [40/60] to 7.5 [40/60]; 8 [100/0] flow: 0.8 mL/min; column temp.: 40 °C, XBridge Shield-RP18, 50*2.1mm 5μm

Method E: mobile phase A : H_2O (0.1%TFA; B:CH_3CN (0.05% TFA) Stop Time : 10 min; Post Time: 0.5 min; gradient time(min) [%A/%B]0 [100/0] to 1 [100/0] to 5

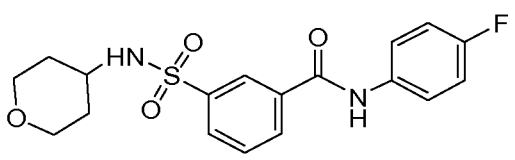
[40/60] to 7.5 [15/85] to 9.5 [100/0]; flow: 0.8 mL/min; column temp.: 50°C, Agilent TC-C18, 50×2.1mm, 5μm

Method F: The LC measurement was performed using an Acquity UPLC (Waters) system with column heater (set at 55 °C). Reversed phase UPLC (Ultra Performance Liquid Chromatography) was carried out on a bridged ethylsiloxane/silica hybrid (BEH) C18 column (1.7 μm, 2.1 x 50 mm; Waters Acquity) with a flow rate of 0.8 mL/min. Two mobile phases (10 mM ammonium acetate in H_2O/acetonitrile 95/5; mobile phase B: acetonitrile) were used to run a gradient condition from 95 % A and 5 % B to 5 % A and 95 % B in 1.3 minutes and hold for 0.3 minutes. An injection volume of 0.5 μl was used. Cone voltage was 10 V for positive ionization mode and 20 V for negative ionization mode.

Method G: The LC measurement was performed using an Acquity UPLC (Waters) with column heater (set at 55 °C). Reversed phase UPLC (Ultra Performance Liquid Chromatography) was carried out on a Acquity UPLC HSS T3 column (1.8 μm, 2.1 x 100 mm; Waters Acquity) with a flow rate of 0.8 mL/min. Two mobile phases (A: 10 mM ammonium acetate in H_2O/acetonitrile 95/5; mobile phase B: acetonitrile) were used to run a gradient condition from 100 % A and 0 % B to 5 % A and 95 % B in 2.1 minutes and subsequently to 0 % A and 100 % B in 0.9 minutes to 5% A and 95% B in 0.5 min. An injection volume of 1 μl was used. Cone voltage was 30 V for positive ionization mode and 30 V for negative ionization mode.

Method H: Reversed phase HPLC was carried out on an Atlantis C18 column (3.5 μm, 4.6 x 100 mm) with a flow rate of 1.6 mL/min. Column heater was set at 45 °C. Two mobile phases (mobile phase A: 70 % methanol + 30 % H_2O; mobile phase B: 0.1 % formic acid in H_2O/methanol 95/5) were employed to run a gradient condition from 100 % B to 5 % B + 95 % A in 9 minutes and hold these conditions for 3 minutes. An injection volume of 10 μl was used. Cone voltage was 10 V for positive ionization mode and 20 V for negative ionization mode.

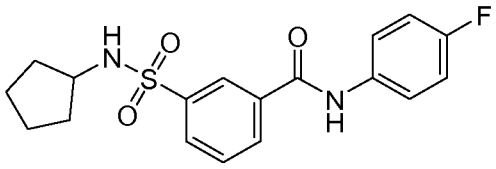
Compounds **21**, **49-55**, **57-62** were purchased from Aurora Fine Chemicals.



Compound **1**

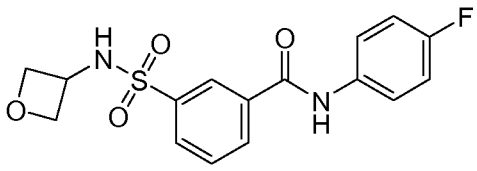
3-(chlorosulfonyl)benzoyl chloride (207 mg, 1 mmol) was dissolved in dichloromethane (3 mL) and 4-fluoroaniline (111 mg, 1.0 mmol) and triethylamine (112 mg, 1.0mmol) in dichloromethane (2 mL) were added to the mixture at 0°C. The mixture was next stirred at 20°C for 1 hour. To this reaction mixture containing 3-(4-fluorophenylcarbamoyl)benzene-1-sulfonyl chloride at 0°C, a solution of triethylamine (121 mg, 1.2 mmol) and 4-aminotetrahydropyran (88 mg, 0.861 mmol) in dichloromethane (3 mL) was added. The mixture was stirred at 20°C for 1 hour. The solvent was removed in vacuo. The residue was purified by high performance liquid chromatography (Column: Phenomenex Synergi C18 150*20mm*5um. A: H_2O+0.1%TFA; B: MeCN). The product fractions were collected and the organic solvent was evaporated. The fraction was neutralized by saturated $NaHCO_3$. The mixture was extracted with dichloromethane. The organic layer was dried over Na_2SO_4 and concentrated resulting in compound **1** (85.4 mg) Method A; Rt: 4.88 min. m/z : 379.2 $(M+H)^+$ Exact mass: 378.1

Following compounds were prepared similarly as compound **1** using the corresponding amines instead of 4-aminotetrahydropyran:



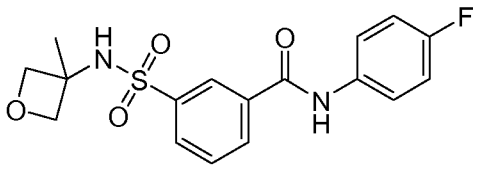
Compound **2**

Method B; Rt: 4.27 min. m/z : 363.1 $(M+H)^+$ Exact mass: 362.1



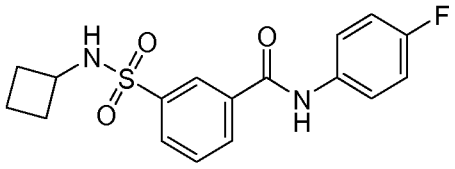
Compound **3**

Method A; Rt: 4.64 min. m/z : 351.1 $(M+H)^+$ Exact mass: 350.1



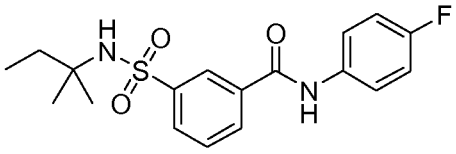
Compound **4**

Method A; Rt: 4.87 min. m/z : 365.1 $(M+H)^+$ Exact mass: 364.1



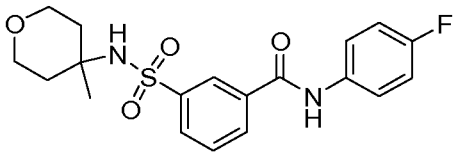
Compound **5**

Method A; Rt: 5.32 min. m/z : 349.1 $(M+H)^+$ Exact mass: 348.1



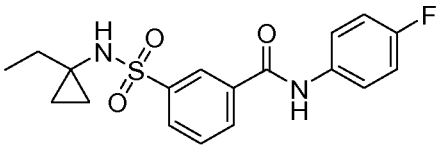
Compound **79**

Method A; Rt: 5.39 min. m/z : 365.2 $(M+H)^+$ Exact mass: 364.1
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.37 (1 H, t, *J*=1.5 Hz), 8.16 (1 H, br. s.), 8.11 (1 H, dm, *J*=8.0 Hz), 8.05 (1 H, dm, *J*=8.0 Hz), 7.57 - 7.70 (3 H, m), 7.08 (2 H, t, *J*=8.7 Hz), 4.78 (1 H, s), 1.55 (2 H, q, *J*=7.5 Hz), 1.18 (6 H, s), 0.84 (3 H, t, *J*=7.5 Hz).



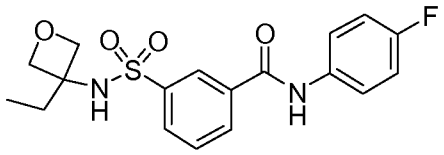
Compound **83**

Method A; Rt: 4.20 min. m/z : 415.0 $(M+Na)^+$ Exact mass: 392.1;
Purified by silica gel chromatography (gradient eluent: petroleum ether/ethyl acetate from 100/1 to 1/1). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.57 (1 H, br. s), 8.33 - 8.47 (1 H, m), 8.19 (1 H, dm, *J*=7.5 Hz), 8.06 (1 H, dm, *J*=7.5 Hz), 7.72 - 7.85 (3 H, m), 7.66 - 7.73 (1 H, br. s), 7.12 - 7.31 (2 H, m), 3.42 - 3.58 (4 H, m), 1.71 - 1.92 (2 H, m), 1.27 - 1.50 (2 H, m), 1.06 (3 H, s).



Compound **87**

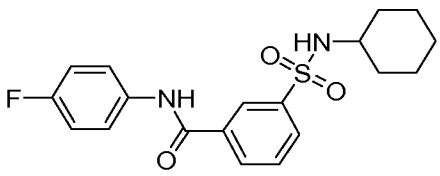
Method B; Rt: 3.94 min. m/z : 363.1 $(M+H)^+$ Exact mass: 362.1
Purified by high performance liquid chromatography over RP-18 (eluent: CH_3CN in water (0.1%TFA) from 25 to 55, v/v). ^{1}H NMR (400 MHz, DMSO-d_6), δ ppm 0.34-0.42 (m, 2 H), 0.46-0.54 (m, 2H), 0.75(t, J=7.3 Hz, 3 H), 1.28 (q, J=7.3 Hz, 2 H), 7.15-7.25 (m,2 H) 7.67-7.83 (m, 3 H), 7.97 (d, J=8.3 Hz; 1 H), 8.14-8.25 (m, 2 H), 8.33 (s, 1 H), 10.55 (s, 1 H).



Compound **89**

Method E; Rt: 4.83 min. m/z : 379.1 $(M+H)^+$ Exact mass: 378.1; ^1H NMR (400 MHz, DMSO-d6), δ ppm 10.60 (s, 1H), 8.48 (br. s., 1H), 8.39 (s, 1H), 8.23 (d, J=7.8 Hz, 1 H), 8.04 (d, J=7.8 Hz, 1 H), 7.74-7.87 (m, 3 H), 7.23 (t, J=9.0 Hz, 2 H), 4.51(d, J= 6.5 Hz, 2 H), 4.20(d, J=6.5 Hz, 2 H), 1.84 (q, J=7.3 Hz, 2 H), 0.64(t, J=7.3 Hz, 3 H). Prepared similarly as described for compound **1**, using 3-ethyloxetan-3-amine instead of 4-aminotetrahydropyran. Synthesis of 3-ethyloxetan-3-amine: 3-ethyloxetane-3-carboxylic acid (3.0g, 23.1 mmol), DPPA (Diphenylphosphoryl azide, 7.61 g, 27.7 mmol), triethylamine (3.0 g, 23.1 mmol) and BnOH (2.99 g, 27.7 mmol) were dissolved in toluene (50 mL). The mixture was stirred at 110°C overnight. The solvent was removed in vacuo. Dichloromethane (50 mL) was added. The mixture was washed with 1N HCl (20 mL). The aqueous layer was extracted with dichloromethane (20 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed in vacuo. The residue was purified by column chromatography over silica gel (eluent: petroleum ether / ethyl acetate from 100/1 to 60/40) resulting in benzyl 3-ethyloxetan-3-ylcarbamate (4.0 g). To a solution of benzyl 3-ethyloxetan-3-yl-carbamate (2.0g, 8.5mmol) and cyclohexa-1, 4-diene (1.02 g, 12.75 mmol) in MeOH (20 mL) was added Pd-C (10%, 0.2 g) under N_2. The mixture was stirred under H_2 balloon at 25°C for 4 hours. After filtration, the filtrate was concentrated resulting in 3-ethyloxetan-3-amine (860 mg), which was used as such in the next reaction.

Synthesis of compound **6**:

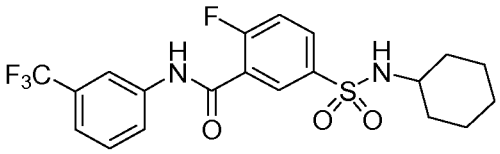


Compound **6**

To a solution of 3-(chlorosulfonyl)benzoic acid (1 g, 4.53 mmol) in CH_2Cl_2 (20 mL) at 5°C, cyclohexanamine (0.899 g, 9.06 mmol) and triethylamine (1.38 g, 13.60 mmol) were successively added drop wise.The solution was stirred at room temperature overnight. The mixture was washed with 1N HCl (50 mL). The organic phase was dried over $MgSO_4$ and concentrated resulting in 3-(N-cyclohexylsulfamoyl)benzoic acid as a white solid (1.2 g), which was used in the next step without purification. To a solution of 3-(N-cyclohexylsulfamoyl)benzoic acid (1.2 g, 4.24 mmol) in DMF

(15 mL) at 5°C, 4-fluoroaniline (0.52 g, 4.66 mmol) and DIPEA (1.64 g, 12.71 mmol) were successively added.. The mixture was stirred for 20 minutes and then HATU (1.93 g, 5.08 mmol) was added. The solution was stirred at room temperature overnight. To the reaction mixture aqueous $NaHCO_3$ (50 mL) was added followed by EtOAc (50 mL). The organic layer washed with HCl (5%; 50 mL) and brine. The organic layer was dried with $MgSO_4$ and concentrated, resulting in a residue. The obtained residue was purified by a silica gel chromatography column (Petroleum ether:EtOAc=2:1) resulting in compound **6** as a white solid (850 mg). Method B; Rt: 4.50 min. m/z : 377.2 $(M+H)^+$ Exact mass: 376.1

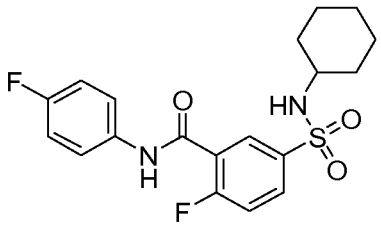
Synthesis of compound **7**



Compound **7**

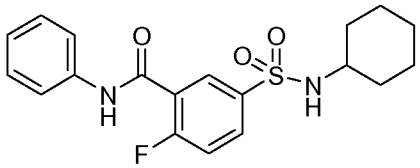
To 5-(chlorosulfonyl)-2-fluorobenzoic acid (10 g, 41.91 mmol) in EtOAc (150 mL) cyclohexanamine (12.47 g, 125.72 mmol) was added at room temperature. The reaction mixture was stirred at room temperature for 10 minutes and washed with 1N HCl (100 mL). The organic phase was dried over $MgSO_4$ and concentrated resulting in 5-(N-cyclohexylsulfamoyl)-2-fluorobenzoic acid as a white solid (10.9 g), which was used in the next steps without further purification. To a solution of 5-(N-cyclohexyl-sulfamoyl)-2-fluorobenzoic acid (1 g, 3.32 mmol) in DMF (15 mL) 3-(trifluoromethyl)-aniline (0.54 g, 3.32 mmol) and DIPEA (1.29 g, 9.96 mmol) were successively added at 5°C. The mixture was stirred for 20 minutes and then HATU (1.51 g, 3.98 mmol) was added. The solution was stirred at room temperature overnight. To the reaction mixture aqueous $NaHCO_3$ (50 mL), was added followed by EtOAc (50 mL). The organic layer was washed with HCl (5%) and brine. The organic layer was dried with $MgSO_4$, concentrated in vacuo, and the obtained residue was purified by preparative HPLC resulting in compound **7** (902 mg) as a white solid. Method B; Rt: 4.85 min. m/z : 445.2 $(M+H)^+$ Exact mass: 444.1; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 10.94 (1 H, br. s), 8.15 - 8.22 (1 H, m), 8.12 (1 H, dd, *J*=6.5, 2.5 Hz), 8.03 (1 H, ddd, *J*=9.0, 4.5, 2.5 Hz), 7.88 - 7.97 (1 H, m), 7.83 (1 H, d, *J*=7.5 Hz), 7.58 - 7.67 (2 H, m), 7.46 - 7.54 (1 H, m), 2.90 - 3.07 (1 H, m), 1.51 - 1.67 (4 H, m), 1.38 - 1.51 (1 H, m), 0.96 - 1.27 (5 H, m)

Examples of compounds prepared similar as compound **7**, using the corresponding anilines instead of 3-(trifluoromethyl)aniline:



Compound **18**

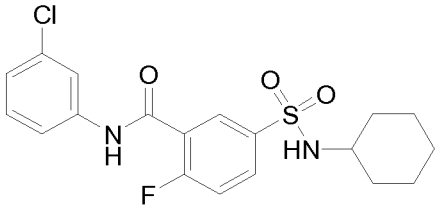
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.68 (1 H, br. s), 8.08 (1 H, dd, *J*=6.0, 2.5 Hz), 8.01 (1 H, ddd, *J*= 8.5, 4.5, 2.5 Hz), 7.83 (1 H, br. s), 7.70 - 7.77 (2 H, m), 7.60 (1 H, app. t, *J*= 9.0 Hz), 7.18 - 7.27 (2H, m), 2.90 - 3.07 (1 H, m), 1.53 - 1.67 (4 H, m), 1.40 - 1.53 (1 H, m), 0.96 - 1.25 (5 H, m). Method C; Rt: 4.21 min. m/z : 395.1 $(M+H)^+$ Exact mass: 394.1



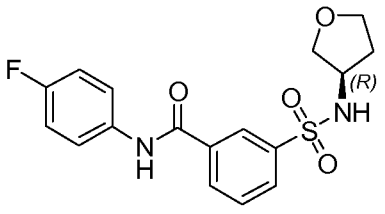
Compound **19**

Method C; Rt: 4.17 min. m/z : 377.1 $(M+H)^+$ Exact mass: 376.1

Compound **43**



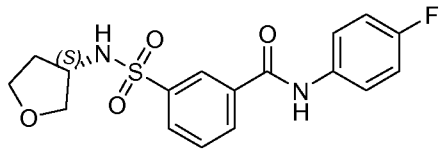
Method C; Rt: 4.53 min. m/z : 411.1 $(M+H)^+$ Exact mass: 410.1



Compound **8**

To a solution of (*R*)-tetrahydrofuran-3-amine (0.87 g, 9.97 mmol) in THF (20 mL) aqueous sodium hydroxide was added (4 mL, 5 N) in ice bath followed by 3-(chloro-sulfonyl)benzoic acid (2.2 g, 9.97 mmol). After stirring at 25°C for 3 hours, the reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (20 mL). The aqueous layer was adjusted to pH=3 by aq. HCl (2 N) and then the resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layer was washed by brine, dried over anhydrous $MgSO_4$ and concentrated in vacuo resulting in

compound (*R*)-3-(N-(tetrahydrofuran-3-yl)sulfamoyl)benzoic acid (900 mg). To a solution of compound (*R*)-3-(N-(tetrahydrofuran-3-yl)sulfamoyl)benzoic acid (0.80 g, 2.95 mmol), 4-fluoroaniline (0.39g, 3.54 mmol), and HATU (3.36 g, 8.85 mmol) in CH_2Cl_2 (10 mL) cooled in an ice bath under N_2 atmosphere,DIPEA (0.57g, 0.44 mmol) was added. The resulting mixture was diluted with CH_2Cl_2 (15 mL) and washed with saturated aqueous $NaHCO_3$ (15 mL) and brine (10 mL). After drying over anhydrous $MgSO_4$ the solvent was removed in vacuo. The obtained residue was purified by preparative high performance liquid chromatography over RP-18 (eluent: CH_3CN in H_2O: from 40% to 80%, v/v; 0.05% TFA as addition). The pure fractions were collected and the volatiles were removed in vacuo. The aqueous layer was adjusted to PH=7 with Amberlite IRA-900 ion exchange resin (OH form), filtrated and lyophilized. The obtained residue was further purified by prep. SFC (Column:Chiralpak AD-3 150×4.6mm I.D., 3um Mobile phase: 40% of methanol (0.05% diethylamine) in CO_2. Flow rate: 2.5 mL/min) resulting in compound **8** (370 mg) Method A; Rt: 4.6 min. m/z : 365.2 $(M+H)^+$ Exact mass: 364.1; $[\alpha]_D^{20} = -13.60$ (*c*=0.11, MeOH) ^1H NMR (400 MHz, DMSO-d_6) δ ppm 10.57 (1 H, br. s), 8.34 - 8.40 (1 H, m), 8.18 - 8.27 (1 H, m), 8.09 (1 H, br. s), 7.99 - 8.06 (1 H, m), 7.74 - 7.84 (3 H, m), 7.13 - 7.33 (2 H, m), 3.64 - 3.83 (2 H, m), 3.50 - 3.64 (2 H, m), 3.35 - 3.39 (1 H, m), 1.80 - 1.99 (1 H, m), 1.51 - 1.68 (1 H, m).

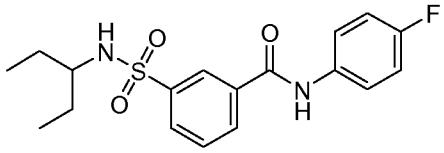


Compound **9**

To an iced-cooled mixture of (*S*)-tetrahydrofuran-3-amine hydrochloride (0.500 g, 4.41 mmol) and NaOH (0.485 g, 12.138 mmol) in H_2O (5 mL) and THF (5 mL) 3-(chlorosulfonyl)benzoic acid (0.893 g, 4.406 mmol) was added in several portions. Then, the reaction mixture was stirred at 20°C for 2 hours. The resulting mixture was diluted with H_2O (10 mL) and extracted with ethyl acetate (10 mL). The pH value of aqueous layer was adjusted to 3 by adding 1N HCl and then the mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic layer was washed by brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure resulting in (*S*)-3-(N-(tetrahydrofuran-3-yl)sulfamoyl)benzoic acid (0.60 g). To an ice cooled mixture of (*S*)-3-(N-(tetrahydrofuran-3-yl)sulfamoyl)benzoic acid (600 mg, 2.212 mmol), 4-fluoroaniline (270 mg, 2.433mmol) and HATU (1.01 g, 2.654 mmol) in DMF (5 mL) DIPEA (1.15 mL, 6.636 mmol) was added under N_2 atmosphere. The resulting mixture was stirred at 20°C for 2 hour. The solvent was removed in vacuo.

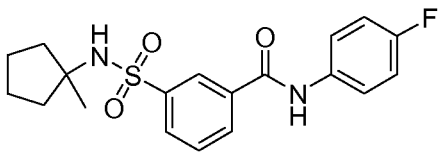
The mixture was washed with saturated aqueous critic acid (10 mL), brine and dried over Na_2SO_4. The solvent was removed in vacuo. The residue was purified by column chromatography over silica gel (gradient eluent: petroleum ether/ethyl acetate from 100/0 to 10/90). The pure fractions were collected and the solvent was removed in vacuo. The residue was further purified by preparative high performance liquid chromatography over RP-18 (eluent: CH_3CN in H_2O from 40% to 80%, v/v; 0.06% NH_4HCO_3 as addition). The pure fractions were collected and the volatiles were removed in vacuo. The aqueous layer was lyophilized to dryness resulting in compound **9** (0.48 g) Method A; Rt: 4.6 min. m/z : 365.2 $(M+H)^+$ Exact mass: 364.1;$[\alpha]_D^{20} = +15.56$ (*c* 0.10, MeOH); ^1H NMR (400 MHz, 80°C, DMSO-d_6) δ ppm 10.35 (1 H, br. s), 8.32 - 8.48 (1 H, m), 8.15 - 8.32 (1 H, m), 8.03 (1 H, br. s), 7.83 - 7.94 (1 H, m), 7.68 - 7.83 (3 H, m), 7.06 - 7.31 (2 H, m), 3.70 - 3.87 (2 H, m), 3.51 - 3.70 (2 H, m), 3.32 - 3.48 (1 H, m), 1.85 - 2.04 (1 H, m), 1.59 - 1.78 (1 H, m)

Compounds prepared similarly as described for compound **8** and **9** from the corresponding amines instead of tetrahydrofuran-3-amine :



Compound **10**

Method B; Rt: 4.24 min. m/z : 365.2 $(M+H)^+$ Exact mass: 364.1;



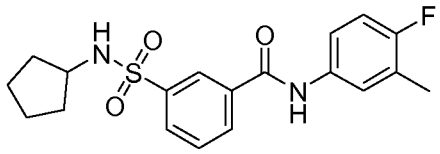
Compound **76**

Using 1-methylcyclopentanamine instead of tetrahydrofuran-3-amine, purified using Gemini 250*20mm*5um (eluent: CH_3CN in H_2O (0.1% TFA) from 40% to 70%, v/v).Method B; Rt: 4.24 min. m/z : 377.2 $(M+H)^+$ Exact mass: 376.1;

Synthesis of 3-(N-cyclopentylsulfamoyl)benzoic acid:

To an iced-cooled mixture of cyclopentanamine (1.93 g, 22.66 mmol) and a solution of NaOH (1.81 g, 45.32 mmol) in H_2O (25 mL) and THF (25 mL) was added 3-(chloro-sulfonyl)benzoic acid (5.0 g, 22.66 mmol) in portions. The reaction mixture was stirred at 20°C for 2 hours. The resulting mixture was diluted with H_2O (20 mL) and extracted with ethyl acetate (30 mL). The aqueous layer was separated and adjusted pH =2 by 4 N HCl and extracted with dichloromethane (3 x 30 mL). The combined organic layer

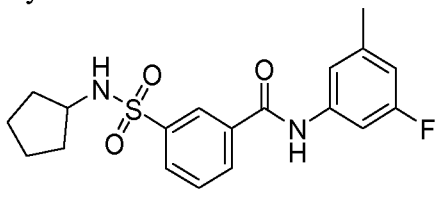
was washed by brine (15 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford 3-(N-cyclopentylsulfamoyl)benzoic acid (4.5 g).



Compound **11**

To an ice cooled mixture of 3-(N-cyclopentylsulfamoyl)benzoic acid (250 mg, 0.928 mmol), 4-fluoro-3-methylaniline (116.2 mg, 0.928 mmol), HATU (388.2 mg, 1.021 mmol) in CH_2Cl_2 (15 mL) DIPEA (359.8 mg, 2.784 mmol) was added under a N_2 atmosphere. The resulting mixture was stirred at 20°C for 16 hours. The solvent was removed in vacuo. The mixture was washed with saturated aqueous critic acid (10 mL), brine and dried over Na_2SO_4. The solvent was removed in vacuo. The residue was purified by column chromatography over silica gel (gradient eluent: petroleum ether/ethyl acetate from 100/0 to 10/90). The pure fractions were collected and the solvent was removed in vacuo. The residue was further purified by preparative high performance liquid chromatography over RP-18 (eluent: CH_3CN in H_2O from 45% to 75%, v/v; 0.01% HCl as addition). The pure fractions were collected and the volatiles were removed in vacuo. The aqueous layer was adjusted to Ph=7 with Amberlite IRA-900 ion exchange resin (OH form), filtrated and lyophilized to dryness to afford compound **11** (170.0 mg). Method B; Rt: 4.31 min. m/z : 377.2 $(M+H)^+$ Exact mass: 376.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.47 (1 H, br. s), 8.33-8.35 (1 H, m), 8.17 (1 H, dm, *J*=8.0), 7.98 (1 H, dm, *J*=8.0), 7.78 (1 H, d, *J*=7.0 Hz), 7.74 (1 H, t, *J*=8.0 Hz), 7.62 - 7.68 (1 H, m), 7.53 - 7.61 (1 H, m), 7.13 (1 H, t, *J*=9.0 Hz), 3.37 - 3.48 (1 H, m), 2.23 (3 H, d, *J*=1.8 Hz), 1.44 - 1.69 (4 H, m), 1.12 - 1.45 (4 H, m)

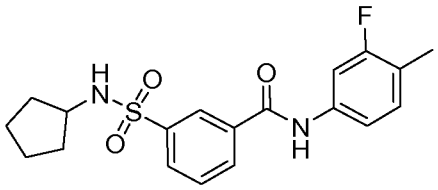
Prepared similarly as compound **11** starting from the corresponding anilines instead of 4-fluoro-3-methylaniline :



Compound **12**

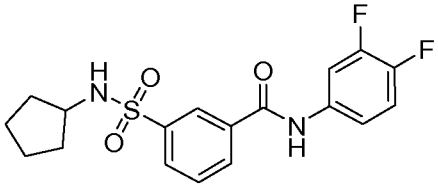
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.60 (1 H, bs), 8.36 (1 H, t, *J*=1.5 Hz), 8.19 (1 H, dm, *J*=7.5 Hz), 8.02 (1 H, dm, *J*=7.5 Hz), 7.81 (1 H, d, *J*=7.5 Hz), 7.78 (1 H, t, *J*=7.5 Hz), 7.55 (1 H, dm, *J*=11.0 Hz), 7.38 - 7.46 (1 H, m), 6.82 (1 H, dm, *J*=9.5 Hz),

3.41 - 3.54 (1 H, m), 2.34 (3 H, s), 1.45 - 1.70 (4 H, m), 1.19 - 1.45 (4 H, m); Method B; Rt: 4.41 min. m/z : 377.2 $(M+H)^+$ Exact mass: 376.1



Compound **13**

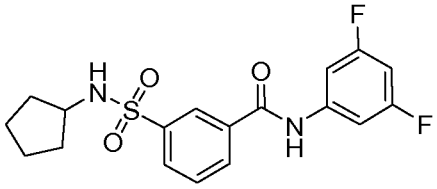
The residue was purified by column chromatography over silica gel (gradient eluent: petroleum ether/ethyl acetate from 100/0 to 40/60). Method B; Rt: 4.41 min. m/z : 377.2 $(M+H)^+$ Exact mass: 376.1



Compound **14**

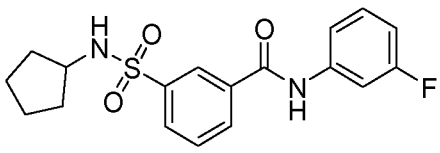
Method B; Rt: 4.34 min. m/z : 381.2 $(M+H)^+$ Exact mass: 380.1

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.20 - 1.44 (m, 4 H), 1.44 - 1.68 (m, 4 H), 3.44 (sxt, *J*=6.8 Hz, 1 H), 7.45 (dt, *J*=10.6, 9.0 Hz, 1 H), 7.51 - 7.60 (m, 1 H), 7.77 (t, *J*=7.8 Hz, 1 H), 7.80 (d, *J*=7.2 Hz, 1 H), 7.93 (ddd, *J*=13.2, 7.5, 2.5 Hz, 1 H), 8.02 (d, *J*=7.8 Hz, 1 H), 8.19 (d, *J*=7.7 Hz, 1 H), 8.35 (t, *J*=1.7 Hz, 1 H), 10.70 (s, 1 H)



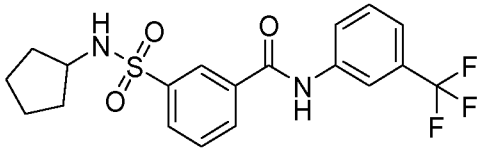
Compound **15**

Method B; Rt: 4.43 min. m/z : 381.2 $(M+H)^+$ Exact mass: 380.1



Compound **77**

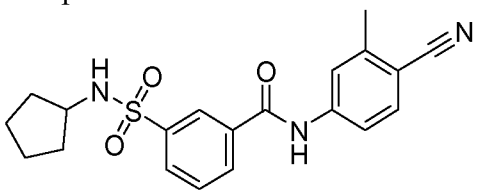
Method B; Rt: 5.45 min. m/z : 363.2 $(M+H)^+$ Exact mass: 362.1



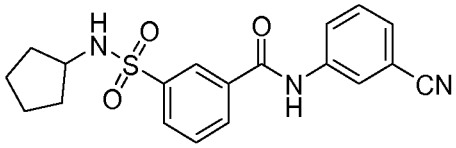
Compound **81**

purified by preparative high performance liquid chromatography (column: Phenomenex Synergi 200mm*77mm, 10um; mobile phase: CH_3CN in water (0.1% TFA) from 45% to 75%,). Method A; Rt: 5.87 min. m/z : 413.2 $(M+H)^+$ Exact mass: 412.1

Compound **16**

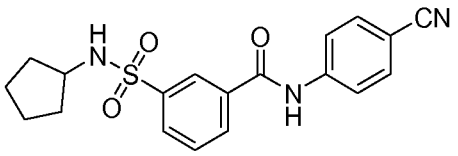


A solution of 3-(N-cyclopentylsulfamoyl)benzoic acid (500 mg, 1.73 mmol) in oxalyl dichloride (10 mL) was stirred at 45°C for 5 hours. The solvent was removed in vacuo. The crude 3-(N-cyclopentylsulfamoyl)benzoyl chloride (600 mg) was used as such in the next step.To an ice cooled mixture of 3-(N-cyclopentylsulfamoyl)benzoyl chloride (600 mg, 1.74 mmol) and 4-amino-2-methylbenzonitrile (230 mg, 1.74 mmol) in CH_2Cl_2 (5 mL) was added pyridine (10 mL) under N_2 atmosphere. The resulting mixture was stirred at 20°C for 16 hours. The solvent was removed in vacuo. The residue was purified by preparative high performance liquid chromatography over RP-18 (eluent: CH_3CN in H_2O from 50% to 80%, v/v; 0.05% TFA as addition). The pure fractions were collected and the volatiles were removed in vacuo. The aqueous layer was adjusted to PH=7 with Amberlite IRA-900 ion exchange resin (OH form), filtrated and lyophilized resulting in compound **16** (250mg). Method B; Rt: 4.23 min. m/z : 384.2 $(M+H)^+$ Exact mass: 383.1.



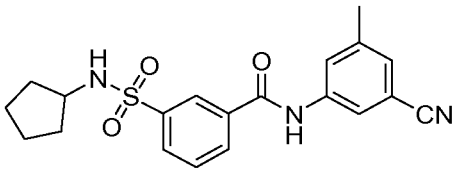
Compound **75**

Prepared similarly as described for compound **16** using 3-aminobenzonitrile instead of 4-amino-2-methylbenzonitrile. Method A; Rt: 5.24 min. m/z : 370.2 $(M+H)^+$ Exact mass: 369.1.



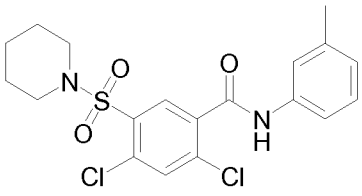
Compound **80**

Prepared similarly as described for compound **16** using 4-aminobenzonitrile instead of 4-amino-2-methylbenzonitrile. Method A; Rt: 5.32 min. m/z : 370.2 $(M+H)^+$ Exact mass: 369.1.



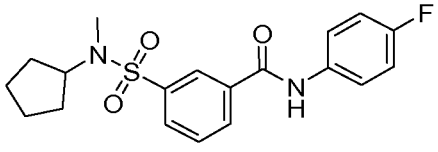
Compound **82**

Prepared similarly as described for compound **16** using 3-amino-5-methylbenzonitrile instead of 4-amino-2-methylbenzonitrile. Method A; Rt: 5.52 min. m/z : 384.2 $(M+H)^+$ Exact mass: 383.1.



Compound **17**

To a solution of compound 2,4-dichloro-5-(piperidin-1-ylsulfonyl)benzoic acid (1.0 g, 2.96 mmol), m-toluidine (0.38 g, 3.55 mmol), and HATU (1.69 g, 4.44 mmol) in CH_2Cl_2 (10 mL) cooled in an ice bath, DIPEA (1.15g, 8.88 mmol) was added under N_2 atmosphere. The resulting mixture was diluted with CH_2Cl_2 (15 mL) and washed with saturated aqueous $NaHCO_3$ (15 mL) and brine (10 mL), dried over anhydrous $MgSO_4$ and the solvent was removed in vacuo. The residue was purified by column chromatography over silica gel (gradient eluent: petroleum ether/ethyl acetate from 100/0 to 40/60). The pure fractions were collected and the solvent was removed in vacuo, resulting in compound **17** (0.65 g). Method B; Rt: 4.70 min. m/z : 427.1 $(M+H)^+$ Exact mass:426.1

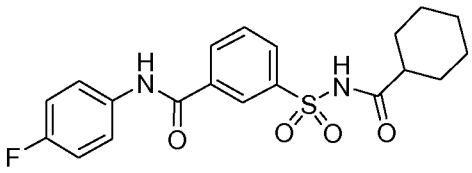


Compound **46**

To a solution of 3-(chlorosulfonyl)benzoic acid (1.10 g, 4.97 mmol) in THF (60mL) sodium hydroxide was added (aq., 2 mL, 5N) in ice bath followed by adding N-methyl-

cyclopentanamine (0.50 g, 4.97 mmol). After stirring at 25°C for 3 hours, the reaction mixture was diluted with H_2O (50mL) and extracted with EtOAc (50mL). The aqueous layer was adjusted to pH=3 by HCl (2N) and extracted with EtOAc (3 x 50mL). The combined organic layer was washed by brine, dried over anhydrous $MgSO_4$ and concentrated in vacuo resulting in 3-(N-cyclopentyl-N-methylsulfamoyl)benzoic acid (0.8 g). To a solution of 3-(N-cyclopentyl-N-methylsulfamoyl)benzoic acid (0.80 g, 2.82 mmol), 4-fluoroaniline (0.31 g, 2.82 mmol), and HATU (1.61 g, 4.24 mmol) in CH_2Cl_2 (10 mL), cooled in an icebath, DIPEA (1.09 g, 8.47mmol) was added under N_2 atmosphere. The resulting mixture was diluted with CH_2Cl_2 (15 mL) and washed with saturated aqueous $NaHCO_3$ (15 mL) and brine (10 mL), dried over anhydrous $MgSO_4$ and the solvent was removed in vacuo. The obtained residue was purified by preparative high performance liquid chromatography over RP-18 (eluent: CH_3CN in H_2O from 30% to 80%, v/v; 0.05% TFA as addition). The pure fractions were collected and the volatiles were removed in vacuo. The aqueous layer was adjusted to Ph=7 with Amberlite IRA-900 ion exchange resin (OH form), filtrated and lyophilized to dryness resulting in compound **46** (0.73g). Method B; Rt: 4.43 min. m/z : 377.2 $(M+H)^+$ Exact mass:376.1

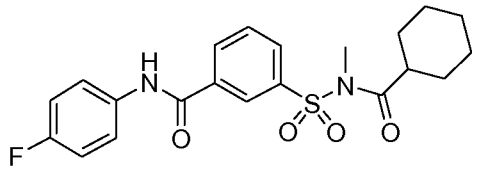
Compound **56**



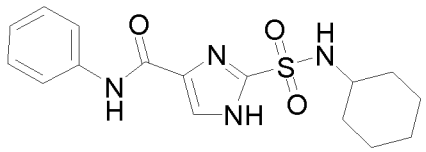
4-fluoroaniline (0.93 g, 8.366 mmol) and DIPEA (2.91 mL, 16.732 mmol) were dissolved in CH_2Cl_2 (20 mL). 3-(chlorosulfonyl)benzoyl chloride (2 g, 8.366 mmol) in CH_2Cl_2 (20 mL) was added in one portion at 0°C. The mixture was stirred for 1 hour at 0°C. The reaction mixture (40 mL) containing 3-(4-fluorophenylcarbamoyl)benzene-1-sulfonyl chloride was used to the next step without further purification. Ammonia (2.52 g, 18 mmol, 25-28% wt) was added to a solution of 3-(4-fluorophenylcarbamoyl)-benzene-1-sulfonyl chloride (obtained as above, 6 mmol) in CH_2Cl_2 (30 mL) at 0°C. The mixture was stirred for 1 hour at 20°C. 1 N HCl (30 mL) was added to the reaction mixture and the volatiles were partely removed in vacuo. The formed precipitate was filtered and co-evaporated with toluene (10 mL), resulting in N-(4-fluorophenyl)-3-sulfamoylbenzamide (1.6 g). A solution of N-(4-fluorophenyl)-3-sulfamoylbenzamide (1.8 g, 6.12 mmol) and cyclohexanecarbonyl chloride (1.79 g, 12.23 mmol) in chloroform (40 mL) with SiO_2 (180 mg) and H_2SO_4 (0.5 mL) was refluxed for 1 hour. Dichloromethane (20 mL) was added and the solid was filtered off. The filtrate was washed with water (10 mL) and dried over Na_2SO_4. The solvent was removed in vacuo. The obtained residue was purified by silica gel column chromatography (gradient

eluent: petroleum ether/ethyl acetate from 100/0 to 70/30). The obtained product (1.2 g, purity 95%) was further washed with methyl t-butyl ether (10 mL) resulting in compound **56** (500 mg, 99.7 % purity). Method A; Rt: 5.51 min. m/z : 405.2 $(M+H)^+$ Exact mass: 404.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.16 (1 H, br. s), 10.62 (1 H, br. s), 8.41 (1 H, t, *J*=2.0 Hz), 8.27 (1 H, dm, *J*=7.5 Hz), 8.09 (1 H, dm, *J*=7.5 Hz), 7.73 - 7.82 (3 H, m), 7.07 - 7.33 (2 H, m), 2.11 - 2.31 (1 H, m), 1.43 - 1.80 (5 H, m), 0.94 - 1.32 (5 H, m)

Compound **48**



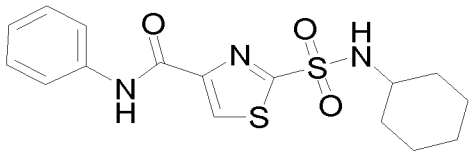
Compound **56** (600 mg) was dissolved in CH_2Cl_2 (6 mL) and MeOH (2 mL) and $TMSCHN_2$ (3.7 mL, 7.415 mmol, 2M in hexane) were added drop wise at 20°C. The mixture was stirred for 2 hours at 20°C. The solvent was removed in vacuo. The residue was purified by flash column (gradient eluent: petroleum ether/ethyl acetate from 100/0 to 70/30) resulting in a residue (0.41 g). The obtained product was further purified by preparative high performance liquid chromatography over RP-18 (eluent: CH_3CN in H_2O (0.1% TFA) from 20% to 50%, v/v). The pure fractions were collected and the volatiles were removed in vacuo. The precipitate was filtered and the residual water was removed by lyophilization resulting in compound **48** (300 mg). Method B; Rt: 4.60 min. m/z : 419.2 $(M+H)^+$ Exact mass:418.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.62 (1 H, br. s), 8.40 - 8.45 (1 H, m), 8.28 (1 H, dm, *J*=7.5 Hz), 8.13 (1 H, dm, *J*=7.5 Hz), 7.66 - 7.95 (3 H, m), 7.07 - 7.33 (2 H, m), 3.40 (3 H, s), 2.73 - 2.92 (1 H, m), 1.42 - 1.77 (5 H, m), 0.90 - 1.35 (5 H, m).



Compound **63**

A mixture of ethyl 2-(chlorosulfonyl)-1H-imidazole-4-carboxylate (1 g, 4.19 mmol), Et_3N (1.27 g, 12.55 mmol) and cyclohexanamine (0.623 g, 6.28 mmol) in THF (25 mL) was stirred at room temperature for 15 hours. The mixture was concentrated and purified by preparative HPLC (Column: C18; Mobile phase A: purified water (0.075%TFA, V/V); Mobile phase B: acetonitrile; Flow rate: 80mL/min; Gradient:

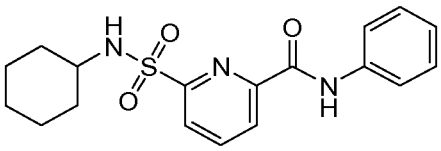
25-55%, 30 min) resulting in ethyl 2-(N-cyclohexylsulfamoyl)-1H-imidazole-4-carboxylate (0.6 g) as a light yellow solid. To a solution of ethyl 2-(N-cyclohexyl-sulfamoyl)-1H-imidazole-4-carboxylate (0.6 g, 1.99 mmol) in EtOH-H_2O (3/1; 20 mL), LiOH (0.145 g, 6.055 mmol) was added. The mixture was stirred at room temperature for 15 hours. The reaction mixture was neutralized with HCl (2M), diluted with water and then extracted into EtOAc, dried over $MgSO_4$, filtered and concentrated resulting in 2-(N-cyclohexylsulfamoyl)-1H-imidazole-4-carboxylic acid (400 mg) as a white solid. A mixture of 2-(N-cyclohexylsulfamoyl)-1H-imidazole-4-carboxylic acid (0.3 g, 1.098 mmol), aniline (0.102 g, 1.098 mmol), DIPEA (0.284 g, 2.196 mmol) and HATU (0.501 g, 1.317 mmol) in DMF (25 mL) was stirred at room temperature for 15 hours. The mixture was purified by preparative HPLC (Column: YMC 150x30mm. Mobile phase A: purified water (0.075%TFA, V/V); Mobile phase B: acetonitrile; Flow rate: 30mL/min; Gradient: 40-70%, 8 min) resulting in compound **63** (218 mg). Method B; Rt: 3.98 min. m/z : 349.2 $(M+H)^+$ Exact mass:348.1. ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 1.26 (s, 5 H) 1.51 - 1.62 (m, 1 H) 1.65 - 1.80 (m, 4 H) 3.23 - 3.29 (m, 1 H) 7.10 - 7.18 (m, 1 H) 7.32 - 7.39 (m, 2 H) 7.67-7.74 (m, 2 H) 7.86 (s, 1 H);



Compound **64**

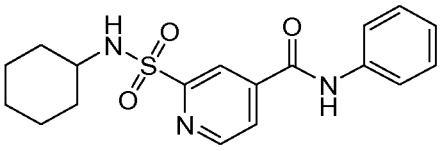
A mixture of ethyl 2-(chlorosulfonyl)thiazole-4-carboxylate (3 g, 11.73 mmol), Et_3N (3.56 g, 35.2 mmol) and cyclohexanamine (1.75 g, 17.65 mmol) in THF (100 mL) was stirred at room temperature for 15 hours. The mixture was concentrated and purified by preparative HPLC resulting in ethyl 2-(N-cyclohexylsulfamoyl)thiazole-4-carboxylate (2 g) as a white solid. To a solution of ethyl 2-(N-cyclohexylsulfamoyl)thiazole-4-carboxylate (2 g) in EtOH-THF (1/1, 60 mL) was added LiOH (0.451 g, 18.83 mmol). The mixture was stirred at room temperature for 15 hours. The reaction mixture was neutralized with HCl (2M), diluted with water and then extracted into EtOAc, dried over $MgSO_4$, filtered and concentrated in vacuo, resulting in 2-(N-cyclohexyl-sulfamoyl)thiazole-4-carboxylic acid (1.7 g) as a white solid. A mixture of 2-(N-cyclo-hexylsulfamoyl)thiazole-4-carboxylic acid (1 g), aniline (0.321 g, 3.44 mmol), DIPEA (1.33 g, 10.29 mmol) and HATU (1.57 g, 4.13 mmol) in DMF (40 mL) was stirred at room temperature for 15 hours. The mixture was concentrated and purified by preparative HPLC (Column: SYNERGI 250*50 10um; Mobile phase A: purified water (0.075%TFA, V/V); Mobile phase B: acetonitrileFlow rate: 80 mL/min Gradient: 35-

65%, 30min) resulting in compound **64** (895 mg) as a white solid. Method B; Rt: 4.45 min. m/z : 366.1 $(M+H)^+$ Exact mass: 365.1



Compound **65**

The mixture of 6-chloro-N-phenylpicolinamide (4 g, 17.19 mmol), phenylmethanethiol (3.23g, 25.79 mmol) and K_2CO_3 (4.75g, 34.38 mmol) in DMF was stirred at 80°C for 18 hour. The reaction mixture was diluted with EtOAc (150 mL), and washed with brine (2 x 200 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography on silica gel (20% EtOAc in petroleum ether) to obtain 6-(benzylthio)-N-phenylpicolinamide (2.8 g). N-Chlorosuccinimide (3.42 g, 25.6 mmol) was added to the mixture of 6-(benzylthio)-N-phenylpicolinamide (2 g, 6.24 mmol) in acetic acid (60 mL) and water (40 mL). The reaction mixture was stirred at room temperature for 3 hours. The reaction was diluted with CH_2Cl_2 (100 mL). After washing with water, the organic layer was added to the mixture of cyclohexanamine (12.4 g, 125 mmol) and Et_3N (50 mL) in CH_2Cl_2 (200 mL). The resulting mixture was stirred at room temperature for 4 hours. The reaction mixture was washed with NH_4Cl (saturated), brine, dried over $MgSO_4$, filtered and concentrated. The obtained residue was purified by preparative HPLC (Column: Synergi 150*30mm*5um; Mobile phase A: purified water (0.075%TFA, V/V); Mobile phase B: acetonitrile; Flow rate: 30mL/min; Gradient: 46-76% (solvent B), 8min) resulting in compound **65** (330 mg). Method B; Rt: 4.46 min. m/z : 360.2 $(M+H)^+$ Exact mass: 359.1. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.00 - 1.31 (m, 5 H) 1.34 - 1.47 (m, 1 H) 1.51 - 1.71 (m, 4 H) 3.02 - 3.13 (m, 1 H) 7.15 - 7.21 (m, 1 H) 7.40 - 7.46 (m, 2 H) 7.82 - 7.88 (m, 2 H) 8.15 (dd, *J*=6.3, 2.5 Hz, 1 H) 8.23 - 8.28 (m, 1 H) 8.29-8.36 (m, 2 H) 10.47 (s, 1 H)

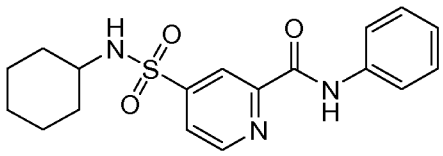


Compound **66**

A mixture of 2-chloro-N-phenylisonicotinamide (2 g, 8.6 mmol), phenylmethanethiol (2.11 g, 17 mmol) and K_2CO_3 (2.35 g, 17 mmol) in DMF was stirred at 80°C for 18 hours. The reaction was diluted with water (200 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$,

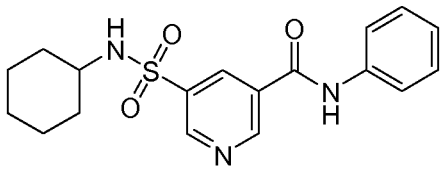
filtered and concentrated. The obtained residue was purified by silica gel chromatography (0-20 % EtOAc in petroleum ether) resulting in 2-(benzylthio)-N-phenylisonicotinamide (1.7 g). N-Chlorosuccinimide (2.56 g, 19.2 mmol) was added to a mixture of 2-(benzylthio)-N-phenylisonicotinamide (1.5 g, 4.68 mmol) in acetic acid (20 mL) and water (10 mL). The reaction mixture was stirred at room temperature for 4 hours. The reaction was diluted with CH_2Cl_2 (20 mL). After washing with water, the organic layer was added to the mixture of cyclohexanamine (4.641g, 46.8 mmol) and Et_3N (10 mL, 71.74 mmol) in CH_2Cl_2 (50mL). The resulting mixture was stirred at room temperature for 4 hours. The reaction mixture was washed with NH_4Cl (saturated), brine, dried over $MgSO_4$, filtered and concentrated. The obtained residue was purified by preparative HPLC (Column: C18-10um; Mobile phase A: purified water (0.075%TFA, V/V); Mobile phase B: acetonitrile; Flow rate: 80mL/min; Gradient: 40-70% (solvent B), 25min) resulting in compound **66** (250 mg). Method B; Rt: 4.22 min. m/z: 360.2 $(M+H)^+$ Exact mass: 359.1. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 0.96 - 1.08 (m, 1 H) 1.08 - 1.24 (m, 4 H) 1.40 - 1.52 (m, 1 H) 1.53 - 1.67 (m, 4 H) 3.11 - 3.22 (m, 1 H) 7.14 - 7.21 (m, 1 H) 7.37 - 7.44 (m, 2 H) 7.78 (d, *J*=7.8 Hz, 2 H) 7.97 (br. s, 1 H) 8.12 (dd, *J*=5.0, 1.5 Hz, 1 H) 8.40 (s, 1 H) 8.94 (d, *J*=5.0 Hz, 1 H) 10.75 (s, 1 H)

Compound **67**



2-chloro-N-cyclohexylpyridine-4-sulfonamide (540 mg, 1.965 mmol), $PdCl_2dppf$ (100 mg, 0.137 mmol) and Et_3N (5.89 mmol) in methanol (50 mL) was stirred at 50°C for 18 hours under CO (50Psi) atmosphere. The solvent was removed under reduced pressure. The obtained residue (700 mg) containing methyl 4-(N-cyclohexylsulfamoyl)-picolinate was used in the next step without further purification. K_2CO_3 (421 mg, 3.05mmol) was added to the mixture of methyl 4-(N-cyclohexylsulfamoyl)picolinate in methanol and water. The mixture was stirred at 20°C for 18 hour. The solvent was removed, the residue was diluted with water (50 mL) and washed with EtOAc (2 x 50 mL). The aqueous layer was then acidified to pH = 3 with 1 M HCl and extracted with EtOAc (2 x 50mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated resulting in 4-(N-cyclohexylsulfamoyl)picolinic acid (380 mg). HATU (0.76 g, 2.0 mmol) was then added to a mixture of 4-(N-cyclohexylsulfamoyl)-picolinic acid (380 mg, 1.34 mmol), aniline (251 mg, 2.7 mmol) and DIPEA (0.517 g, 4.0 mmol) in DMF (50 mL) at room temperature The resulting mixture was stirred at

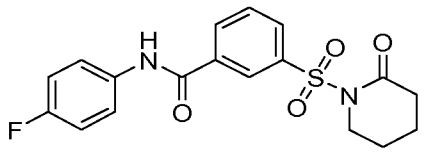
room temperature for 18 hour. The mixture was diluted with water (200 mL), and extracted with EtOAc. The organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The obtained residue was purified by silica gel chromatography (10-20% EtOAc in petroleum ether) resulting in compound **67** as a white solid (330 mg). Method B; Rt: 4.58 min. m/z : 360.2 $(M+H)^+$ Exact mass: 359.1. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 0.93 - 1.26 (m, 5 H) 1.37 - 1.50 (m, 1 H) 1.50 - 1.69 (m, 4 H) 2.98-3.12 (m, 1 H) 7.15 (t, *J*=7.2 Hz, 1 H) 7.32-7.45 (m, 2 H) 7.86-7.97 (m, 2 H) 8.03 (dd, *J*=5.0, 1.5 Hz, 1 H) 8.25 (d, *J*=7.3 Hz, 1 H) 8.47 (d, *J*=1.5 Hz, 1 H) 9.00 (d, *J*=5.0 Hz, 1 H) 10.78 (s, 1 H)



Compound **68**

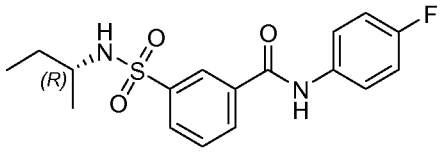
Thionyl chloride (10 mL, 137 mmol) was added drop wise to water (60 mL) at 0-5°C. The mixture was stirred at room temperature for 16 hour. CuCl(40 mg, 0.4 mmol) was added, and the mixture (mixture A) was cooled to -5°C. To a mixture of 5-amino-nicotinic acid in con. HCl (35 mL), a solution of $NaNO_2$ (2.76g, 40 mmol) in of water (40 mL) at -5°C to 0°C, was added (mixture B). The mixture B was added portionwise to the mixture A over 30 minutes, maintaining temperature at -5°C to 0°C.After stirring at 0°C for 1 hour, the solid was collected by filtration, washed with water, and dried in vacuo resulting in 5-(chlorosulfonyl)nicotinic acid (1.05 g). The mixture of 5-(chlorosulfonyl)nicotinic acid (1 g, 4.5 mmol), cyclohexanamine (0.893g, 9 mmol) and Et_3N (1.37 mmol, 13.5 mmol) in CH_2Cl_2 (30 mL) was stirred at room temperature for 18 hours. The solvent was removed under reduced pressure. The residue was purified by HPLC (Column: C18 10um; Mobile phase A: purified water (0.075%TFA, V/V); Mobile phase B: acetonitrile; Flow rate: 80mL/min; Gradient: 30-60% (solvent B), 30 min) resulting in 5-(N-cyclohexylsulfamoyl)nicotinic acid as a white solid (1 g). HATU (2.6g, 7mmol) was added to the mixture of 5-(N-cyclohexylsulfamoyl)nicotinic acid (1 g, 3.5 mmol), aniline (391 mg, 4.2 mmol) and DIPEA (1.36 g, 10.5 mmol) in DMF (50 mL) at room temperature The resulting mixture was stirred at room temperature for 18 hour. The mixture was diluted with of water (200 mL) and extracted with EtOAc. The organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel chromatography (10-100% EtOAc in petroleum ether) resulting in compound **68** (708 mg) as white solid. Method B; Rt: 4.58 min. m/z : 360.2 $(M+H)^+$ Exact mass: 359.1

Compound **69**



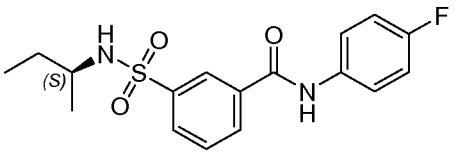
To an ice-cooled solution of 5-aminopentanoic acid (1.2 g, 3.44 mmol) and 1N NaOH (8 mL) in THF (16 mL) was added 3-(4-fluorophenylcarbamoyl)benzene-1-sulfonyl chloride (0.444 g, 3.78mmol). Then the reaction mixture was stirred at 25°C overnight. The resulting mixture was diluted with 1N HCl (10 mL) and extracted with ethyl acetate (2 x 30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (gradient eluent: petroleum ether: ethyl acetate: from 100: 0 to 65:35) resulting in 5-(3-(4-fluorophenylcarbamoyl)phenylsulfonamido) pentanoic acid (0.9 g). A mixture of 5-(3-(4-fluorophenylcarbamoyl)phenylsulfonamido) pentanoic acid (400 mg, 0.913 mmol), acetic anhydride (0.466 g, 4.57 mmol) and AcOK (1.79 g, 18.3 mmol) in toluene (25 mL) was heated by microwave irradiation at 150°C for 30 minutes. The formed precipitate was filtered off and the filtrate was concentrated in vacuo. The residue was purified by preparative high performance liquid chromatography (eluent: CH_3CN in H_2O (0.05% HCl) from 0% to 35%, v/v). The pure fractions were collected and adjusted to pH=7 with Amberlite IRA-900(OH)anionic exchange resin. The resin was filtered off and the filtrate was lyophilized to dryness resulting in compound **69** (200 mg). Method A; Rt: 4.97 min. m/z : 377.2 $(M+H)^+$ Exact mass: 376.1; ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.78 - 1.87 (m, 2 H), 1.90 - 1.99 (m, 2 H), 2.44 (t, *J*=6.8 Hz, 2 H), 3.95 (t, *J*=6.0 Hz, 2 H), 7.08 (t, *J*=8.7 Hz, 2 H), 7.55 - 7.70 (m, 3 H), 8.15 (d, *J*=8.0 Hz, 1 H), 8.20 (d, *J*=7.8 Hz, 1 H), 8.26 (br. s., 1 H), 8.49 (s, 1 H)

Compound **70**



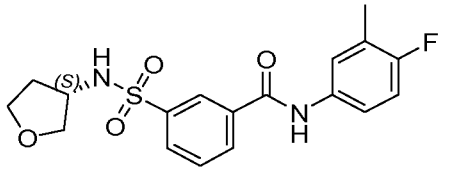
To an iced-cooled mixture of (*R*)-butan-2-amine (0.500 g, 6.837 mmol) and NaOH (0.547 g, 13.67 mmol) in H_2O (15 mL) and THF (15 mL), 3-(chlorosulfonyl)benzoic acid was added (1.508 g, 6.84 mmol) in portions. The reaction mixture was stirred at 20°C for 2 hours. The resulting mixture was diluted with H_2O (15 mL) and extracted with ethyl acetate (15 mL). The aqueous layer was separated and pH was adjusted to 3 by 1 N HCl and extracted with ethyl acetate (3 x 10 mL). The combined organic layer

was washed by brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure resulting in (*R*)-3-(N-sec-butylsulfamoyl)benzoic acid (0.73 g).
To an ice cooled mixture of (*R*)-3-(N-sec-butylsulfamoyl)benzoic acid (730 mg), 4-fluoroaniline (347 mg, 3.121mmol), HATU (1.294 g, 3.404 mmol) in DMF (10 mL) DIPEA (1.48 mL, 8.51 mmol) was added under N_2 atmosphere. The resulting mixture was stirred at 20°C for 2 hour. The solvent was removed in vacuo. The mixture was washed with saturated aqueous critic acid (10 mL), brine and dried over Na_2SO_4. The solvent was removed in vacuo. The residue was purified by column chromatography over silica gel (gradient eluent: petroleum ether/ethyl acetate from 100/0 to 55/45). The pure fractions were collected and the solvent was removed in vacuo. The residue was purified by SFC separation (Chiralcel OJ, 20 µm; Supercritical CO_2 : MeOH (0.2% diethylamine)). The pure fractions were collected and the solvent was removed in vacuo, resulting in compound **70** (300 mg). Method A; Rt: 5.25 min. m/z : 351.2 $(M+H)^+$ Exact mass: 350.1. $[\alpha]_D^{20}$ = - (*c*= 0.2, MeOH). $[\alpha]_D^{20}$ = -9.9 (c 0.435 w/v %, DMF); Column: Chiralpak AD-3 150×4.6mm I.D., 3um; Mobile phase: methanol (0.05% diethylamine) in CO_2 from 5% to 40%; Flow rate: 2.5 mL/min; Rt: 7.58 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.70 (t, *J*=7.4 Hz, 3 H), 0.88 (d, *J*=6.5 Hz, 3 H), 1.30 (quin, *J*=7.2 Hz, 2 H), 3.01 - 3.18 (m, 1 H), 7.21 (t, *J*=8.8 Hz, 2 H), 7.67 (br. d, *J*=5.5 Hz, 1 H), 7.75 (t, *J*=7.8 Hz, 1 H), 7.78 (dd, *J*=8.8, 5.1 Hz, 2 H), 8.00 (d, *J*=7.8 Hz, 1 H), 8.19 (d, *J*=7.8 Hz, 1 H), 8.36 (s, 1 H), 10.55 (s, 1 H).



Compound **71**

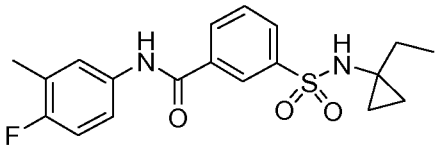
Prepared similar as described for compound **70** starting from (*S*)-butan-2-amine instead of (*R*)-butan-2-amine.Method B; Rt: 4.03 min. m/z : 351.2 $(M+H)^+$ Exact mass: 350.1 ($[\alpha]_D^{20}$ = + (*c*= 0.2, MeOH). $[\alpha]_D^{20}$ = + 9.49 (c 0.611 w/v %, DMF), Column: Chiralpak AD-3 150×4.6mm I.D., 3um; Mobile phase: methanol (0.05% diethylamine) in CO_2 from 5% to 40%; Flow rate: 2.5 mL/min; Rt: 7.73 min. $[\alpha]_{589}^{20}$ +9.49 ° (c 0.61 w/v %, MeOH)



Compound **72**

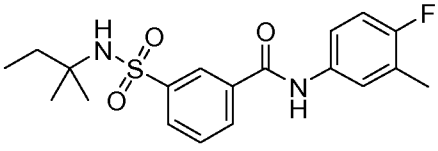
3-(chlorosulfonyl)benzoyl chloride (1200 mg, 5.0 mmol) was dissolved in dichloromethane (15 mL). A solution of 4-fluoro-3-methylaniline (625 mg, 5.0 mmol) and triethylamine (606 mg, 6.0 mmol) in dichloromethane (15 mL) was added to the mixture at 0°C. The mixture was stirred at 25°C for 1 hour. The reaction mixture was used to the next step without further purification. To the above reaction mixture a solution of triethylamine (606 mg, 6.0 mmol) and (*S*)-tetrahydrofuran-3-amine (460.0 mg, 5.3 mmol) in dichloromethane (15 mL) was added at 0°C. The mixture was stirred at 25°C for 1 hour. The solvent was removed in vacuo. The residue was purified by reversed phase high performance liquid chromatography (eluent: CH_3CN in water (0.1% TFA) from 25 to 55, v/v). The pure fractions were collected and the organic solvent was evaporated. The aqueous layer was neutralized with saturated aqueous $NaHCO_3$ to pH=7-8. The mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo resulting in compound **72** (620 mg). Method A; Rt: 4.88 min. m/z : 379.2 $(M+H)^+$ Exact mass: 378.1. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.56 - 1.65 (m, 1 H), 1.85 - 1.94 (m, 1 H), 2.22 - 2.28 (m, 3 H), 3.33 - 3.39 (m, 1 H), 3.52 - 3.65 (m, 2 H), 3.65 - 3.73 (m, 1 H), 3.73 - 3.79 (m, 1 H), 7.14 (t, *J*=9.2 Hz, 1 H), 7.56 - 7.62 (m, 1 H), 7.67 (dd, *J*=7.0, 2.3 Hz, 1 H), 7.78 (t, *J*=7.8 Hz, 1 H), 8.02 (d, *J*=7.8 Hz, 1 H), 8.10 (d, *J*=4.5 Hz, 1 H), 8.21 (d, *J*=7.8 Hz, 1 H), 8.37 (s, 1 H), 10.49 (s, 1 H)

Compound **85**



Prepared similarly as described for compound **72** using 1-ethylcyclopropanamine hydrochloride instead of (*S*)-tetrahydrofuran-3-amine. Compound **85** was purified by preparative high performance liquid chromatography over RP-18 (eluent: CH_3CN in H_2O (0.5% NH_4HCO_3) from 43% to 73%, v/v). Method B; Rt: 4.17 min. m/z : 377.1 $(M+H)^+$ Exact mass: 376.1. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 0.35-0.45 (m, 2 H), 0.49-0.58 (m, 2 H), 0.77 (t, *J*=7.2 Hz, 3 H), 1.31 (q, *J*=7.1 Hz, 2 H), 2.26 (s, 3 H), 7.15 (t, *J*=9.3 Hz, 1 H), 7.55 - 7.64 (m, 1 H) 7.69 (d, *J*=7.0 Hz, 1 H), 7.76 (t, *J*=7.8 Hz, 1 H), 7.98 (d, *J*=7.8 Hz, 1 H), 8.16 - 8.25 (m, 2 H), 8.35 (s, 1 H), 10.50 (s, 1 H).

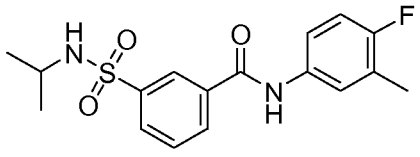
Compound **86**



Prepared similarly as described for compound **72** using 2-methylbutan-2-aminehydrochloride instead of (*S*)-tetrahydrofuran-3-amine. Purified by high performance liquid chromatography over RP-18 (eluent: CH_3CN in water from 47% to 77%, v/v). Method D; Rt: 5.97 min. m/z : 379.1 $(M+H)^+$ Exact mass: 378.1. ^1H NMR (400 MHz, DMSO-d_6), δ = 0.73 (t, *J*=7.5 Hz, 3 H), 1.02 (s, 6 H), 1.44 (q, *J*=7.5 Hz, 2 H), 2.23 (d, *J*=1.0 Hz, 3 H), 7.12 (t, *J*=9.3 Hz, 1 H), 7.52 - 7.61 (m, 2 H), 7.64 - 7.77 (m, 2 H), 8.01 (d, *J*=7.8 Hz, 1 H), 8.14 (d, *J*=7.8 Hz, 1 H), 8.36 (s, 1 H). 10.45 (s, 1 H).

Alternative synthesis of compound **72**:

A mixture of 3-(chlorosulfonyl)benzoyl chloride (4.61 g ,19.28mmol) in toluene (45 mL) was refluxed under a gentle flow of nitrogen. 4-fluoro-3-methylaniline (2.19 g, 17.53 mmol) in toluene (15 mL) was added drop wise to the refluxing solution. After addition, the mixture was refluxed for another 30 minutes. The mixture was next cooled to room temperature, and a mixture of (S)-3-aminotetrahydrofuran tosylate (5 g, 19.28 mmol) and diisopropylethylamine (15 mL) in toluene (15 mL) and CH_2Cl_2 (10 mL) was added drop wise. After addition, the mixture was stirred for 4 hours at room temperature.The resulting mixture was washed with HCl (2 x 100 mL, 1M aq), water (2 x 100 mL) and $NaHCO_3$ (2 x 100 mL, sat. aq). The organic layer was dried on $MgSO_4$, filtered and concentrated under reduced pressure. The obtained residue was purified using silica gel chromatography (CH_2Cl_2-MeOH 100:0 to 95:5) yielding 3-(4-fluoro-3-methylphenylcarbamoyl)benzene-1-sulfonyl chloride (1.07 g) during CH_2Cl_2 elution, followed by compound **72** (2.85 g) as a white solid after removal of the solvent (dried in a vacuum oven at 55°C for 20 hours). ($[\alpha]_D^{20}$ = - 5.21 (c 0.67 w/v %, MeOH), Method F; Rt: 0.88 min. m/z : 379.1 $(M+H)^+$ Exact mass: 378.1. The compound was crystallized from CH_2Cl_2: DSC (From 30 to 300 °C at 10°C/min): 149°C. $[\alpha]_D^{20}$ = + 3.21 (c 0.65 w/v %, DMF).

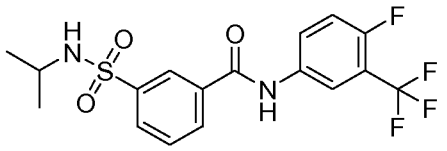


Compound **73**

To an iced-cooled solution of 3-(chlorosulfonyl)benzoic acid (50.0 g, 226.6 mmol) in ethylacetate (1000 mL) was added isopropylamine (67.0 g, 1.13 mol) in one portion. The reaction mixture was stirred at 25°C for 3 hours. The resulting mixture was diluted with 1N HCl (500 mL) and extracted with ethyl acetate (2 x 500 mL). The combined organic layers were washed with brine (400 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure resulting 3-(N-isopropylsulfamoyl)benzoic acid

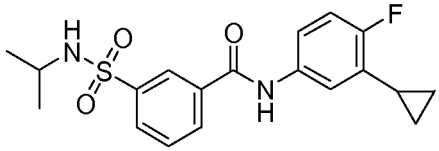
(46 g). To an ice-cooled mixture of 3-(N-isopropylsulfamoyl)benzoic acid (7.0 g, 28.77 mmol), 4-fluoro-3-methylaniline (3.6 g, 28.77 mmol) and DIPEA (18.6 g, 143.91 mmol) in CH_2Cl_2 (70 mL) HATU (12.0 g, 31.56 mmol) was added under N_2 atmosphere. The resulting mixture was stirred at 20° for 16 hours. The solvent was removed in vacuo. The mixture was washed with saturated aqueous critic acid (30 mL), brine (20 mL) and dried over Na_2SO_4. The solvent was removed in vacuo. The residue was purified by preparative high performance liquid chromatography on SYNERGI 250*50 10um (eluent: CH_3CN in H_2O (0.05% TFA) from 35% to 65%, v/v). The pure fractions were collected and adjusted to pH=7 with Amberlite IRA-900(OH) anionic exchange resin. The resin was filtered off. The filtrate was lyophilized to dryness resulting in compound **73** (7.5 g). Method B; Rt: 3.44 min. m/z : 351.1 $(M+H)^+$ Exact mass: 350.1 ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.49 (1 H, br. s), 8.36 (1 H, t, *J*=1.5 Hz), 8.19 (1 H, ddd, *J*=7.8, 1.5, 1.0 Hz), 8.01 (1 H, ddd, *J*=7.8, 1.5, 1.0 Hz), 7.76 (1 H, t, *J*=7.8 Hz), 7.68 (1 H, dd, *J*=7.0, 3.0 Hz), 7.75 (1 H, bs), 7.59 (1 H, ddd, *J*=9.0, 4.5, 3.0 Hz), 7.15 (1 H, t, *J*=9.0 Hz), 3.14 - 3.33 (1 H, m), 2.25 (3 H, d, *J*=1.5 Hz), 0.96 (6 H, d, *J*=6.5 Hz).

Compound **74**



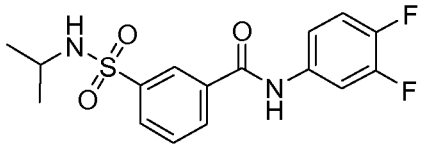
Prepared similarly as described for compound **73**, using 4-fluoro-3-(trifluoromethyl)-aniline instead of 4-fluoro-3-methylaniline. Purified on HPLC Synergi 150x30mmx5u (eluent: CH_3CN in H_2O (0.05% HCl) from 45% to 75%, v/v). Method A; Rt: 5.62 min. m/z : 405.2 $(M+H)^+$ Exact mass: 404.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.82 (1 H, s), 8.39 (1 H, t, *J*=1.5 Hz), 8.17 - 8.30 (2 H, m), 8.07 - 8.17 (1 H, m), 8.03 (1 H, d, *J*=7.8), 7.73-7.83 (2 H, m), 7.55 (1 H, t, *J*=10.0 Hz), 3.20 - 3.33 (1 H, m), 0.95 (6 H, d, *J*=6.5 Hz).

Compound **84**



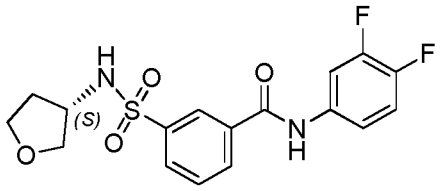
A mixture of N-(3-bromo-4-fluorophenyl)-3-(N-isopropylsulfamoyl)benzamide (prepared similarly as described for compound **73,** using 3-bromo-4-fluoroaniline instead of 4-fluoro-3-methylaniline and purified via preparative high performance liquid chromatography over RP-18 (eluent: CH_3CN in H_2O (0.05% NH_4HCO_3) from 40% to 70%, v/v); 700 mg, 1.69 mmol), cyclopropylboronic acid (0.22 g, 2.529 mmol),

$Pd(PPh_3)_4$ (0.20 g, 0.169 mmol) and Na_2CO_3 (1.43 g, 13.49 mmol) in water (7 mL), EtOH (7 mL) and toluene (7 mL) was heated by microwave irradiation for 40 minutes at 100°C under N_2. The reaction mixture was filtered through celite. Water (10 mL) was added to the filtrate and the mixture was extracted with ethyl acetate (2 x 10 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed in vacuo. The residue was purified by preparative high performance liquid chromatography over RP-18 (eluent: CH_3CN in H_2O (0.1% TFA) from 20% to 50%, v/v). The pure fractions were collected and the volatiles were removed in vacuo. The aqueous layer was adjusted to pH=7 with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate (2 x 20 mL). The combined organic layers were dried over Na_2SO_4. The solvent was removed in vacuo and the obtained residue was further purified by supercritical fluid chromatography (Column: Chiralpak AD-3 150×4.6mm I.D., 3um Mobile phase: methanol (0.05% diethylamine) in CO_2 from 5% to 40%. Flow rate: 2.5mL/min). The pure fractions were collected and the volatiles were removed in vacuo. The residue was suspended in water (5 mL) and lyophilized to dryness resulting in compound **84** (35 mg) Method B; Rt: 4.18 min. m/z : 377.1 $(M+H)^+$ Exact mass: 376.1; ^1H NMR (400 MHz, chloroform-d) δ ppm 8.34 (s, 1 H), 8.12 (d, J=8.0 Hz, 1 H), 7.97 - 8.07 (m, 2 H), 7.65 (t, J=8.0 Hz, 1 H), 7.36 - 7.46 (m, 1 H), 7.15-7.22 (m, 1 H), 7.01 (t, J=9.3 Hz, 1 H), 4.65 (d, J=7.5 Hz, 1 H), 3.44-3.58 (m, 1 H), 2.04 - 2.16 (m, 1 H), 1.10 (d, J=6.5 Hz, 6 H), 0.96 - 1.06 (m, 2 H), 0.71 - 0.82 (m, 2 H).



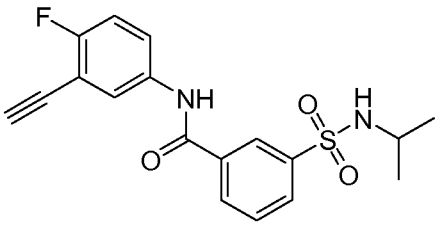
Compound **88**

Prepared similarly as described for compound **73**, using 3,4-difluoroaniline instead of 4-fluoro-3-methylaniline. Method E; Rt: 5.31 min. m/z : 355.1 $(M+H)^+$ Exact mass: 354.1; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 10.71 (s, 1 H), 8.36 (t, *J*=1.5 Hz, 1 H), 8.19 (d, *J*=7.8 Hz, 1 H), 7.98 - 8.08 (m, 1 H), 7.94 (ddd, *J*=13.2, 7.5, 2.4 Hz, 1 H), 7.71 - 7.83 (m, 2 H), 7.53 - 7.59 (m, 1 H), 7.42 - 7.51 (m, 1 H), 3.21 - 3.29 (m, 1 H), 0.96 (d, *J*=6.5 Hz, 6 H).



Compound **90**

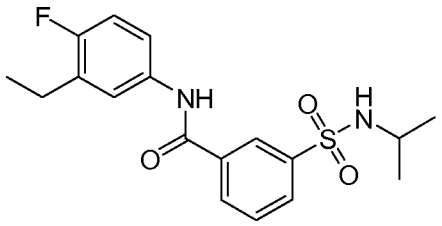
3-(chlorosulfonyl)benzoyl chloride (1200 mg, 5.0 mmol) was dissolved in dichloromethane (15 mL). A solution of 3,4-difluoroaniline (650 mg, 5.0 mmol) and triethylamine (606 mg, 6.0mmol) in dichloromethane (15 mL) was added to the mixture at 0°C. The mixture was stirred at 25°C for 1 hour. To the obtained reaction mixture a solution of triethylamine (606 mg, 6.0 mmol) and (S)-tetrahydrofuran-3-amine (460.0 mg, 5.3mmol) in dichloromethane (15 mL) was added at 0°C. The mixture was stirred at 25°C for 1 hour. The solvent was removed in vacuo. The obtained residue was purified by high performance liquid chromatography over RP-18 (eluent: CH_3CN in water (0.1%TFA) from 30 to 60, v/v). The pure fractions were collected and the organic solvent was evaporated. The aqueous layer was neutralized with saturated aqueous $NaHCO_3$ to pH=7-8. The mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo resulting in compound **90** (710 mg) Method A; Rt: 4.16 min. m/z : 383.0 $(M+H)^+$ Exact mass: 382.1; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.54 - 1.63 (m, 1 H), 1.83 - 1.93 (m, 1 H), 3.32 - 3.38 (m, 1 H), 3.52 - 3.63 (m, 2 H), 3.63 - 3.77 (m, 2 H), 7.45 (dt, *J*=10.5, 9.0 Hz, 1 H), 7.51 - 7.57 (m, 1 H), 7.78 (t, *J*=7.8 Hz, 1 H), 7.92 (ddd, *J*=13.3, 7.5, 2.5 Hz, 1 H), 8.02 (d, *J*=7.8Hz, 1 H), 8.09 (d, *J*=6.5 Hz, 1 H), 8.20 (d, *J*=7.8 Hz, 1 H), 8.35 (s, 1 H), 10.70 (s, 1 H). SFC: Column: Chiralcel OJ-H 250×4.6mm I.D., 5um; Flow: 2.35 mL/min; Mobile phase: methanol (0.05% diethylamine) in CO_2 from 5% to 40%; Rt: 5.61 Min.$[\alpha]_D^{20}$ = + 3.21 (c 0.624 w/v %, DMF)



Compound **91**

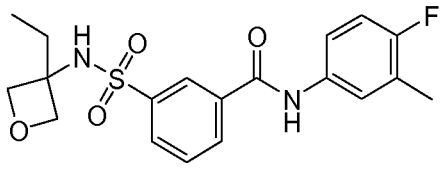
N-(3-bromo-4-fluorophenyl)-3-(N-isopropylsulfamoyl)benzamide (1.5 g, 3.61 mmol), ethynyltrimethylsilane (1.77 g, 18.06 mmol), $Pd(PPh_3)_2Cl_2$ (0.127g, 0.181mmol) and copper iodide (34.4 mg, 0.181mmol) were dissolved in diisopropylamine (10 mL). The mixture was stirred at 80°C in autoclave for 24 hours. The solvent was removed in vacuo and dichloromethane (30 mL) was added. The mixture was washed with water (20 mL) and the aqueous layer was extracted with dichloromethane (20 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed in vacuo. The obtained residue was purified by silica gel column chromatography (eluent: petroleum ether / ethyl acetate from 100/1 to 60/40) resulting in N-(4-fluoro-3-((trimethylsilyl)ethynyl)phenyl)-3-(N-isopropylsulfamoyl)benzamide

(0.8 g). N-(4-fluoro-3-((trimethylsilyl)ethynyl)phenyl)-3-(N-isopropylsulfamoyl)-benzamide (0.8 g, 1.66 mmol) and TFA (4 mL) were dissolved in anhydrous CH_2Cl_2 (16 mL). The mixture was stirred at 25°C overnight and next concentrated in vacuo. The obtained residue was purified by silica gel column chromatography (gradient eluent: petroleum ether/ethyl acetate from 100/0 to 75/25) resulting in compound **91** (220 mg). Method A; Rt: 5.12 min. m/z : 361.3 $(M+H)^+$ Exact mass: 360.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.60 (1 H, s), 8.35 (1 H, t, *J*=1.5 Hz), 8.18 (1 H, d, *J*=8.0 Hz), 8.00 (1 H, d, *J*=8.0 Hz), 7.97 (1 H, dd, *J*=6.5, 3.0 Hz), 7.77 - 7.84 (1 H, m), 7.70 - 7.79 (2 H, m), 7.32 (1 H, t, *J*=9.0 Hz), 4.52 (1H, s) 3.22 - 3.31 (1 H, m), 0.94 (6 H, d, *J*=6.5 Hz).



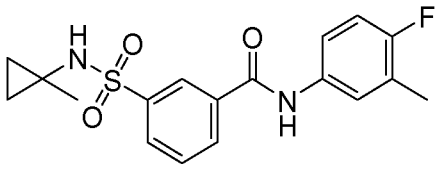
Compound **92**

N-(4-fluoro-3-((trimethylsilyl)ethynyl)phenyl)-3-(N-isopropylsulfamoyl)benzamide (0.8g, 1.66mmol) and TFA (4 mL) were dissolved in anhydrous CH_2Cl_2 (16 mL). The mixture was stirred at 25° overnight. The mixture was concentrated resulting in crude N-(3-ethynyl-4-fluorophenyl)-3-(N-isopropylsulfamoyl)benzamide which was used as such in the next step (650 mg). To a solution of N-(3-ethynyl-4-fluorophenyl)-3-(N-isopropylsulfamoyl)benzamide (0.6 g) in MeOH (20 mL) was added Pd-C (10%, 0.2 g) under N_2 atmosphere. The mixture was stirred under hydrogen atmosphere (50 psi) at 25°C for 4 hours. After filtration on celite, the solvent was removed in vacuo and the obtained residue was purified by preparative high performance liquid chromatography on reversed phase C-18 (eluent: CH_3CN in H_2O (0.05% HCl) from 42% to 72%, v/v). The pure fractions were collected and the volatiles were removed in vacuo. The aqueous layer was adjusted to PH=7 with Amberlite IRA-900 anionic exchange resin (OH form), filtered and lyophilized to dryness resulting in compound **92** (160 mg). Method B; Rt: 4.13 min. m/z : 365.3 $(M+H)^+$ Exact mass: 364.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.48 (1 H, s), 8.35 (1 H, t, *J*=1.5 Hz), 8.18 (1 H, d, *J*=8.0 Hz), 7.99 (1 H, d, *J*=8.0 Hz), 7.70 - 7.78 (2 H, m), 7.65 - 7.70 (1 H, m), 7.57 - 7.65 (1 H, m), 7.13 (1 H, t, *J*=9.0 Hz), 3.21 - 3.32 (1 H, m), 2.62 (2 H, q, *J*=7.5 Hz), 1.18 (3 H, t, *J*=7.5 Hz), 0.94 (6 H, d, *J*=6.5 Hz).



Compound **93**

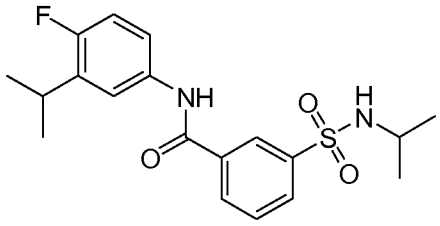
To a solution of 3-(chlorosulfonyl)benzoyl chloride (0.50 g, 2.09 mmol) in CH_2Cl_2 (10 mL), DIPEA was added (1.35 g, 10.45 mmol) followed by slow addition of 4-fluoro-3-methylaniline (0.25 g, 1.99 mmol). After stirring at 25°C for 0.5 hour, 3-ethyloxetan-3-amine (0.21 g, 2.09 mmol) was added. After 1 hour, the resulting mixture was diluted with CH_2Cl_2 (15 mL), washed with saturated aqueous $NaHCO_3$ (15 mL) and brine (10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the obtained residue was purified by silica gel column chromatography (gradient eluent: petroleum ether/ethyl acetate from 100/0 to 80/20) resulting in compound **93** (70 mg). Method B; Rt: 3.79 min. m/z : 393.3 $(M+H)^+$ Exact mass: 392.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.50 (1 H, s), 8.47 (1 H, br. s), 8.38 (1 H, t, *J*=1.5 Hz), 8.22 (1 H, d, *J*=8.0 Hz), 8.03 (1 H, d, *J*=8.0 Hz), 7.78 (1 H, t, *J*=8.0 Hz), 7.68 (1 H, dd, *J*=7.5, 2.5 Hz), 7.56 - 7.64 (1 H, m), 7.15 (1 H, t, *J*=9.0 Hz), 4.51 (2 H, d, *J*=6.5 Hz), 4.19 (2 H, d, *J*=6.5 Hz), 2.25 (3 H, d, *J*=1.5 Hz), 1.84 (2 H, q, *J*=7.0 Hz), 0.64 (3 H, t, *J*=7.0 Hz).



Compound **94**

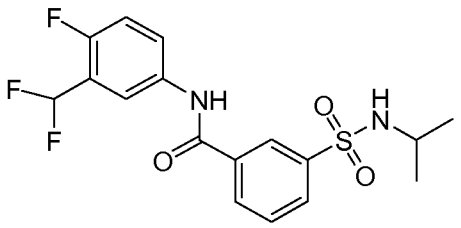
3-(chlorosulfonyl)benzoyl chloride (1200 mg, 5.0 mmol) was dissolved in dichloromethane (15 mL). A solution of 4-fluoro-3-methylaniline (625 mg, 5.0 mmol) and triethylamine (606 mg, 6.0 mmol) in dichloromethane (15 mL) was added to the mixture at 0°C. The mixture was stirred at 25°C for 1 hour. The reaction mixture was used to the next step without further purification (crude, 30 mL). To the above reaction mixture was added a solution of triethylamine (606 mg, 6.0 mmol) and 1-methylcyclopropanamine (425.0 mg, 5.9 mmol) in dichloromethane (15 mL) at 0°C. The mixture was stirred at 25°C for 1 hour. The solvent was removed in vacuo. The residue was purified by high performance liquid chromatography on reversed phase (eluent: CH_3CN in water from 40% to 70%, v/v). The pure fractions were collected and the organic solvent was evaporated. The aqueous layer was neutralized with saturated aqueous $NaHCO_3$ to pH=7-8. The mixture was extracted with dichloromethane (3 x

15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo resulting in compound **94** (365 mg). Method B; Rt: 3.40 min. m/z : 363.0 $(M+H)^+$ Exact mass: 362.1; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 10.49 (1 H, s), 8.35 (1 H, t, *J*=1.5 Hz), 8.17 - 8.23 (2 H, m), 7.99 (1 H, d, *J*=8.0 Hz), 7.76 (1 H, t, *J*=8.0 Hz), 7.68 (1 H, dd, *J*=7.0, 2.5 Hz), 7.56 - 7.62 (1 H, m), 7.14 (1 H, t, *J*=9.0 Hz), 2.25 (3 H, d, *J*=1.5 Hz), 1.06 (3 H, s), 0.58 - 0.63 (2 H, m), 0.37 - 0.42 (2 H, m)



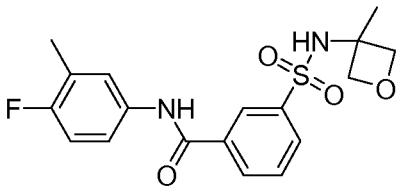
Compound **95**

A mixture of N-(3-bromo-4-fluorophenyl)-3-(N-isopropylsulfamoyl)benzamide (800 mg, 1.93 mmol), 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (0.65 g, 3.85 mmol), $Pd(PPh_3)_4$ (111 mg, 0.096 mmol)) and K_2CO_3 (0.53 g, 3.85 mmol) in dioxane (8 mL) and water (2 mL) was heated by microwave irradiation for 110 minutes at 120°C under N_2 atmosphere. The reaction mixture was diluted with ethyl acetate (20 mL) and the catalyst was filtered off. The filtrate was concentrated in vacuo. Water (20 mL) was added and the aqueous layer was extracted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed in vacuo and the obtained residue was purified by preparative high performance liquid chromatography over reversed phase C-18 (eluent: CH_3CN in H_2O (0.1% TFA) from 40% to 70%, v/v). The pure fractions were collected and the organic solvent was removed in vacuo. The aqueous layer was lyophilized to dryness resulting in N-(4-fluoro-3-(prop-1-en-2-yl)phenyl)-3-(N-isopropylsulfamoyl)benzamide (300 mg). N-(4-fluoro-3-(prop-1-en-2-yl)phenyl)-3-(N-isopropylsulfamoyl)benzamide (180 mg) and Pd/C(wet) (20 mg) were stirred in methanol (4 mL) under a hydrogen atmosphere at 25°C for 3 hours. The mixture was filtered over celite and the filtrate was evaporated to dryness in vacuo. The residue was purified by silica gel column chromatography (gradient eluent: petroleum ether/ethyl acetate from 100/0 to 70/30). The volatiles were removed in vacuo, resulting in compound **95** (175 mg). Method B; Rt: 4.33 min. m/z : 379.3 $(M+H)^+$ Exact mass: 378.1;



Compound **96**

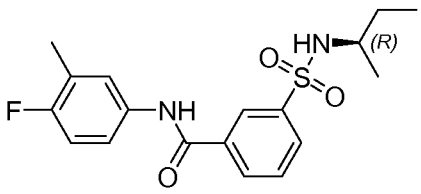
3-(difluoromethyl)-4-fluoroaniline (1.20 g, 7.448 mmol), 3-(N-isopropylsulfamoyl)-benzoic acid (0.90 g, 3.699 mmol) and DIPEA (1.93 mL, 11.10 mmol) were dissolved in CH_2Cl_2 (10 mL) and HATU (1.41 g, 3.699 mmol) was added at 0°C. The mixture was stirred at 20 °C for 2 hours. The mixture was diluted with CH_2Cl_2 (10 mL) and H_2O (10 mL). The organic layer was separated, washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL) and dried over Na_2SO_4. The solvent was removed in vacuo and the obtained residue was purified by preparative high performance liquid chromatography over reversed phase C-18 (eluent: CH_3CN in H_2O (0.1‰ NH_4HCO_3) from 45% to 75%, v/v). The pure fractions were collected and the organic solvent was removed in vacuo. The aqueous layer was lyophilized to dryness resulting in compound **96** (0.885 g). Method A; Rt: 5.16 min. m/z : 387.3 $(M+H)^+$ Exact mass: 386.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.72 (1 H, s), 8.38 (1 H, t, *J*= 1.5 Hz), 8.21 (1 H, d, *J*= 8.0 Hz), 8.06 - 8.13 (1 H, m), 8.02 (1 H, d, *J*= 8.0 Hz), 7.92 - 8.00 (1 H, m), 7.72 - 7.82 (2 H, m), 7.40 (1 H, t, *J*= 9.5 Hz), 7.25 (1 H, t, *J*= 55 Hz), 3.23 - 3.32 (1 H, m), 0.95 (6 H, d, *J*= 6.5 Hz).



Compound **97**

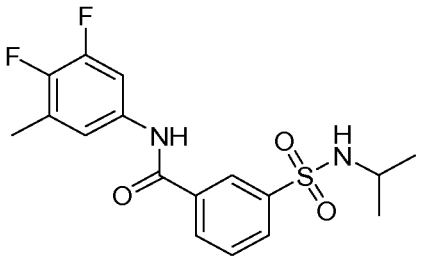
To 3-(4-fluoro-3-methylphenylcarbamoyl)benzene-1-sulfonyl chloride (500 mg, 1.53 mmol) in toluene (10 mL) at room temperature, a solution of diisopropyl-ethylamine (0.657 mL, 141.6 mmol) and 3-methyl-3-oxetanamine hydrochloride (207 mg, 1.68 mmol) in toluene (5 mL) and dichloromethane (10 mL) was added drop wise. After 2 hours, the reaction mixture was washed with 1M hydrochloric acid (2 x 10 mL, saturated $NaHCO_3$ (2 x 10 mL) and brine (2 x 10 mL). The organic layer was dried on $MgSO_4$, filtered and concentrated under reduced pressure until only toluene remained. The formed white precipitate was filtered and recrystallised out of diisopropylether and acetonitrile. The crystals were dried in a vacuum oven at 55°C for 20 hours yielding compound **97** (361 mg) as a white solid. Method F; Rt: 0.89 min. m/z : 379.0 $(M+H)^+$ Exact mass: 378.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.41 (s, 3

H), 2.25 (d, *J*=1.5 Hz, 3 H), 4.14 (d, *J*=6.3 Hz, 2 H), 4.56 (d, *J*=6.3 Hz, 2 H), 7.14 (t, *J*=9.0 Hz, 1 H), 7.52 - 7.64 (m, 1 H), 7.68 (dd, *J*=7.0, 2.2 Hz, 1 H), 7.77 (t, *J*=8.0 Hz, 1 H), 7.99 - 8.06 (m, 1 H), 8.20 (d, *J*=8.0 Hz, 1 H), 8.37 (t, *J*=1.5 Hz, 1 H), 8.50 (br. s., 1 H), 10.48 (s, 1 H).



Compound **98**

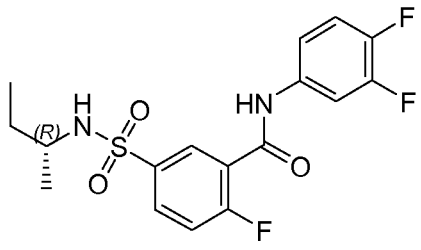
To 3-(4-fluoro-3-methylphenylcarbamoyl)benzene-1-sulfonyl chloride (500 mg, 1.53 mmol) in toluene (10 mL) at room temperature, a solution of diisopropylethylamine (0.657 mL, 141.6 mmol) and (*R*)-(-)-2-aminobutane (130 mg, 1.83 mmol) in toluene (5 mL) and dichloromethane (10 mL) was added drop wise. After 2 hours, the reaction mixture was washed with 1M aqueous HCl (2 x10 mL), $NaHCO_3$ (2 x 10 mL) and brine (2 x 10 mL). The organic layer was dried on $MgSO_4$, filtered and concentrated under reduced pressure until only toluene remained. The formed white precipitate was filtered, recrystallised (diisopropylether and acetonitrile) and dried in vacuo at 55°C for 20 hours resulting in compound **98** (257 mg) as a white solid. Method F; Rt: 1.04 min. m/z : 382.1 $(M+NH_4)^+$ Exact mass: 364.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.71 (t, *J*=7.5 Hz, 3 H), 0.88 (d, *J*=6.6 Hz, 3 H), 1.31 (quin, *J*=7.5 Hz, 2 H), 2.25 (d, *J*=1.8 Hz, 3 H), 3.05-3.18 (m, 1 H), 7.14 (t, *J*=9.0 Hz, 1 H), 7.55 - 7.62 (m, 1 H), 7.63 - 7.72 (m, 2 H), 7.75 (t, *J*=8.0 Hz, 1 H), 8.00 (d, *J*=8.0 Hz, 1 H), 8.18 (d, *J*=8.0 Hz, 1 H), 8.36 (t, *J*=1.5 Hz, 1 H), 10.46 (s, 1 H).



Compound **99**

A mixture of 3-(N-isopropylsulfamoyl)benzoic acid (2.3 g, 9.615 mmol), 3-bromo-4,5-difluoroaniline (2 g, 9.615 mmol) and DIPEA (5 mL) in CH_2Cl_2 (30 mL) was cooled to 0°C and HATU (4.39 g, 11.538 mmol) was added. The mixture was stirred for 2 hours at 20°C. The mixture was washed with 1N HCl (30 mL) and brine (30 mL) and dried over Na_2SO_4. The solvent was removed in vacuo. The residue was purified by silica gel column chromatography (gradient eluent: petroleum ether/ethyl acetate from 100/0 to

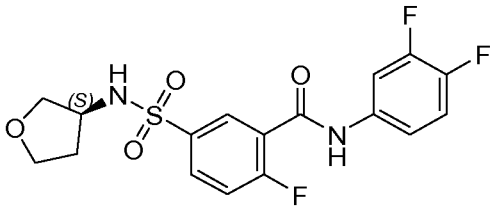
70/30) resulting in crude N-(3-bromo-4,5-difluorophenyl)-3-(N-isopropylsulfamoyl)-benzamide (4 g). A mixture of N-(3-bromo-4,5-difluorophenyl)-3-(N-isopropyl-sulfamoyl)benzamide (1 g, 2.308 mmol), methylboronic acid (1 g, 4.616 mmol), Cs_2CO_3 (2.26 g, 6.924 mmol), 2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl (95 mg, 0.231 mmol) and Tris(dibenzylideneacetone)dipalladium(0) (0.21 g, 0.231 mmol) in dioxane (15 mL) was heated by microwave irradiation for 40 minutes at 120°C under N_2 atmosphere. After cooling, the mixture was filtered through celite and the filtrate was evaporated to dryness. The obtained residue was purified by silca gel column chromatography (gradient eluent: petroleum ether/ethyl acetate from 100/0 to 70/30) and further purified by preparative high performance liquid chromatography over reversed phase C-18 (eluent: CH_3CN in H_2O (0.1% TFA) from 38% to 68%, v/v). The pure fractions were collected and half of the volatiles were removed in vacuo. The mixture was adjusted to pH=7 with Amberlite IRA-900 (OH) anionic exchange resin and the resin was filtered off. The organic solvent was concentrated in vacuo and the aqueous layer was lyophilized to dryness. The obtained product was further purified by silica gel chromatography (gradient eluent: petroleum ether/ethyl acetate from 100/0 to 70/30) resulting in compound **99** (190 mg). Method A; Rt: 6.09 min. m/z : 369.2 $(M+H)^+$ Exact mass: 368.1, ^1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.35 (1 H, t, *J*=1.5 Hz), 8.09 - 8.17 (2 H, m), 8.04 (1 H, dt, *J*=8.0, 1.5 Hz), 7.66 (1 H, t, *J*=8.0 Hz), 7.54 (1 H, ddd, *J*=11.5, 6.5, 3.0 Hz), 7.14 - 7.22 (1 H, m), 4.72 (1 H, d, *J*=8.0 Hz), 3.43-3.60 (1 H, m), 2.32 (3 H, d, *J*=2.0 Hz), 1.10 (6 H, d, *J*=6.5 Hz).



Compound **100**

5-(chlorosulfonyl)-2-fluorobenzoic acid (7g, 29.3 mmol) was dissolved in dichloro-methane (70 mL). DMF (0.7 mL) was added, followed by drop wise addition of oxalyl chloride (4.46 g, 35.16 mmol) at 0°C. The mixture was stirred for 1 hour at 20°C. The mixture was concentrated in vacuo and the crude 5-(chlorosulfonyl)-2-fluorobenzoyl chloride was dissolved in dichloromethane (15 mL). A solution of 3,4-difluoroaniline (3.6g, 27.87 mmol) and DIPEA (4.6g, 35.20 mmol) in dichloromethane (60 mL) was added to the mixture at 0°C. The mixture was stirred at 25°C for 1 hour and used to the next step directly. To the above reaction mixture, a solution of (*R*)-(-)-2-aminobutane (2.2 g, 29.34 mmol) and DIPEA (4.6g, 35.20 mmol) in dichloromethane (60 mL) was

added at 0°C. The resulting mixture was stirred at 25°C for 1 hour. The mixture was concentrated in vacuo and the obtained residue was purified by high performance liquid chromatography on reversed phase (eluent: CH_3CN in water (0.1% TFA) from 25% to 55%, v/v). The pure fractions were collected and the organic solvent was evaporated. The aqueous solution was adjusted to pH =7 with saturated aqueous $NaHCO_3$. The mixture was extracted with dichloromethane (3 x 200 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The obtained residue was suspended in water (10 mL) and the aqueous layer was lyophilized to dryness resulting in compound **100** (4.7 g). Method B; Rt: 4.70 min. m/z : 387.2 $(M+H)^+$ Exact mass: 386.1.

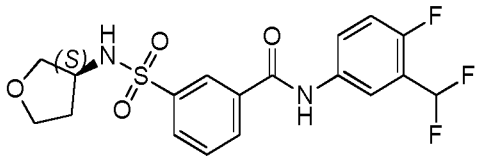


Compound **101**

(S)-tetrahydrofuran-3-amine hydrochloride (5.17 g, 42 mmol) and NaOH (5 g, 126 mmol) were dissolved in THF (50 mL) and H_2O (50 mL). 5-(chlorosulfonyl)-2-fluorobenzoic acid (10 g, 42 mmol) was added at 0°C. The mixture was stirred at 20°C for 4 hours. The mixture was washed with ethyl acetate (3 x 20 mL). The aqueous layer was separated and adjusted to pH=3 with 1N HCl. The aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed in vacuo resulting in (S)-2-fluoro-5-(N-(tetrahydrofuran-3-yl)sulfamoyl)benzoic acid (2.1 g) . (S)-2-fluoro-5-(N-(tetrahydrofuran-3-yl)sulfamoyl)benzoic acid (1 g, 3.457 mmol), 3,4-difluoroaniline (0.53 g, 4.15 mmol) and triethylamine (0.7 g, 6.9 mmol) were dissolved in DMF (400 mL) and HATU (1.57 g , 4.15 mmol) was added at 0°C. The mixture was next stirred at 20°C for 6 hours. The solvent was removed in vacuo and the obtained residue was purified by silica gel chromatography (eluent: petroleum ether: ethyl acetate=5:1) resulting in compound **101** (0.8 g). Method B; Rt: 4.15 min. m/z : 401.3 $(M+H)^+$ Exact mass: 400.1

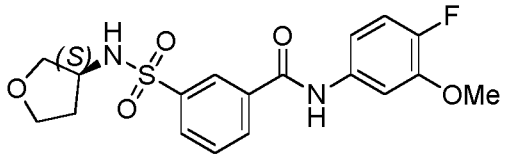
Synthesis of 3-[[(3*S*)-tetrahydrofuran-3-yl]sulfamoyl]benzoic acid:

(3*S*)-tetrahydrofuran-3-amine hydrochloride (5.6 g, 45.3 mmol) and NaOH (5.2 g, 130 mmol) were dissolved in THF (50 mL) and H_2O (50 mL). 3-(chlorosulfonyl)-benzoic acid (10 g, 45.325 mmol) was added at 0°C. The mixture was stirred at 20°C for 4 hours. The aqueous layer was separated and the pH was adjusted to 2 with 1N HCl. The mixture was washed with ethyl acetate (3 x 100 mL).The combined organic layers were concentrated in vacuo resulting in 3-[[(3*S*)-tetrahydrofuran-3-yl]sulfamoyl]benzoic acid (11.2 g).



Compound **102**

A mixture of (*S*)-tetrahydrofuran-3-amine hydrochloride (11.2 g, 90.7 mmol) and NEt_3 (50.5 mL, 362.6 mmol) in dry CH_2Cl_2 (400 mL) was stirred for 5 minutes at 20° C. 3-(chlorosulfonyl)benzoic acid (20 g, 90.7 mmol) was added and the mixture was stirred overnight at 20°C. The reaction mixture was washed with 1N HCl (100 mL), the aqueous layer was extracted with dichloromethane (2 x 200 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed in vacuo, resulting in 3-[[(3*S*)-tetrahydrofuran-3-yl]sulfamoyl]benzoic acid (16.3 g). 3-[[(3*S*)-tetrahydrofuran-3-yl]sulfamoyl]benzoic acid (3 g, 11.058 mmol), 3-(difluoromethyl)-4-fluoroaniline (2.1 g, 13.3 mmol) and triethylamine (3.3 g, 33 mmol) were dissolved in DMF (400 mL). PyBrOP (132705-51-2, 6.2 g , 13.3 mmol) was added at 0°C. The mixture was stirred at 50°C for 12 hours. The solvent was removed in vacuo and the obtained residue was purified by reversed phase high performance liquid chromatography (mobile phase: CH_3CN in water (0.1% TFA) from 30% to 60%). The pure fractions were collected and neutralized with solid $NaHCO_3$. The organic solvent was removed in vacuo and the formed precipitate was filtered, washed with H_2O (5 mL) and dried under high vacuum. The obtained residue was suspended in water (5 mL) and lyophilized to dryness resulting in compound **102** (2.3 g). Method A; Rt: 5.32 min. m/z : 415.2 $(M+H)^+$ Exact mass: 414.1. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.53 - 1.68 (m, 1 H) 1.82 - 1.99 (m, 1 H) 3.27 - 3.42 (m, 1 H) 3.51 - 3.90 (m, 4 H) 7.26 (t, *J*=55 Hz, 1 H) 7.36 - 7.51 (m, 1 H) 7.80 (t, *J*=7.8 Hz, 1 H) 7.92 - 8.00 (m, 1 H) 8.01 - 8.08 (m, 1 H) 8.08 - 8.15 (m, 2 H) 8.25 (d, *J*=7.8 Hz, 1 H) 8.40 (s, 1 H) 10.75 (s, 1 H).



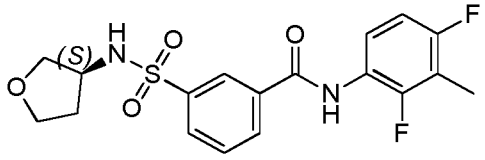
Compound **103**

3-[[(3*S*)-tetrahydrofuran-3-yl]sulfamoyl]benzoic acid (400 mg, 1.47 mmol) was dissolved in DMF (0.5 mL) and CH_2Cl_2 (10 mL). $(COCl)_2$ (223 mg, 1.76 mmol) was added at 0°C. The mixture was stirred at 20°C for 2 hours. The solvent was removed in vacuo and the obtained residue was co-evaporated with toluene (2 x 10 mL) resulting in crude 3-[[(3S)-tetrahydrofuran-3-yl]sulfamoyl]benzoyl chloride (400 mg).The crude product was used in the next step without purification. 3-[[(3S)-tetrahydrofuran-3-yl]-

sulfamoyl]benzoyl chloride (200 mg) was dissolved in dichloromethane (5 mL). 4-fluoro-3-methoxy-aniline (78 mg, 0.552 mmol) and triethylamine (167 mg, 165 mmol) were added at 0°C. The mixture was stirred at 20°C for 2 hours, washed with H_2O (5 mL) and the waterlayer extracted with dichloromethane (3 x 10 mL). The combined organic layers were concentrated in vacuo. The obtained residue was purified by reversed phase high performance liquid chromatography (mobile phase: CH_3CN in water (0.1% TFA) from 30% to 60%). The pure fractions were collected and neutralized with solid $NaHCO_3$. The organic solvent was removed in vacuo. The obtained precipitate was filtered, washed with H_2O (5 mL) and dried under high vacuum. The residue was suspended in water (5 mL) lyophilized to dryness resulting in compound **103** (140 mg). Method A; Rt: 4.98 min. m/z : 395.2 $(M+H)^+$ Exact mass: 394.1

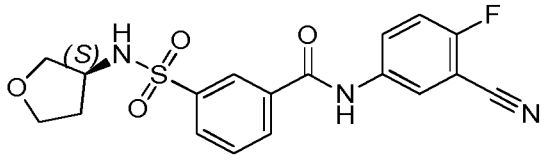
Prepared similarly as described for compound **103:**

Compound **104**



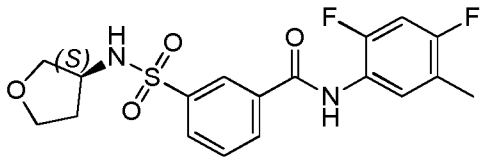
Method A; Rt: 5.17 min. m/z: 397.3 $(M+H)^+$ Exact mass: 396.1

Compound **105**



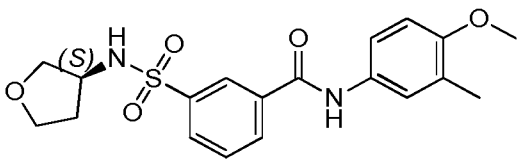
Method A; Rt: 5.10 min. m/z: 389.1 $(M+H)^+$ Exact mass: 390.2

Compound **106**



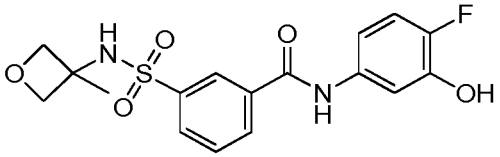
Method A; Rt: 5.18 min. m/z : 397.2 $(M+H)^+$ Exact mass: 396.1

^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.54 - 1.69 (m, 1 H) 1.82 - 1.98 (m, 1 H) 2.24 (s, 3 H) 3.35 - 3.40 (m, 1 H) 3.52 - 3.66 (m, 2 H) 3.66 - 3.83 (m, 2 H) 7.32 (t, *J*=10.0 Hz, 1 H) 7.49 (t, *J*=8.5 Hz, 1 H) 7.79 (t, *J*=7.8 Hz, 1 H) 8.04 (d, *J*=8.0 Hz, 1 H) 8.07 - 8.18 (m, 1 H) 8.23 (d, *J*=7.8 Hz, 1 H) 8.39 (s, 1 H) 10.40 (br. s, 1 H)



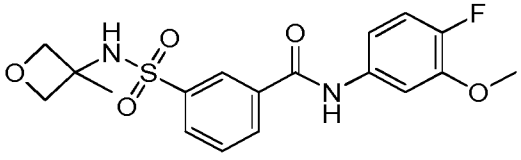
Compound **107**

3-[[(3*S*)-tetrahydrofuran-3-yl]sulfamoyl]benzoic acid (270 mg, 1.0 mmol) was dissolved in dichloromethane (5 mL). 3-methyl-4-methoxyaniline (165 mg, 1.2 mmol) and triethylamine (145 mg, 1.4 mmol) were added to the mixture at 20°C. The mixture was stirred at 20°C for 5 minutes. HATU (456 mg, 1.2 mol) was added and the mixture was further stirred at 20°C for 8 hours. The solvent was removed in vacuo and the obtained residue was purified by high performance liquid chromatography (Column: Phenomenex Synergi C18 150*20mm*5um.. A: H_2O+0.1%TFA B: MeCN from 30% to 60 % B in A). The product fractions were collected and the organic solvent was evaporated in vacuo. The aqueous layer was neutralized with saturated aqueous $NaHCO_3$ and extracted with dichloromethane (2 x 10 mL). The combine organic layers was dried over Na_2SO_4 and concentrated in vacuo resulting in compound **107** (135 mg). Method A; Rt: 5.24 min. m/z : 391.3 $(M+H)^+$ Exact mass: 390.1



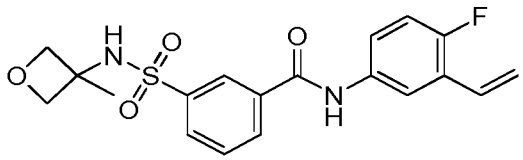
Compound **108**

5-amino-2-fluoro-phenol (234 mg, 1.84 mmol) and 3-[(3-methyloxetan-3-yl)-sulfamoyl]benzoic acid (500 mg, 1.84 mmol) were dissolved in dichloromethane (8 mL). PyBrOP (132705-51-2, 1030 mg, 2.21 mmol) was added followed by drop wise addition of DIPEA (714 mg, 5.53 mmol) at 0°C. The mixture was stirred for 1 hour at 25°C. The mixture was washed with saturated aqueous citric acid (15 mL), saturated aqueous $NaHCO_3$ (15 mL) and brine and dried over Na_2SO_4. The solvent was removed in vacuo. The obtained residue was purified by reversed phase preparative high-performance liquid chromatography (mobile phase: CH_3CN in water (0.05% NH_4HCO_3) from 29% to 39%). The pure fractions were collected and the volatiles were removed in vacuo. The residual aqueous layer was lyophilized to dryness re sulting in compound **108** (60 mg). Method A; Rt: 4.47 min. m/z: 381.2 $(M+H)^+$ Exact mass: 380.1



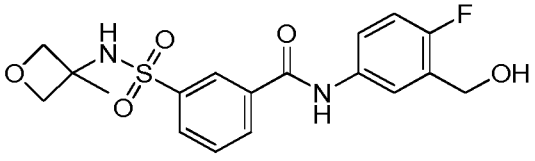
Compound **109**

Prepared similarly as described for compound **108**, using 4-fluoro-3-methoxy-aniline instead of 5-amino-2-fluoro-phenol. Method A; Rt: 5.03 min. m/z: 395.2 $(M+H)^+$ Exact mass: 394.1



Compound **110**

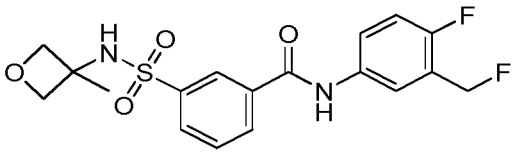
DIPEA (2.85 g, 22.08 mmol) was added to a solution of 3-[(3-methyloxetan-3-yl)-sulfamoyl]benzoic acid (3.0 g, 11.06 mmol) and HATU (4.20 g, 11.05 mmol) in DMF (100 mL) at 25°C. After 30 minutes, 3-bromo-4-fluoro-aniline (2.1 g, 11.05 mmol) was added to the solution. The reaction mixture was stirred at 25°C overnight. The solvent was removed in vacuo and the obtained residue was purified by silica gel column chromatography (gradient eluent: petroleum ether/ethyl acetate from 10/1 to 5/1). The pure fractions were collected and the solvent was removed in vacuo resulting in N-(3-bromo-4-fluoro-phenyl)-3-[(3-methyloxetan-3-yl)sulfamoyl]benzamide (compound **160**, 2.5 g). A mixture of N-(3-bromo-4-fluoro-phenyl)-3-[(3-methyloxetan-3-yl)sulfamoyl]benzamide (0.3 g, 0.68 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (54.2 mg, 0.35 mmol), Pd (dppf) Cl_2 (50 mg, 0.068 mmol), KOAc (108 mg, 1.1 mmol) and Na_2CO_3 (100 mg, 0.94 mmol) in CH_3CN (10 mL) and H_2O (2 mL) was heated by microwave irradiation for 30 minutes at 130°C under a N_2 atmosphere. The reaction mixture was filtered through Celite and the filter cake was washed with ethyl acetate (2 x 10 mL). The organic layer was separated from the filtrate, washed with brine and dried over Na_2SO_4. The solvent was removed in vacuo. The obtained residue was purified by reversed phase preparative high performance liquid chromatography (eluent: CH_3CN in H_2O (0.05% $NH_3.H_2O$) from 30% to 80%, v/v). The pure fractions were collected and the volatiles were removed in vacuo. The aqueous layer was lyophilized to dryness resulting in compound **110** (70 mg). Method B; Rt: 4.19 min. m/z : 391.3 $(M+H)^+$ Exact mass: 390.1.



Compound **111**

3-[(3-methyloxetan-3-yl)sulfamoyl]benzoic acid (3 g, 11.06 mmol), methyl 5-amino-2-fluoro-benzoate (2.33 g, 13.2 mmol) and DIPEA (2.84 g, 22 mmol) were dissolved in

DMF (40 mL). HATU (5.02 g , 13.2 mmol) was added at 0°C. The mixture was stirred at 20°C for 2 hours. The solvent was removed in vacuo and the obtained residue was purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate=3:1) resulting in methyl 2-fluoro-5-[[3-[(3-methyloxetan-3-yl)sulfamoyl]-benzoyl]amino]benzoate (2.3 g). Methyl 2-fluoro-5-[[3-[(3-methyloxetan-3-yl)-sulfamoyl]benzoyl]amino]benzoate (0.3 g, 0.71 mmol) was dissolved in THF (5 mL) and ethanol (5 mL). $NaBH_4$ (53 mg, 1.4 mmol) was added at 0°C. The mixture was stirred for 2 hours at 20°C. The solvent was removed in vacuo and the obtained residue was purified by reversed phase high performance liquid chromatography (mobile phase: CH_3CN in water (0.1% TFA) from 34% to 64%). The pure fractions were collected and neutralized with solid $NaHCO_3$. The organic solvent was removed in vacuo. The precipitate was filtered, washed with H_2O (5 mL) and dried under high vacuum. The residue was suspended in water (5 mL) and the aqueous layer was lyophilized to dryness resulting in compound **111** (220 mg). Method A; Rt: 4.34 min. m/z : 395.3 $(M+H)^+$ Exact mass: 394.1.

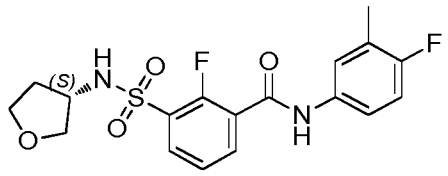


Compound **127**

(2-fluoro-5-nitro-phenyl)methanol (4.3 g, 25.1 mmol) was dissolved in dichloro-methane (50 mL). Diethylaminosulfur trifluoride (4.5 g, 27.9 mmol) was added drop wise to the mixture at -30°C. The mixture was stirred at 10° C for 4 hours. Methanol (10 mL) was added to the mixture and the mixture was further stirred at 10°C for 30 minutes. The mixture was washed with brine (30mL) and the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo, resulting in 1-fluoro-2-(fluoromethyl)-4-nitro-benzene (3.9 g). A mixture of 1-fluoro-2-(fluoromethyl)-4-nitro-benzene (3.1 g, 17.9 mmol), iron (4.0 g, 71.6 mmol) and methanol (30 mL) was stirred at 65° for 8 hours. The mixture was filtrated and the filtrate was concentrated in vacuo, resulting in 4-fluoro-3-(fluoromethyl)aniline (1.5 g). 3-(chlorosulfonyl)benzoyl chloride (300 mg, 1.2 mmol) and triethylamine (150 mg, 1.5 mmol) were dissolved in dichloromethane (20 mL). 4-fluoro-3-(fluoromethyl)aniline (175 mg, 1.22 mmol) was added to the mixture at 0° C. The mixture was stirred at 10°C for 30 minutes. The mixture was used to the next step without further purification.Triethylamine (152 mg, 1.5 mmol) and 3-methyl-3-oxetanamine (131 mg. 1.5 mmol) were added to the above obtained reaction mixture at 0° C. The mixture was stirred at 20° C for 1 hour. The solvent was

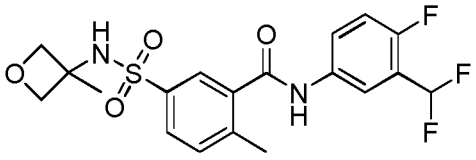
removed in vacuo and the obtained residue was purified by reversed phase high performance liquid chromatography (Column: Gemini 250*20mm*5um.. A: H_2O+0.1%TFA B: MeCN. 27% to 57% B in A). The product fractions were collected and the organic solvent was removed in vacuo. The fraction was neutralized by saturated $NaHCO_3$. The mixture was extracted with dichloromethane (3 x 20 mL) and the combined organic layer was dried over Na_2SO_4 and concentrated in vacuo, resulting in compound **127** (91.1 mg). Method A; Rt: 4.95 min. m/z : 397.3 $(M+H)^+$ Exact mass: 396.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.41 (s, 3 H) 4.14 (d, *J*=6.3 Hz, 2 H) 4.56 (d, *J*=6.3 Hz, 2 H) 5.52 (d, *J*=48 Hz, 2 H) 7.31 (t, *J*=9.4 Hz, 1 H) 7.72 - 7.89 (m, 2 H) 7.92-7.97 (m, 1 H) 8.03 (d, *J*=8.0 Hz, 1 H) 8.23 (d, *J*=7.8 Hz, 1 H) 8.39 (s, 1 H) 8.55 (s, 1 H) 10.67 (s, 1 H).

Compound **112**



Compound **123** (255 mg, 0.592 mmol) and Pd/C (50 mg) were stirred in methanol (25 mL) under a hydrogen atmosphere for 3 hours. The reaction mixture was filtered, concentrated and the obtained residue dried in vacuo at 50°C resulting in compound **112** as a colorless resin.(174 mg). Method G; Rt: 1.57 min. m/z : 397.1 $(M+H)^+$ Exact mass: 396.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.65 - 1.80 (m, 1 H), 1.91 - 2.04 (m, 1 H), 2.24 (d, J=1.5 Hz, 3 H), 3.43 (dd, J=9.0, 4.6 Hz, 1 H), 3.55 - 3.79 (m, 3 H), 3.80 - 3.91 (m, 1 H), 7.14 (t, J=9.2 Hz, 1 H), 7.45 - 7.57 (m, 2 H), 7.64 (dd, J=7.0, 2.4 Hz, 1 H), 7.85 - 8.02 (m, 2 H), 8.40 (d, J=6.8 Hz, 1 H), 10.62 (s, 1 H)

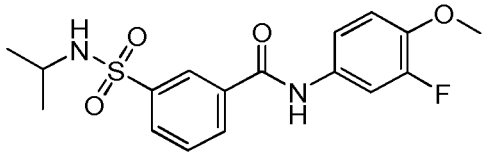
Compound **113**



3-methyloxetan-3-amine hydrochloride (210 mg, 1.7 mmol) and NaOH (204 mg, 5.1 mmol) were dissolved in 2-methyltetrahydrofuran (5 mL) and H_2O (5 mL). 5-chlorosulfonyl-2-methyl-benzoic acid (400 mg, 1.7 mmol) was added at 0°C. The mixture was stirred at 20°C for 4 hours. The aqueous layer was separated and adjusted to pH=3 by aq.HCl (1N).The mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were concentrated in vacuo resulting in 2-methyl-5-[(3-methyloxetan-3-yl)sulfamoyl]benzoic acid (250 mg). 2-methyl-5-[(3-methyloxetan-

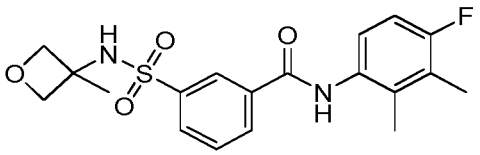
3-yl)sulfamoyl]benzoic acid (250 mg, 0.876 mmol), 3-(difluoromethyl)-4-fluoro-aniline (178 mg, 1.1 mmol) and DIPEA (232 mg, 1.8 mmol) were dissolved in DMF (5 mL). HATU (399 mg , 1.05 mmol) was added at 0°C. The mixture was stirred at 20°C for 2 hours. The solvent was removed in vacuo and the obtained residue was purified by reversed phase high performance liquid chromatography (mobile phase: CH_3CN in water (0.1% TFA) from 34% to 64%). The pure fractions were collected and neutralized with solid $NaHCO_3$. The organic solvent was removed in vacuo and the formed precipitate was filtered, washed with H_2O (5 mL) and dried under high vacuum. The residue was suspended in water (5 mL) and the aqueous layer was lyophilized to dryness resulting in compound **113** (220 mg). Method A; Rt: 5.28 min. m/z : 429.3 $(M+H)^+$ Exact mass: 428.1. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.44 (s, 3 H) 2.47 (s, 3 H) 4.15 (d, *J*=6.3 Hz, 2 H) 4.57 (d, *J*=6.0 Hz, 2 H) 7.24 (t, *J*=54.5 Hz, 1 H) 7.40 (t, *J*=9.5 Hz, 1 H) 7.56 (d, *J*=8.0 Hz, 1 H) 7.71 - 7.98 (m, 3 H) 8.09 (d, *J*=4.3 Hz, 1 H) 8.37 (br. s., 1 H) 10.74 (br. s., 1 H)

Compound **114**



3-(isopropylsulfamoyl)benzoic acid (190 mg, 0.78 mmol) was dissolved in dichloromethane (5 mL). 3-fluoro-4-methoxyaniline (139 mg, 0.94 mmol) and triethylamine (112 mg, 1 mmol) were added to the mixture at 20°C. The mixture was stirred at 20°C for 5 minutes. HATU (358 mg, 0.94 mmol) was added to the mixture at 20°C. The mixture was stirred at 20°C for 8 hours. The solvent was removed in vacuo and the obtained residue was purified by high performance liquid chromatography (Column: Phenomenex Synergi C18 150*20mm*5um.. A: H_2O+0.1%TFA B: MeCN 30% to 60% B in A). The product fractions were collected and the organic solvent was evaporated. The aqueous layer was neutralized with saturated aqueous $NaHCO_3$. The mixture was extracted with dichloromethane (2 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo resulting in compound **114** (135 mg). Method A; Rt: 5.60 min. m/z: 367.2 $(M+H)^+$ Exact mass: 366.1

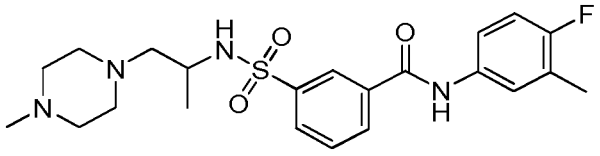
Compound **115**



Prepared similarly as desribed for compound **127** using 4-fluoro-2,3-dimethyl-aniline

instead of 4-fluoro-3-(fluoromethyl)aniline. Method A; Rt: 4.98 min. m/z : 393.3 $(M+H)^+$ Exact mass: 392.1.

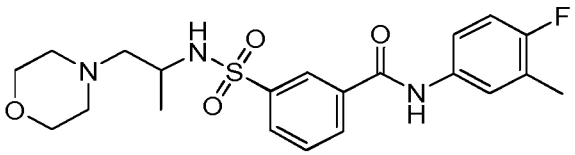
Compound **116**



4-fluoro-3-methyl-aniline (9.04 g, 72.2 mmol) was added drop wise to a solution of 3-(chlorosulfonyl) benzoyl chloride (19.0g, 79.47 mmol) in toluene (300 mL) at 110°C. The resultant mixture was stirred at 110°C for 1 hour and allowed to cool to 20°C overnight. The precipitate was filtered and recrystallized from dry toluene resulting in 3-[(4-fluoro-3-methyl-phenyl)carbamoyl]benzenesulfonyl chloride (20 g). 3-[(4-fluoro-3-methyl-phenyl)carbamoyl]benzenesulfonyl chloride (15 g, 45.77 mmol) was added drop wise at 0°C to a solution of 2-aminopropan-1-ol (3.437 g, 45.77 mmol) and triethylamine (6.946 g) in THF (200 mL). The resultant mixture was stirred for 10 minutes and then allowed to warm to 20°C during 2 hours. The reaction mixture was quenched with 1N HCl (50 mL). The mixture was extracted with dichloromethane (3 x 30 mL).The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (gradient eluent: petroleum ether / ethyl acetate from 100/1 to 50/50), resulting in N-(4-fluoro-3-methyl-phenyl)-3-[(2-hydroxy-1-methyl-ethyl)sulfamoyl]-benzamide (15.6 g). Diethyl diazene-1,2-dicarboxylate (4.91 g, 28.19 mmol) was added drop wise to a solution of N-(4-fluoro-3-methyl-phenyl)-3-[(2-hydroxy-1-methyl-ethyl)sulfamoyl]benzamide (7.8 g, 21.29 mmol) and PPh_3 (6.14 g, 23.41 mmol) in THF (500 mL) at -70°C under Argon. The resultant mixture was stirred for 1 hour and then allowed to warm to 20°C overnight. The reaction mixture was quenched with 1N HCl (300 mL). The mixture was extracted with dichloromethane (4 x 400 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The obtained residue was purified by silica gel column chromatography (gradient eluent: petroleum ether / ethyl acetate from 100/1 to 60/40) resulting in N-(4-fluoro-3-methyl-phenyl)-3-(2-methylaziridin-1-yl)sulfonyl-benzamide (6.5 g). A mixture of N-(4-fluoro-3-methyl-phenyl)-3-(2-methylaziridin-1-yl)sulfonyl-benzamide (300 mg, 0.861 mmol) and 1-methylpiperazine (862 mg, 8.61 mmol) in 1.4-dioxane (3 mL) was heated by microwave irradiation at 150°C for 30 minutes. The volatiles were removed in vacuo. The obtained residue was purified by silica gel column chromatography (gradient eluent: petroleum ether/ethyl acetate from 100/1 to 1/100). The pure fractions were collected and the solvent was removed in vacuo. The

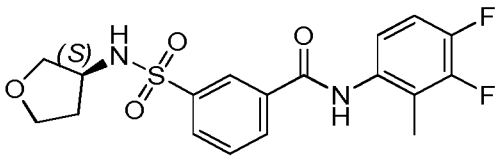
obtained residue was purified by preparative high-performance liquid chromatography (column: Luna 150*30mm*5u, mobile phase: CH_3CN in water (0.1% NH_4HCO_3) from 44% to 74%). The pure fractions were collected, concentrated in vacuo and the residual aqueous solution was lyophilized to dryness resulting in compound **116** (250 mg). Method A; Rt: 4.26 min. m/z : 449.4 $(M+H)^+$ Exact mass: 448.2

Compound **117**



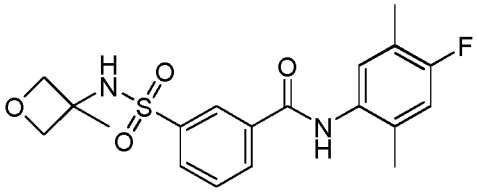
Prepared similarly as desribed for compound **116** using morpholine instead of 1-methylpiperazine. Method A; Rt: 4.45 min. m/z : 436.3 $(M+H)^+$ Exact mass: 435.2

Compound **118**



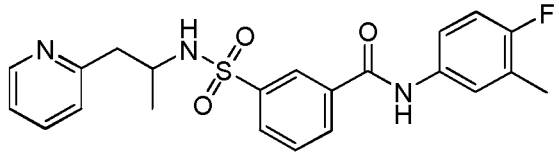
To a stirred solution of 3,4-difluoro-2-methyl-aniline (369 mg, 2.6 mmol), 3-[[(3*S*)-tetrahydrofuran-3-yl]sulfamoyl]benzoic acid (700 mg, 2.58 mmol) and N,N-diisopropylethylamine(1.35 ml, 7.74 mmol) in DMF (10 mL), Pybrop (132705-51-2, 1.82 g, 3.9 mmol) was added at 0° C. The resulting mixture was stirred overnight at 18 °C. The mixture was concentrated in vacuo, ethyl acetate (15 mL) was added and the organic layer was washed with 1N HCl (15 ml) and saturated aqueous $NaHCO_3$ (15 mL). After drying over Na_2SO_4 and concentration in vacuo, the crude residue was purified by reversed phase preparative high-performance liquid chromatography (eluent: CH_3CN in H2O (0.05% $NH_3.H_2O$) from 37% to 37%, v/v). The pure fractions were collected and the volatiles were removed in vacuo. The aqueous layer was lyophilized to dryness, resulting in compound **118** (238 mg). Method D; Rt: 5.01 min. m/z : 396.9 $(M+H)^+$ Exact mass: 396.1

Compound **119**



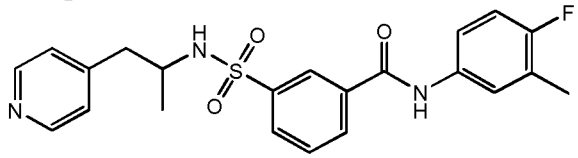
Prepared similarly as described for compound **127** using 4-fluoro-2,5-dimethyl-aniline instead of 4-fluoro-3-(fluoromethyl)aniline, and DIPEA instead of NEt_3. Method A; Rt: 5.27 min. m/z: 393.3 $(M+H)^+$ Exact mass: 392.1

Compound **120**



A mixture of 1-(2-pyridyl)propan-2-amine (207.8 mg, 1.53 mmol) and DIPEA (0.532 mL, 3.05 mmol) were dissolved in CH_2Cl_2 (10 mL). 3-[(4-fluoro-3-methyl-phenyl)carbamoyl]benzenesulfonyl chloride (500 mg, 1.53 mmol) was added portion wise at 0°C and the mixture was stirred at 0°C for 1 hour. The mixture was washed with saturated citric acid (10 mL), saturated aqueous $NaHCO_3$ (10 mL), brine and dried over Na_2SO_4. The solvent was removed in vacuo and the obtained residue was purified by silica gel column chromatography (gradient eluent: petroleum ether/ethyl acetate from 100/1 to 1/100).The pure fractions were collected and the solvent was removed in vacuo. The obtained solid was suspended in water (10 mL) and acetonitrile (10 mL) and the solution was lyophilized to dryness resulting in compound **120** (550 mg). Method B; Rt: 3.36 min. m/z: 428.3 $(M+H)^+$ Exact mass: 427.1. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 0.95 (d, *J*=6.5 Hz, 3 H) 2.26 (d, *J*=1.5 Hz, 3 H) 2.69 (dd, *J*=13.6, 7.3 Hz, 1 H) 2.80 (dd, *J*=13.6, 7.0 Hz, 1 H) 3.64 - 3.74 (m, 1 H) 7.08 - 7.19 (m, 3 H) 7.55-7.64 (m, 2 H) 7.64 - 7.71 (m, 2 H) 7.84 - 7.89 (m, 1 H) 7.89 - 7.95 (m, 1 H) 8.12 - 8.17 (m, 1 H) 8.25 (t, *J*=1.5 Hz, 1 H) 8.32 - 8.36 (m, 1 H) 10.45 (s, 1 H).

Compound **224**

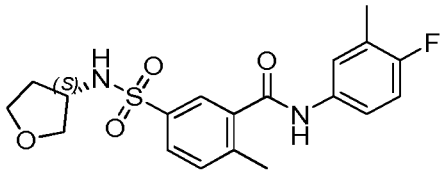


Compound **224** was prepared similarly as described for compound **223**, using 1-(4-pyridyl)propan-2-amine instead of 1-(2-pyridyl)propan-2-amine. Compound **224** was purified by preparative high-performance liquid chromatography (column: Luna 150*30mm*4u, mobile phase: CH_3CN in water (0.05% NH_4HCO_3) from 40% to 70%). Method A; Rt: 4.6 min. m/z: 428.3 $(M+H)^+$ Exact mass: 427.1.

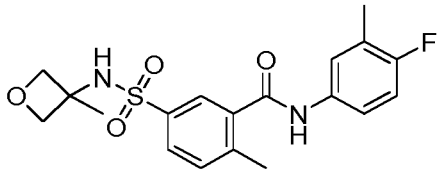
Synthesis of 5-chlorosulfonyl-2-methyl-benzoyl chloride and 3-[(4-fluoro-3-methyl-phenyl)carbamoyl]-4-methyl-benzenesulfonyl chloride

5-(chlorosulfonyl)-2-methylbenzoic acid (10 g, 42.61 mmol) was dissolved in dichloromethane (200 mL). N,N-dimethylformamide (166 µL, 2.13 mmol) was added and the mixture was stirred at room temperature under a nitrogen atmosphere. Oxalyl chloride (18.3 mL, 213 mmol) was added in four portions over one hour. The resulting mixture was stirred for one hour at room temperature. The mixture was concentrated in vacuo and co-evaporated twice using toluene (2 x 100 mL) yielding 5-chlorosulfonyl-2-methyl-benzoyl chloride as a yellow oil which was used as such. 5-chlorosulfonyl-2-methyl-benzoyl chloride (10.7 g, 42.3 mmol) was dissolved in toluene (220 mL) and this was heated to reflux and stirred under a gentle flow of nitrogen. 4-fluoro-3-methylaniline (4.76 g, 38.1 mmol) in toluene (80 mL) was added drop wise using a syringe pump (0,8 mL / min). The resulting mixture was stirred for 30 minutes while heating was continued. Then the mixture was cooled to room temperature. A precipitation was formed and collected on a glass filter. The obtained solid was dried in vacuo at 55°C, yielding 3-[(4-fluoro-3-methyl-phenyl)carbamoyl]-4-methyl-benzenesulfonyl chloride (10.4 g) as a solid which was used as such in the next step.

Compound **121**

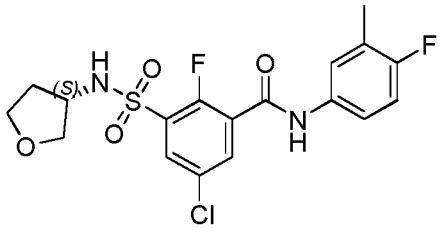


A solution of (*S*)-3-aminotetrahydrofuran tosylate (0.76 g, 2.93 mmol) and diisopropylethylamine (1.26 mL, 7.31 mmol) in dichloromethane (10 mL) was added drop wise to a solution of 3-[(4-fluoro-3-methyl-phenyl)carbamoyl]-4-methyl-benzenesulfonyl chloride (1 g, 2.93 mmol) in dichloromethane (10 mL). The resulting mixture was stirred for 1 hour at room temperature. The mixture was quenched using HCl (aq / 14.6 mL, 14.6 mmol). The layers were separated and the water layer was extracted with dichloromethane (2 x 20 mL). The combined organics were concentrated in vacuo and purified using silica gel column chromatography (gradient elution: EtOAc-heptane 0:100 to 100:0). The desired fractions were concentrated in vacuo and dried in vacuo at 55°C yielding compound **121** as a bright white solid. Method F; Rt: 0.90 min. m/z: 393.2 $(M+H)^+$ Exact mass: 392.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.58 - 1.69 (m, 1 H), 1.85 - 1.98 (m, 1 H), 2.24 (d, J=1.3 Hz, 3 H), 2.45 (s, 3 H), 3.38 (dd, J=8.8, 4.4 Hz, 1 H), 3.53 - 3.65 (m, 2 H), 3.66 - 3.76 (m, 2 H), 7.13 (t, J=9.2 Hz, 1 H), 7.46 - 7.59 (m, 2 H), 7.66 (dd, J=7.0, 2.2 Hz, 1 H), 7.75 - 7.87 (m, 2 H), 7.96 (br. s., 1 H), 10.46 (s, 1 H).



Compound **122**

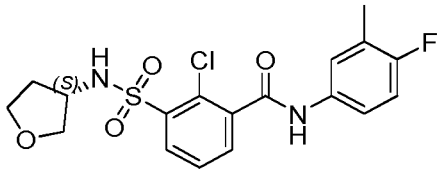
A solution of 3-methyl-3-oxetanamine hydrochloride (0.4 g, 3.22 mmol) and diisopropylethylamine (1.26 mL, 7.31 mmol) in of dichloromethane (10 mL) was added drop wise to a solution of 3-[(4-fluoro-3-methyl-phenyl)carbamoyl]-4-methyl-benzenesulfonyl chloride (1 g, 2.93 mmol) in dichloromethane(10 mL). The resulting mixture was stirred for 1 hour at room temperature. The mixture was quenched using HCl (aq / 14.63 mL, 14.63 mmol). The layers were separated and the water layer was extracted using dichloromethane (2 x 20 mL). The combined organic layers were concentrated in vacuo and purified using column chromatography (gradient elution: EtOAc-heptane 0:100 to 100:0). The desired fractions were concentrated in vacuo and dried in a vacuum oven at 55°C yielding compound **122** as a bright white solid. Method F; Rt: 0.90 min. m/z: 410.2 $(M+NH_4)^+$ Exact mass: 392.1.^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.43 (s, 3 H), 2.19 - 2.29 (m, 3 H), 2.44 (s, 3 H), 4.14 (d, J=6.4 Hz, 2 H), 4.56 (d, J=6.2 Hz, 2 H), 7.13 (t, J=9.1 Hz, 1 H), 7.42 - 7.57 (m, 2 H), 7.59 - 7.71 (m, 1 H), 7.74 - 7.90 (m, 2 H), 8.36 (s, 1 H), 10.46 (s, 1 H).



Compound **123**

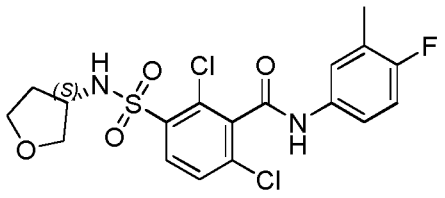
Compound **123** was prepared similarly as described for compound **121** starting from 5-chloro-3-chlorosulfonyl-2-fluoro-benzoic acid (commercial from Enamine EN300-35191) via 5-chloro-3-chlorosulfonyl-2-fluoro-benzoyl chloride (^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 8.23 (dd, J=5.4, 2.8 Hz, 1 H), 8.37 (dd, J=5.5, 2.6 Hz, 1 H)). After silica gel column chromatography (gradient elution: EtOAc-heptane 10:90 to 100:0) compound **123** was crystallised by addition of H_2O to a hot iPrOH solution of compound **123**, resulting in compound **123** as white solid (3153 mg). Method G; Rt: 1.81 min. m/z: 431.0 $(M+H)^+$ Exact mass: 430.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.65 - 1.79 (m, 1 H), 1.93 - 2.06 (m, 1 H), 2.25 (d, J=1.8 Hz, 3 H), 3.44 (dd, J=9.0, 4.4 Hz, 1 H), 3.62 (td, J=8.0, 5.9 Hz, 1 H), 3.69 (dd, J=8.9, 6.3 Hz, 1 H), 3.71 - 3.79 (m, 1 H), 3.84 - 3.98 (m, 1 H), 7.15 (t, J=9.1 Hz, 1 H), 7.45 - 7.55 (m, 1 H), 7.61 (dd,

J=6.9, 2.3 Hz, 1 H), 7.91 (dd, J=5.7, 2.6 Hz, 1 H), 8.07 (dd, J=5.2, 2.8 Hz, 1 H), 8.57 (d, J=6.8 Hz, 1 H), 10.68 (s, 1 H)



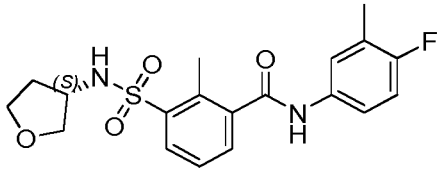
Compound **124**

Compound **125** (167 mg,0.371 mmol) and Pd/C (25 mg) were stirred in methanol (19 mL) under hydrogen atmosphere during 80 minutes. The reaction mixture was filtered and concentrated. The obtained residue was purified by preparative SFC (Stationary phase: Chiralpak Diacel AD 30 x 250 mm), Mobile phase: CO_2, MeOH with 0.2% $iPrNH_2$), the desired fractions were collected, evaporated, dissolved in MeOH and evaporated again resulting in compound **124** (67 mg). Method G; Rt: 1.61 min. m/z: 430.0 $(M+NH_4)^+$ Exact mass: 412.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.68 - 1.83 (m, 1 H), 1.89 - 2.03 (m, 1 H), 2.24 (d, J=1.5 Hz, 3 H), 3.45 (dd, J=8.9, 4.7 Hz, 1 H), 3.56 - 3.69 (m, 2 H), 6 3.70 - 3.86 (m, 2 H), 7.14 (t, J=9.1 Hz, 1 H), 7.45 - 7.55 (m, 1 H), 7.60 - 7.69 (m, 2 H), 7.82 (dd, J=7.6, 1.7 Hz, 1 H), 8.09 (dd, J=7.8, 1.7 Hz, 1 H), 8.34 (s, 1 H), 10.62 (s, 1 H)



Compound **125**

Compound **125** was prepared similarly as described for compound **126** starting from 2,6-dichloro-3-chlorosulfonyl-benzoic acid instead of 3-chlorosulfonyl-2-methyl-benzoic acid. Method G; Rt: 1.77 min. m/z: 464.0 $(M+NH_4)^+$ Exact mass: 446.0. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.75-1.86 (m, 1 H), 2.04 - 2.16 (m, 1 H), 2.30 (d, J=1.8 Hz, 3 H), 3.57 - 3.65 (m, 1 H), 3.66 - 3.76 (m, 2 H), 3.82 - 3.95 (m, 2 H), 5.45 (d, J=7.5 Hz, 1 H), 7.01 (t, J=8.9 Hz, 1 H), 7.30 - 7.38 (m, 1 H), 7.47 - 7.56 (m, 2 H), 7.83 (s, 1 H), 8.05 (d, J=8.6 Hz, 1 H).



Compound **126**

3-chlorosulfonyl-2-methyl-benzoic acid (commercial from Enamine EN300-109516; 508.4 mg, 2.17 mmol) was dissolved in dichloromethane (50 mL). DMF (1 drop) and oxalylchloride (1375mg, 10.83 mmol) were added and the mixture was stirred for 4 hours under an inert atmosphere. The reaction mixture was concentrated resulting in 3-chlorosulfonyl-2-methyl-benzoyl chloride as a yellow oil (554 mg) which was used as such in the next step. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 2.92 - 3.01 (m, 3 H), 7.60 (t, *J*=7.9 Hz, 1 H), 8.27 - 8.41 (m, 2 H). 4-Fluoro-3-methylaniline (227 mg, 1.98 mmol) dissolved in dichloromethane (10 mL) was added drop wise, over 5 minutes, to a solution of 3-chlorosulfonyl-2-methyl-benzoyl chloride (550 mg, 2.17 mmol) in toluene (50 mL) at reflux. The reaction mixture was refluxed for 30 minutes and next cooled in an icebath. A solution of (S)-3-aminotetrahydrofuran tosylate (564 mg, 2.17 mmol) and DIPEA (0.85 ml, 4.94 mmol) dissolved in dichloromethane (10 mL) was added and the obtained mixture was stirred for 30 minutes. The resulting mixture was washed with HCl (2 x 100 mL / 1M aq), water (2 x 100 mL) and $NaHCO_3$ (2 x 100 mL / sat. aq). The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The obtained residue was purified using silica gel column chromatography (CH_2Cl_2-MeOH 100:0 to 90:10) and repurified by applying a gradient from 10 till 100% EtOAc in heptane. The product fractions were concentrated and dried overnight in vacuo at 50°C yielding compound **126** as colourless oil (16.6 mg). Method G; Rt: 1.65 min. m/z: 393.1 $(M+H)^+$ Exact mass: 392.1. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.73 - 1.87 (m, 1 H), 2.06 - 2.20 (m, 1 H), 2.30 (d, J=1.8 Hz, 3 H), 2.69 (s, 3 H), 3.54 - 3.63 (m, 1 H), 3.65 - 3.78 (m, 2 H), 3.83 - 3.97 (m, 2 H), 4.99 (d, J=8.1 Hz, 1 H), 7.01 (t, J=8.9 Hz, 1 H), 7.31 - 7.44 (m, 2 H), 7.51 (dd, J=6.7, 2.5 Hz, 1 H), 7.58 - 7.69 (m, 2 H), 8.06 (dd, J=8.0, 1.2 Hz, 1 H)

Procedure S1: A solution of 3-[(4-fluoro-3-methyl-phenyl)carbamoyl]benzenesulfonyl chloride (0.50 g, 1.52 mmol, 1 eq) in toluene (10 mL) was added to a flask containing an amine (1.1 eq). DIPEA (657 µL, 3.81 mmol, 2.5 eq) was added and the reaction mixture was stirred for 1 hour. Next, 1M HCl (5 mL) was added to the reaction mixture.

Procedure S2: A tube was charged with 3-[(4-fluoro-3-methyl-phenyl)carbamoyl]-benzenesulfonyl chloride (250 mg, 0.76 mmol) and an amine (1.1 eq) and CH_2Cl_2 (5 mL) was added. The solution was stirred, DIPEA (329 µL, 1.9 mmol, 2.5 eq) was added and the mixture was further stirred for 30 minutes.Then, HCl (1M aq / 5 mL) was added and the mixture was stirred for 5 minutes more.

Procedure S3: To a solution of 3-[(4-fluoro-3-methyl-phenyl)carbamoyl]benzene-sulfonyl chloride (0.50 g, 1.52 mmol, 1 eq) and DIPEA (657 µL, 3.81 mmol, 2.5 eq) in

CH_2Cl_2 (10 mL), an amine (1.1 eq) was added. The reaction mixture was stirred for 1 hour. Next, 1M HCl (5 mL) was added to the reaction mixture.

Procedure S4: 3-[(4-fluoro-3-methyl-phenyl)carbamoyl]benzenesulfonyl chloride (250 mg, 0.76 mmol) and DIPEA (329 µL, 1.9 mmol, 2.5 eq) dissolved in CH_2Cl_2 (5 mL) were added to a tube containing an amine (1.1 eq). The reaction mixture was stirred for 3 hours. 1M HCl (5 mL) was added.

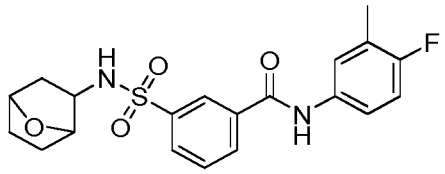
Workup W1: A precipitate was formed. The precipitate was filtered off , rinced with diisopropylether and dried in a vacuum oven at 55 °C.

Workup W2: The organic layer was separated and concentrated in vacuo. The obtained residue was purified by silica gel column chromatography using a heptane to EtOAc gradient as eluent.

Workup W3: The layers were separated and the organic layer was loaded on a silica gel column for purification (with gradient elution: CH_2Cl_2-methanol 100:0 to 97:3).

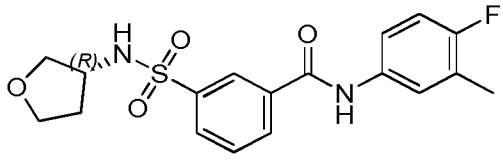
Workup W4: The organic layer was separated and loaded on a silica gel column. The mixture was purified using gradient elution from heptane to EtOAc.

Compound **128**



Synthesis following procedure S4 with 7-oxabicyclo[2.2.1]heptan-2-amine. as amine, workup W4. Method F; Rt: 0.94 min. m/z: 422.1 $(M+NH_4)^+$ Exact mass: 404.1.^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.22 - 1.48 (m, 5 H), 1.68 (dd, J=12.5, 7.9 Hz, 1 H), 2.25 (d, J=1.8 Hz, 3 H), 3.25 - 3.29 (m, 1 H), 4.14 (d, J=4.8 Hz, 1 H), 4.44 (t, J=4.8 Hz, 1 H), 7.14 (t, J=9.2 Hz, 1 H), 7.54 - 7.63 (m, 1 H), 7.68 (dd, J=7.2, 2.3 Hz, 1 H), 7.74 - 7.80 (m, 1 H), 7.86 (d, J=6.8 Hz, 1 H), 7.98 - 8.03 (m, 1 H), 8.20 (dt, J=7.8, 1.4 Hz, 1 H), 8.35 (t, J=1.5 Hz, 1 H), 10.46 (s, 1 H).

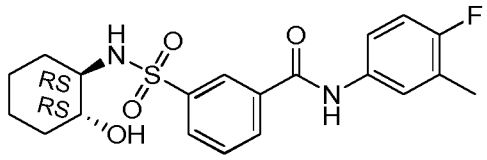
Compound **129**



Synthesis following procedure S3 with R-(+)-3-aminotetrahydrofuran toluene-4-sulfonate as amine, workup W2.

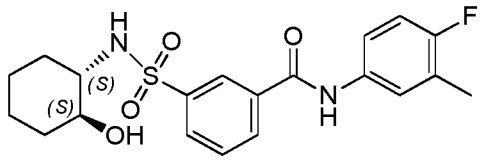
Method F; Rt: 0.89 min. m/z: 396.1 $(M+NH_4)^+$ Exact mass: 378.1. ^{1} H NMR (400 MHz, DMSO-d_6) ppm 1.56 - 1.65 (m, 1 H), 1.85 - 1.94 (m, 1 H), 2.25 (d, J=1.8 Hz, 3 H), 3.36 (dd, J=9.0, 4.4 Hz, 1 H), 3.52 - 3.65 (m, 2 H), 3.65 - 3.73 (m, 1 H), 3.73 - 3.79

(m, 1 H), 7.14 (t, J=9.2 Hz, 1 H), 7.56 - 7.62 (m, 1 H), 7.67 (dd, J=7.0, 2.3 Hz, 1 H), 7.78 (t, J=7.8 Hz, 1 H), 7.99 - 8.05 (m, 1 H), 8.08 (bs, 1 H), 8.20-8.23(m, 1 H), 8.37 (t, J=1.7 Hz, 1 H), 10.47 (s, 1 H), $[\alpha]_D^{20}$= + 5.8 (c 0.61 w/v %, MeOH)



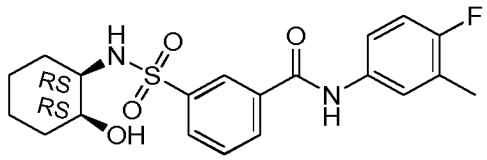
Compound **130**

Method F; Rt: 0.95 min. m/z: 424.2 $(M+NH_4)^+$ Exact mass: 406.1.
Synthesis following procedure S3 with racemic trans-2-aminocyclohexanol hydrochloride as amine, workup W2.



Compound **131**

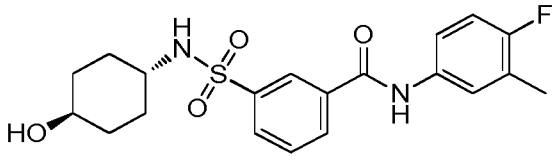
Synthesis following procedure S3 with (1*S*,2*S*)-trans-2-aminocyclohexanol hydrochloride as amine, workup W2.
Method F; Rt: 0.95 min. m/z: 424.2 $(M+NH_4)^+$ Exact mass: 406.1.
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.01 - 1.23 (m, 4 H), 1.41 - 1.58 (m, 2 H), 1.59 - 1.70 (m, 1 H), 1.71 - 1.83 (m, 1 H), 2.25 (d, J=1.3 Hz, 3 H), 2.77 - 2.90 (m, 1 H), 3.15 - 3.27 (m, 1 H), 4.50 (d, J=4.6 Hz, 1 H), 7.14 (t, J=9.2 Hz, 1 H), 7.54 - 7.64 (m, 2 H), 7.64 - 7.69 (m, 1 H), 7.72 (t, J=7.9 Hz, 1 H), 8.04 (d, J=7.7 Hz, 1 H), 8.16 (d, J=7.9 Hz, 1 H), 8.39 (s, 1 H), 10.43 (s, 1 H)



Compound **132**

Synthesis following procedure S3 with racemic cis-2-aminocyclohexanol hydrochloride as amine, workup W2. Method F; Rt: 0.96 min. m/z: 424.1 $(M+NH_4)^+$ Exact mass: 406.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.01 - 1.26 (m, 4 H), 1.26 - 1.36 (m, 1 H), 1.38 - 1.62 (m, 3 H), 2.25 (d, J=1.8 Hz, 3 H), 3.03 - 3.14 (m, 1 H), 3.57 (br. s., 1 H), 4.52 (d, J=4.2 Hz, 1 H), 7.14 (t, J=9.1 Hz, 1 H), 7.46 (d, J=7.9 Hz, 1 H), 7.56 - 7.62 (m, 1 H), 7.68 (dd, J=7.0, 2.6 Hz, 1 H), 7.73 (t, J=7.8 Hz, 1 H), 8.05 (dt, J=8.1, 1.2 Hz, 1 H), 8.14 - 8.19 (m, 1 H), 8.39 (t, J=1.7 Hz, 1 H), 10.43 (s, 1 H)

Compound **133**

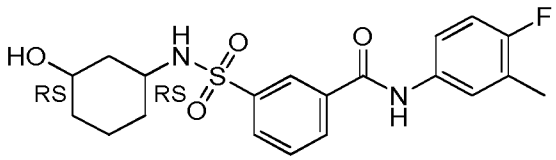


Synthesis following procedure S3 with trans-4-aminocyclohexanol hydrochloride as amine, workup W2.

Method F; Rt: 0.84 min. m/z: 424.2 $(M+NH_4)^+$ Exact mass: 406.1.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.01 - 1.31 (m, 4 H), 1.57 (d, J=10.3 Hz, 2 H), 1.69 (d, J=12.5 Hz, 2 H), 2.25 (d, J=1.8 Hz, 3 H), 2.84 - 3.01 (m, 1 H), 3.22 - 3.29 (m, 1 H), 4.46 (d, J=4.4 Hz, 1 H), 7.14 (t, J=9.1 Hz, 1 H), 7.53 - 7.64 (m, 1 H), 7.68 (dd, J=7.0, 2.2 Hz, 1 H), 7.72 - 7.79 (m, 2 H), 7.95 - 8.04 (m, 1 H), 8.18 (dt, J=7.7, 1.3 Hz, 1 H), 8.36 (t, J=1.7 Hz, 1 H), 10.46 (s, 1 H)

Compound **134**



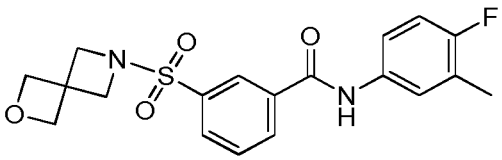
Method F; Rt: 0.89 min. m/z: 424.2 $(M+NH_4)^+$ Exact mass: 406.1.

Synthesis following procedure S3 with 3-amino-cyclohexanol as amine, workup W2.

Compound **134** was separated in it's isomers by preparative SFC (Stationary phase: Chiralpak Daicel IC 20 x 250 mm), Mobile phase: CO_2, iPrOH with 0.4% $iPrNH_2$), the desired fractions were collected, evaporated, dissolved in MeOH and evaporated again, yielding **134a**, **134b**, **134c**, **134d.** SFC Columns: ID-H 250 mm x 4.6 mm Flow: 3 ml/min Mobile phase: 25 % iPrOH (containing 0.2% iPrNH2) hold 18.0 min. Temperature: 30°C; Rt: **134 a** (10.0 min), **134b** (11.1 min), **134c** (13.6 min), **134d** (14.7 min). Cis: Enantiomers **134a** and **134b** N-(4-fluoro-3-methyl-phenyl)-3-[[(1R,3S)-3-hydroxycyclohexyl]sulfamoyl]benzamide or N-(4-fluoro-3-methyl-phenyl)-3-[[(1S,3R)-3-hydroxycyclohexyl]sulfamoyl]benzamide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.84 - 1.14 (m, 4 H), 1.48 - 1.60 (m, 2 H), 1.60-1.72 (m, 1 H), 1.72 - 1.82 (m, 1 H), 2.26 (d, *J*=1.8 Hz, 3 H), 2.93 - 3.07 (m, 1 H), 3.20 - 3.30 (m, 1 H), 4.58 (d, *J*=4.6 Hz, 1 H), 7.14 (t, *J*=9.1 Hz, 1 H), 7.55 - 7.64 (m, 1 H), 7.69 (dd, *J*=7.0, 2.2 Hz, 1 H), 7.76 (t, *J*=7.8 Hz, 1 H), 7.83 (br. s., 1 H), 7.96 - 8.06 (m, 1 H), 8.13 - 8.24 (m, 1 H), 8.38 (t, *J*=1.7 Hz, 1 H), 10.47 (s, 1 H)

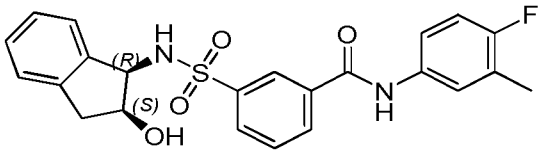
Trans: enantiomers **134c** and **134d** N-(4-fluoro-3-methyl-phenyl)-3-[[(1R,3R)-3 hydroxycyclohexyl]sulfamoyl]benzamide or N-(4-fluoro-3-methyl-phenyl)-3-[[(1S,3S)-3-hydroxycyclohexyl]sulfamoyl]benzamide ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.08 - 1.20 (m, 1 H), 1.25 - 1.42 (m, 4 H), 1.42 - 1.58 (m, 3 H), 2.25 (d, *J*=1.8

Hz, 3 H), 3.36 - 3.45 (m, 1 H), 3.71 - 3.89 (m, 1 H), 4.38 (d, *J*=3.5 Hz, 1 H), 7.14 (t, *J*=9.1 Hz, 1 H), 7.51 (br. s., 1 H), 7.56 - 7.63 (m, 1 H), 7.69 (dd, *J*=7.2, 2.3 Hz, 1 H), 7.73 - 7.78 (m, 1 H), 7.97 - 8.05 (m, 1 H), 8.19 (dt, *J*=7.9, 1.2 Hz, 1 H), 8.37 (t, *J*=1.7 Hz, 1 H), 10.47 (br. s., 1 H)



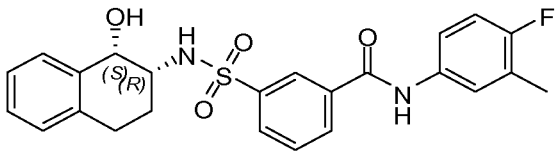
Compound **135**

Synthesis following procedure S3 with 2-oxa-6-azaspiro[3.3]heptane as amine, workup W2. Method F; Rt: 0.91 min. m/z: 389.1 $(M-H)^-$ Exact mass: 390.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.26 (d, J=1.8 Hz, 3 H), 3.95 (s, 4 H), 4.44 (s, 4 H), 7.15 (t, J=9.2 Hz, 1 H), 7.57 - 7.65 (m, 1 H), 7.68 (dd, J=7.0, 2.4 Hz, 1 H), 7.85 (t, J=7.8 Hz, 1 H), 8.01 (dt, J=8.0, 1.3 Hz, 1 H), 8.28 - 8.38 (m, 2 H), 10.51 (s, 1 H).



Compound **136**

Synthesis following procedure S1 with (1*R*,2*S*)-(+)-cis-1-aminoindan-2-ol as amine, workup W1. Method G; Rt: 1.79 min. m/z: 439.0 $(M-H)^-$ Exact mass: 440.1. ^{1} H NMR (400 MHz, DMSO-d_6) δ ppm 2.25 (d, J=1.8 Hz, 3 H), 2.72 (d, J=15.0 Hz, 1 H), 2.93 (dd, J=16.1, 4.6 Hz, 1 H), 4.15 (qd, J=4.7, 1.8 Hz, 1 H), 4.69 (dd, J=8.7, 4.7 Hz, 1 H), 4.96 (d, J=4.4 Hz, 1 H), 6.87 (d, J=7.3 Hz, 1 H), 7.04 - 7.10 (m, 1 H), 7.10 - 7.21 (m, 3 H), 7.55 - 7.64 (m, 1 H), 7.68 (dd, J=7.0, 2.4 Hz, 1 H), 7.77 (t, J=7.8 Hz, 1 H), 7.93 (d, J=9.0 Hz, 1 H), 8.15 (dt, J=8.1, 1.2 Hz, 1 H), 8.21 (dd, J=7.7, 1.5 Hz, 1 H), 8.48 (t, J=1.7 Hz, 1 H), 10.44 (s, 1 H)

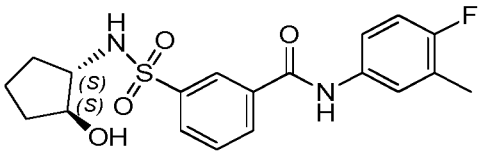


Compound **137**

Synthesis following procedure S4 with (1*S*,2*R*)-2-aminotetralin-1-ol hydrochloride as amine, workup W4. Method F; Rt: 1.03 min. m/z: 472.2 $(M+NH_4)^+$ Exact mass: 454.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.35 - 1.46 (m, 1 H), 1.96 (qd, J=11.8, 6.2 Hz, 1 H), 2.25 (d, J=1.5 Hz, 3 H), 2.62 (ddd, J=17.2, 10.9, 6.3 Hz, 1 H), 2.70 - 2.82 (m, 1 H), 3.34 - 3.45 (m, 1 H), 4.39 (br. s., 1 H), 5.29 (d, J=5.7 Hz, 1 H), 7.04 (d, J=6.8

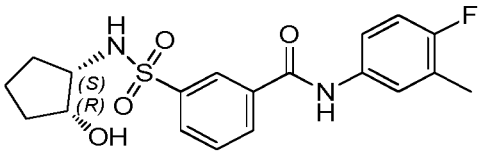
Hz, 1 H), 7.09 - 7.24 (m, 4 H), 7.55 - 7.63 (m, 1 H), 7.62-7.70 (m, 2 H), 7.75 (t, J=7.8 Hz, 1 H), 8.06 - 8.13 (m, 1 H), 8.19 (d, J=8.1 Hz, 1 H), 8.43 (t, J=1.5 Hz, 1 H), 10.44 (s, 1 H), $[\alpha]_D^{20}$: +66 ° (c 0.55 w/v %, DMF). DSC (From 30 to 300 °C at 10°C/min): 170°C.

Compound **138**



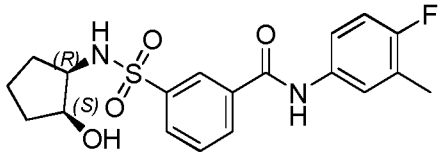
Synthesis following procedure S1 with trans-(1*S*,2*S*)-2-aminocyclopentanol hydrochloride as amine, workup W1. Method F; Rt: 0.88 min. m/z: 410.4 $(M+NH_4)^+$ Exact mass: 392.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.16 - 1.29 (m, 1 H), 1.29 - 1.40 (m, 1 H), 1.50 (quin, J=7.4 Hz, 2 H), 1.61 - 1.78 (m, 2 H), 2.25 (d, J=1.8 Hz, 3 H), 3.16 - 3.26 (m, 1 H), 3.74 - 3.82 (m, 1 H), 4.67 (d, J=4.4 Hz, 1 H), 7.14 (t, J=9.2 Hz, 1 H), 7.55 - 7.63 (m, 1 H), 7.65 - 7.72 (m, 2 H), 7.75 (t, J=7.8 Hz, 1 H), 7.98 - 8.04 (m, 1 H), 8.18 (dt, J=7.9, 1.3 Hz, 1 H), 8.36 (t, J=1.7 Hz, 1 H), 10.45 (s, 1 H)

Compound **139**

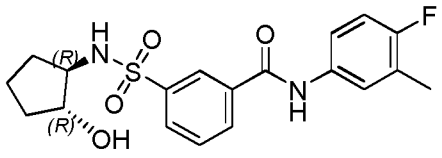


Synthesis following procedure S1 with cis-(1*R*,2*S*)-2-aminocyclopentanol hydrochloride as amine, workup W1. Method F; Rt: 0.92 min. m/z: 410.1 $(M+NH_4)^+$ Exact mass: 392.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.25 - 1.51 (m, 4 H), 1.51 - 1.67 (m, 2 H), 2.25 (d, J=1.5 Hz, 3 H), 3.21 - 3.28 (m, 1 H), 3.72 - 3.79 (m, 1 H), 4.63 (d, J=4.0 Hz, 1 H), 7.14 (t, J=9.2 Hz, 1 H), 7.42 (d, J=8.1 Hz, 1 H), 7.55 - 7.63 (m, 1 H), 7.68 (dd, J=7.3, 2.4 Hz, 1 H), 7.73 (t, J=7.8 Hz, 1 H), 8.06 (dt, J=8.1, 1.2 Hz, 1 H), 8.17 (d, J=8.1 Hz, 1 H), 8.40 (t, J=1.5 Hz, 1 H), 10.43 (s, 1 H)

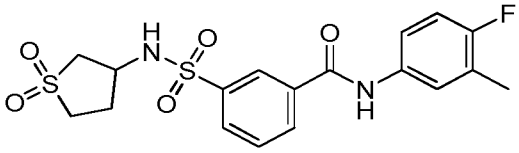
Compound **172**



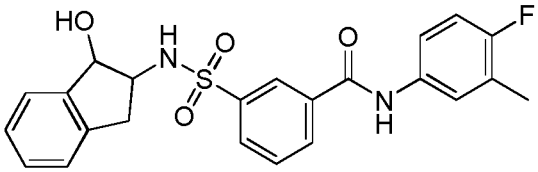
Synthesis following procedure S2 with cis-(1*S*,2*R*)-2-aminocyclopentanol hydrochloride as amine.The formed precipitate was collected on a glassfilter and rinsed with CH_2Cl_2 (2 x 5 mL). The precipitate was further purified using silica gel column chromatography (gradient elution: EtOAc-heptane 0:100 to 100:0). Drying in vacuo at 55°C resulted in compound **172** as a bright white powder. Method G; Rt: 1.65 min. m/z: 392.9 $(M+H)^+$ Exact mass: 392.1. DSC (From 30 to 300 °C at 10°C/min):145 °C.

Compound **173** 

Synthesis following procedure S4 (reaction time= 20 hours instead of 3 hours) with trans-(1*R*,2*R*)-2-aminocyclopentanol as amine, workup W4. Method F; Rt: 0.87 min. m/z: 410.1 $(M+NH_4)^+$ Exact mass: 392.1.

Compound **140** 

Synthesis following procedure S1 with 1,1-dioxothiolan-3-amine hydrochloride as amine, workup W1. Method F; Rt: 0.85 min. m/z: 444.2 $(M+NH_4)^+$ Exact mass: 426.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.90 - 2.04 (m, 1 H), 2.16 - 2.24 (m, 1 H), 2.25 (d, J=1.8 Hz, 3 H), 2.81 (dd, J=13.4, 7.0 Hz, 1 H), 3.08 (ddd, J=13.1, 9.1, 7.5 Hz, 1 H), 3.15 - 3.26 (m, 2 H), 3.94 - 4.06 (m, 1 H), 7.15 (t, J=9.2 Hz, 1 H), 7.55 - 7.63 (m, 1 H), 7.68 (dd, J=7.2, 2.3 Hz, 1 H), 7.79 (t, J=7.8 Hz, 1 H), 8.01 - 8.07 (m, 1 H), 8.23 (dt, J=7.7, 1.3 Hz, 1 H), 8.38 (t, J=1.7 Hz, 1 H), 8.40 (br. s., 1 H), 10.48 (s, 1 H)

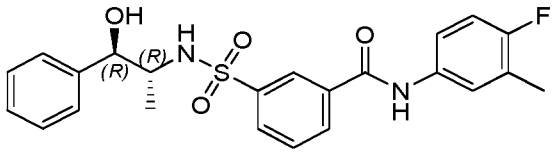
Compound **141** 

Synthesis following procedure S4 with 2-aminoindan-1-ol hydrochloride as amine, workup W4. Method F; Rt: 0.98 and 1.01 min. m/z: 458.1 $(M+NH_4)^+$ Exact mass: 440.1. Compound **141** was separated in it's isomers by preparative SFC (Stationary phase: Chiralcel Diacel OD 20 x 250 mm), Mobile phase: CO_2, MeOH with 0.2% $iPrNH_2$), the desired fractions were collected, evaporated, dissolved in MeOH and evaporated again. SFC, Column: OD-H (Diacel) 250 mm x 4.6 mm
Flow: 5 mL/min, Mobile phase: 30% MeOH (containing 0.2% $iPrNH_2$) hold 4.00 min, up to 50% in 1 min and hold 2.00 min @ 50% Temperature: 40°C.Rt: **141a** (1.8 min), **141b** (2.1 min), **141c** (2.5 min), **141d** (2.7 min).
141a, 141c: N-(4-fluoro-3-methyl-phenyl)-3-[[(1S,2S)-1-hydroxyindan-2-yl]-sulfamoyl]benzamide or N-(4-fluoro-3-methyl-phenyl)-3-[[(1R,2R)-1-hydroxyindan-2-yl]sulfamoyl]benzamide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.25 (d, J=1.5 Hz, 3 H), 2.43-2.55 (m, 1 H), 2.83 (dd, J=15.7, 7.8 Hz, 1 H), 3.59 - 3.70 (m, 1 H), 4.83 (d,

J=6.8 Hz, 1 H), 5.58 (br. s., 1 H), 7.03 - 7.27 (m, 5 H), 7.56 - 7.65 (m, 1 H), 7.68 (dd, J=7.0, 2.4 Hz, 1 H), 7.78 (t, J=7.8 Hz, 1 H), 8.05 - 8.11 (m, 1 H), 8.16 (br. s., 1 H), 8.22 (d, J=8.1 Hz, 1 H), 8.43 (t, J=1.7 Hz, 1 H), 10.47 (br. s., 1 H) Method F; Rt: 0.98 m/z: 458.3 $(M+NH_4)^+$ Exact mass: 440.1.

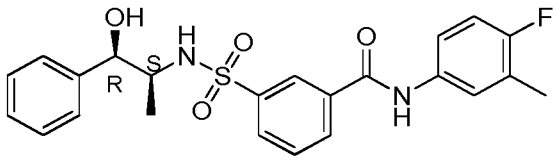
141b, 141d: N-(4-fluoro-3-methyl-phenyl)-3-[[(1*R*,2*S*)-1-hydroxyindan-2-yl]sulfamoyl]benzamide or N-(4-fluoro-3-methyl-phenyl)-3-[[(1S,2R)-1-hydroxyindan-2-yl]sulfamoyl]benzamide. ^{1}H NMR (600 MHz, ACETONE-d_6, -14 °C) δ ppm 2.25 (d, J=1.9 Hz, 3 H), 2.80 - 2.90 (m, 2 H), 3.94 - 3.99 (m, 1 H), 4.72 (d, J=5.3 Hz, 1 H), 4.87 (d, J=3.8 Hz, 1 H), 6.96 (d, J=5.0 Hz, 1 H), 7.08 (t, J=9.2 Hz, 1 H), 7.14 - 7.19 (m, 2 H), 7.21 (td, J=7.3, 1.2 Hz, 1 H), 7.29 (d, J=7.3 Hz, 1 H), 7.65 - 7.70 (m, 1 H), 7.74 (dt, J=6.8, 3.1 Hz, 1 H), 7.79 (t, J=7.8 Hz, 1 H), 8.19 (ddd, J=7.8, 1.8, 1.1 Hz, 1 H), 8.27 (ddt, J=7.8, 1.8, 0.9, 0.9 Hz, 1 H), 8.54 (q, J=1.6 Hz, 1 H), 10.09 (s, 1 H) Method F; Rt: 1.00 m/z: 458.2 $(M+NH_4)^+$ Exact mass: 440.1.

Compound **142**

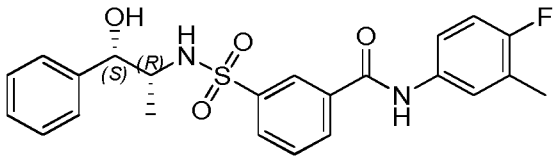


Synthesis following procedure S4 with (1*R*,2*R*)-2-amino-1-phenyl-propan-1-ol as amine, workup W4. Method F; Rt: 1.00 min. m/z: 460.1 $(M+NH_4)^+$ Exact mass: 442.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.76 (d, J=6.8 Hz, 3 H), 2.25 (d, J=1.3 Hz, 3 H), 3.37 - 3.46 (m, 1 H), 4.56 (d, J=4.6 Hz, 1 H), 5.41 (br. s., 1 H), 7.14 (t, J=9.2 Hz, 1 H), 7.18 - 7.23 (m, 1 H), 7.23 - 7.32 (m, 4 H), 7.49 (br. s., 1 H), 7.56 - 7.64 (m, 1 H), 7.64 - 7.72 (m, 2 H), 7.88 - 7.96 (m, 1 H), 8.15 (d, J=7.9 Hz, 1 H), 8.31 (t, J=1.5 Hz, 1 H), 10.42 (s, 1 H).

Compound **143**

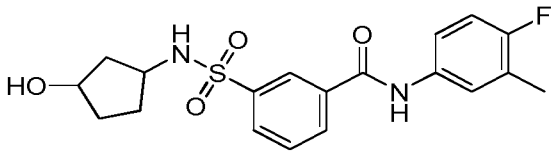


Synthesis following procedure S1 with (1*R*,2*S*)-(-)-norephedrine as amine, workup W1. Method F; Rt: 1.01 min. m/z: 460.1 $(M+NH_4)^+$ Exact mass: 442.1. ^{1} H NMR (400 MHz, DMSO-d_6) δ ppm 0.79 (d, J=6.8 Hz, 3 H), 2.25 (d, J=1.8 Hz, 3 H), 3.33 - 3.37 (m, 1 H), 4.48 (t, J=4.6 Hz, 1 H), 5.42 (d, J=4.6 Hz, 1 H), 7.10 - 7.27 (m, 6 H), 7.55 - 7.63 (m, 1 H), 7.64 - 7.71 (m, 2 H), 7.78 (d, J=8.4 Hz, 1 H), 7.91 (dt, J=8.2, 1.2 Hz, 1 H), 8.12 - 8.18 (m, 1 H), 8.30 (t, J=1.7 Hz, 1 H), 10.42 (s, 1 H)



Compound **144**

Synthesis following procedure S1 with (1*S*, 2*R*)-(+)-norephedrine as amine, workup W1. Method F; Rt: 1.01 min. m/z: 460.2 $(M+NH_4)^+$ Exact mass: 442.1.
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.79 (d, J=6.8 Hz, 3 H), 2.25 (d, J=1.8 Hz, 3 H), 3.32 - 3.38 (m, 1 H), 4.48 (t, J=4.6 Hz, 1 H), 5.42 (d, J=4.8 Hz, 1 H), 7.10 - 7.27 (m, 6 H), 7.56 - 7.63 (m, 1 H), 7.65 - 7.71 (m, 2 H), 7.78 (d, J=8.4 Hz, 1 H), 7.89 - 7.94 (m, 1 H), 8.15 (dt, J=7.8, 1.3 Hz, 1 H), 8.30 (t, J=1.7 Hz, 1 H), 10.42 (s, 1 H)

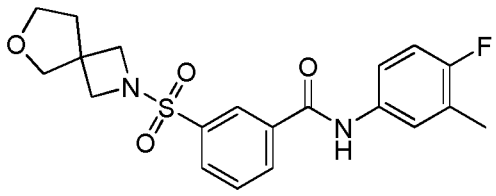


Compound **145**

Synthesis following procedure S4 with 3-aminocyclopentanol as amine, after completion, the reaction mixture was directly loaded on a silica gel column for purification, using a heptane to EtOAc gradient yielding compound **145** as a 83 (**145a**, **145b**): 17 (**145c**, **145d**) mixture of diastereomers. Method F; Rt: 0.82 and 0.86 min. m/z: 410.2 $(M+NH_4)^+$ Exact mass: 392.1. Compound **145** was separated in it's isomers by preparative SFC (Stationary phase: Chiralpak Diacel AD 30 x 250 mm), Mobile phase: CO_2, MeOH with 0.4% $iPrNH_2$), the desired fractions were collected, evaporated, dissolved in MeOH and evaporated again yielding compound **145a** (238 mg) and **145b** (236 mg) and a mixture of compound **145c** and **145d**. The mixture of **145c** and **145d** was further purified by Preparative SFC (Stationary phase: Chiralpak Diacel AD 30 x 250 mm), Mobile phase: CO_2, EtOH with 0.4% $iPrNH_2$), the desired fractions were collected, evaporated, dissolved in MeOH and evaporated again yielding **145c** (29 mg) and **145d** (27 mg). **145a** and **145b**: N-(4-fluoro-3-methyl-phenyl)-3-[[(1*R*,3*S*)-3-hydroxycyclopentyl]sulfamoyl]benzamide or N-(4-fluoro-3-methyl-phenyl)-3-[[(1*S*,3*R*)-3-hydroxycyclopentyl]sulfamoyl]benzamide.
Method F; Rt: 0.85 min. m/z: 410.2 $(M+NH_4)^+$ Exact mass: 392.1.
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.21 (ddd, J=13.3, 7.8, 6.1 Hz, 1 H), 1.36 - 1.64 (m, 4 H), 1.84 - 1.95 (m, 1 H), 2.25 (d, J=1.1 Hz, 3 H), 3.37 - 3.47 (m, 1 H), 3.85 - 3.96 (m, 1 H), 4.25-5.00 (1H, br. s), 7.14 (t, J=9.2 Hz, 1 H), 7.35-7.75 (1H, br. s), 7.54 - 7.63 (m, 1 H), 7.68 (dd, J=7.0, 2.2 Hz, 1 H), 7.75 (t, J=7.8 Hz, 1 H), 8.01 (d, J=7.9 Hz, 1 H), 8.19 (d, J=7.7 Hz, 1 H), 8.36 (s, 1 H), 10.46 (br. s., 1 H)
145c and **145d**: N-(4-fluoro-3-methyl-phenyl)-3-[[(1*S*,3*S*)-3-hydroxycyclopentyl]-sulfamoyl]benzamide or N-(4-fluoro-3-methyl-phenyl)-3-[[(1*R*,3*R*)-3-hydroxycyclo-

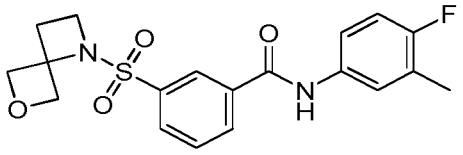
pentyl]sulfamoyl]benzamide. Method F; Rt: 0.82 min. m/z: 410.2 $(M+NH_4)^+$ Exact mass: 392.1.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.17 - 1.35 (m, 2 H), 1.41 (ddd, J=13.4, 8.0, 5.7 Hz, 1 H), 1.56 (ddd, J=13.2, 7.3, 2.6 Hz, 1 H), 1.69 - 1.83 (m, 2 H), 2.25 (d, J=1.8 Hz, 3 H), 3.59 - 3.72 (m, 1 H), 3.99 - 4.09 (m, 1 H), 4.43 (d, J=3.5 Hz, 1 H), 7.14 (t, J=9.2 Hz, 1 H), 7.55 - 7.63 (m, 1 H), 7.68 (dd, J=7.0, 2.2 Hz, 1 H), 7.73 - 7.84 (m, 2 H), 7.96 - 8.02 (m, 1 H), 8.20 (dt, J=7.9, 1.2 Hz, 1 H), 8.36 (t, J=1.7 Hz, 1 H), 10.48 (br. s., 1 H) **145a:** $[\alpha]_D^{20}$: +5.2 ° (c 0.56 w/v %, DMF); **145b:** $[\alpha]_D^{20}$: -5.4 ° (c 0.60 w/v %, DMF); **145c:** $[\alpha]_D^{20}$: -3.5 ° (c 0.46 w/v %, DMF); **145d:** $[\alpha]_D^{20}$: +2.5 °(c 0.44 w/v %, DMF)



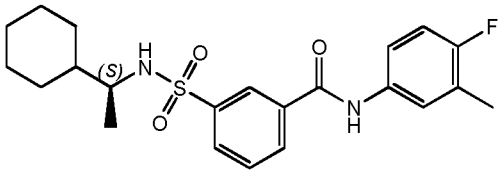
Compound **146**

Synthesis following procedure S2 with 6-oxa-2-azaspiro[3.4]octane oxalate as amine, after completion, the reaction mixture was directly loaded on a silica gel column for purification, using a heptane to EtOAc gradient yielding compound **146**. Method F; Rt: 0.93 min. m/z: 422.3 $(M+NH_4)^+$ Exact mass: 404.1. ^{1} H NMR (400 MHz, DMSO-d_6) ppm 1.81 (t, J=6.9 Hz, 2 H), 2.26 (d, J=1.8 Hz, 3 H), 3.46 (s, 2 H), 3.57 (t, J=6.9 Hz, 2 H), 3.72 - 3.80 (m, 4 H), 7.15 (t, J=9.1 Hz, 1 H), 7.58 - 7.64 (m, 1 H), 7.69 (dd, J=7.0, 2.2 Hz, 1 H), 7.87 (t, J=7.8 Hz, 1 H), 8.04 (dt, J=8.0, 1.3 Hz, 1 H), 8.32 - 8.41 (m, 2 H), 10.53 (s, 1 H).



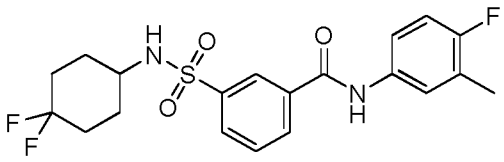
Compound **147**

Synthesis following procedure S2 with 6-oxa-1-azaspiro[3.3]heptane as amine, after completion, the reaction mixture was directly loaded on a silica gel column for purification, using a heptane to EtOAc gradient yielding compound **147.** Method F; Rt: 0.92 min. m/z: 408.2 $(M+NH_4)^+$ Exact mass: 390.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.25 (d, *J*=1.8 Hz, 3 H), 2.53 (t, *J*=7.3 Hz, 2 H), 3.73 (t, *J*=7.4 Hz, 2 H), 4.53 (d, *J*=7.9 Hz, 2 H), 5.01 (d, *J*=7.9 Hz, 2 H), 7.15 (t, *J*=9.1 Hz, 1 H), 7.56 - 7.64 (m, 1 H), 7.68 (dd, *J*=7.0, 2.2 Hz, 1 H), 7.82 (t, *J*=7.8 Hz, 1 H), 8.05 - 8.11 (m, 1 H), 8.29 (dt, *J*=7.8, 1.3 Hz, 1 H), 8.40 (t, *J*=1.7 Hz, 1 H), 10.51 (s, 1 H)



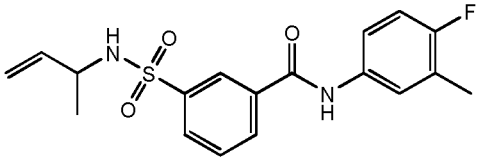
Compound **148**

Synthesis following procedure S4 with (*S*)-(+)-1-cyclohexylethylamine as amine, workup W4. Method F; Rt: 1.23 min. m/z: 436.2 $(M+NH_4)^+$ Exact mass: 418.2



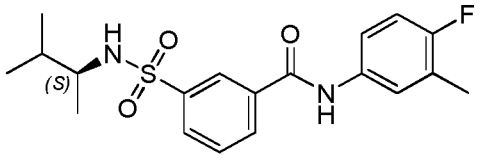
Compound **149**

Synthesis following procedure S4 with 4,4-difluorocyclohexylamine as amine, workup W4. Method F; Rt: 1.06 min. m/z: 444.5 $(M+NH_4)^+$ Exact mass: 426.1.



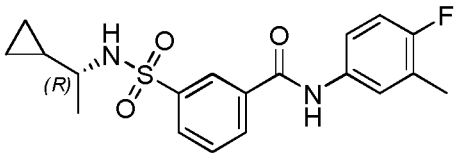
Compound **150**

Synthesis following procedure S4 with 3-buten-2-amine, hydrochloride as amine, workup W4. Method F; Rt: 1.01 min. m/z: 380.3 $(M+NH_4)^+$ Exact mass: 362.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.03 (d, J=6.8 Hz, 3 H), 2.25 (d, J=1.8 Hz, 3 H), 3.74 - 3.87 (m, 1 H), 4.87 (dt, J=10.5, 1.4 Hz, 1 H), 5.00 (dt, J=17.3, 1.4 Hz, 1 H), 5.61 (ddd, J=17.3, 10.5, 6.1 Hz, 1 H), 7.14 (t, J=9.2 Hz, 1 H), 7.55 - 7.63 (m, 1 H), 7.68 (dd, J=7.2, 2.3 Hz, 1 H), 7.74 (t, J=7.8 Hz, 1 H), 7.93 (d, J=7.9 Hz, 1 H), 7.96 - 8.01 (m, 1 H), 8.18 (dt, J=7.7, 1.3 Hz, 1 H), 8.35 (t, J=1.7 Hz, 1 H), 10.45 (s, 1 H).



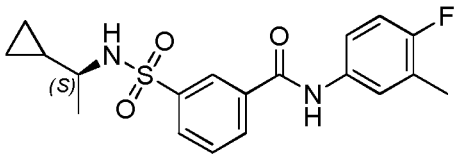
Compound **151**

Synthesis following procedure S4 (stirred for 20 hours instead of 3 hours) with (*S*)-(+)-2-amino-3-methylbutane as amine, workup W4. Method F; Rt: 1.11 min. m/z: 396.2 $(M+NH_4)^+$ Exact mass: 378.1. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 0.81 (d, J=6.8 Hz, 6 H), 0.95 (d, J=6.8 Hz, 3 H), 1.57 - 1.67 (m, 1 H), 2.28 (d, J=1.8, 3 H), 3.13 - 3.28 (m, 1 H), 4.85 (d, J=8.6 Hz, 1 H), 6.98 (t, J=9.0 Hz, 1 H), 7.36 - 7.46 (m, 1 H), 7.49 - 7.57 (m, 1 H), 7.61 (t, J=7.8 Hz, 1 H), 8.00 (dt, J=7.9, 1.5 Hz, 1 H), 8.12 (dt, J=7.9, 1.5 Hz, 1 H), 8.25 (s, 1 H), 8.39 (t, J=1.9 Hz, 1 H).



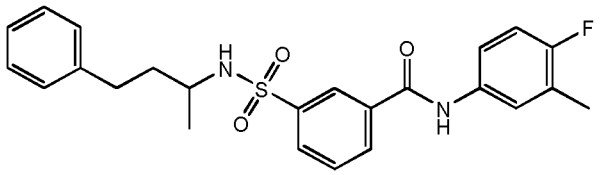
Compound **152**

Synthesis following procedure S4 (stirred for 20 hours instead of 3 hours) with (1*R*)-1-cyclopropylethylamine as amine, workup W4. ^{1} H NMR (400 MHz, CHLOROFORM-d) δ ppm -0.05 - 0.05 (m, 1 H), 0.09-0.16 (m, 1 H), 0.20 - 0.36 (m, 1 H), 0.38 - 0.51 (m, 1 H), 0.69-0.81 (m, 1 H), 1.13 (d, J=6.6 Hz, 3 H), 2.27 (d, J=1.8 Hz, 3 H), 2.63 - 2.85 (m, 1 H), 5.10 (d, J=6.8 Hz, 1 H), 6.98 (t, J=8.9 Hz, 1 H), 7.37-7.45 (m, 1 H), 7.52 (dd, J=6.6, 2.4 Hz, 1 H), 7.60 (t, J=7.8 Hz, 1 H), 7.98-8.02 (m, 1 H), 8.08-8.13 (m, 1 H), 8.25 (s, 1 H), 8.38 (t, J=1.7 Hz, 1 H). Method F; Rt: 1.07 min. m/z: 394.2 $(M+NH_4)^+$ Exact mass: 376.1.



Compound **174**

Synthesis following procedure S4 (stirred for 20 hours instead of 3 hours) with (1*R*)-1-cyclopropylethylamine as amine, workup W4. The obtained residue was recrystallised from disopropylether/acetonitrile. The precipitate was collected and dried in vacuo at 55°C, resulting in compound **174.** ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm -0.11 - -0.01 (m, 1 H), 0.07 - 0.23 (m, 2 H), 0.29 - 0.38 (m, 1 H), 0.70 - 0.82 (m, 1 H), 0.99 (d, J=6.6 Hz, 3 H), 2.21 - 2.30 (m, 3 H), 2.66 (quin, J=6.8 Hz, 1 H), 7.14 (t, J=9.1 Hz, 1 H), 7.56 - 7.64 (m, 1 H), 7.68 (dd, J=7.0, 2.4 Hz, 1 H), 7.75 (t, J=7.8 Hz, 1 H), 7.85 (br. s., 1 H), 7.93 - 8.07 (m, 1 H), 8.18 (d, J=7.9 Hz, 1 H), 8.37 (t, J=1.7 Hz, 1 H), 10.46 (br. s., 1 H)

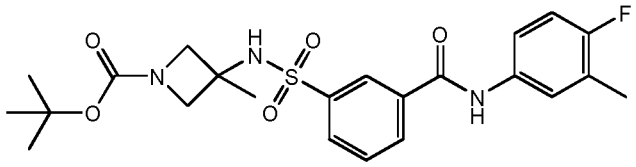


Compound **153**

Synthesis following procedure S4 (stirred for 20 hours instead of 3 hours) with 3-amino-1-phenylbutane as amine, workup W4. Method F; Rt: 1.19 min. m/z: 458.2 $(M+NH_4)^+$ Exact mass: 440.2. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.06 (d, J=6.6 Hz, 3 H), 1.62 - 1.76 (m, 2 H), 2.25 (d, J=1.8 Hz, 3 H), 2.44 - 2.64 (m, 2 H), 3.30 - 3.43 (m, 1 H), 5.05 (d, J=8.4 Hz, 1 H), 6.96 (t, J=8.9 Hz, 1 H), 7.00-7.04 (m, 2 H), 7.09 - 7.17 (m, 1 H), 7.17 - 7.25 (m, 2 H), 7.36-7.42 (m, 1 H), 7.50 (dd, J=6.8, 2.4

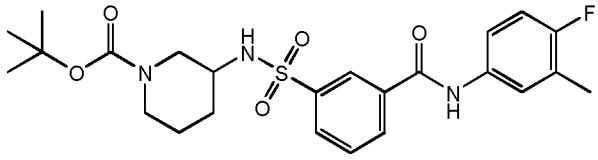
Hz, 1 H), 7.57 (t, J=7.8 Hz, 1 H), 7.95 (m, J=7.8, 1 H), 8.10 (m, J=7.8 Hz, 1 H), 8.25 (s, 1 H), 8.37 (t, J=1.5 Hz, 1 H)

Compound **154**



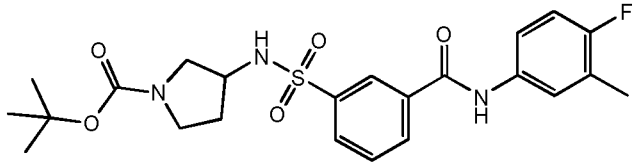
3-[(4-fluoro-3-methyl-phenyl)carbamoyl]benzenesulfonyl chloride (500 mg, 1.53 mmol) and DIPEA (657 µL, 3.8 mmol, 2.5 eq) dissolved in CH_2Cl_2 (15 mL) were added to a tube containing 3-amino-1-Boc-3-methyl-azetidine (1.1 eq). The reaction mixture was stirred for 20 hours. 1M HCl (5 mL) was added and the mixture was stirred for 5 minutes. The organic layer was separated and loaded on a silica gel column. The mixture was purified using gradient elution from heptane to EtOAc, resulting in compound **154** (721 mg). Method F; Rt: 1.11 min. m/z: 478.2 $(M+H)^+$ Exact mass: 477.2.

Compound **155**

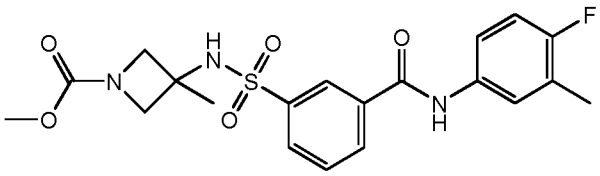


Prepared as described for compound **154** using 1-Boc-3-aminopiperidine instead of 3-amino-1-Boc-3-methyl-azetidine. Method F; Rt: 1.13 min. m/z: 492.1 $(M+H)^+$ Exact mass: 491.2.

Compound **156**

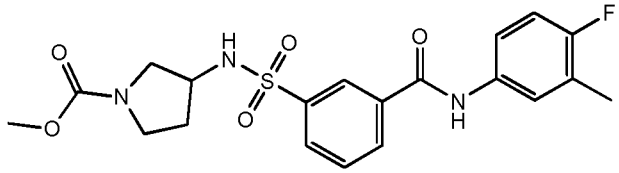


Prepared as described for compound **154** using (+/-)-3-amino-1-N-Boc-pyrrolidine instead of 3-amino-1-Boc-3-methyl-azetidine. Method F; Rt: 1.08 min. m/z: 478.2 $(M+H)^+$ Exact mass: 477.2 ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.36 (s, 9 H), 1.71 - 1.92 (m, 1 H), 1.92 - 2.15 (m, 1 H), 2.28 (d, *J*=1.8 Hz, 3 H), 3.10-3.24 (m, 1 H), 3.24-3.44 (m, 3 H), 3.81 - 3.94 (m, 1 H), 5.50 - 6.00 (m, 1 H), 6.98 (t, *J*=9.0 Hz, 1 H), 7.40 - 7.48 (m, 1 H), 7.52 - 7.71 (m, 2 H), 7.93-8.03 (m, 1 H), 8.04 - 8.17 (m, 1 H), 8.31 (br. s., 1 H), 8.45 - 8.88 (m, 1 H).



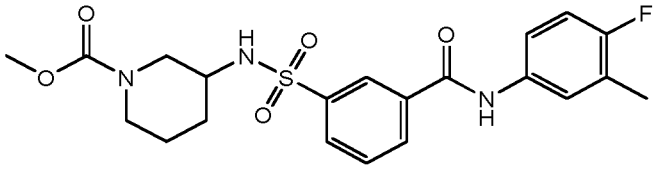
Compound **157**

Compound **154** (721 mg, 1.51 mmol) was dissolved in CH_2Cl_2 (10 mL) and HCl (6M in iPrOH, 2.5 mL) was added. The mixture was stirred overnight and the volatiles were removed in vacuo, resulting in N-(4-fluoro-3-methyl-phenyl)-3-[(3-methylazetidin-3-yl)sulfamoyl]benzamide hydrochloride as a white solid (0.57 g). To N-(4-fluoro-3-methyl-phenyl)-3-[(3-methylazetidin-3-yl)sulfamoyl]benzamide hydrochloride (150 mg) in CH_2Cl_2 (10 mL), DIPEA (263 µL, 1.5 mmol) and methyl chloroformate (44 µL, 0.57 mmol) were added. The mixture was concentrated under a gentle flow of nitrogen at 55°C until only 2 mL remained. This residue was purified using silica gel column chromatography (gradient elution: EtOAc-heptane 0:100 to 100:0). The desired fractions were concentrated under reduced pressure and the obtained product was dried in a vacuum oven at 55°C yielding compound **157** (74.2 mg) as a bright white powder. Method F; Rt: 0.93 min. m/z: 436.1 $(M+H)^+$ Exact mass: 435.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.36 (s, 3 H), 2.25 (d, J=1.5 Hz, 3 H), 3.52 (s, 3 H), 3.56-3.68 (m, 2 H), 3.83-3.93 (m, 2 H), 7.14 (t, J = 9.2 Hz, 1 H), 7.57 - 7.62 (m, 1 H), 7.68 (dd, J=6.8, 2.4 Hz, 1 H), 7.77 (t, J=7.9 Hz, 1 H), 8.01 (m, J=7.9 Hz, 1 H), 8.21 (m, J=7.9 Hz, 1 H), 8.37 (t, J=1.5 Hz, 1 H), 8.48 (bs, 1 H), 10.49 (s, 1 H)



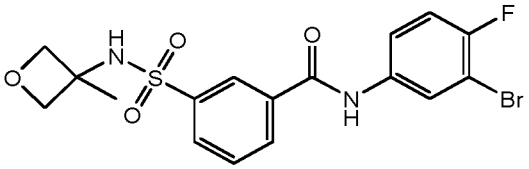
Compound **158**

Prepared similarly as described for compound **157**, starting from compound **156** instead of compound **154**, via intermediate N-(4-fluoro-3-methyl-phenyl)-3-(pyrrolidin-3-yl-sulfamoyl)benzamide hydrochloride. Method F; Rt: 0.91 min. m/z: 436.2 $(M+H)^+$ Exact mass: 435.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.61-1.77 (m, 1 H), 1.80-1.98 (m 1 H), 2.25 (d, J=1.5 Hz, 3 H), 3.00-3.12 (m, 1 H), 3.14 - 3.27 (m, 1 H), 3.26 - 3.39 (m, 2 H), 3.50-3.58 (m, 3 H), 3.67 - 3.76 (m, 1 H), 7.14 (t, J=9.2 Hz, 1 H), 7.57 - 7.63 (m, 1 H), 7.68 (dd, J=7.2, 2.3 Hz, 1 H), 7.78 (t, J=7.8 Hz, 1 H), 7.97 - 8.04 (m, 1 H), 8.04 - 8.18 (m, 1 H), 8.18 - 8.25 (m, 1 H), 8.37 (t, J=1.5 Hz, 1 H), 10.48 (s, 1 H)



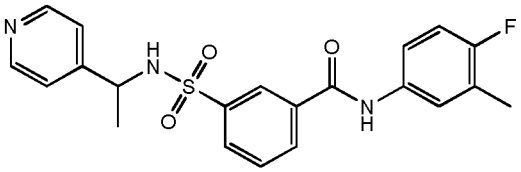
Compound **159**

Prepared similarly as described for compound **157**, starting from compound **155** instead of compound **154**, via intermediate N-(4-fluoro-3-methyl-phenyl)-3-(3-piperidyl-sulfamoyl)benzamide hydrochloride. Method F; Rt: 0.96 min. m/z: 467.1 $(M+NH_4)^+$ Exact mass: 449.1. The racemic compound **159** was separated by Preparative SFC (Stationary phase: Chiralpak Daicel IC 20 x 250 mm), Mobile phase: CO_2, MeOH with 0.2% $iPrNH_2$), the desired fractions were collected, evaporated, dissolved in methanol and evaporated again, resulting in enantiomer **159a** and **159b**.
Columns: ID-H (Daicel) 250 mm x 4.6 mm; Flow: 3 mL/min; Mobile phase: 20% EtOH (containing 0.2% $iPrNH_2$) hold 15.00 min; Temperature: 30°C ; Rt: 9.6 min (**159a**), Rt: 11.0 min (**159b**)



Compound **160**

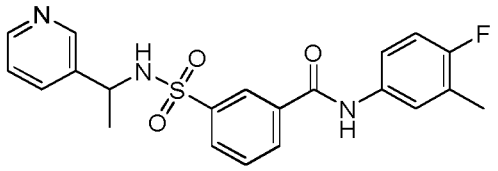
Method B; Rt: 4 min. m/z: 443.1 $(M+H)^+$ Exact mass: 442.0
^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.41 (s, 3 H) 4.14 (d, J= 6.3 Hz, 2 H) 4.56 (d, J=6.0 Hz, 2 H) 7.42 (t, J=8.8 Hz, 1 H) 7.74 - 7.82 (m, 2 H) 8.04 (s, 1 H) 8.15 - 8.24 (m, 2 H) 8.37 (t, J=1.5 Hz, 1 H) 8.54 (br. s, 1 H) 10.67 (br. s, 1 H).



Compound **161**

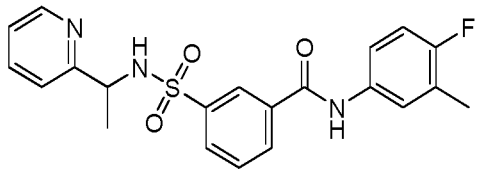
1-pyridin-4-yl-ethylamine (220 mg, 1.8 mmol) and 3-[(4-fluoro-3-methyl-phenyl)-carbamoyl]benzenesulfonyl chloride (500 mg, 1.53 mmol) were dissolved in CH_2Cl_2 (10 mL). DIPEA (6.2 mmol) was added at 0°C and the mixture was stirred at 25°C for 4 hours. The mixture was washed with water (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed in vacuo and the obtained residue was purified by reversed phase high performance liquid chromatography (mobile phase: CH_3CN in water (0.1% TFA) from 30% to 60%).

The pure fractions were collected and neutralized with solid $NaHCO_3$. The organic solvent was removed in vacuo and the formed precipitate was filtered, washed with H_2O (5 mL) and dried under high vacuum. The obtained residue was suspended in water (5 mL) and the aqueous layer was lyophilized to dryness, resulting in compound **161** (410 mg). Method A; Rt: 4.34 min. m/z: 414.3 $(M+H)^+$ Exact mass: 413.1. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.23 (d, *J*=7.0 Hz, 3 H) 2.26 (d, *J*=1.5 Hz, 3 H) 4.34 - 4.50 (m, 1 H) 7.15 (t, *J*=9.3 Hz, 1 H) 7.20 - 7.24 (m, 2 H) 7.56 - 7.66 (m, 2 H) 7.68 (dd, *J*=7.0, 2.3 Hz, 1 H) 7.86 (m, *J*=7.8 Hz, 1 H) 8.13 (m, *J*=7.8 Hz, 1 H) 8.26 (t, *J*=1.3 Hz, 1 H) 8.32 - 8.39 (m, 2 H) 8.55 (d, *J*=8.3 Hz, 1 H) 10.41 (s, 1 H).



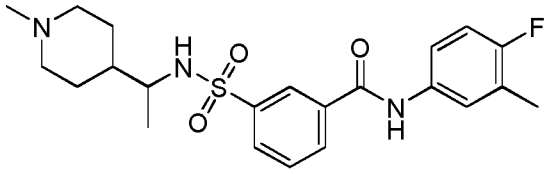
Compound **162**

Prepared similarly as described for compound **161**, using 1-(3-pyridyl)ethanamine instead of 1-pyridin-4-yl-ethylamine. Method D; Rt: 5.16 min. m/z: 414.3 $(M+H)^+$ Exact mass: 413.1.



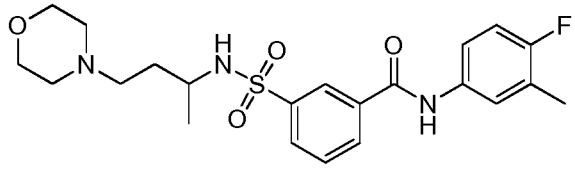
Compound **163**

Prepared similarly as described for compound **161**, using 1-(2-pyridyl)ethanamine instead of 1-pyridin-4-yl-ethylamine. Method A; Rt: 4.60 min. m/z: 414.3 $(M+H)^+$ Exact mass: 413.1.



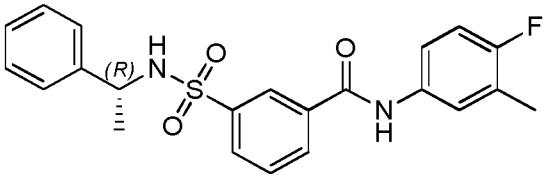
Compound **164**

Prepared similarly as described for compound **161**, using 1-(1-methyl-4-piperidyl)ethanamine instead of 1-pyridin-4-yl-ethylamine. Method B; Rt: 3.35 min. m/z: 434.4 $(M+H)^+$ Exact mass: 433.2.



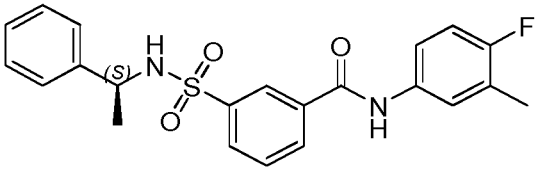
Compound **165**

Prepared similarly as described for compound **161**, using 4-morpholinobutan-2-amine instead of 1-pyridin-4-yl-ethylamine. Method B; Rt: 3.33 min. m/z: 450.3 $(M+H)^+$ Exact mass: 449.2.



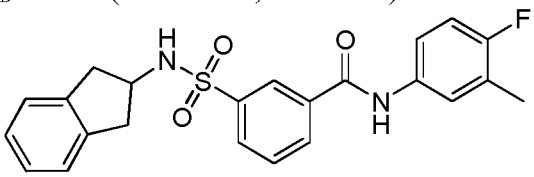
Compound **166**

Prepared similarly as described for compound **161**, using (*R*)-1-phenylethanamine instead of 1-pyridin-4-yl-ethylamine. The impure compound was purified by preparative high-performance liquid chromatography (column: Luna 150*30mm*5u, mobile phase: CH_3CN in water (0.1% NH_4HCO_3) from 40% to 70%, flow rate: 35 ml/min). Method B; Rt: 4.45 min. m/z: 413.3 $(M+H)^+$ Exact mass: 412.1. $[\alpha]_D^{20}$: + 55° (c 0.12 w/v, methanol).



Compound **167**

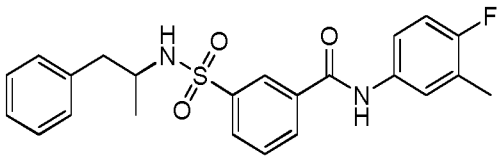
Prepared similarly as described for compound **166**, using (*S*)-1-phenylethanamine instead of (*R*)-1-phenylethanamine. Method B; Rt: 4.45 min. m/z: 413.3 $(M+H)^+$ Exact mass: 412.1. $[\alpha]_D^{20}$: - 57° (c 0.12 w/v, methanol).



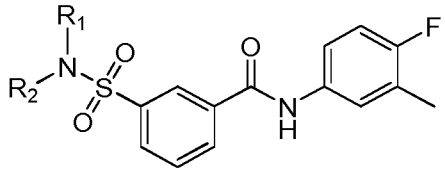
Compound **168**

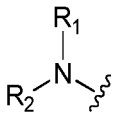
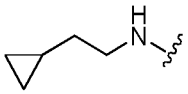
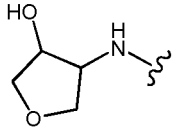
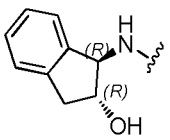
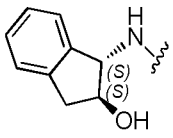
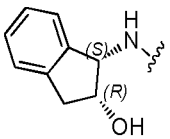
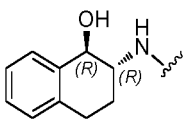
Synthesis following procedure S4 (20 hours reaction time instead of 3 hours) with 2-aminoindane as amine, workup W4. The obtained residue was recrystallised from Diisopropylether/acetonitrile, resulting in compound **168**. Method F; Rt: 1.14 min. m/z: 442.2 $(M+NH_4)^+$ Exact mass: 424.1. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.25 (d, J=1.8 Hz, 3 H), 2.72 (dd, J=15.6, 7.0 Hz, 2 H), 2.96 (dd, J=15.8, 7.5 Hz, 2 H), 3.95 (quin, J=7.3 Hz, 1 H), 7.08 - 7.17 (m, 5 H), 7.57 - 7.63 (m, 1 H), 7.68 (dd, J=6.9, 2.3 Hz, 1 H), 7.79 (t, J=7.8 Hz, 1 H), 8.03 - 8.12 (m, 1 H), 8.13 - 8.28 (m, 2 H), 8.41 (t, J=1.7 Hz, 1 H), 10.49 (br. s., 1 H)

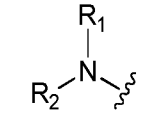
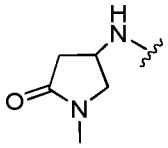
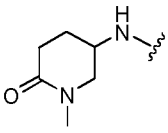
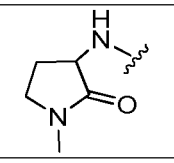
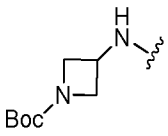
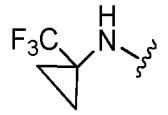
Compound **169**



Prepared similarly as described for compound **166**, using 1-phenylpropan-2-amine instead of (*R*)-1-phenylethanamine. Method B; Rt: 4.60 min. m/z: 427.3 $(M+H)^+$ Exact mass: 426.1.



#		Amine used	Synthetic/ work up Procedure	LC-MS method	Rt (min.)	$[M+NH_4]^+$ or $[M+H]^+$	Exact mass
170		2-cyclopropyl-ethanamine	S4/W4	H	8.63	377.1	376.1
171		4-aminotetra-hydrofuran-3-ol	S4/W4	F	0.79	412.1	394.1
175		(1R,2R)-1-amino-2,3-dihydro-1H-inden-2-ol	S4*/W4	F	0.97	458.1	440.1
176		(1S,2S)-1-Amino-2,3-dihydro-1H-inden-2-ol	S4*/W4	F	1.01	458.1	440.1
177		(1S,2R)-(-)-Cis-1-amino-2-indanol	S4*/W4	F	0.97	458.4	440.1
178		(1R,2R)-2-aminotetralin-1-ol hydrochloride	S4*/W4	F	1.01	472.2	454.1

#		Amine used	Synthetic/ work up Procedure	LC-MS method	Rt (min.)	$[M+NH_4]^+$ or $[M+H]^+$	Exact mass
179		4-Amino-1-methyl-pyrrolidin-2-one	S4*/W4	F	0.81	406.1	405.1
180		5-Amino-1-methyl-piperidin-2-one	S4*/W4	F	0.81	420.2	419.1
181		3-Amino-1-methylpyrrolidin-2-one	S4/W4	F	0.84	423.1	405.1
182		3-Amino-1-N-boc-azetidine	S4*/W4	F	1.06	481.2	463.2
183		1-(trifluoro-methyl)cyclo-propanamine	S4*/W4	F	1.03	434.1	416.1

S4*: reaction time 20 hours instead of 3 hours

Compound **175**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.25 (d, J=1.5 Hz, 3 H), 2.62 (dd, J=15.7, 6.5 Hz, 1 H), 3.07 (dd, J=15.7, 6.7 Hz, 1 H), 4.11 (quin, J=6.2 Hz, 1 H), 4.50 (dd, J=7.9, 6.2 Hz, 1 H), 5.14 (d, J=5.7 Hz, 1 H), 6.92 (d, J=7.5 Hz, 1 H), 7.06 - 7.24 (m, 4 H), 7.55 - 7.65 (m, 1 H), 7.69 (dd, J=7.0, 2.4 Hz, 1 H), 7.77 (t, J=7.8 Hz, 1 H), 8.05 - 8.15 (m, 1 H), 8.19 - 8.26 (m, 1 H), 8.31 (d, J=8.4 Hz, 1 H), 8.47 (t, J=1.7 Hz, 1 H), 10.45 (s, 1 H)

Compound **178**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.51 - 1.72 (m, 1 H), 1.86 - 1.99 (m, 1 H), 2.22 - 2.31 (m, 3 H), 2.60-2.74 (m, 1 H), 2.74 - 2.85 (m, 1 H), 3.26 - 3.41 (m, 1 H), 4.38 (t, J=6.2 Hz, 1 H), 5.32 - 5.39 (m, 1 H), 6.96 - 7.09 (m, 1 H), 7.11 - 7.21 (m, 3 H), 7.28 - 7.37 (m, 1 H), 7.51 - 7.65 (m, 1 H), 7.69 (dd, J=7.0, 2.4 Hz, 1 H), 7.72 - 7.82 (m, 2 H), 8.05 - 8.12 (m, 1 H), 8.17 - 8.24 (m, 1 H), 8.43 (t, J=1.7 Hz, 1 H), 10.48 (s, 1 H)

Compound **179**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.99 (dd, J=5.1, 16.7 Hz, 1 H), 2.25 (d, J=1.8 Hz, 3 H), 2.35 (dd, J=8.4, 16.7 Hz, 1 H), 2.66 (s, 3 H), 3.10 (dd, J=10.1, 4.6 Hz, 1 H), 3.47 (dd, J=10.3, 7.3 Hz, 1 H), 3.80 - 3.92 (m, 1 H), 7.14 (t, J=9.2 Hz, 1 H), 7.53 - 7.63 (m, 1 H), 7.68 (dd, J=7.0, 2.2 Hz, 1 H), 7.74 - 7.86 (m, 1 H), 7.97 - 8.08 (m, 1 H), 8.15 - 8.32 (m, 2 H), 8.37 (s, 1 H), 10.48 (s, 1 H). Racemic compound **179**

was separated in enantiomers **179a** and **179b** by Preparative SFC (Stationary phase: Chiralpak Diacel AD 30 x 250 mm), Mobile phase: CO_2, iPrOH with 0.4% $iPrNH_2$) The collected fractions were concentrated in vacuo resulting in compound **179a** and **179b**. Columns: AD-H (diacel) 250 mm x 4.6 mm; Flow: 5 mL/min; Mobile phase: 30% iPrOH (containing 0.2% $iPrNH_2$) hold 4.00 min, up to 50% in 1 min and hold 2.00 min @ 50%; Temperature: 40°C Rt: 2.2 min (**179a**); 2.9 min (**179b**). **179a**: +6.1 ° (589 nm, c 0.6225 w/v %, MeOH, 20 °C). **179b**: -6.1 ° (589 nm, c 0.506 w/v %, MeOH, 20°C).

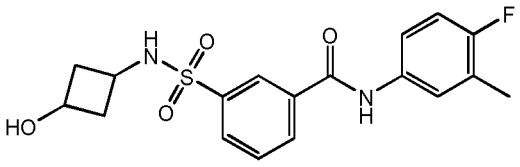
Compound **180**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.55 - 1.79 (m, 2 H), 2.01 - 2.36 (m, 5 H), 2.68 (s, 3 H), 3.06 (dd, J=12.3, 6.8 Hz, 1 H), 3.25 - 3.30 (m, 1 H), 3.46 - 3.58 (m, 1 H), 7.14 (t, J=9.1 Hz, 1 H), 7.52 - 7.63 (m, 1 H), 7.64 - 7.71 (m, 1 H), 7.78 (t, J=7.8 Hz, 1 H), 8.01 - 8.09 (m, 1 H), 8.11 - 8.27 (m, 2 H), 8.39 (t, J=1.7 Hz, 1 H), 10.47 (s, 1 H)

Compound **181**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.59 (dq, J=12.4, 9.3 Hz, 1 H), 1.93 - 2.16 (m, 1 H), 2.25 (d, J=1.5 Hz, 3 H), 2.69 (s, 3 H), 3.06 - 3.24 (m, 2 H), 4.00 (t, J=9.1 Hz, 1 H), 7.14 (t, J=9.2 Hz, 1 H), 7.54 - 7.64 (m, 1 H), 7.65 - 7.71 (m, 1 H), 7.74 (t, J=7.8 Hz, 1 H), 7.99 - 8.09 (m, 1 H), 8.25 (br. s, 1 H), 8.11 - 8.20 (m, 1 H), 8.44 (t, J=1.7 Hz, 1 H), 10.42 (s, 1 H).

Compound **182**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.12 - 1.52 (m, 9 H), 2.26 (d, J=1.3 Hz, 3 H), 3.40-3.60 (m 2 H), 3.80-4.00 (m, 2 H), 4.02 - 4.19 (m, 1 H), 7.15 (t, J=9.2 Hz, 1 H), 7.57 - 7.66 (m, 1 H), 7.70 (dd, J=7.0, 2.2 Hz, 1 H), 7.80 (t, J=7.8 Hz, 1 H), 8.01 (m, J=8.1 Hz, 1 H), 8.26 (m, J=7.9 Hz, 1 H), 8.38 (t, J=1.0 Hz, 1 H), 8.51 (d, J=8.4 Hz, 1 H), 10.50 (s, 1 H).

Compound **183**. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.19 - 1.43 (m, 4 H), 2.28 (d, J=1.8 Hz, 3 H), 5.74 (br. s., 1 H), 6.99 (t, J=8.8 Hz, 1 H), 7.37 (m, J=8.4, 3.7 Hz, 1 H), 7.45 - 7.54 (m, 1 H), 7.64 (t, J=7.8 Hz, 1 H), 7.88 (br. s., 1 H), 8.03 (m, J=8.1 Hz, 1 H), 8.10 (m, J=7.9 Hz, 1 H), 8.29 - 8.38 (m, 1 H)

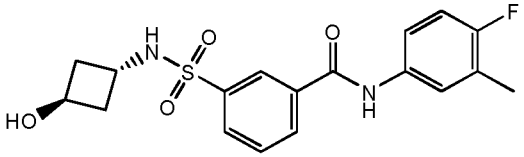
Compound **184**



Synthesis following procedure S4 with 3-aminocyclobutanol as amine, 1 hour reaction time instead of 3 hour, workup W4. Method F; Rt: 0.81 min. m/z: 396.2 $(M+NH_4)^+$ Exact mass: 378.1. SFC: Columns: Diacel AD-H (250 mm x 4.6 mm); Flow: 5 mL/min Mobile phase: 30% MeOH (containing 0.2% $iPrNH_2$) hold 4.00 min, up to 50% in 1 min and hold 2.00 min at 50%; Temperature: 40°C; Rt: **184a** (2.5

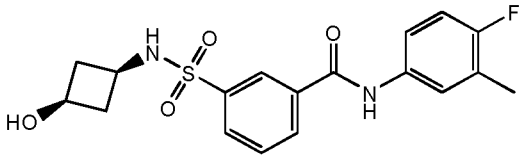
min), **184b** (3.4 min). The diastereomeric mixture of compound **184** was separated in diastereoisomers (Prep SFC (Stationary phase: Chiralpak Diacel AD 30 x 250 mm), Mobile phase: CO_2, MeOH with 0.4% $iPrNH_2$). The obtained fractions were concentrated under reduced pressure and dried in vacuo at 55°C, resulting in compound **184a** and **184b**.

Compound **184a**



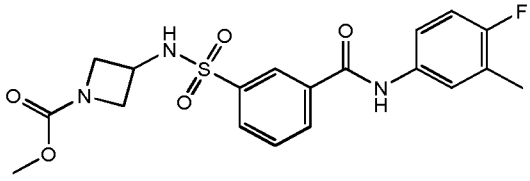
^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.84 - 1.91 (m, 2 H), 1.92 - 1.98 (m, 2 H), 2.25 (d, J=1.8 Hz, 3 H), 3.77 (quin, J=6.9 Hz, 1 H), 4.10 - 4.14 (m, 1 H), 4.93 (d, J=4.9 Hz, 1 H), 7.14 (t, J=9.2 Hz, 1 H), 7.59 (ddd, J=8.8, 4.6, 2.7 Hz, 1 H), 7.68 (dd, J=7.1, 2.7 Hz, 1 H), 7.76 (t, J=7.8 Hz, 1 H), 7.96 (ddd, J=7.8, 1.9, 1.1 Hz, 1 H), 8.06 (br. s., 1 H), 8.20 (dt, J=7.8, 1.5 Hz, 1 H), 8.33 (t, J=1.8 Hz, 1 H), 10.49 (br. s., 1 H).

Compound **184b**

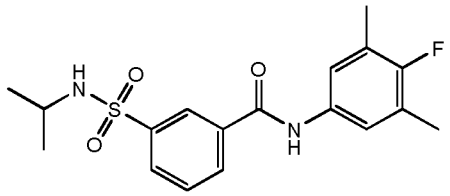


^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.54 - 1.60 (m, 2 H), 2.19 - 2.24 (m, 2 H), 2.25 (d, J=1.8 Hz, 3 H), 3.09 - 3.19 (m, 1 H), 3.62 - 3.68 (m, 1 H), 5.00 (d, J=5.6 Hz, 1 H), 7.14 (t, J=9.2 Hz, 1 H), 7.59 (ddd, J=8.5, 4.5, 2.8 Hz, 1 H), 7.68 (dd, J=7.0, 2.2 Hz, 1 H), 7.75 (t, J=7.8 Hz, 1 H), 7.97 (ddd, J=7.8, 1.9, 1.0 Hz, 1 H), 8.02 (br. s., 1 H), 8.19 (ddd, J=7.8, 1.8, 1.1 Hz, 1 H), 8.34 (t, J=1.6 Hz, 1 H), 10.48 (s, 1 H)

Compound **185**



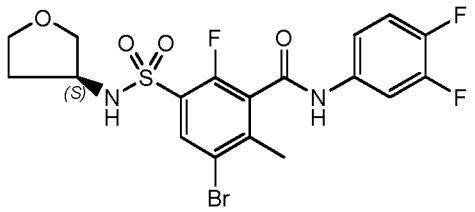
Prepared similarly as described for compound **157**, starting from compound **182** instead of compound **154**, via intermediate 3-(azetidin-3-ylsulfamoyl)-N-(4-fluoro-3-methyl-phenyl)benzamide hydrochloride. Method F; Rt: 0.89 min. m/z: 439.2 $(M+NH_4)^+$ Exact mass: 421.1.^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.25 (d, J=1.8 Hz, 3 H), 3.45-3.60 (m, 5 H), 3.85-4.05 (m, 2 H), 4.07 - 4.17 (m, 1 H), 7.15 (t, J=9.1 Hz, 1 H), 7.53 - 7.64 (m, 1 H), 7.65 - 7.71 (m, 1 H), 7.78 (t, J=7.8 Hz, 1 H), 7.94 - 8.03 (m, 1 H), 8.23 (m, J=7.9 Hz, 1 H), 8.33 (t, J=1.7 Hz, 1 H), 8.44 - 8.63 (br. s, 1 H), 10.49 (s, 1 H).



Compound **186**

3-(isopropylsulfamoyl)benzoic acid (250 mg, 1.03 mmol), 4-fluoro-3,5-dimethyl-aniline (157 mg, 1.13 mmol) and DIPEA (398 mg, 3.08 mmol) were mixed in acetonitrile (10 mL) at room temperature under a nitrogen atmosphere. HATU (430 mg, 1.13 mmol) was added and the mixture was stirred overnight. EtOAc (100 mL) was added and the mixture was washed with 1M HCl, sat $NaHCO_3$ and brine. After drying over $MgSO_4$ and evaporation to dryness in vacuo, the obtained residue was crystallized from MeOH (10 mL) to provide a white solid (216 mg). Method F; Rt: 1.04 min. m/z: 382.2 $(M+NH_4)^+$ Exact mass: 364.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.96 (d, J=6.6 Hz, 6 H), 2.23 (d, J=2.0 Hz, 6 H), 3.23 - 3.29 (m, 1 H), 7.48 (d, J=6.6 Hz, 2 H), 7.66 - 7.80 (m, 2 H), 7.95 - 8.04 (m, 1 H), 8.18 (d, J=7.9 Hz, 1 H), 8.35 (t, J=1.7 Hz, 1 H), 10.37 (s, 1 H).

Compound **187**

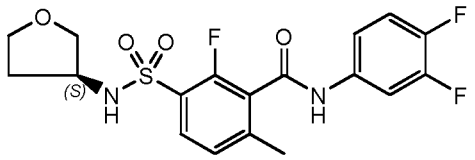


A solution of 2-fluoro-6-methylbenzoic acid (10 g, 0.0649 mol) in HOAc (300 mL) was stirred on a water-bath containing a bit of ice. At ~ 15°C, HNO_3 (65%, 32.7 mL) was added dropwise. After addition, H_2O (30 mL) was added slowly. After addition, Br_2 (3.7 mL) was added dropwise. A solution of silver nitrate (14.33 g, 0.0844 mol) in H_20 (100 mL) was added dropwise over a period of 30 minutes. After addition, the reaction mixture was stirred at room temperature for 3 hours 30 minutes. The reaction mixture was poured into H_2O (850 mL), and EtOAc (300 mL) was added. The mixture was stirred vigorously for 5 minutes. Both upper liquid layers were decanted from a residue. The separated water layer was combined with the residue, and extracted with EtOAc. Both upper liquid layers were decanted from the residue. The separated water layer was combined with the residue, and extracted again with EtOAc. The organic layers were combined, washed with satured NaCl and dried with Na_2SO_4, filtered off, evaporated, and co-evaporated with toluene. The obtained solid residue was stirred in a small amount of diisopropylether, filtered off, washed with diisopropylether, resulting

in 3-bromo-6-fluoro-2-methyl-benzoic acid (4 g).The filtrate was evaporated. The residue was stirred in heptane, filtered off, washed with heptanes (3x), and dried at 50°C in vacuo, resulting in a mixture of bromo-6-fluoro-2-methyl-benzoic acid and 2-fluoro-6-methylbenzoic acid (12 g, 1/0.4 ratio). 3-bromo-6-fluoro-2-methyl-benzoic acid (4 g, 0.0172 mol) was added portionwise to stirring chlorosulfonic acid (25 mL). The resulting solution was stirred at 115°C for 2 hours, left standing at room temperature overnight and next stirred at 115°C for 3 hours more. The reaction mixture was allowed to reach room temperature, and added dropwise to a stirring mixture of crushed ice (150 g) and H_2O (50 mL). The product was extracted with EtOAc (2 x). The combined organic layers were washed with brine, dried with Na_2SO_4, filtered off, and evaporated, resulting in a crude mixture containing 5-bromo-3-chlorosulfonyl-2-fluoro-6-methyl-benzoic acid (4.4 g) (Na_2CO_3, 1.407 g, 0.0133 mol) was dissolved in water (25 mL). A solution of (S)-3-aminotetrahydrofuran (2.312 g, 0.0265 mol) in THF (20 mL) was added, and the reaction mixture was cooled to 0°C on an ice-bath. A solution of crude 5-bromo-3-chlorosulfonyl-2-fluoro-6-methyl-benzoic acid (4.4 g) in THF (30 mL) was added dropwise at 0°C. After addition, the reaction mixture was stirred at 0°C for 1 hour, and at room temperature for 2 hours. The mixture was concentrated till ~ 35 mL remained, then left standing for 70 hours. The solid was filtered off and washed with H_2O (2x). The filtrate was washed with Et_2O. The separated waterlayer was acidified with 1N HCl (30 mL), and the product was extracted with 2-MeTHF. The separated waterlayer was acidified further till pH ~ 2 and extracted with 2-MeTHF. The organic layer was washed with brine, dried with Na_2SO_4 and filtered, resulting in crude 5-bromo-2-fluoro-6-methyl-3-[[(3S)-tetrahydrofuran-3-yl]sulfamoyl]benzoic acid (6.5 g). To a stirring solution of crude 5-bromo-2-fluoro-6-methyl-3-[[(3S)-tetrahydrofuran-3-yl]sulfamoyl]benzoic acid (1.3 g) in CH_3CN (30 mL) under N_2-atm triethylamine (1.42 mL, 0.0102 mol), 3,4-difluoroaniline (0.446 mL, 4.42 mmol) and HATU (1.55 g, 4.08 mmol) were successively added. The reaction mixture was stirred at room temperature for 16 hours. The volatiles were evaporated and the obtained residue was purified by silica gel chromatography (heptane-EtOAc 100/0 to 0/100], resulting in compound **187** (0.45 g).An impure fraction was further purified by Preparative HPLC (Stationary phase: RP XBridge Prep C18 OBD-10µm,30x150mm), Mobile phase: 0.25% NH_4HCO_3 solution in water, CH_3CN), resulting in more compound **187** (0.048 g)

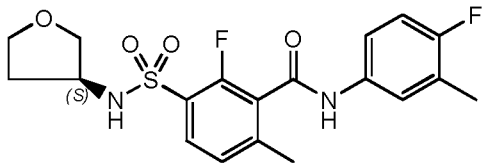
Method F; Rt: 1.06 min. m/z: 491.0 $(M-H)^-$ Exact mass:492.0. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.66 - 1.76 (m, 1 H), 1.94 - 2.05 (m, 1 H), 2.41 (s, 3 H), 3.43 (dd, J=8.9, 4.5 Hz, 1 H), 3.58 - 3.65 (m, 1 H), 3.68 (dd, J=8.9, 6.3 Hz, 1 H), 3.71 - 3.78 (m, 1 H), 3.83 - 3.92 (m, 1 H), 7.36 - 7.42 (m, 1 H), 7.43 - 7.52 (m, 1 H), 7.85 (ddd, J=12.8, 7.5, 2.4 Hz, 1 H), 8.02 (d, J=6.8 Hz, 1 H), 8.55 (s, 1 H), 11.09 (s, 1 H)

Compound **188**



Compound **187** (0.45 g, 0.912 mmol) was dissolved in MeOH (20 mL) and THF (30 mL). To the resulting solution, triethylamine (0.254 mL, 1.82 mmol) was added and the mixture was stirred with 10% Pd/C (0.2 g) under hydrogen atmosphere at room temperature. After 3 hours, the catalyst was filtered off over dicalite, and washed with MeOH (3x) and THF (1x). The volatiles were removed in vacuo and the obtained residue was dissolved in hot MeOH (10 mL) and hot H_2O (10 mL) was added. The volume was concentrated till ~ 15 mL, and left standing for 1 hour. The precipitated product was filtered off, washed with H_2O (3x), and dried at 50°C in vacuo, resulting in compound **188** (245 mg). Method F; Rt: 0.93 min. m/z: 413.2 $(M-H)^-$ Exact mass: 414.1.[19] F NMR (377 MHz, DMSO-d_6) δ ppm -143.7 - -143.2 (m, 1 F), -137.1 - -136.5 (m, 1 F), -114.8 (d, J=7.9 Hz, 1 F). [1] H NMR (400 MHz, DMSO-d_6) δ ppm 1.66 - 1.77 (m, 1 H), 1.91 - 2.03 (m, 1 H), 2.39 (s, 3 H), 3.43 (dd, J=9.0, 4.6 Hz, 1 H), 3.57 - 3.70 (m, 2 H), 3.70 - 3.77, (m, 1 H), 3.78 - 3.86 (m, 1 H), 7.35 (d, J=8.1 Hz, 1 H), 7.39 - 7.52 (m, 2 H), 7.79 (t, J=7.8 Hz, 1 H), 7.87 (ddd, J=12.9, 7.5, 2.1 Hz, 1 H), 8.32 (br. s., 1 H), 11.00 (s, 1 H).

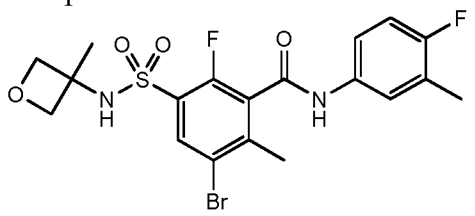
Compound **189**



Compound **189** was prepared similarly as described for compound **188**, using 4-fluoro-3-methylaniline instead of 3,4-difluoroaniline. Method F; Rt: 0.94 min. m/z: 409.2 $(M-H)^-$ Exact mass:410.1. [19]F NMR (377 MHz, DMSO-d_6) δ ppm -122.40 (dtd, J=9.3, 4.6, 4.6, 2.1 Hz, 1 F), -114.96 (d, J=7.2 Hz, 1 F). [1]H NMR (400 MHz, DMSO-d_6) δ ppm 1.67 - 1.77 (m, 1 H), 1.92 - 2.03 (m, 1 H), 2.24 (d, J=1.5 Hz, 3 H), 2.38 (s, 3 H), 3.43 (dd, J=8.8, 4.6 Hz, 1 H), 3.58 - 3.64 (m, 1 H), 3.65 - 3.70 (m, 1 H), 3.70 - 3.77 (m, 1 H), 3.78 - 3.86 (m, 1 H), 7.14 (dd, J=9.1 Hz, 1 H), 7.34 (d, J=8.1 Hz, 1 H), 7.45 - 7.53 (m, 1 H), 7.63 (dd, J=7.0, 2.4 Hz, 1 H), 7.77 (dd, J=7.9 Hz, 1 H), 8.30 (br. s., 1 H), 10.72 (s, 1 H). Differential scanning calorimetry From 30 to 300 °C at 10°C/min:

Peak at 157.0 °C

Compound **190**

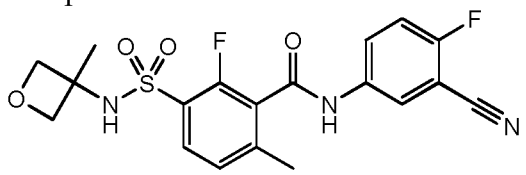


Na_2CO_3 (1.60 g, 0.0151 mol) was dissolved in water (25 mL). A solution of 3-methyloxetan-3-amine (2.63 g, 0.0302 mol) in THF (20 mL) was added, and the reaction mixture was cooled to 0°C on an ice-bath. A solution of crude 5-bromo-3-chlorosulfonyl-2-fluoro-6-methyl-benzoic acid (5 g) in THF (30 mL) was added dropwise at 0°C. After addition, the reaction mixture was stirred vigorously at 0°C for 30 minutes, and at room temperature for 2 hours. The organic volatiles were evaporated, and the remaining ~ 30 mL was washed with Et_2O (50 mL). The separated waterlayer was acidified with 1N HCl (40 mL), and the product was extracted with 2-MeTHF (2x). The combined organic layers were washed with brine, dried with Na_2SO_4, filtered off, evaporated, and co-evaporated with CH_3CN, resulting in crude 5-bromo-2-fluoro-6-methyl-3-[(3-methyloxetan-3-yl)sulfamoyl]benzoic acid (3.6 g) To a solution of crude 5-bromo-2-fluoro-6-methyl-3-[(3-methyloxetan-3-yl)sulfamoyl]benzoic acid (0.72 g, 0.00188 mol) in CH_3CN (15 mL) under N_2-atm was successively added NEt_3 (0.786 mL, 0.00565 mol), 4-fluoro-3-methylaniline (0.313 g, 0.00245 mol), and HATU (0.86 g, 0.00226 mol). The reaction mixture was stirred at room temperature for 20 hours. More 4-fluoro-3-methylaniline (0.1 g) and HATU (0.3 g) were added, and the reaction was continued for 20 hours. The volatiles were evaporated. The residue was purified by silica gel Chromatography (heptane-EtOAc 100/0 to 0/100). The desired fractions were combined and evaporated. The residue was stirred in diisopropylether, filtered off, washed with diisopropylether (3x), and dried at 50°C, resulting in compound **190** (0.38 g). m/z: 486.9 $(M-H)^-$ Exact mass:488.0. ^{19}F NMR (377 MHz, DMSO-d_6) δ ppm -122.15 - -121.89 (m, 1 F), -116.05 (d, J=6.4 Hz, 1 F). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.47 (s, 3 H), 2.25 (d, J=1.5 Hz, 3 H), 2.40 (s, 3 H), 4.22 (d, J=6.6 Hz, 2 H), 4.62 (d, J=6.4 Hz, 2 H), 7.16 (dd, J=9.2 Hz, 1 H), 7.44 - 7.51 (m, 1 H), 7.61 (dd, J=6.9, 2.3 Hz, 1 H), 8.01 (d, J=6.8 Hz, 1 H), 8.86 (br. s., 1 H), 10.81 (s, 1 H)

Synthesis of 2-fluoro-6-methyl-3-[(3-methyloxetan-3-yl)sulfamoyl]benzoic acid

A solution of 5-bromo-2-fluoro-6-methyl-3-[(3-methyloxetan-3-yl)sulfamoyl]benzoic acid (0.9 g) and triethylamine (0.98 mL, 7.1 mmol) in MeOH (30 mL) was stirred with Pd/C 10% (0.1 g) at room temperature under a hydrogen atmosphere. After the calculated amount of hydrogen was taken up, the catalyst was filtered off. The filtrate was concentrated in vacuo, and co-evaporated with CH_3CN. The obtained residue containing 2-fluoro-6-methyl-3-[(3-methyloxetan-3-yl)sulfamoyl]benzoic acid was used as such. Method F; Rt: 0.38 min. m/z: 302.0 $(M-H)^-$ Exact mass:303.1

Compound **191**



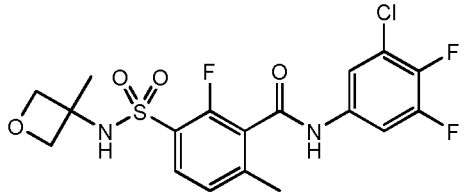
Triethylamine (0.206 mL, 0.00149 mol) was added to a stirring mixture of 2-fluoro-6-methyl-3-[(3-methyloxetan-3-yl)sulfamoyl]benzoic acid (0.15 g, 0.000495 mol) and CH_3CN (10 mL) under N_2-atm. To the resulting solution was added HATU (0.207 g, 0.545 mmol). After stirring for 5 minutes, 5-amino-2-fluorobenzonitrile, (79.9 mg, 0.569 mmol) was added, and the reaction mixture was stirred at room temperature for 20 hours. The reaction was next continued at 50°C for 4 hours. The volatiles were evaporated and the obtained residue was dissolved in CH_2Cl_2 (2.5 mL) and purified by silica gel Chromatography (heptane-EtOAc 100/0 to 0/100) followed by repurification with CH_2Cl_2-MeOH 100/0 to 98/2 as eluent. The desired fractions were combined and evaporated, and co-evaporated with EtOAc. The residue was dried further at 50°C in vacuo, resulting in compound **191** (63 mg). Method F; Rt: 0.88 min. m/z: 420.1 $(M-H)^-$ Exact mass:421.1. ^1H NMR (400 MHz, DMSO-d_6) d ppm 1.46 (s, 3 H), 2.40 (s, 3 H), 4.19 (d, J=6.6 Hz, 2 H), 4.62 (d, J=6.2 Hz, 2 H), 7.36 (d, J=8.1 Hz, 1 H), 7.58 (t, J=9.1 Hz, 1 H), 7.80 (t, J=7.9 Hz, 1 H), 7.96 (ddd, J=9.1, 4.8, 2.8 Hz, 1 H), 8.22 (dd, J=5.7, 2.6 Hz, 1 H), 8.64 (s, 1 H), 11.16 (s, 1 H). ^{19}F NMR (377 MHz, DMSO-d_6) δ ppm -115.10 (d, J=7.9 Hz, 1 F), -113.61 (dt, J=8.9, 5.2 Hz, 1 F).

Synthesis of 3-chloro-4,5-difluoro-aniline

3-chloro-4,5-difluorobenzoic acid (commercial from astatech, 25.5 g, 0.132 mol) was dissolved in tert-butyl alcohol (200 mL) at 50°C. Et_3N (20.2 mL, 0.146 mol) was added. Diphenylphosphoryl azide, 30.0 mL, 0.139 mol) was added slowly, and the reaction mixture was stirred and refluxed for 18 hours. The volatiles were evaporated, and co-evaporated with EtOAc. The residue was stirred in Et_2O (300 mL)/Sat. $NaHCO_3$ (300 mL) /H_2O (50 mL) for 15 minutes. The separated organic layer was dried with

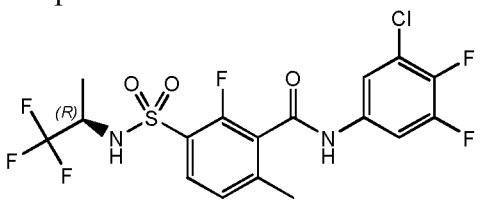
$MgSO_4$, filtered off, and evaporated. The solid residue was stirred in diisopropylether (20 mL), filtered off, washed with diisopropylether (3x) and dried at 50°C, resulting in tert-butyl N-(3-chloro-4,5-difluoro-phenyl)carbamate (8.5 g). The filtrate was concentrated in vacuo. The residue was stirred in CH_2Cl_2 (20 mL) + heptanes (20 mL), filtered off, washed with CH_2Cl_2-heptane 1/1 (2x) and heptanes (2x), and dried at 50°C in vacuo, resulting in more tert-butyl N-(3-chloro-4,5-difluoro-phenyl)carbamate, 11.8 g). tert-butyl N-(3-chloro-4,5-difluoro-phenyl)carbamate (8.5 g, 0.0322 mol) was added portion wise to stirring HCl (40 mL, 0.16 mol, 4 M in dioxane). The mixture was stirred at room tempertaure for 2 hours, then left standing for 65 hours. Stirring was continued for another 2 hours. The formed precipitate was filtered off , washed with dioxane (4x) and dried at 50°C in vacuo, resulting in 3-chloro-4,5-difluoro-aniline hydrochloride (5.95 g). A mixture of 3-chloro-4,5-difluoro-aniline hydrochloride (1 g, 0.005 mol), NaOH (1M in H_2O, 10 mL, 0.01 mol) and toluene (15 mL) was stirred at room temperature for 1 hour. The separated organic layer was dried with $MgSO_4$, filtered off, and evaporated. The obtained 3-chloro-4,5-difluoro-aniline (0.81 g) was used as such.

Compound **192**



Compound **192** was prepared similarly as described for compound **191**, using 3-chloro-4,5-difluoro-aniline hydrochloride instead of 5-amino-2-fluorobenzonitrile.^{19}F NMR (377 MHz, DMSO-d_6) d ppm -144.93 (br. s., 1 F), -134.02 - -133.17 (m, 1 F), -115.09 (d, J=7.9 Hz, 1 F). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.45 (s, 3 H), 2.38 (s, 3 H), 4.18 (d, J=6.4 Hz, 2 H), 4.61 (d, J=6.2 Hz, 2 H), 7.35 (d, J=8.1 Hz, 1 H), 7.71 - 7.83 (m, 3 H), 8.64 (br. s., 1 H), 11.14 (br. s., 1 H). Method F; Rt: 1.05 min. m/z: 447.1 $(M-H)^-$ Exact mass:448.0.

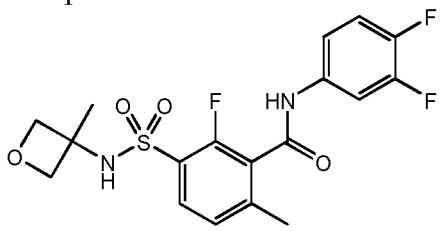
Compound **193**



Oxalyl chloride (12.3 mL, 0.143 mol) was added dropwise to a stirring solution of 5-bromo-3-chlorosulfonyl-2-fluoro-6-methyl-benzoic acid (9.5 g) and DMF (0.111 mL)

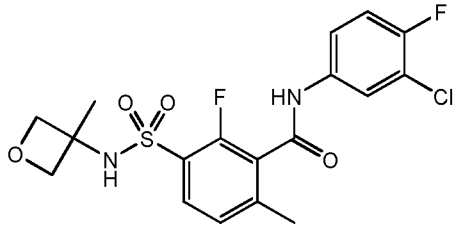
in CH_2Cl_2 (100 mL). After addition, the reaction mixture was stirred at room temperature for 2 hours and 30 minutes. The volatiles were removed in vacuo, and co-evaporated with toluene. The obtained residue containing 5-bromo-3-chlorosulfonyl-2-fluoro-6-methyl-benzoyl chloride was used as such. A solution of 5-bromo-3-chlorosulfonyl-2-fluoro-6-methyl-benzoyl chloride (1.75 g) in toluene (20 mL) was stirred at reflux under N_2-flow. A solution of 3-chloro-4,5-difluoroaniline (0.818 g, 0.005 mol) in toluene (10 mL) was added dropwise. After addition, the reaction mixture was refluxed for 45 minutes, then allowed to reach room temperature, and left standing for 18 hours. A precipitate (0.51 g) was filtered off, washed with toluene (2 x), and dried at 50°C in vacuo. (*R*)-1,1,1-trifluoro-2-propylamine (0.181 g, 0.0016 mol) was dissolved in CH_3CN (5 mL) under N_2-atm. 5-bromo-3-[(3-chloro-4,5-difluoro-phenyl)carbamoyl]-2-fluoro-4-methyl-benzenesulfonyl chloride (0.51 g) was added, then DIPEA (0.461 mL, 0.00267 mol). The mixture was stirred in a sealed tube at 80°C for 20 hours. The reaction mixture was allowed to reach room temperature, and left standing for 2 hours. The mixture was filtered and the filtrate was evaporated. The residue was dissolved in CH_2Cl_2 (2 mL), and purified by silica gel chromatography [heptane-EtOAc 100/0 to 0/100]. The fractions containing the desired compound were combined and evaporated, and co-evaporated with EtOH, resulting in crude 5-bromo-N-(3-chloro-4,5-difluoro-phenyl)-2-fluoro-6-methyl-3-[[(1R)-2,2,2-trifluoro-1-methyl-ethyl]sulfamoyl]benzamide (0.12 g).To a solution of 5-bromo-N-(3-chloro-4,5-difluoro-phenyl)-2-fluoro-6-methyl-3-[[(1R)-2,2,2-trifluoro-1-methyl-ethyl]sulfamoyl]benzamide (0.1 g) in EtOH (11 mL) was added H_2O (3.5 mL), then K_2CO_3 aq. sat. sol., (1.25 mL) and next Palladium(0)tetrakis(triphenylphosphine (26.1 mg, 0.023 mmol). The mixture was stirred 150°C by microwave irradiation for 45 minutes. The reaction mixture was combined with a similar reaction mixture starting from 20 mg 5-bromo-N-(3-chloro-4,5-difluoro-phenyl)-2-fluoro-6-methyl-3-[[(1R)-2,2,2-trifluoro-1-methyl-ethyl]sulfamoyl]benzamide) allowed to reach room temperature and left standing for 15 minutes. The upper layer was isolated by means of a separation funnel, and evaporated. The obtained residue was purified by silica gel chromatography (heptane-EtOAc 100/0 to 0/100, also CH_2Cl_2-MeOH 100/0 to 98/2), followed by separation by preparative HPLC (Stationary phase: RP Vydac Denali C18 - 10μm, 200g, 5cm), Mobile phase: 0.25% NH_4HCO_3 solution in water, CH_3CN) , resulting in compound **193** (11.4 mg). Method F; Rt: 1.17 min. m/z: 473.0 $(M-H)^-$ Exact mass:474.0. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.17 (d, J=6.8 Hz, 3 H), 2.38 (s, 3 H), 4.00-4.15 (m, 1 H), 7.35 (d, J=8.4 Hz, 1 H), 7.71 - 7.78 (m, 2 H), 7.82 (t, J=7.8 Hz, 1 H), 9.00 (br. s., 1 H), 11.13 (s, 1 H). ^{19}F NMR (377 MHz, DMSO-d_6) d ppm -145.3 to -144.5 (m, 1 F), -134.4 to -132.8 (m, 1 F), -114.9 (br. s., 1 F), -76.0 (d, J=7.2 Hz, 3 F).

Compound **194**



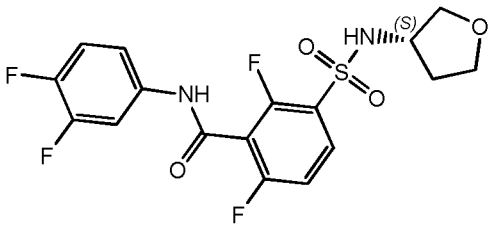
2-fluoro-6-methyl-3-[(3-methyloxetan-3-yl)sulfamoyl]benzoic acid (0.15 g, 0.473 mmol) was dissolved in DMF (5 mL) and triethylamine (0.2 mL) and HATU (233 mg, 0.61 mmol) were added to the reaction mixture. The reaction mixture was stirred for 10 minutes and 3,4-difluoroaniline (123 mg, 0.945 mmol) was added. The reaction mixture was stirred at room temperature for 42 hours. The reaction mixture was poured into ice water (50 mL). The mixture was extracted with Me-THF (3 x 20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified using silica gel column chromatography (ethyl acetate in heptane from 0 to 100% and methanol in dichloromethane from 0 to 2%) to afford compound **194** (79 mg) as a white powder which was dried in vacuum oven overnight. Method F; Rt: 0.94 min. m/z: 413.2 $(M-H)^-$ Exact mass: 414.1. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.45 (s, 3 H), 2.39 (s, 3 H), 4.18 (d, J=6.6 Hz, 2 H), 4.62 (d, J=6.2 Hz, 2 H), 7.35 (d, J=8.1 Hz, 1 H), 7.39 - 7.51 (m, 2 H), 7.79 (t, J=7.8 Hz, 1 H), 7.87 (ddd, J=12.9, 7.4, 2.0 Hz, 1 H), 8.64 (br. s., 1 H), 11.00 (s, 1 H)

Compound **195**



Compound **195** (98 mg) was prepared similarly as described for compound **194**, using 3-chloro-4-fluoroaniline instead of 3,4-difluoroaniline. Method F; Rt: 0.99 min. m/z: 429.1 $(M-H^-)^-$ Exact mass:430.1. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.45 (s, 3 H), 2.39 (s, 3 H), 4.18 (d, J=6.4 Hz, 2 H), 4.62 (d, J=6.2 Hz, 2 H), 7.35 (d, J=8.1 Hz, 1 H), 7.45 (t, J=9.0 Hz, 1 H), 7.60 (ddd, J=9.0, 4.3, 2.5 Hz, 1 H), 7.79 (t, J=7.9 Hz, 1 H), 8.02 (dd, J=6.8, 2.6 Hz, 1 H), 8.63 (br. s., 1 H), 10.99 (s, 1 H)

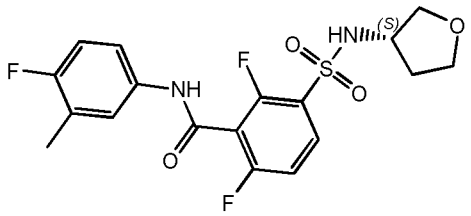
Compound **196**



Sodium carbonate (2.07 g, 19.48 mmol) was dissolved in distilled water (30 mL). To this was added (*S*)-3-aminotetrahydrofuran (3.4 g, 38.97 mmol) at once followed by THF (30 mL). The obtained solution was stirred and cooled in an ice bath. 3-(chlorosulfonyl)-2,6-difluorobenzoic acid (5 g, 19.48 mmol) was dissolved in THF (40 mL) and this was added drop wise to the stirring solution. The resulting mixture was stirred for 30 minutes while cooling was continued. Then the mixture was stirred for 3 hours at room temperature. The mixture was concentrated in vacuo until only water remained. Water (20 mL) was added and the mixture was acidified with HCl (1M / aq; 40 mL). This was extracted using Me-THF (3 x 50 mL). The combined organics were washed with of brine (50 mL), dried on Na_2SO_4, filtered and concentrated in vacuo yielding 2,6-difluoro-3-[[(3S)-tetrahydrofuran-3-yl]sulfamoyl]benzoic acid as a yellow powder (5.9 g). Method F, Rt: 0.33 min. m/z : 306.0 $(M-H)^-$ Exact mass: 307.0. 2,6-difluoro-3-[[(3S)-tetrahydrofuran-3-yl]sulfamoyl]benzoic acid (1 g, 2.99 mmol) was dissolved in N,N-dimethylformamide (5 mL). HATU (1.42 g, 3.74 mmol) was added followed by diisopropylethylamine (1.55 mL, 8.98 mmol). The resulting mixture was stirred for 30 minutes at room temperature. Then, 3,4-difluoroaniline (0.77 g, 5.99 mmol) was added. The resulting mixture was stirred for 24 hours and next poured in water (50 mL) and extracted using Me-THF (3 x 50 mL). The combined organics were washed with brine, dried on Na_2SO_4, filtered and concentrated in vacuo. The obtained residue was purified by silica gel column chromatography using gradient elution from heptane to EtOAc. (100:0 to 0:100). The desired fractions were concentrated in vacuo and dried in a vacuum oven at 55°C for 24 hours yielding compound **196**. Method F, Rt: 0.92 min. m/z : 417.1 $(M-H)^-$ Exact mass: 418.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.64 - 1.79 (m, 1 H), 1.92 - 2.07 (m, 1 H), 3.43 (dd, J=9.0, 4.6 Hz, 1 H), 3.56 - 3.79 (m, 3 H), 3.80 - 3.92 (m, 1 H), 7.32 - 7.43 (m, 1 H), 7.44 - 7.54 (m, 2 H), 7.84 (ddd, J=12.7, 7.4, 2.5 Hz, 1 H), 8.01 (td, J=8.6, 6.2 Hz, 1 H), 8.49 (br. s., 1 H), 11.21 (br. s., 1 H)

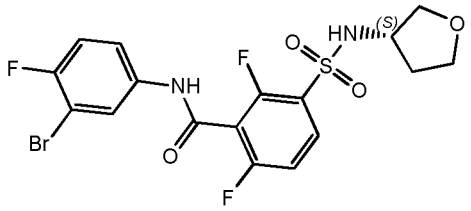
Compound **197** to **201** were prepared as described for compound **196**, using the corresponding aniline instead of 3,4-difluoroaniline:

Compound **197**



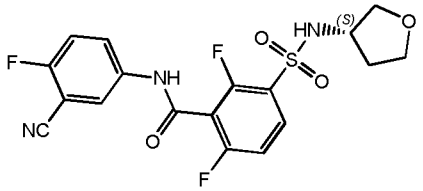
4-fluoro-3-methylaniline was used as aniline. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.64 - 1.76 (m, 1 H), 1.91 - 2.05 (m, 1 H), 2.25 (d, J=1.8 Hz, 3 H), 3.42 (dd, J=8.9, 4.7 Hz, 1 H), 3.56 - 3.78 (m, 3 H), 3.79 - 3.88 (m, 1 H), 7.16 (t, J=9.1 Hz, 1 H), 7.41 - 7.51 (m, 2 H), 7.60 (dd, J=7.0, 2.2 Hz, 1 H), 7.97 (td, J=8.6, 6.2 Hz, 1 H), 8.49 (br. s, 1 H), 10.93 (s, 1 H). Method F, Rt: 0.93 min. m/z : 413.2 (M-H)- Exact mass: 414.1

Compound **198**



3-bromo-4-fluoroaniline was used as aniline. Method G, Rt: 1.74 min. m/z : 478.8 $(M-H)^-$ Exact mass: 480.0. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.67 - 1.77 (m, 1 H), 1.93 - 2.05 (m, 1 H), 3.43 (dd, J=9.0, 4.6 Hz, 1 H), 3.57 - 3.78 (m, 3 H), 3.80 - 3.89 (m, 1 H), 7.43 (t, J=8.7 Hz, 1 H), 7.49 (m, J=8.7, 8.7 Hz, 1 H), 7.61 (ddd, J=9.0, 4.4, 2.6 Hz, 1 H), 8.00 (td, J=8.6, 6.2 Hz, 1 H), 8.11 (dd, J=6.3, 2.5 Hz, 1 H), 8.49 (br. s., 1 H), 11.19 (br. s., 1 H)

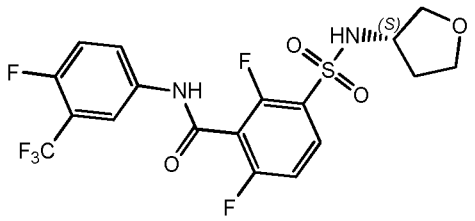
Compound **199**



5-amino-2-fluorobenzonitrile was used as aniline

Method G, Rt: 1.56 min. m/z : 423.9 $(M-H)^-$ Exact mass: 425.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.65-1.80 (m, 1 H), 1.94 - 2.06 (m, 1 H), 3.43 (dd, J=9.0, 4.6 Hz, 1 H), 3.57 - 3.78 (m, 3 H), 3.80 - 3.91 (m, 1 H), 7.49 (t, J=8.5 Hz, 1 H), 7.59 (t, J=9.1 Hz, 1 H), 7.94 (ddd, J=9.2, 4.8, 2.6 Hz, 1 H), 8.02 (td, J=8.6, 6.2 Hz, 1 H), 8.19 (dd, J=5.7, 2.9 Hz, 1 H), 8.50 (br. s., 1 H), 11.37 (br. s., 1 H).

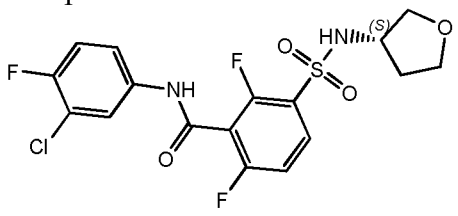
Compound **200**



4-fluoro-3-(trifluoromethyl)aniline was used as aniline

Method F, Rt: 1.02 min. m/z : 467.1 (M-H)- Exact mass: 468.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.72 (ddt, J=12.6, 7.2, 5.6, 5.6 Hz, 1 H), 1.93 - 2.08 (m, 1 H), 3.43 (dd, J=9.0, 4.6 Hz, 1 H), 3.58 - 3.79 (m, 3 H), 3.80 - 3.91 (m, 1 H), 7.49 (t, J=8.4 Hz, 1 H), 7.58 (t, J=9.7 Hz, 1 H), 7.93 (s, 1 H), 8.02 (td, J=8.6, 6.2 Hz, 1 H), 8.16 (dd, J=6.4, 2.6 Hz, 1 H), 8.50 (br. s., 1 H), 11.35 (br. s., 1 H)

Compound **201**

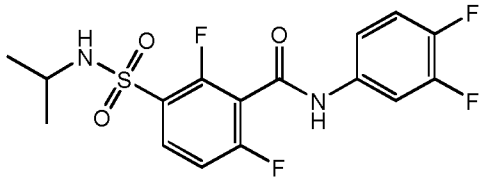


3-chloro-4-fluoroaniline was used as aniline.

Method F, Rt: 0.97 min. m/z: 433.1 (M-H)- Exact mass: 434.0. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.72 (ddt, J=12.5, 7.2, 5.6, 5.6 Hz, 1 H), 1.92 - 2.12 (m, 1 H), 3.43 (dd, J=8.8, 4.6 Hz, 1 H), 3.55 - 3.79 (m, 3 H), 3.80 - 3.91 (m, 1 H), 7.35 - 7.52 (m, 2 H), 7.53 - 7.67 (m, 1 H), 7.90 - 8.12 (m, 2 H), 8.49 (br. s., 1 H), 11.20 (br. s., 1 H)

Compound **202** and **203** were prepared similarly as described for compound **196**, using isopropyl amine instead of (*S*)-3-aminotetrahydrofuran and for compound **203**, using 3-(trifluoromethyl)aniline instead of 3,4-difluoroaniline.

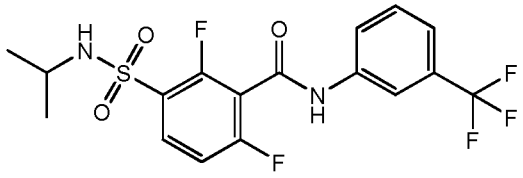
Compound **202**



Method G, Rt: 1.80 min. m/z : 388.9 (M-H)- Exact mass: 390.1.

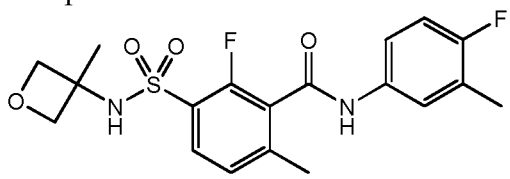
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.03 (d, J=6.6 Hz, 8 H), 3.34 - 3.46 (m, 1 H), 7.36 - 7.53 (m, 3 H), 7.84 (ddd, J=12.7, 7.4, 2.5 Hz, 1 H), 8.00 (td, J=8.6, 6.2 Hz, 1 H), 8.09 (br. s., 1 H), 11.20 (br. s., 1 H)

Compound **203**



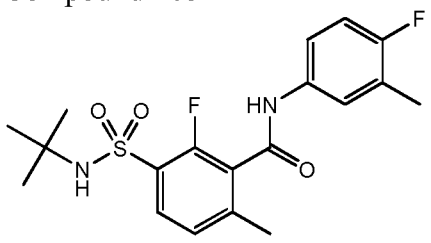
Method G, Rt: 1.82 min. m/z : 421.1 (M-H)- Exact mass: 422.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.04 (d, J=6.6 Hz, 6 H), 3.34 - 3.46 (m, 1 H), 7.47 (t, J=8.6 Hz, 1 H), 7.54 (d, J=7.9 Hz, 1 H), 7.65 (t, J=7.9 Hz, 1 H), 7.87 (d, J=8.4 Hz, 1 H), 8.01 (td, J=8.6, 6.2 Hz, 1 H), 8.11 (d, J=7.5 Hz, 1 H), 8.15 (s, 1 H), 11.32 (s, 1 H).

Compound **204**



Compound **204** (0.19 g) was prepared starting from compound **190** (0.34 g), similar as described for the conversion of compound **187** to compound **188**. Compound **204** was crystallised from Et_2O, filtered off, washed with 3x Et_2O, and dried at 50°C in vacuo. Method F; Rt: 0.94 min. m/z: 409.1 $(M-H)^-$ Exact mass:410.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.46 (s, 3 H), 2.24 (d, J=1.8 Hz, 3 H), 2.38 (s, 3 H), 4.18 (d, J=6.6 Hz, 2 H), 4.62 (d, J=6.2 Hz, 2 H), 7.14 (dd, J=9.1 Hz, 1 H), 7.33 (d, J=8.1 Hz, 1 H), 7.45 - 7.53 (m, 1 H), 7.63 (dd, J=7.0, 2.2 Hz, 1 H), 7.77 (t, J=7.9 Hz, 1 H), 8.61 (br. s., 1 H), 10.72 (s, 1 H).

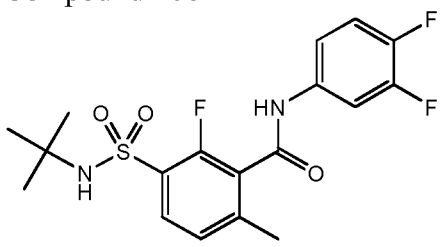
Compound **205**



3-(tert-butylsulfamoyl)-2-fluoro-6-methyl-benzoic acid was prepared similarly as described for 2-fluoro-6-methyl-3-[(3-methyloxetan-3-yl)sulfamoyl]benzoic acid, using tert-butylamine instead of 3-methyloxetan-3-amine. Compound **205** was prepared similar as described for compound **194**, using 4-fluoro-3-methylaniline instead of 3,4-difluoroaniline and starting from 3-(tert-butylsulfamoyl)-2-fluoro-6-methyl-benzoic acid instead of 2-fluoro-6-methyl-3-[(3-methyloxetan-3-yl)sulfamoyl]benzoic acid. Method F; Rt: 1.08 min. m/z: 395.2 $(M-H)^-$ Exact mass: 396.1.^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.16 (s, 9 H), 2.24 (d, J=1.8 Hz, 3 H), 2.37 (s, 3 H), 7.14 (t, J=9.2

Hz, 1 H), 7.30 (d, J=8.1 Hz, 1 H), 7.50 (ddd, J=9.0, 4.7, 2.3 Hz, 1 H), 7.64 (dd, J=6.9, 2.3 Hz, 1 H), 7.73 - 7.84 (m, 2 H), 10.70 (br. s, 1 H).

Compound **206**



Compound **206** was prepared similar as described for for compound **194**, starting from 3-(tert-butylsulfamoyl)-2-fluoro-6-methyl-benzoic acid instead of 2-fluoro-6-methyl-3-[(3-methyloxetan-3-yl)sulfamoyl]benzoic acid. Method F; Rt: 1.08 min. m/z: 399.1 $(M-H)^-$ Exact mass:400.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.16 (s, 9 H), 2.31 (s, 3 H), 7.32 (d, J=8.1 Hz, 1 H), 7.40 - 7.51 (m, 2 H), 7.76 - 7.82 (m, 2 H), 7.88 (ddd, J=13.0, 7.5, 2.4 Hz, 1 H), 10.97 (br. s., 1 H)

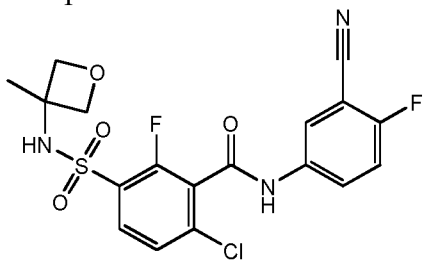
Synthesis of 6-chloro-2-fluoro-3-[(3-methyloxetan-3-yl)sulfamoyl]benzoic acid and 2-chloro-6-fluoro-3-[(3-methyloxetan-3-yl)sulfamoyl]benzoic acid

2-chloro-6-fluorobenzoic acid (2 g, 11.46 mmol) was treated with chlorosulfonic acid (10 mL, 150.44 mmol) and this was heated to 100°C and stirred for 5 hours. The resulting mixture was cooled to room temperature and added dropwise to ice-water (1 liter). This was then extracted using dichloromethane (2 x 500 mL). The combined organics were dried on Na_2SO_4, filtered and concentrated in vacuo yielding an isomeric mixture of 2-chloro-3-chlorosulfonyl-6-fluoro-benzoic acid and 6-chloro-3-chlorosulfonyl-2-fluoro-benzoic acid (3.1 gram) as a slightly yellow powder which was used as such.Method F, Rt: 0.47 min and 0.49 min. m/z : 270.9 (M-H)- Exact mass: 271.9. Sodium carbonate (1.21 g, 11.4 mmol) was dissolved in distilled water (22 mL). To this was added 3-methyl-3-oxetanamine (1.19 g, 13.68 mmol) at once followed by THF (20 mL). The obtained solution was stirred and cooled in an ice bath. An isomeric mixture of 2-chloro-3-chlorosulfonyl-6-fluoro-benzoic acid and 6-chloro-3-chlorosulfonyl-2-fluoro-benzoic acid (3.1 g, 11.4 mmol) was dissolved in THF (30 mL) and this was added drop wise to the stirring solution. The resulting mixture was stirred for 30 minutes while cooling was continued. Then, the mixture was stirred for 3 hours at room temperature.The mixture was concentrated in vacuo untill only water remained. Then water (20 mL) was added and the mixture was acidified with HCl (46 mL, 1M / aq). This was extracted using Me-THF (3 X 50 mL). The combined organics were dried on Na_2SO_4, filtered and concentrated in vacuo. The residue was purified, and isomers

were separated using preparative HPLC (Stationary phase: Uptisphere C18 ODB - 10µm, 200g, 5cm), Mobile phase: 0.25% NH_4HCO_3 solution in water, MeOH) , yielding 6-chloro-2-fluoro-3-[(3-methyloxetan-3-yl)sulfamoyl]benzoic acid as a white powder. Method G, Rt: 0.40 min. m/z : 322.0 $(M-H)^-$ Exact mass: 323.0. 1H NMR (400 MHz, DMSO-d) ppm 1.42 (s, 3 H), 4.15 (d, J=6.6 Hz, 2 H), 4.61 (d, J=5.9 Hz, 13 H), 7.29 (dd, J=8.5, 0.8 Hz, 1 H), 7.36 - 7.73 (m, 5 H).
and 2-chloro-6-fluoro-3-[(3-methyloxetan-3-yl)sulfamoyl]benzoic acid as a white powder. Method G, Rt: 0.34 min. m/z : 321.9 $(M-H)^-$ Exact mass: 323.0

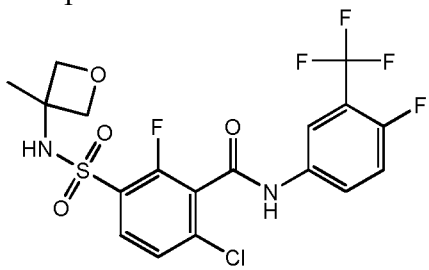
Compound **207** to **210** were prepared similarly as described for compound **196** using 6-chloro-2-fluoro-3-[(3-methyloxetan-3-yl)sulfamoyl]benzoic acid instead of 2,6-difluoro-3-[[(3*S*)-tetrahydrofuran-3-yl]sulfamoyl]benzoic acid and the corresponding aniline instead of 3,4-difluoroaniline.

Compound **207**



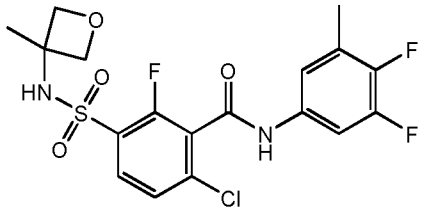
Using 5-amino-2-fluorobenzonitrile as aniline. Method F, Rt: 0.92 min. m/z : 440.0 $(M-H)^-$ Exact mass: 441.0. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.46 (s, 2 H), 4.21 (d, J=6.4 Hz, 2 H), 4.61 (d, J=6.2 Hz, 2 H), 7.59 (t, J=9.1 Hz, 1 H), 7.66 (d, J=8.8 Hz, 1 H), 7.89 - 7.99 (m, 2 H), 8.18 (dd, J=5.6, 2.8 Hz, 1 H), 8.93 (br. s, 1 H), 11.37 (br. s., 1 H)

Compound **208**



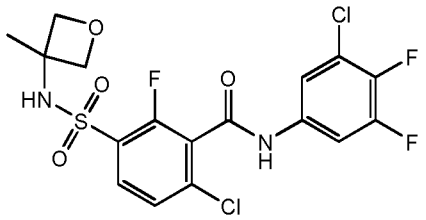
Using 4-fluoro-3-(trifluoromethyl)aniline as aniline. Method F, Rt: 1.06 min. m/z : 483 $(M-H)^-$ Exact mass: 484.0. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.46 (s, 2 H), 4.20 (d, J=6.2 Hz, 2 H), 4.61 (d, J=6.2 Hz, 2 H), 7.58 (t, J=9.9 Hz, 1 H), 7.66 (d, J=8.6 Hz, 1 H), 7.94 (m, J=8.1, 8.1 Hz, 2 H), 8.07 - 8.25 (m, 1 H), 8.91 (br. s, 1 H), 11.34 (br. s., 1 H)

Compound **209**



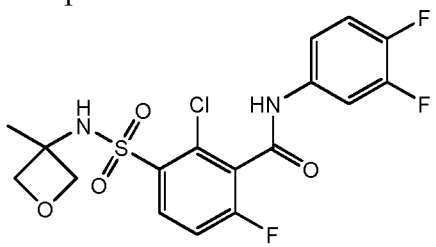
Using 3,4-difluoro-5-methyl-aniline as aniline. Method F, Rt: 1.03 min. m/z : 447.1 $(M-H)^-$ Exact mass: 448.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.45 (s, 3 H), 2.30 (d, J=2.0 Hz, 3 H), 4.20 (d, J=6.4 Hz, 2 H), 4.61 (d, J=6.2 Hz, 2 H), 7.32 (m, J=5.9 Hz, 1 H), 7.54 - 7.69 (m, 2 H), 7.91 (t, J=8.3 Hz, 1 H), 8.92 (br. s, 1 H), 11.09 (br. s, 1 H)

Compound **210**



Using 3-chloro-4,5-difluoro-aniline hydrochloride as aniline. Method F, Rt: 1.07 min. m/z : 467.0 $(M-H)^-$ Exact mass: 468.0. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.45 (s, 3 H), 4.20 (d, J=6.6 Hz, 2 H), 4.60 (d, J=6.2 Hz, 2 H), 7.64 (d, J=8.6 Hz, 1 H), 7.67 - 7.79 (m, 2 H), 7.93 (t, J=8.1 Hz, 1 H), 9.08 (br. s, 1 H), 11.34 (br. s., 1 H)

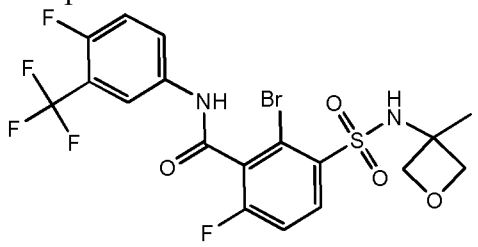
Compound **211**



Compound **211** was prepared similarly as described for compound **196** using 2-chloro-6-fluoro-3-[(3-methyloxetan-3-yl)sulfamoyl]benzoic acid instead of 2,6-difluoro-3-[[(3*S*)-tetrahydrofuran-3-yl]sulfamoyl]benzoic acid. Method F, Rt: 0.94 min. m/z : 433.1 $(M-H)^-$ Exact mass: 434.0. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.46 (s, 3 H), 4.20 (d, J=6.6 Hz, 2 H), 4.62 (d, J=6.4 Hz, 2 H), 7.30 - 7.43 (m, 1 H), 7.43 - 7.54 (m, 1 H), 7.61 (t, J=8.6 Hz, 1 H), 7.84 (ddd, J=12.7, 7.4, 2.3 Hz, 1 H), 8.17 (dd, J=9.0, 5.9 Hz, 1 H), 8.75 (br. s, 1 H), 11.18 (br. s, 1 H).

2-bromo-6-fluoro-3-[(3-methyloxetan-3-yl)sulfamoyl]benzoic acid and 6-bromo-2-fluoro-3-[(3-methyloxetan-3-yl)sulfamoyl]benzoic acid were prepared similarly as described for 2-chloro-6-fluoro-3-[(3-methyloxetan-3-yl)sulfamoyl]benzoic acid and 6-chloro-2-fluoro-3-[(3-methyloxetan-3-yl)sulfamoyl]benzoic acid, starting from 2-bromo-6-fluorobenzoic acid instead of 2-chloro-6-fluorobenzoic acid.

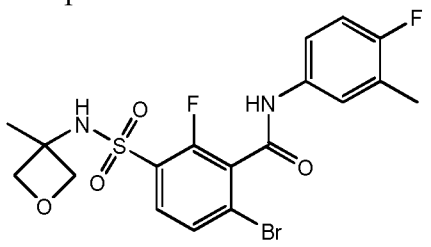
Compound **212**



Compound **212** was prepared similarly as described for compound **196** using 2-bromo-6-fluoro-3-[(3-methyloxetan-3-yl)sulfamoyl]benzoic acid instead of 2,6-difluoro-3-[[(3*S*)-tetrahydrofuran-3-yl]sulfamoyl]benzoic acid and 4-fluoro-3-(trifluoromethyl)aniline instead of 3,4-difluoroaniline. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.48 (s, 3 H), 4.20 (d, J=6.6 Hz, 2 H), 4.64 (d, J=6.2 Hz, 2 H), 7.57 (t, J=9.7 Hz, 1 H), 7.65 (t, J=8.6 Hz, 1 H), 7.93 (dt, J=8.4, 3.7 Hz, 1 H), 8.08 - 8.31 (m, 2 H), 8.70 (br. s., 1 H), 11.29 (br. s., 1 H).

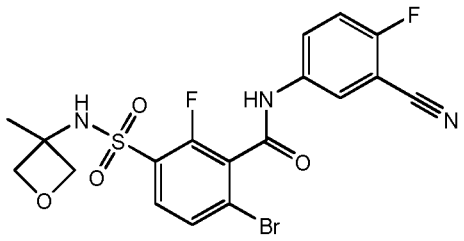
Compound **213** to **216** were prepared similarly as described for compound **196** using 6-bromo-2-fluoro-3-[(3-methyloxetan-3-yl)sulfamoyl]benzoic acid instead of 2,6-difluoro-3-[[(3*S*)-tetrahydrofuran-3-yl]sulfamoyl]benzoic acid the corresponding aniline instead of 3,4-difluoroaniline.

Compound **213**



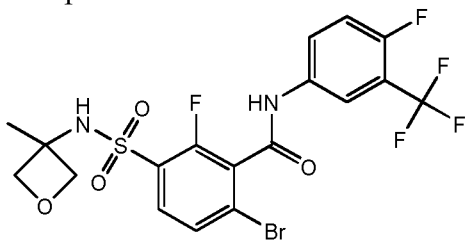
Using 4-fluoro-3-methylaniline as aniline. Method F, Rt: 0.99 min. m/z: 473.0 $(M-H)^-$ Exact mass: 474.0. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.46 (s, 3 H), 2.25 (d, J=1.5 Hz, 3 H), 4.20 (d, J=6.4 Hz, 2 H), 4.62 (d, J=6.2 Hz, 2 H), 7.16 (t, J=9.1 Hz, 1 H), 7.42 - 7.52 (m, 1 H), 7.60 (dd, J=7.0, 2.4 Hz, 1 H), 7.68 - 7.93 (m, 2 H), 8.65 (br. s, 1 H), 10.82 (br. s, 1 H).

Compound **214**



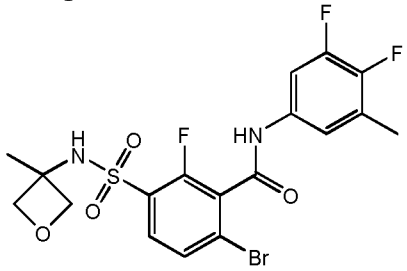
Using 5-amino-2-fluorobenzonitrile as aniline. Method F, Rt: 0.92 min. m/z : 484.0 $(M-H)^-$ Exact mass: 485.0. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.39 - 1.55 (m, 3 H), 4.20 (d, J=6.6 Hz, 2 H), 4.61 (d, J=6.4 Hz, 2 H), 7.59 (t, J=9.1 Hz, 1 H), 7.77 - 7.89 (m, 2 H), 7.95 (ddd, J=9.2, 4.8, 2.8 Hz, 1 H), 8.18 (dd, J=5.7, 2.6 Hz, 1 H), 8.90 (br. s, 1 H), 11.34 (br. s., 1 H).

Compound **215**



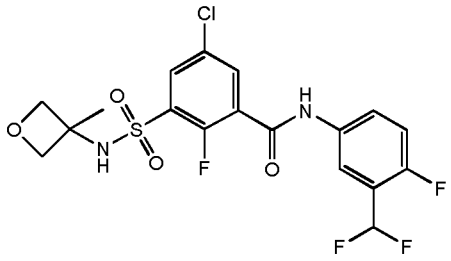
Using 4-fluoro-3-(trifluoromethyl)aniline as aniline. Method F,Rt: 1.07 min. m/z : 527.0 $(M-H)^-$ Exact mass: 528.0. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.46 (s, 3 H), 4.20 (d, J=6.6 Hz, 2 H), 4.61 (d, J=6.2 Hz, 2 H), 7.58 (t, J=9.8 Hz, 1 H), 7.74 - 7.89 (m, 2 H), 7.90 - 7.98 (m, 1 H), 8.16 (dd, J=6.3, 2.5 Hz, 1 H), 8.84 (br. s, 1 H), 11.31 (br. s., 1 H).

Compound **216**



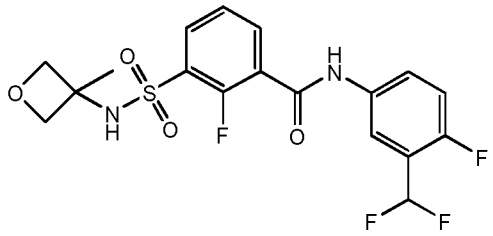
Using 3,4-difluoro-5-methyl-aniline as aniline. Method F, Rt: 1.03 min. m/z : 491.0 $(M-H)^-$ Exact mass: 492.0. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.46 (s, 3 H), 2.30 (d, J=1.8 Hz, 3 H), 4.20 (d, J=6.6 Hz, 2 H), 4.61 (d, J=6.4 Hz, 2 H), 7.32 (m, J=5.7 Hz, 1 H), 7.61 (ddd, J=12.3, 6.9, 2.6 Hz, 1 H), 7.72 - 7.89 (m, 2 H), 8.86 (br. s., 1 H), 11.07 (br. s, 1 H).

Compound **217**



A solution of 3-(difluoromethyl)-4-fluoro-aniline (1.02 mL, 8.58 mmol) in dry toluene (10 mL) was added dropwise (over 15 min) to a refluxing solution of 5-chloro-3-chlorosulfonyl-2-fluoro-benzoyl chloride (2500 mg, 8.576 mmol) in dry toluene (100 mL). After the addition, the reaction mixture was left to stir at reflux for 1 h. The reaction mixture was left to cool to room temperature under nitrogen atmosphere while stirring.The brown solution containing 5-chloro-3-[[3-(difluoromethyl)-4-fluoro-phenyl]carbamoyl]-2-fluoro-benzenesulfonyl chloride was used without further purification. 3-methyl-3-oxetanamine (580 mg, 6.66 mmol) was added dropwise to the above solution at room temperature. Et_3N (2.10 mL 15.14 mmol) was then added dropwise to the reaction mixture and the reaction mixture was stirred at room temperature for 45 minutes. The solvent was evaporated and the residue was taken up in EtOAc. HCl (0.5 N, 30 mL) was added to the reaction mixture and the layers were separated. The organic layer was washed again with NaOH (0.5 N, 30 mL).
The organic layer was dried on $MgSO_4$ and was evaporated. The obtained residue was purified by silica gel column chromatography (eluent: CH_2Cl_2:MeOH 100:0 -> 95:5), resulting in compound **217** (1.8 g). ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 1.45 (s, 3 H) 4.23 (d, J=6.2 Hz, 2 H) 4.63 (d, J=6.2 Hz, 2 H) 7.27 (t, J=54.3 Hz, 1 H) 7.43 (t, J=9.7 Hz, 1 H) 7.83 (dt, J=8.1, 4.0 Hz, 1 H) 7.95 (dd, J=5.9, 2.6 Hz, 1 H) 8.04 (dd, J=6.0, 2.4 Hz, 1 H) 8.13 (dd, J=5.3, 2.7 Hz, 1 H) 8.98 (s, 1 H) 10.98 (s, 1 H)
Method F, Rt: 1.03 min. m/z : 465.1 $(M-H)^-$ Exact mass: 466.0.

Compound **218**

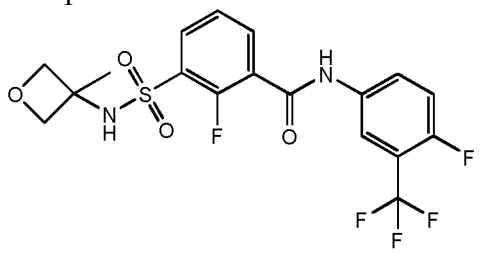


Pd/C (10%) (716 mg) was suspended in a solution of compound **217** (345 mg, 0.673 mmol) and Et_3N (0.467 mL) in MeOH (100 mL) at room temperature under nitrogen atmosphere.The reaction mixture was next stirred at room temperature under an

atmosphere of hydrogen until one equivalent of hydrogen was absorbed.The reaction mixture was filtered on decalite and the solvent was evaporated.The obtained residue was purified by silica gel column chromatography (CH_2Cl_2:MeOH 100:0 -> 95:5) resulting in compound **218** (206 mg) as a white solid, dried in vacuo at 50 °C.

^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 1.44 (s, 3 H) 4.19 (d, J=6.6 Hz, 2 H) 4.63 (d, J=6.2 Hz, 2 H) 7.26 (t, J=54.3 Hz, 1 H) 7.42 (t, J=9.5 Hz, 1 H) 7.52 (t, J=7.7 Hz, 1 H) 7.86 (dd, J=8.1, 3.7 Hz, 1 H) 7.93 - 8.01 (m, 2 H) 8.06 (dd, J=6.4, 2.4 Hz, 1 H) 8.77 (s, 1 H) 10.92 (s, 1 H). Method F, Rt: 0.92 min. m/z : 431.1 $(M-H)^-$ Exact mass: 432.1.

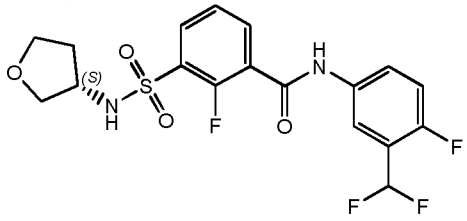
Compound **219**



Compound **219** (828 mg), was prepared similar as described for compound **217** and **218**. Using 4-fluoro-3-(trifluoromethyl)aniline instead of 3-(difluoromethyl)-4-fluoro-aniline. Method F, Rt: 1.00 min. m/z : 449.1 $(M-H)^-$ Exact mass: 450.1.

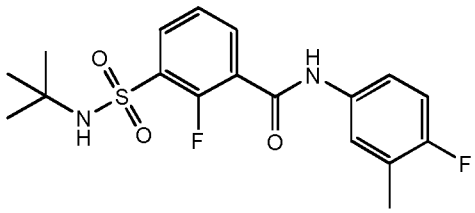
^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 1.44 (s, 3 H) 4.19 (d, J=5.9 Hz, 2 H) 4.62 (d, J=6.2 Hz, 2 H) 7.53 (t, J=7.9 Hz, 1 H) 7.57 (t, J=9.9 Hz, 1 H) 7.94 - 8.02 (m, 3 H) 8.20 (dd, J=6.4, 2.7 Hz, 1 H) 8.78 (s, 1 H) 11.02 (s, 1 H).

Compound **220**



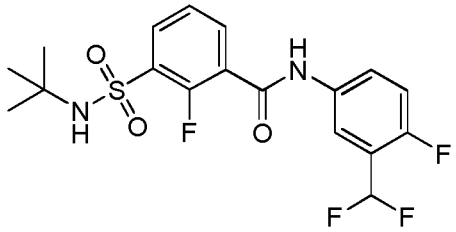
Compound **220** was prepared similar as described for compound **217** and **218**, using (*S*)-3-aminotetrahydrofuran instead of 3-methyl-3-oxetanamine. Method F, Rt: 0.90 min. m/z : 431.1 $(M-H)^-$ Exact mass: 432.1. ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 1.66 - 1.77 (m, 1 H) 1.91 - 2.03 (m, 1 H) 3.43 (dd, J=8.8, 4.8 Hz, 1 H) 3.57 - 3.70 (m, 2 H) 3.70 - 3.78 (m, 1 H) 3.79 - 3.90 (m, 1 H) 7.26 (t, J=54.2 Hz, 1 H) 7.42 (t, J=9.5 Hz, 1 H) 7.53 (t, J=7.7 Hz, 1 H) 7.81 - 7.88 (m, 1 H) 7.94 - 8.00 (m, 2 H) 8.07 (dd, J=6.4, 2.4 Hz, 1 H) 8.45 (d, J=6.6 Hz, 1 H) 10.92 (s, 1 H).

Compound **221**



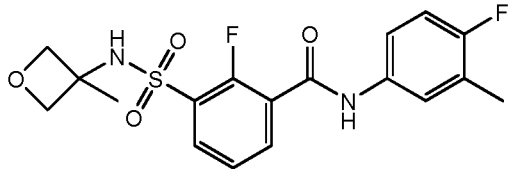
Compound **221** was prepared similar as described for compound **217** and **218**, using 2-methylpropan-2-amine instead of 3-methyl-3-oxetanamine, and 4-fluoro-3-methyl-aniline instead of 3-(difluoromethyl)-4-fluoro-aniline Method F, Rt: 1.06 min. m/z : 381.2 $(M-H)^-$ Exact mass: 382.1. 1 H NMR (360 MHz, DMSO-d_6) δ ppm 1.15 (s, 9 H) 2.24 (d, J=1.5 Hz, 3 H) 7.15 (t, J=9.1 Hz, 1 H) 7.47 (t, J=7.7 Hz, 1 H) 7.43 - 7.55 (m, 1 H) 7.65 (dd, J=7.0, 2.6 Hz, 1 H) 7.87 (ddd, J=7.8, 6.1, 1.8 Hz, 1 H) 7.93 (s, 1 H) 7.90 - 7.99 (m, 1 H) 10.63 (s, 1 H).

Compound **243**



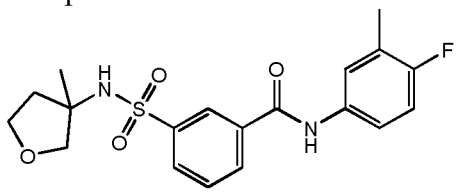
Compound **243** was prepared similar as described for compound **217** and **218**, using tert-butylamine instead of 3-methyl-3-oxetanamine. Method G, Rt: 1.76 min. m/z : 417.1 $(M-H)^-$ Exact mass: 418.1. ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 1.15 (s, 9 H) 7.41 (t, J=9.7 Hz, 1 H) 7.26 (t, J=54.5 Hz, 1 H) 7.49 (t, J=7.7 Hz, 1 H) 7.85 (ddd, J=8.6, 4.4, 3.1 Hz, 1 H) 7.88 - 8.01 (m, 3 H) 8.08 (dd, J=6.2, 2.6 Hz, 1 H) 10.90 (s, 1 H).

Compound **222**



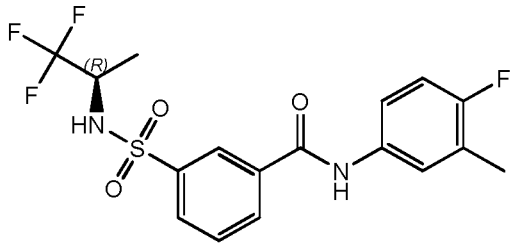
Compound **222** was prepared similar as described for compound **221**, using 3-methyl-3-oxetanamine instead of 2-methylpropan-2-amine. Method F, Rt: 0.91 min. m/z : 395.1 $(M-H)^-$ Exact mass: 396.1. ^{1} H NMR (360 MHz, DMSO-d_6) δ ppm 1.44 (s, 3 H) 2.24 (d, J=1.5 Hz, 3 H) 4.19 (d, J=6.6 Hz, 2 H) 4.62 (d, J=6.2 Hz, 2 H) 7.15 (t, J=9.3 Hz, 1 H) 7.46 - 7.55 (m, 2 H) 7.63 (dd, J=7.0, 2.6 Hz, 1 H) 7.88 - 7.99 (m, 2 H) 8.75 (s, 1 H) 10.65 (s, 1 H).

Compound **223**



3-methyloxolan-3-amine hydrochloride (165.9 mg, 1.21 mmol) was added to a solution of 3-[(4-fluoro-3-methyl-phenyl)carbamoyl]benzenesulfonyl chloride (499 mg, 1.096 mmol) in dry CH_2Cl_2 (20 mL) at room temperature. Et_3N (381 µL) was then added dropwise to the reaction mixture and the reaction mixture was stirred at room temperature for 1 hour.The reaction mixture was diluted with EtOAc (250 mL). HCl 0.5 N (50 mL) was added and the layers were separated. The organic layer was washed again with NaOH 0.5 N (30 mL). The organic layer was dried on $MgSO_4$ and was evaporated. The obtained residue was purified t by silica gel column chromatography (CH_2Cl_2:MeOH 100:0 -> 95:5) and by preparative HPLC (Stationary phase: RP XBridge Prep C18 OBD-10µm,30x150mm), Mobile phase: 0.25% NH_4HCO_3 solution in water, MeOH) resulting in compound **223** (257 mg) as a white solid after drying in vacuo at 50°C. Method F, Rt: 0.93 min. m/z : 391.2 $(M-H)^-$ Exact mass: 392.1.[1] H NMR (360 MHz, DMSO-d_6) ppm 1.17 (s, 3 H) 1.72 (dt, J=12.8, 7.7 Hz, 1 H) 2.14 (ddd, J=12.8, 7.1, 6.0 Hz, 1 H) 2.25 (d, J=1.8 Hz, 3 H) 3.30-3.40 (m, 1 H) 3.61 - 3.77 (m, 3 H) 7.15 (t, J=9.3 Hz, 1 H) 7.55 - 7.64 (m, 1 H) 7.69 (dd, J=7.0, 2.2 Hz, 1 H) 7.75 (t, J=7.9 Hz, 1 H) 8.04 (d, J=8.0 Hz, 1 H) 8.10 (br. s., 1 H) 8.18 (dt, J=7.7, 1.3 Hz, 1 H) 8.39 (t, J=1.6 Hz, 1 H) 10.49 (br. s., 1 H).

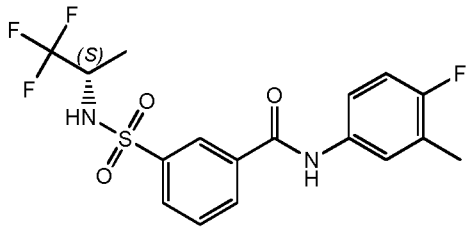
Compound **225**



3-[(4-fluoro-3-methyl-phenyl)carbamoyl]benzenesulfonyl chloride (0.5 g, 1.53 mmol) and (*R*)-1,1,1-trifluoro-2-propylamine (0.38 g, 3.36 mmol) were dissolved in of dichloromethane (10 mL). Then diisopropylethylamine (0.66 mL, 3.81 mmol) was added and the resulting mixture was stirred for two hours. Then 1M HCl (5 mL) was added and the organic layer was separated, loaded on silica and subjected to silica gel column chromatography using gradient elution from heptane to EtOAc. (100:0 to 0:100). The desired fractions were concentrated in vacuo and dried in a vacuum oven at 55°C for 24 hours compound **225** (233 mg) as a white powder. Method F, Rt: 1.05 min.

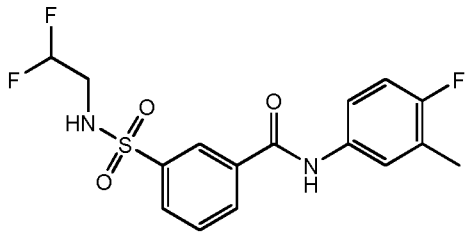
m/z : 403.1 $(M-H)^-$ Exact mass: 404.1. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.01 (d, J=6.8 Hz, 3 H), 2.25 (d, J=1.8 Hz, 3 H), 4.06 - 4.22 (m, 1 H), 7.15 (t, J=9.2 Hz, 1 H), 7.51 - 7.63 (m, 1 H), 7.67 (dd, J=7.2, 2.3 Hz, 1 H), 7.78 (t, J=7.8 Hz, 1 H), 8.00 - 8.10 (m, 1 H), 8.16 - 8.28 (m, 1 H), 8.40 (t, J=1.7 Hz, 1 H), 8.66 (br. s., 1 H), 10.46 (s, 1 H).

Compound **226**



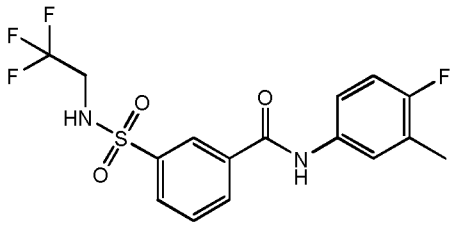
Compound **226** (416 mg) was prepared as described for compound **225**, using (*S*)-1,1,1-trifluoro-2-propylamine instead of (*R*)-1,1,1-trifluoro-2-propylamine. Method F, Rt: 1.05 min. m/z : 403.1 $(M-H)^-$ Exact mass: 404.1.

Compound **227**



Compound **227** (444 mg) was prepared similarly as described in synthetic procedure S3 (using 2,2-difluoroethylamine as amine), workup W4. Method F, Rt: 0.93 min. m/z : 371.1 $(M-H)^-$ Exact mass: 372.1. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.25 (d, J=1.8 Hz, 3 H), 3.26 (td, J=15.8, 3.7 Hz, 2 H), 6.00 (tt, J=55.2, 3.5 Hz, 1 H), 7.14 (t, J=9.0 Hz, 1 H), 7.52 - 7.62 (m, 1 H), 7.63 - 7.70 (m, 1 H), 7.77 (t, J=7.9 Hz, 1 H), 7.96 - 8.06 (m, 1 H), 8.14 - 8.25 (m, 1 H), 8.30-8.45 (m, 2 H), 10.46 (s, 1 H)

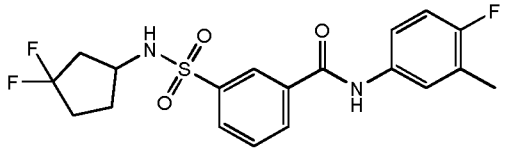
Compound **228**



Compound **228** (238 mg) was prepared similarly as described in synthetic procedure S3

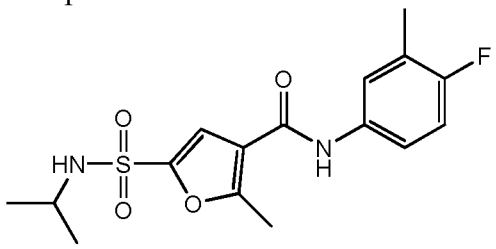
(using 2,2-difluoroethylamine as amine), workup W4, followed by preparative HPLC (SunFire Prep C18 OBD-10µm,30x150mm). Mobile phase (0.25% NH_4HCO_3 solution in water, MeOH). Method F, Rt: 0.97 min. m/z : 389.1 $(M-H)^-$ Exact mass: 390.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.25 (d, J=1.8 Hz, 3 H), 3.74 (q, J=9.5 Hz, 2 H), 7.15 (t, J=9.2 Hz, 1 H), 7.48 - 7.62 (m, 1 H), 7.64 - 7.71 (m, 1 H), 7.77 (t, J=7.8 Hz, 1 H), 7.94 - 8.10 (m, 1 H), 8.20 (m, J=8.1 Hz, 1 H), 8.37 (t, J=1.7 Hz, 1 H), 8.49 - 9.15 (bs, 1 H), 10.45 (s, 1 H)

Compound **229**



Compound **243** (239 mg) was prepared similar to synthetic procedure S2 (using 3,3-difluoro-cyclopentanamine as amine), workup W4. Method F, Rt: 1.03 min. m/z : 411.2 $(M-H)^-$ Exact mass: 412.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.50-1.165 (m, 1 H), 1.81 - 2.04 (m, 3 H), 2.04 - 2.23 (m, 2 H), 2.25 (s, 3 H), 3.63 - 3.76 (m, 1 H), 7.14 (t, J=9.1 Hz, 1 H), 7.59 (dt, J=8.1, 3.9 Hz, 1 H), 7.65 - 7.72 (m, 1 H), 7.78 (t, J=7.8 Hz, 1 H), 8.02 (d, J=7.9 Hz, 1 H), 8.14 (d, J=6.8 Hz, 1 H), 8.22 (d, J=7.7 Hz, 1 H), 8.37 (s, 1 H), 10.47 (s, 1 H).

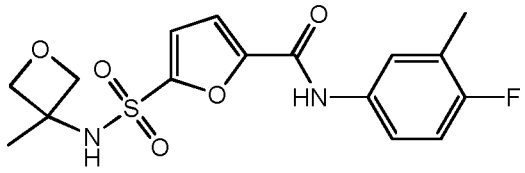
Compound **230**



2-methyl-3-furoic acid (4.2 g, 32.6 mmol) was dissolved in CH_2Cl_2 (100 mL) and cooled with an ice-bath to -5°C. Then chlorosulfonic acid (10.85 mL, 163.2 mmol) was added dropwise at a rate of 0.250 mL/min. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was quenched on ice and extracted with 2-MeTHF. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated to dryness yielding crude 5-chlorosulfonyl-2-methyl-furan-3-carboxylic acid (420 mg) as a brown oil. 5-chlorosulfonyl-2-methyl-furan-3-carboxylic acid (420 mg) was dissolved in CH_2Cl_2 (10 mL). Hunig's base (0.64 mL, 3.74 mmol) and isopropylamine (0.478 mL, 5.61 mmol) were added and the reaction mixture was stirred overnight at room temperature. The volatiles were removed under reduced pressure and the residue was used as such in the next step. The above residue

was dissolved in CH_2Cl_2 (20 mL), 4-fluoro-3-methylaniline (228 mg, 1.82 mmol), HATU (830 mg, 2.18 mmol) and N,N-diisopropylethylamine (0.94 mL, 5.46 mmol) were added and the reaction mixture was stirred for 30 minutes. The volatiles were removed under reduced pressure and the residue was purified on silica using a heptane to EtOAc gradient resulting in compound **230** (174 mg) as a white powder. Method F, Rt: 1.00 min. m/z : 353.1 $(M-H)^-$ Exact mass: 354.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.03 (d, J=6.4 Hz, 6 H), 2.23 (s, 3 H), 2.64 (s, 3 H), 3.35 - 3.43 (m, 1 H), 7.11 (t, J=9.2 Hz, 1 H), 7.53 (dd, J=7.9, 4.0 Hz, 1 H), 7.59 - 7.69 (m, 1 H), 7.72 (s, 1 H), 8.06 (d, J=5.5 Hz, 1 H), 9.87 (s, 1 H).

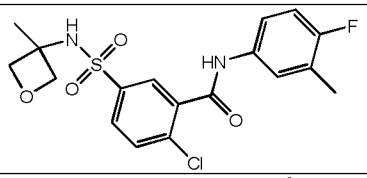
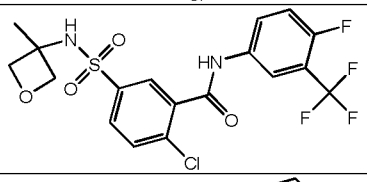
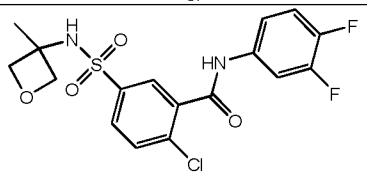
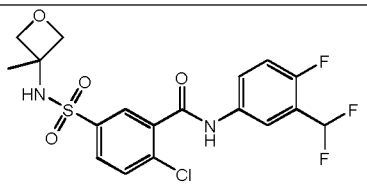
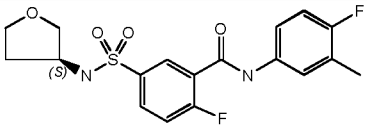
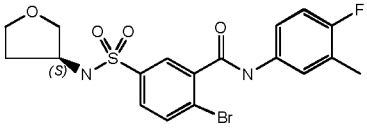
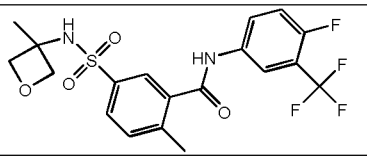
Compound **231**

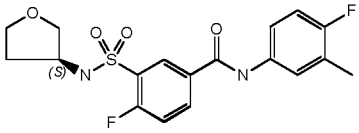


3-methyl-3-oxetanamine hydrochloride (302.6 mg, 2.45 mmol) and Hunig's base (1.15 mL, 6.68 mmol) dissolved in CH_2Cl_2 (2 mL) were added to a solution of methyl 5-(chlorosulfonyl)-2-furoate (thermo scientific, 500 mg, 2.23 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred overnight at room temperature. The volatiles were removed under reduced pressure and the obtained residue was used as such.
The residue was dissolved in THF (10 mL). LiOH (60.2 mg, 2.514 mmol), dissolved in H_2O (1 mL), was added to the reaction mixture, MeOH (1 mL) was added and this was stirred overnight at room temperature. The volatiles were removed under reduced pressure and the residue was dissolved water (25 mL). 1M HCl (2.5 mL) was added and then 2-MeTHF (50 mL) was added. The aqueous layer was removed and the organic layer was washed with brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness yielding an oil which was used as such in the next step. The oil and HATU (573 mg, 1.51 mmol) were stirred in CH_2Cl_2 (5 mL) and 4-fluoro-3-methylaniline (157.3 mg,1.26 mmol) and N,N-diisopropylethylamine (0.65 mL, 3.77 mmol) were added. The reaction mixture was stirred overnight at room temperature. The volatiles were removed under reduced pressure and the residue was purified on silica using a heptane to EtOAc gradient followed by by preparative HPLC (Stationary phase: RP Vydac Denali C18 - 10µm, 200g, 5cm), Mobile phase: 0.25% NH_4HCO_3 solution in water, CH_3CN), the desired fractions were collected, evaporated, dissolved in MeOH and evaporated again. This fraction was triturated in MeOH (4 mL), filtered and dried in the oven yielding compound **231** (305 mg) as a white solid. Method F, Rt: 0.89 min. m/z: 367.1 $(M-H)^-$ Exact mass: 368.1. ^{1}H NMR (400 MHz,

DMSO-d_6) δ ppm 1.53 (s, 3 H), 2.24 (d, J=1.8 Hz, 3 H), 4.21 (d, J=6.6 Hz, 2 H), 4.61 (d, J=6.2 Hz, 2 H), 7.14 (t, J=9.2 Hz, 1 H), 7.26 (d, J=3.7 Hz, 1 H), 7.50 (d, J=3.7 Hz, 1 H), 7.51 - 7.57 (m, 1 H), 7.60 (dd, J=7.0, 2.4 Hz, 1 H), 8.92 (s, 1 H), 10.34 (s, 1 H).

Compound **232** to **239** were prepared by slow addition of an aniline to a refluxing toluene solution of a 3-chlorosulfonylbenzoyl chloride derivative, followed by reaction with an amine in the presence of a base like NEt_3 or DIPEA, as described above.

	Structure	**Aniline**	**Amine**	**3-chlorosulfonyl benzoyl chloride derivative**
232		4-fluoro-3-methylaniline	3-methyl-3-oxetanamine	2-chloro-5-(chlorosulfonyl)benzoyl chloride
233		4-fluoro-3-(trifluoromethyl)aniline	3-methyl-3-oxetanamine	2-chloro-5-(chlorosulfonyl)benzoyl chloride
234		3,4-difluoroaniline	3-methyl-3-oxetanamine	2-chloro-5-(chlorosulfonyl) benzoyl chloride
235		3-(difluoromethyl)-4-fluoro-aniline	3-methyl-3-oxetanamine	2-chloro-5-(chlorosulfonyl) benzoyl chloride
236		4-fluoro-3-methylaniline	(*S*)-3-aminotetrahydrofuran tosylate	5-chlorosulfonyl-2-fluoro-benzoyl chloride
237		4-fluoro-3-methylaniline	(*S*)-3-aminotetrahydrofuran tosylate	2-bromo-5-chlorosulfonyl-benzoyl chloride
238		4-fluoro-3-(trifluoromethyl)aniline	3-methyl-3-oxetanamine	5-chlorosulfonyl-2-methyl-benzoyl chloride

	Structure	Aniline	Amine	3-chlorosulfonyl benzoyl chloride derivative
239		4-fluoro-3-methylaniline	(S)-tetrahydrofuran-3-amine hydrochloride	3-chlorosulfonyl-4-fluoro-benzoyl chloride

Compound	LC method	Rt (min)	m/z $(M-H)^-$	Exact mass
232	G	1.67	410.8	412.1
233	G	1.83	464.9	466.0
234	G	1.68	414.9	416.0
235	G	1.69	446.9	448.1
236	F	0.90	395.1	396.1
237	F	0.93	457.1	458.0
238	F	1.03	445.1	446.1
239	G	1.64	394.9	396.1

Compound	^{1}H-NMR
232	^{1}H NMR (360MHz , DMSO-d_6) δ ppm 10.67 (s, 1 H), 8.57 (s, 1 H), 7.96 - 7.88 (m, 2 H), 7.84 - 7.79 (m, 1 H), 7.62 (dd, J = 2.6, 7.0 Hz, 1 H), 7.54 - 7.46 (m, 1 H), 7.15 (t, J = 9.1 Hz, 1 H), 4.56 (d, J = 6.2 Hz, 2 H), 4.17 (d, J = 6.2 Hz, 2 H), 2.24 (d, J = 1.8 Hz, 3 H), 1.43 (s, 3 H)
233	^{1}H NMR (360MHz , DMSO-d_6) δ ppm 1.44 (s, 3 H) 4.18 (d, J=6.6 Hz, 2 H) 4.57 (d, J=6.0Hz, 2 H) 7.57 (t, J=9.9 Hz, 1 H) 7.85 (d, J=8.4 Hz, 1 H) 7.91 - 7.98 (m, 2 H) 8.02 (d, J=2.2 Hz, 1 H) 8.20 (dd, J=6.2, 2.6 Hz, 1 H) 8.58 (s, 1 H) 11.06 (s, 1H)
234	^{1}H NMR (360 MHz, CHLOROFORM-d) δ ppm 1.64 (s, 3 H) 4.37 (d, J=6.5Hz, 2 H) 4.66 (d, J=6.5 Hz, 2 H) 5.74 (s, 1 H) 7.09 - 7.24 (m, 2 H) 7.59 (d, J=8.2 Hz, 1 H) 7.70 (ddd, J=11.8, 7.0, 2.4 Hz, 1 H) 7.88 (dd, J=8.4, 2.2 Hz, 1 H) 8.19 (d, J=2.2 Hz, 1 H) 8.30 (s, 1 H)
235	^{1}H NMR (360MHz , DMSO-d_6) δ ppm 1.44 (s, 3 H) 4.18 (d, J=6.2 Hz, 2 H) 4.57 (d, J=6.2 Hz, 2 H) 7.26 (t, J=54.2 Hz, 1 H) 7.36 - 7.46 (m, 1 H) 7.84 (d, J=8.4 Hz, 2 H) 7.91 (d, J=2.2 Hz, 1 H) 8.00 (d, J=2.2 Hz, 1 H) 8.03 - 8.10 (m, 1 H) 8.58 (s, 1 H) 10.95 (s, 1 H)

Compound	^{1}H-NMR
236	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.57 - 1.70 (m, 1 H), 1.87 - 2.04 (m, 1 H), 2.25 (d, J=1.0 Hz, 3 H), 3.38 (m, 1 H), 3.54 - 3.81 (m, 4 H), 7.15 (t, J=9.1 Hz, 1 H), 7.47 - 7.56 (m, 1 H), 7.57 - 7.72 (m, 2 H), 7.95-8.20 (ddd, J=8.6, 4.6, 2.4 Hz, 1 H), 8.06 - 8.19 (m, 2 H), 10.60 (s, 1 H)
237	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.60 - 1.70 (m, 1 H), 1.89 - 2.00 (m, 1 H), 2.24 (d, J=1.6 Hz, 3 H), 3.38 (dd, J=8.9, 4.4 Hz, 1 H), 3.55-3.62 (m, 1 H), 3.63 - 3.67 (m, 1 H), 3.68-3.72 (m, 1 H), 3.73 - 3.80 (m, 1 H), 7.14 (t, J=9.3 Hz, 1 H), 7.49 (ddd, J=8.9, 4.4, 2.8 Hz, 1 H), 7.63 (dd, J=6.9, 2.4 Hz, 1 H), 7.80 (dd, J=8.3, 2.2 Hz, 1 H), 7.89 (d, J=2.4 Hz, 1 H), 7.97 (d, J=8.5 Hz, 1 H), 8.12 (br. s., 1 H), 10.63 (s, 1 H)
238	^{1}H NMR (360MHz , DMSO-d_6) δ ppm 1.42 (s, 3 H) 2.46 (s, 3 H) 4.14 (d, J=6.2 Hz, 2 H) 4.56 (d, J=6.2 Hz, 2 H) 7.51 - 7.59 (m, 2 H) 7.84 (dd, J=8.1, 1.8 Hz, 1 H) 7.89 (d, J=1.8 Hz, 1 H) 7.95 - 8.02 (m, 1 H) 8.24 (dd, J=6.6, 2.6 Hz, 1 H) 8.42 (s, 1 H) 10.87 (s, 1 H)
239	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.65 - 1.74 (m, 1 H), 1.90 - 2.00 (m, 1 H), 2.25 (d, J=1.5 Hz, 3 H), 3.41 (dd, J=8.9, 4.7 Hz, 1 H), 3.57 - 3.77 (m, 3 H), 3.83 - 3.91 (m, 1 H), 7.14 (dd, J=9.2 Hz, 1 H), 7.54 - 7.61 (m, 1 H), 7.61 - 7.69 (m, 2 H), 8.29 (ddd, J=8.5, 4.6, 2.3 Hz, 1 H), 8.40 (dd, J=7.0, 2.2 Hz, 1 H), 8.44 (br. s., 1 H), 10.47 (s, 1 H)

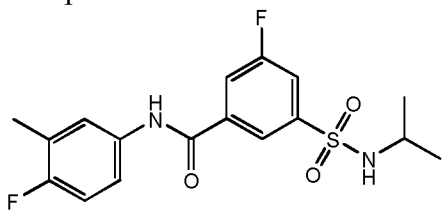
Differential scanning calorimetry From 30 to 300 °C at 10°C/min:

Compound **232**: Peak at 169.6 °C

Optical rotation:

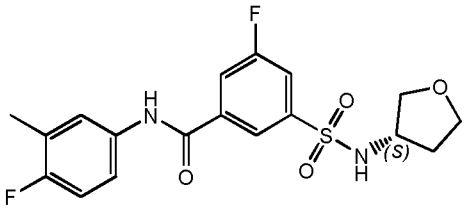
Compound **236**: $[\alpha]_D^{20}$ = - 5.83 (c 0.67 w/v %, MeOH).

Compound **240**



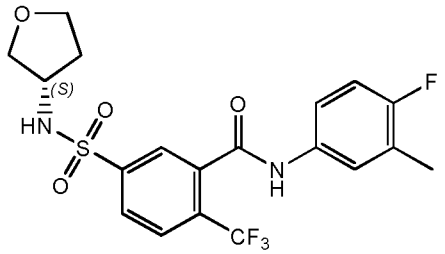
$SOCl_2$ (20.1 mL, 277.2 mmol) was added slowly to water (125 mL) cooled to 5 °C, maintaining the temperature between 4 and 7 °C (addition took about 1.5 hour). The solution was then kept stirring overnight while the temperature was allowed to slowly reach room temperature. Copper(I) chloride (76.6 mg, 0.774 mmol) was then added to the solution and it was cooled to -10 °C (dry ice/acetone bath), (resulting in solution A). In another flask cooled to 0 °C, HCl (37% in H_2O, 65 mL) was added dropwise to 3-amino-5-fluorobenzoic acid (10 g, 64.46 mmol), keeping the temperature below 20 °C. This slurry was cooled to -10 °C (dry ice/acetone bath) and a solution of sodium nitrite (4.803 g, 69.62 mmol) in H_2O (20 mL) was added very slowly (1 drop/5 sec) to the slurry, keeping the temperature below -5°C.
After addition, the orange mixture was allowed to warm to -2 °C for 5 min before cooling back to -15 °C (solution B). Solution B was then added portionwise (plastic pipette) to solution A, cooled to -10 °C. After addition (~30 min), the reaction mixture was stirred at 0 °C for 2 h. The resulting orange solid was filtered and rinsed with water (2 x 25 mL) resulting in 3-chlorosulfonyl-5-fluoro-benzoic acid as an orange solid (dried at 35 °C in vacuo). Et_3N (1.22 mL, 8.8 mmol) was slowly added to a solution of 3-chlorosulfonyl-5-fluoro-benzoic acid (525 mg, 2.2 mmol) in dry CH_2Cl_2 (10 mL). Isopropylamine (198 µL, 2.42 mmol) was then added dropwise at room temperature to the reaction mixture.The reaction mixture was stirred at room temperature for 30 min.The brown reaction mixture was diluted with CH_2Cl_2 and water. HCl 1N was added to pH 2. The layers were separated and the aqueous layer was extracted twice with CH_2Cl_2.The organic layer was dried on $MgSO_4$, filtered, and evaporated resulting in 3-fluoro-5-(isopropylsulfamoyl)benzoic acid as an orange solid, which was used without further purification. HATU (356.7 mg, 0.94 mmol) was added to a solution of crude 3-fluoro-5-(isopropylsulfamoyl)benzoic acid (190 mg), 4-fluoro-3-methylaniline (78.3 mg, 0.625 mmol) and N,N-diisopropylethylamine (326.8 µL, 1.88 mmol) in CH_2Cl_2 (30 mL)at room temperature. The mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with CH_2Cl_2, washed with HCl 0.5 N, filtered on Extrelut NT3 and evaporated. The obtained residue was purified by column chromatography on silica gel (Grace Resolv 12g, eluent: CH_2Cl_2:MeOH 100:0 -> 95:5) resulting in compound **240** (136 mg) as a white solid, dried at 50 °C in vacuo.
Method G, Rt: 1.87 min. m/z: 366.9 $(M-H)^-$ Exact mass: 368.1.^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 0.97 (d, J=6.2 Hz, 6 H) 2.25 (d, J=1.5 Hz, 3 H) 3.30-3.39 (m, 1H), 7.16 (t, J=9.3 Hz, 1 H) 7.55 - 7.62 (m, 1 H) 7.67 (dd, J=7.1, 2.4 Hz, 1H) 7.83 (dt, J=8.0, 1.9 Hz, 1 H) 7.88 (d, J=7.0 Hz, 1 H) 8.08 (dt, J=9.3, 1.7 Hz, 1 H) 8.22 (s, 1 H) 10.52 (s, 1 H).

Compound **241**



Compound **241** was prepared similarly as described for compound **240** using (S)-3-aminotetrahydrofuran tosylate instead of isopropylamine. Method G, Rt: 1.70 min. m/z: 394.9 $(M-H)^-$ Exact mass: 396.1. ^1H NMR (360 MHz, DMSO-d_6) d ppm 1.55 - 1.67 (m, 1 H) 1.93 (dq, J=12.8, 7.4 Hz, 1 H) 2.25 (d, J=1.8 Hz, 3 H) 3.37 (dd, J=9.0, 4.2 Hz, 1 H) 3.55 - 3.75 (m, 3 H) 3.75 - 3.85 (m, 1 H) 7.16 (t, J=9.1 Hz, 1 H) 7.56 - 7.62 (m, 1 H) 7.67 (dd, J=7.3, 2.6 Hz, 1 H) 7.82 - 7.88 (m, 1 H) 8.08 - 8.13 (m, 1 H) 8.20 - 8.25 (m, 2 H) 10.53 (s, 1 H).

Compound **242**



Compound **237** (400 mg, 0.87 mmol) was dissolved in a mixture of DMF (2.5 mL) and N-methylpyrrolidine (0.12 mL) containing Copper(I)iodide (45.43 mg, 0.24 mmol) and 2,2-difluoro-2-fluorosulfonyl acetic acid methylester (0.21 g, 1.09 mmol).
The resulting mixture was stirred at room temperature for 2 hours. An extra amount of 2,2-difluoro-2-fluorosulfonyl acetic acid methylester (0.21 g, 1.09 mmol) was added and the mixture was stirred at 60°C for 1 hour. The mixture was stirred at 60°C for 18 hours. Saturated ammonium chloride solution (10 mL) was added to the reaction mixture. Then this was extracted using EtOAc (3 x 15mL). The combined extracts were dried on Na_2SO_4, filtered and concentrated in vacuo. The obtained residue was purified using column chromatography on silica (gradient elution: ethylacetate: heptane from 0 to 100%). All desired fractions were combined and concentrated under reduced pressure and then dried at 50°C in a vacuum oven overnight yielding compound **242** (314 mg) as a white powder. Method G, Rt: 1.73 min. m/z: 445.0 $(M-H)^-$ Exact mass: 446.1.

Biological examples – anti-HBV activity of compounds of Formula (I)

The anti-HBV activity was measured using a stable transfected cell line, HepG2.2.15. This cell line was described to secrete relatively consistent high levels of

HBV virion particles, which have been shown to cause both acute and chronic infection and disease in chimpanzees.

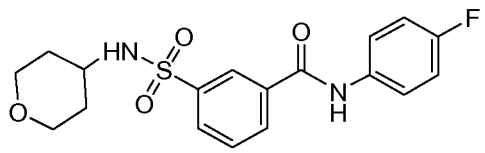
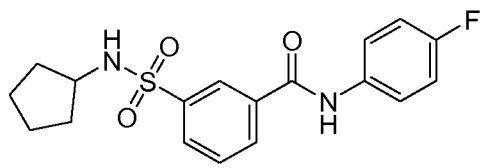
For the antiviral, assay cells were treated twice for three days with serially diluted compound in 96-well plates in duplicate. After 6 days of tretament the antiviral activity was determined by quantification of purified HBV DNA from secreted virions using realtime PCR and an HBV specific primer set and probe.

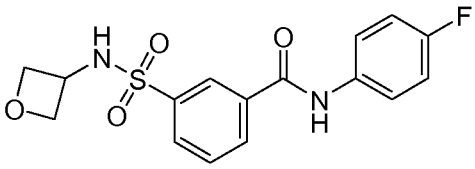
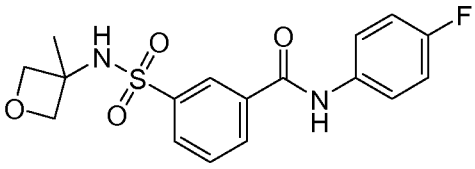
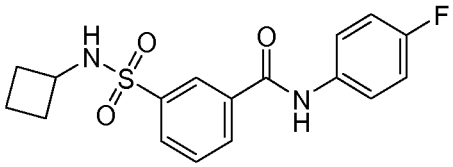
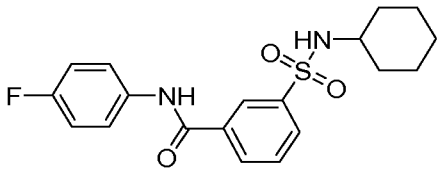
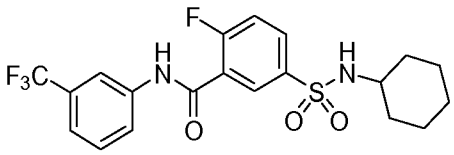
Cytotoxicity of the compounds was tested in HepG2 cells using CellTiter-Blue, with the same incubation period and dose range as in the HepG2.2.15 assay.

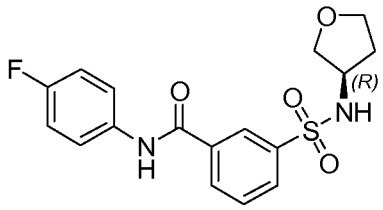
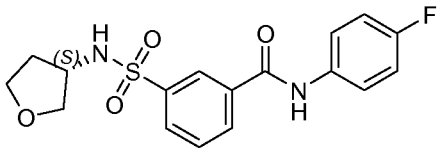
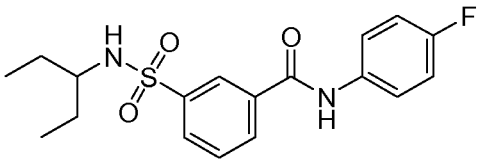
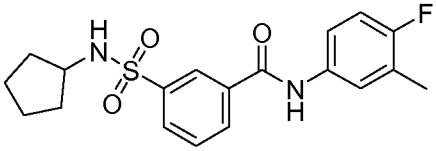
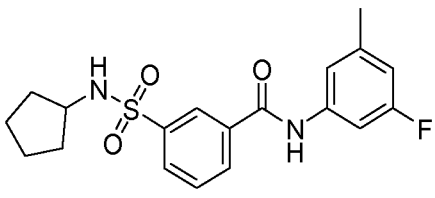
The anti HBV activity was also measured using the HepG2.117 cell line, a stable, inducibly HBV producing cell line, which replicates HBV in the absence of doxicycline (Tet-off system). For the antiviral assay, HBV replication was induced, followed by a treatment with serially diluted compound in 96-well plates in duplicate. After 3 days of treatment, the antiviral activity was determined by quantification of intracellular HBV DNA using realtime PCR and an HBV specific primer set and probe.

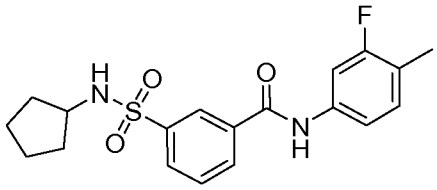
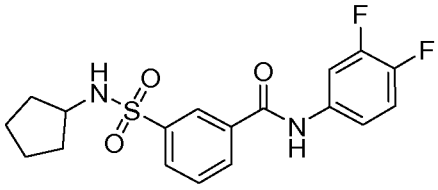
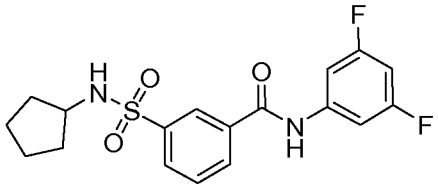
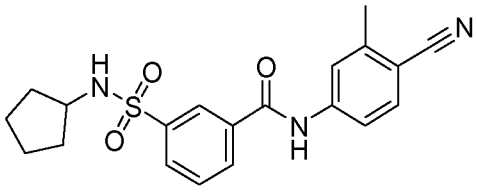
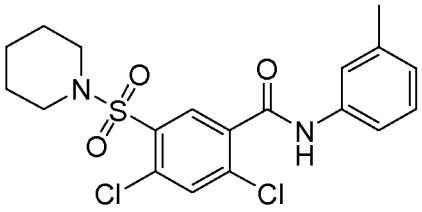
Cytotoxicity of the compounds was tested using HepG2 cells, incubated for 4 days in the presence of compounds. The viability of the cells was assessed using a Resazurin assay. Results are displayed in Table 1.

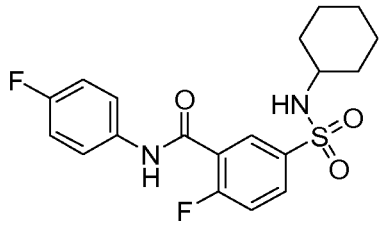
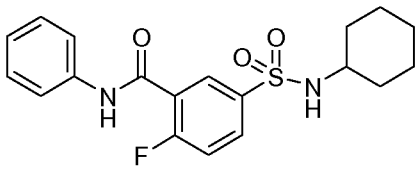
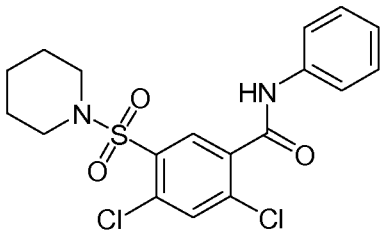
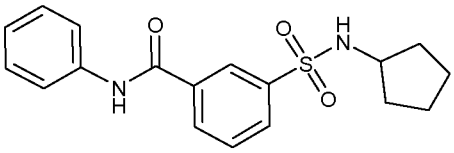
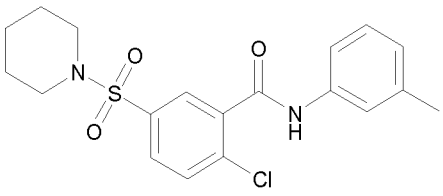
Table 1.

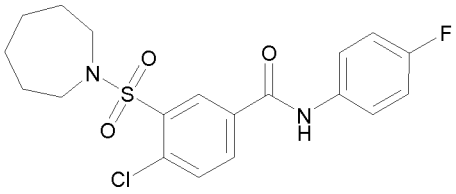
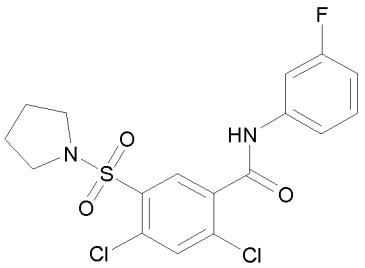
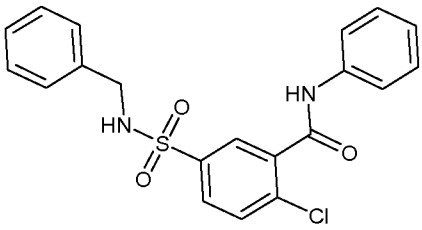
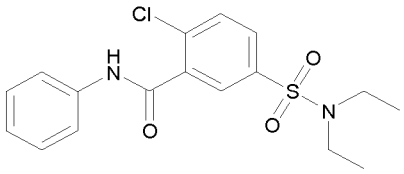
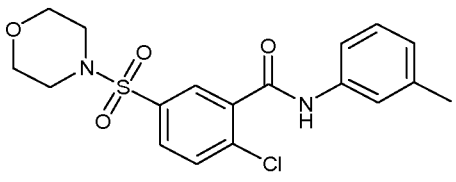
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**1**	0.93		1.67	>100
	**2**	0.47		0.56	32.7

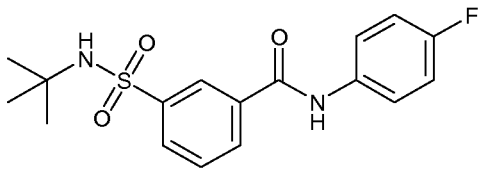
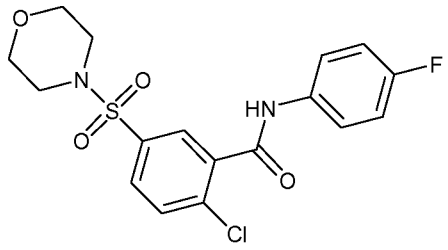
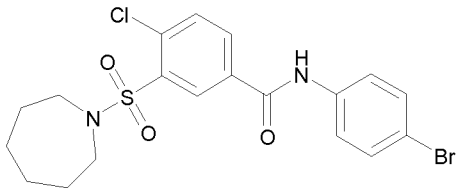
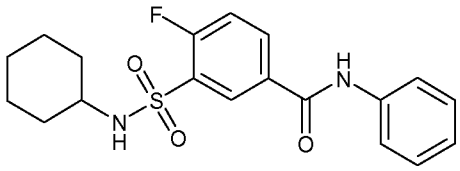
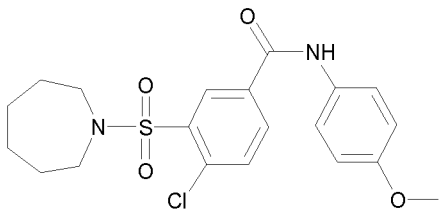
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**3**	2.10		3.05	>100
	**4**	0.96		0.93	>100
	**5**	0.83		0.90	57.7
	**6**			0.58	>25
	**7**	0.66	-	0.56	11.4

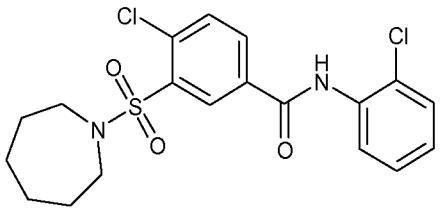
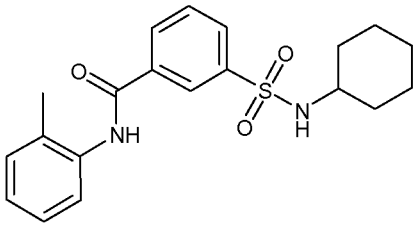
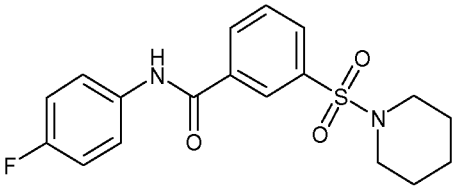
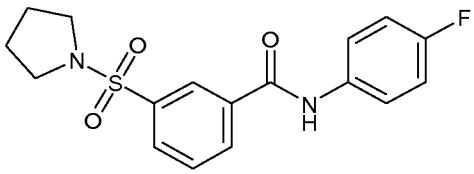
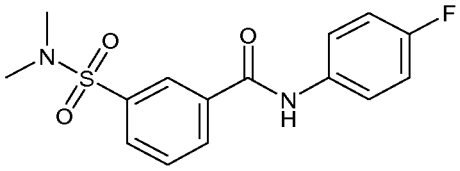
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**8**	1.18		2.03	>100
	**9**	0.54		1.36	>100
	**10**	0.75		3.63	40.3
	**11**	0.10		0.42	19.6
	**12**	0.11		1.51	13.3

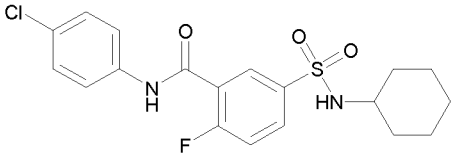
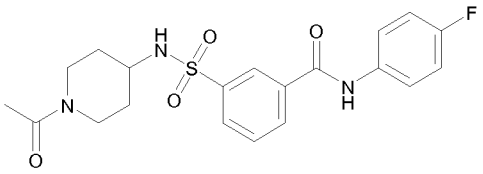
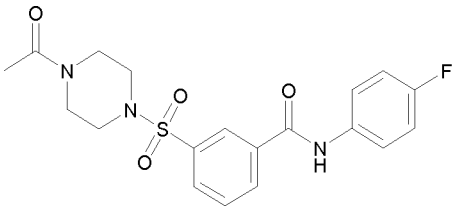
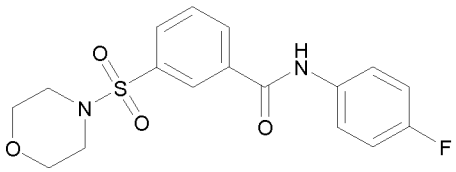
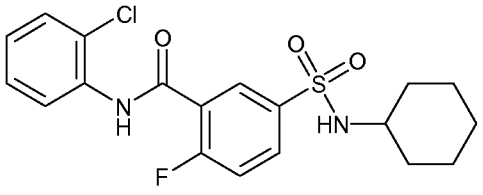
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**13**	1.99		15.31	13.8
	**14**	0.09		0.36	11.7
	**15**	0.28		0.78	10.1
	**16**	1.21		2.8	10.3
	**17**	0.56		2.65	>100

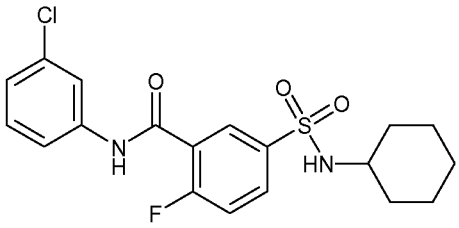
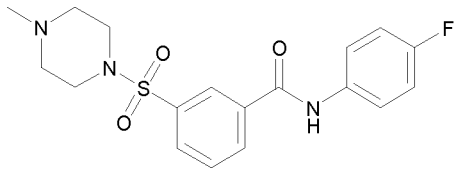
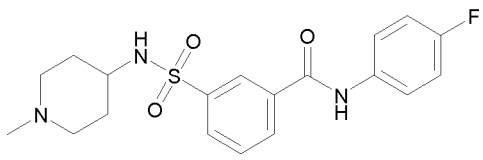
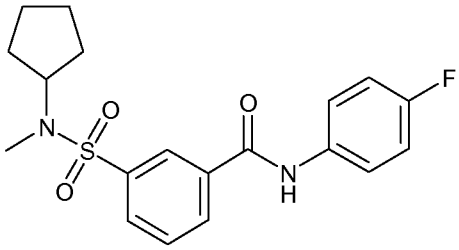
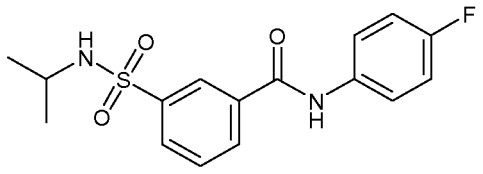
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**18**	0.78	51.6	1.30	>50
	**19**	0.66	42.5	0.60	>25
	**20**	0.50	>25	1.00	79.6
	**21**	0.60	27.2	0.76	41.1
	**22**	0.52	>25		

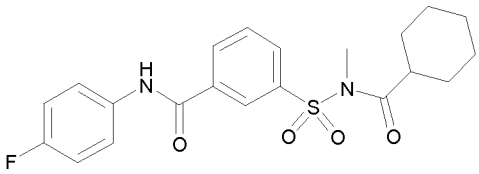
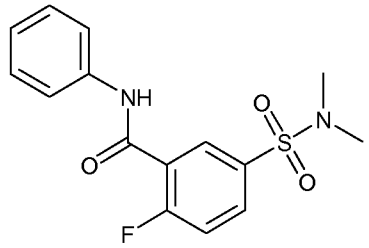
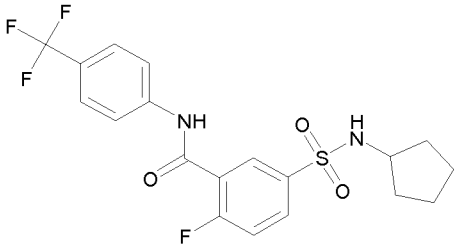
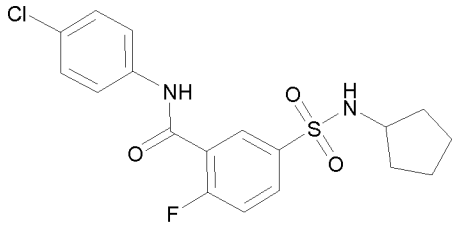
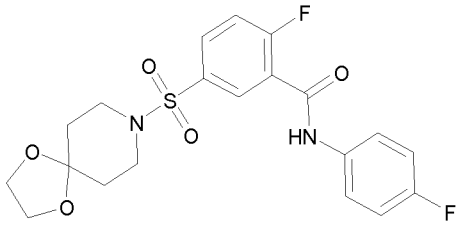
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**23**	0.66	17.0	1.30	19.6
	**24**	0.79	>25		
	**25**	0.80	>25	1.02	>6.25
	**26**	1.04	>25		
	**27**	1.13	>25		

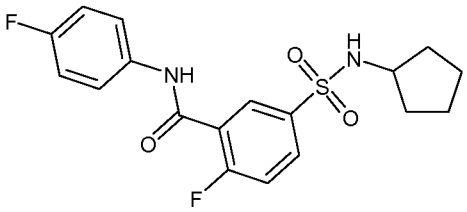
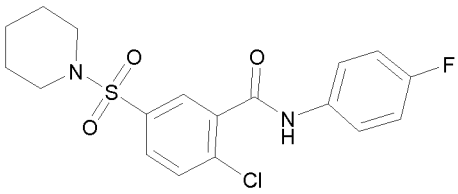
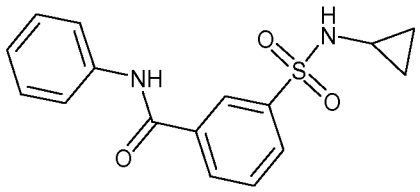
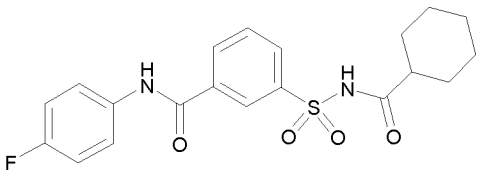
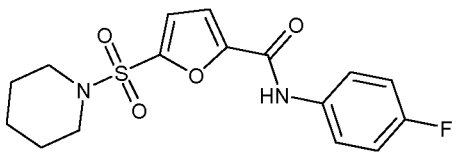
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**28**	1.24		2.28	52.5
	**29**	1.39	>25		
	**30**	1.67	>25		
	**31**	2.23	16.4		
	**32**	2.59	9.9	4.58	>25

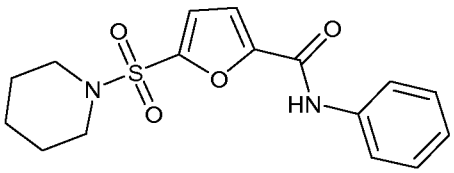
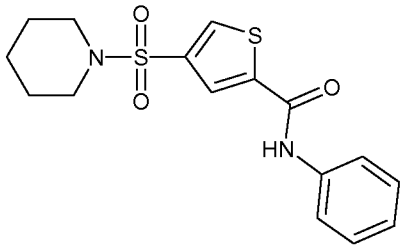
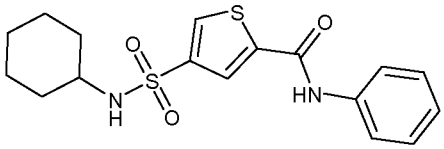
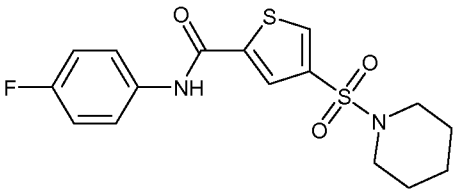
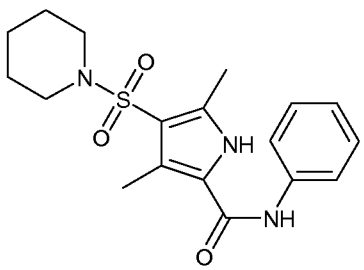
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**33**	3.56	>25		
	**34**	4.18	>25		
	**35**	4.50		2.70	70.4
	**36**	4.53		3.03	97.0
	**37**	5.02		2.99	>100

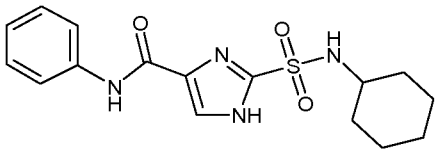
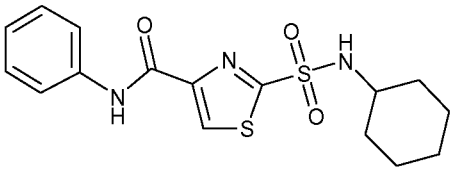
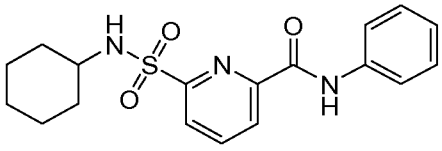
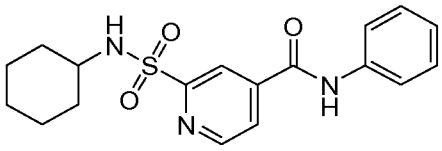
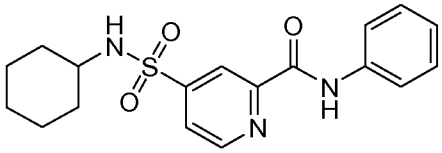
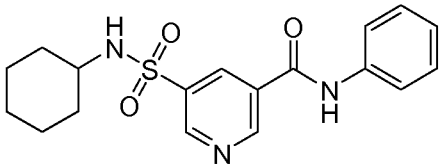
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**38**	<6.25	18.4	15.54	22.10
	**39**	6.77		4.68	>100
	**40**	7.10		6.29	>100
	**41**	8.49	-	10.95	>100
	**42**	11.64	37.2	>25	

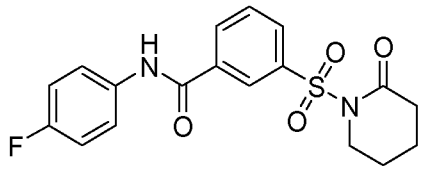
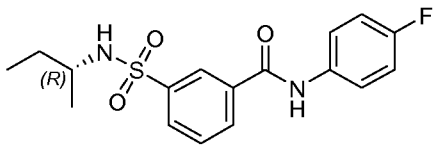
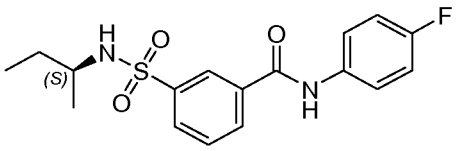
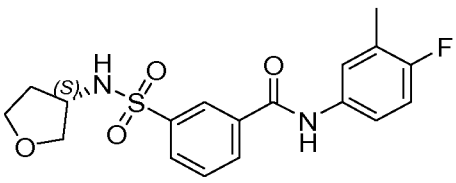
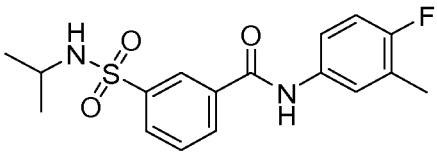
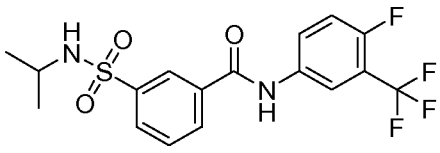
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**43**	15.13	36.3	>25	>25
	**44**	26.49		11.08	>100
	**45**	59.33		16.03	>100
	**46**	2.61		11.09	23.8
	**47**	0.74		0.96	57.5

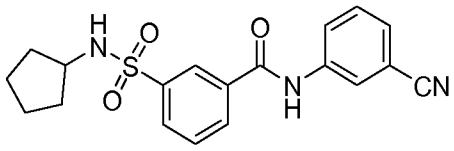
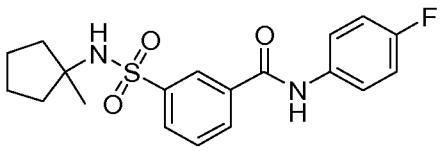
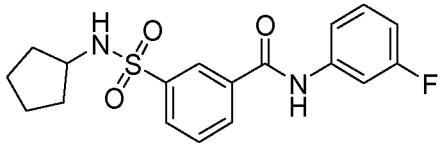
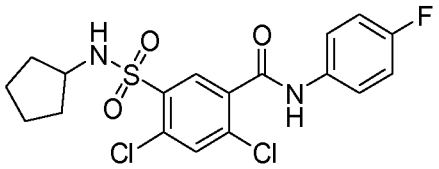
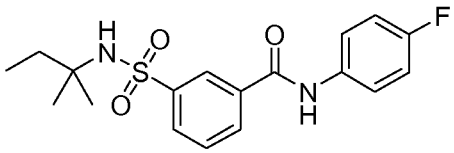
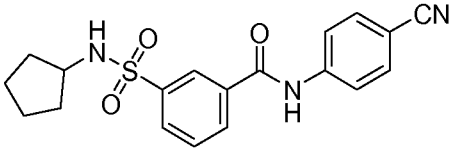
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**48**	2.92		1.88	97.2
	**49**	13.4		9.15	>100
	**50**	45.9		15.80	11.3
	**51**	3.98		9.44	20.8
	**52**	1.94		2.44	>50

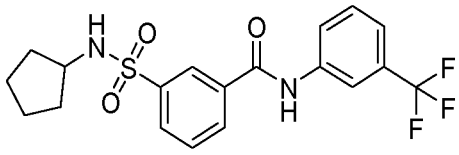
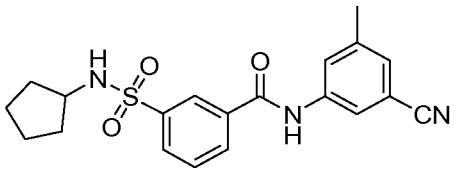
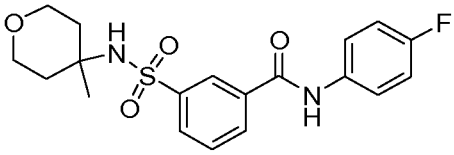
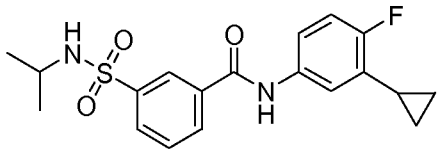
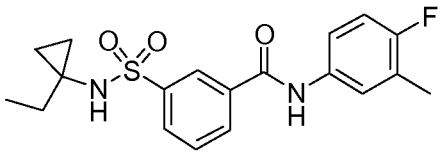
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**53**	0.36		0.44	>50
	**54**	1.63		1.55	>50
	**55**	3.06		3.26	>100
	**56**	1.64		5.45	>100
	**57**	15.53		12.74	52.1

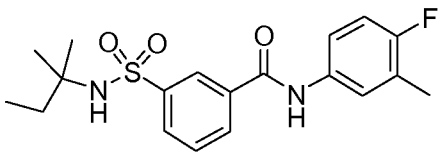
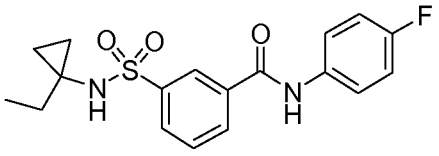
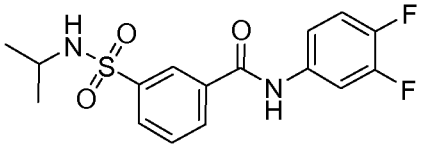
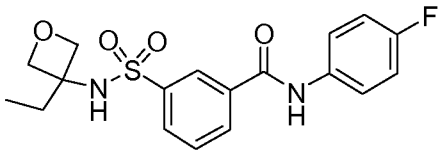
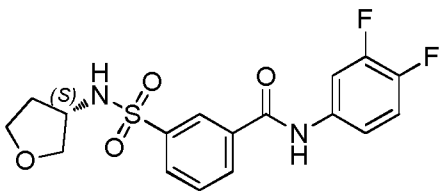
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**58**	14.62		19.94	62.5
	**59**	12.79		19.27	46.7
	**60**	0.85		0.67	29.1
	**61**	7.07		15.44	35.7
	**62**	7.06		10.07	>50

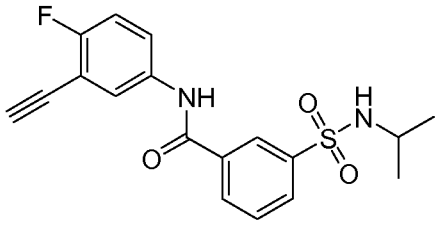
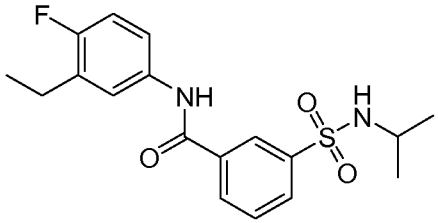
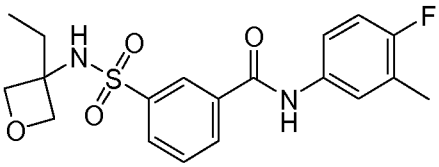
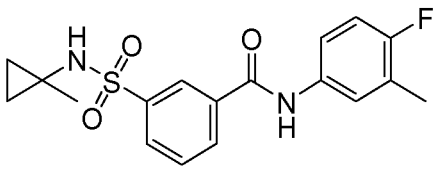
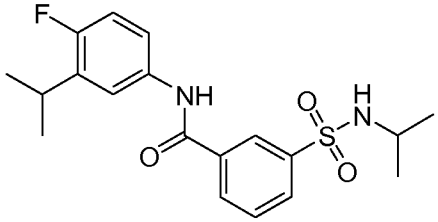
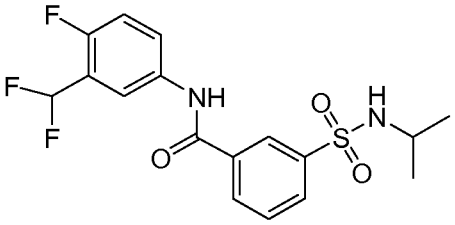
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**63**	9.94		21.12	>100
	**64**			7.83	>25
	**65**	10.76		>25	35.3
	**66**	4.27		14.49	>100
	**67**	11.10		18.55	>100
	**68**	18.60		>25	68.0

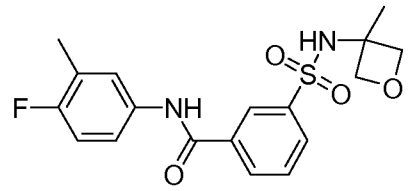
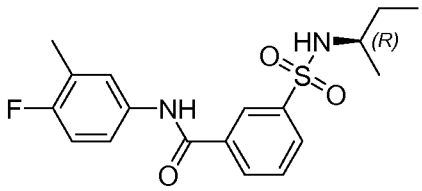
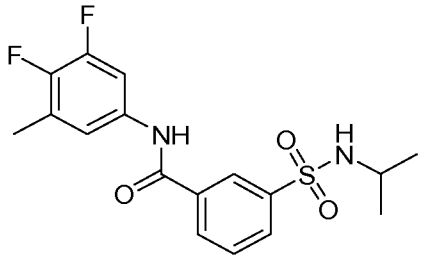
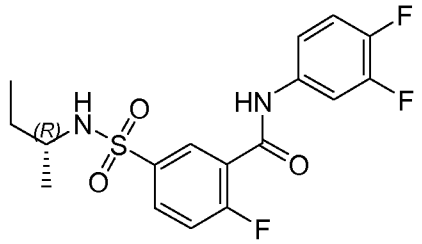
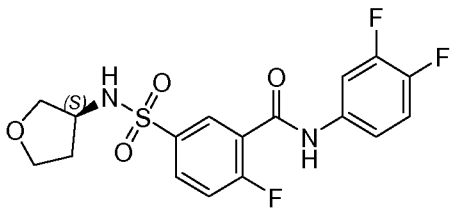
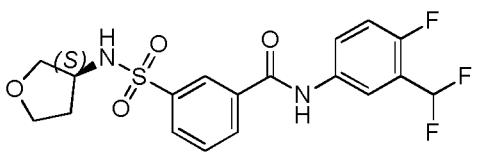
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**69**	3.90		10.38	>25
	**70**	0.34		0.89	>25
	**71**	0.75		8.63	>25
	**72**	0.12		0.37	>25
	**73**	0.073		0.15	>25
	**74**	0.64		0.53	>25

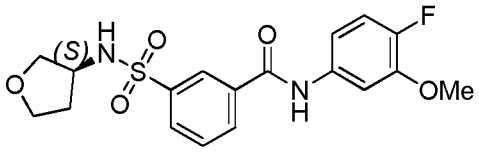
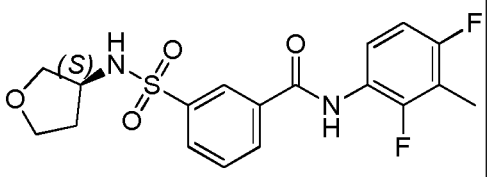
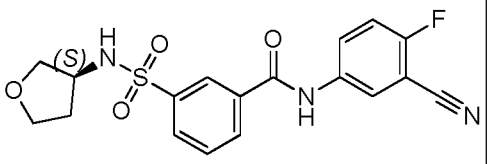
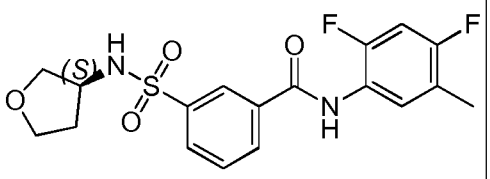
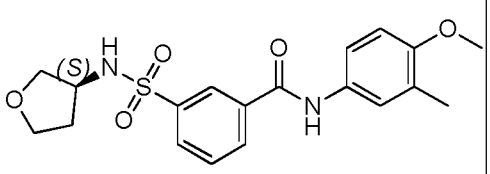
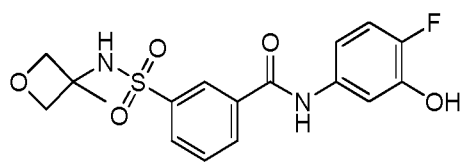
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**75**	0.39		0.82	>25
	**76**	0.72		2.5	>25
	**77**	0.27		0.43	>25
	**78**	0.90		0.65	>25
	**79**	0.96		1.69	>25
	**80**	8.4		17.9	>25

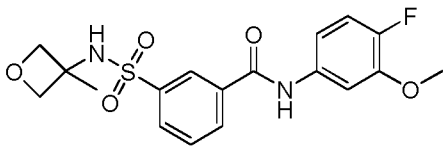
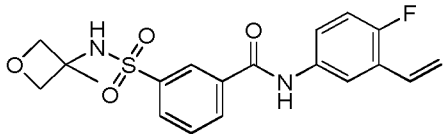
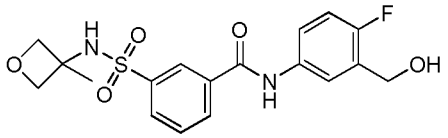
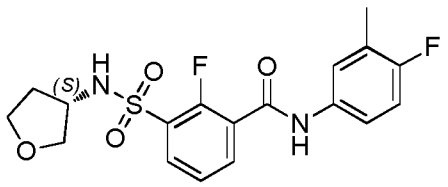
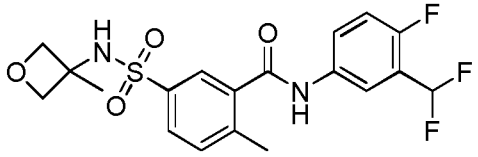
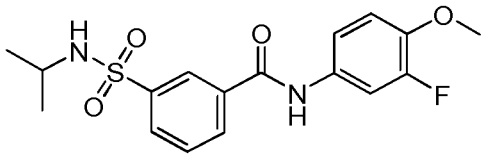
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**81**	0.24		0.81	15.3
	**82**	1.20		3.13	>25
	**83**	1.04		1.23	>25
	**84**	0.32		0.91	>25
	**85**	0.05		0.38	>25

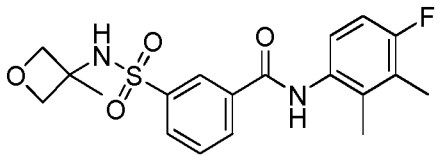
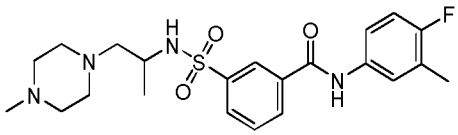
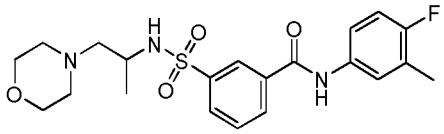
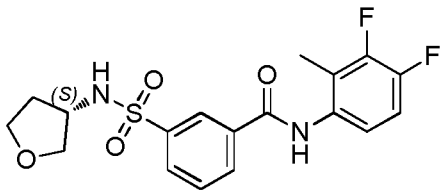
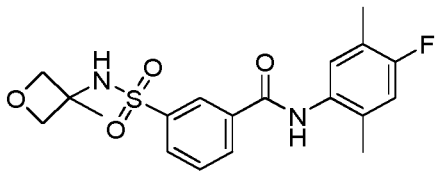
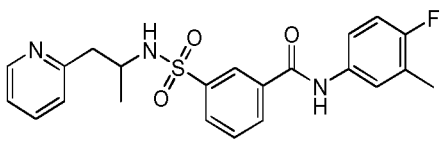
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**86**	0.14		0.11	>25
	**87**	0.41		0.89	>25
	**88**	0.21		0.40	>25
	**89**	0.54		0.72	>25
	**90**	0.38		0.51	>25

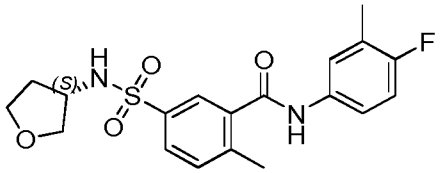
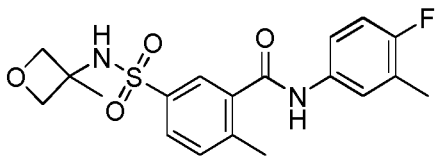
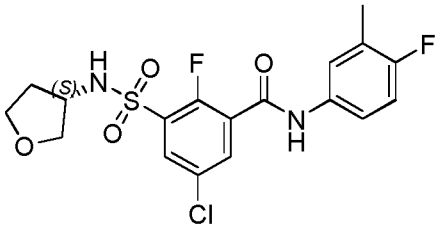
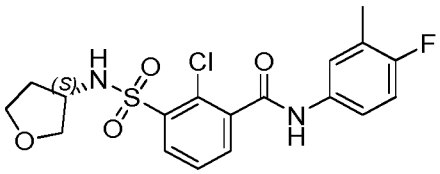
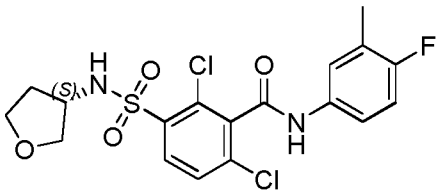
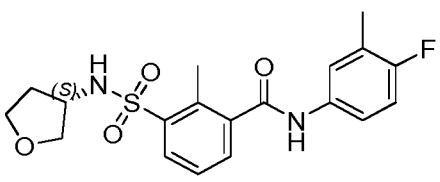
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**91**	0.53		0.77	>25
	**92**	0.31		2.59	>25
	**93**	0.07		0.22	>25
	**94**	0.15		0.23	>25
	**95**	1.4		2.79	>25
	**96**	0.10		0.29	>25

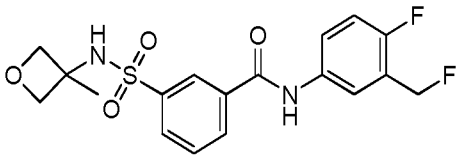
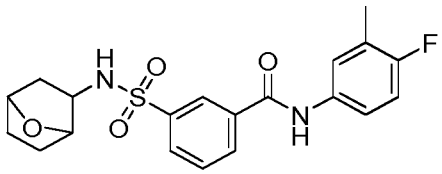
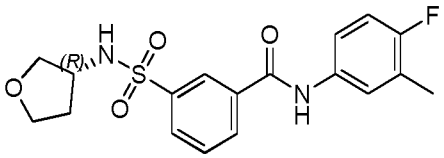
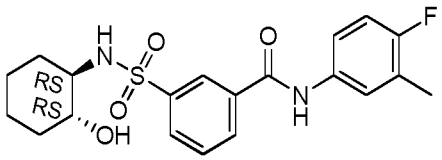
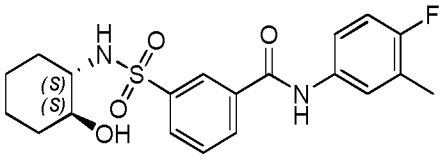
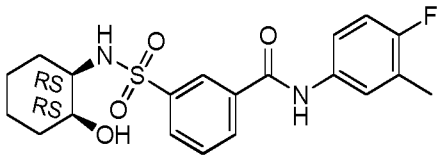
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**97**	0.12		0.37	>25
	**98**	0.10		0.31	>25
	**99**	0.09		0.46	>25
	**100**	0.13		0.43	>25
	**101**	0.43		1.51	>25
	**102**	0.18		0.33	>25

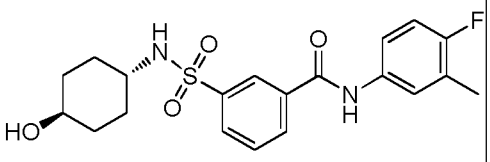
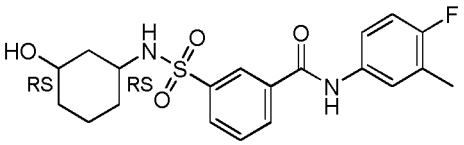
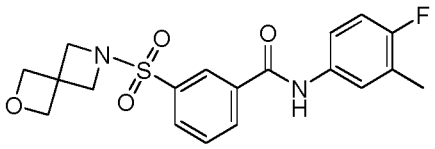
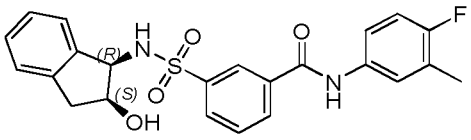
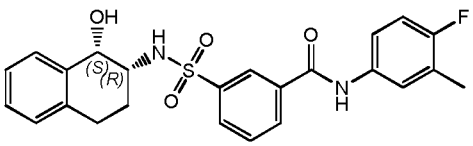
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**103**	2.33		2.66	>25
	**104**	0.29		0.78	>25
	**105**	0.81		0.98	>25
	**106**	2.22		3.30	>25
	**107**	7.82		13.82	>25
	**108**	7.20		9.27	>25

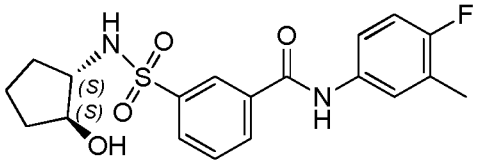
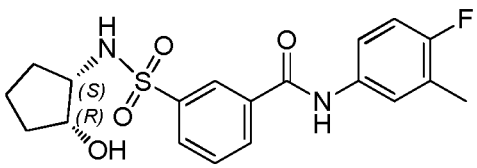
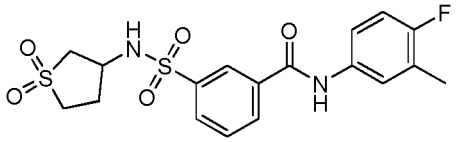
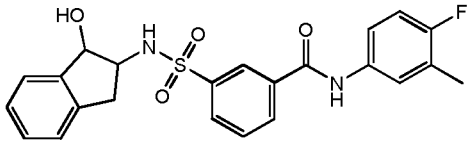
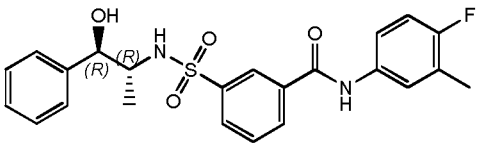
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**109**	1.23		2.53	>25
	**110**	0.66		0.85	>25
	**111**	4.48		1.48	>25
	**112**	0.03		0.14	>25
	**113**	0.15		0.18	>25
	**114**	1.35		3.15	>25

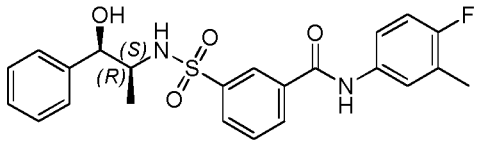
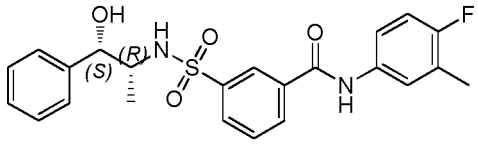
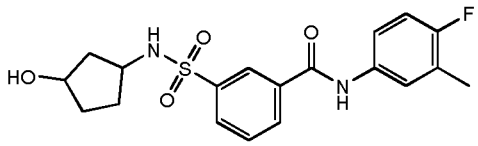
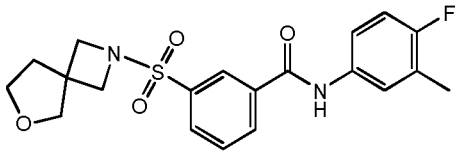
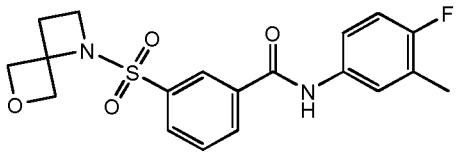
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**115**	2.74		1.65	>25
	**116**	1.94		0.90	>25
	**117**	0.88		0.50	>25
	**118**	3.63		1.91	>25
	**119**	3.06		1.91	>25
	**120**	0.53		0.51	>25

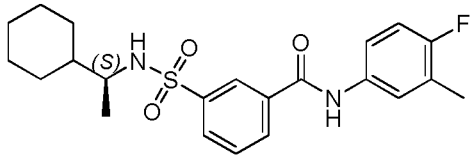
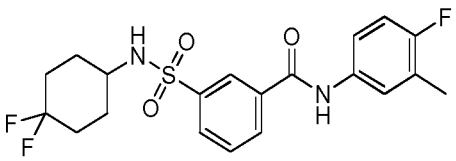
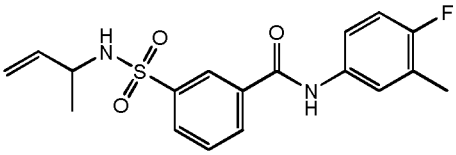
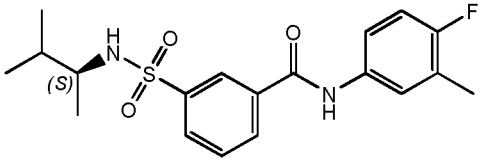
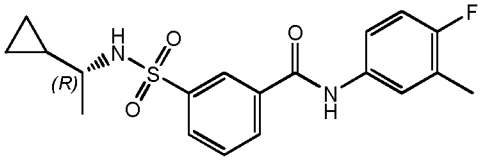
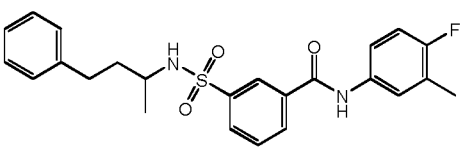
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**121**	0.16		0.13	>25
	**122**	0.13		0.18	>25
	**123**	0.15		0.3	>25
	**124**	0.33		0.68	>25
	**125**	1.44		1.15	>25
	**126**	1.38		0.89	>25

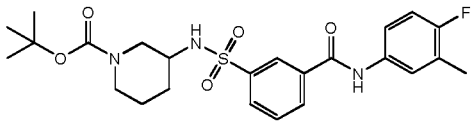
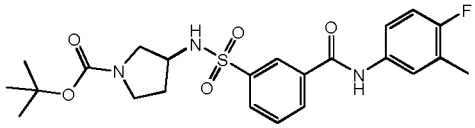
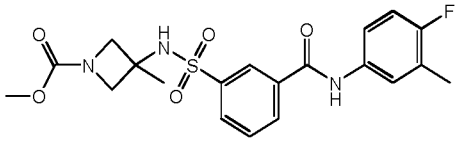
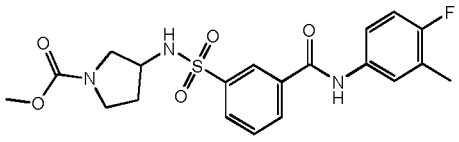
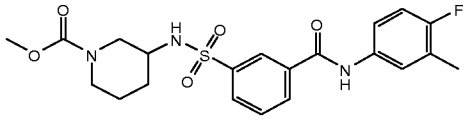
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**127**	0.23		0.58	>25
	**128**	0.23		0.54	>25
	**129**	0.35		0.78	>25
	**130**	0.88		1.03	>25
	**131**	2.63		1.74	>25
	**132**	0.59		0.73	>25

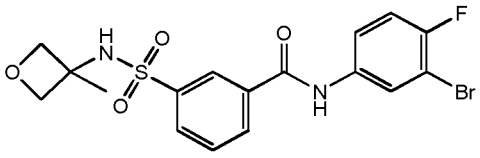
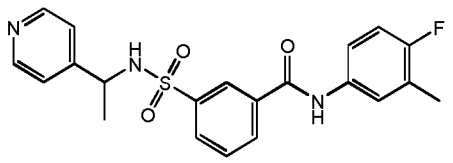
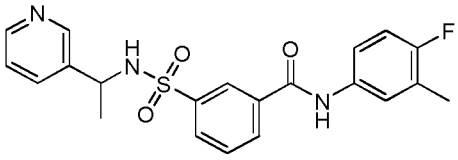
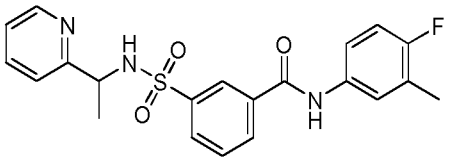
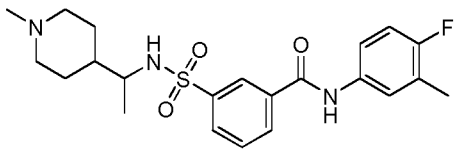
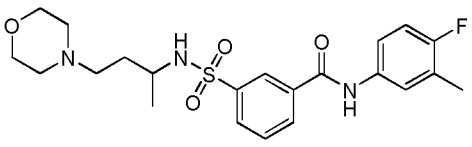
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**133**	0.60		1.69	>25
	**134**	0.18		0.57	>25
	134a	0.66		0.72	
	134b	0.57		0.20	
	134c	0.49		0.38	
	134d	0.25		1.22	
	**135**	0.56		0.36	>25
	**136**	0.47		0.81	>25
	**137**	0.66		0.92	23.7

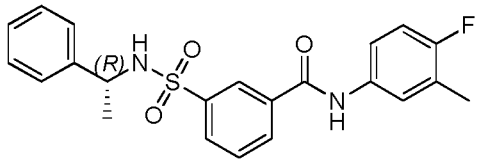
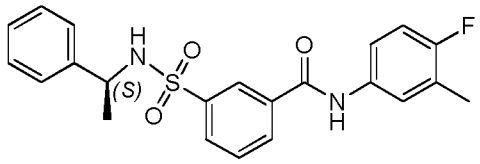
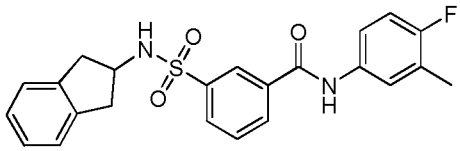
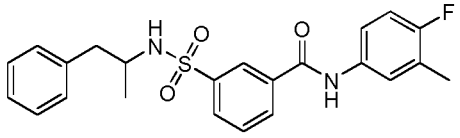
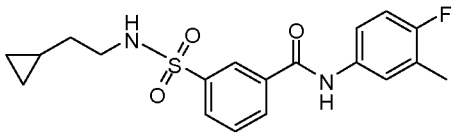
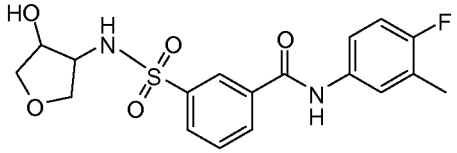
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**138**	1.28		2.27	>25
	**139**	1.00		1.75	>25
	**140**	1.10		1.12	>25
	**141**	0.36		0.60	>25
	141a	0.70		1.65	>25
	141b	0.27		0.23	>25
	141c	0.17		0.29	>25
	141d	0.56		1.14	>25
	**142**	0.14		0.56	>25

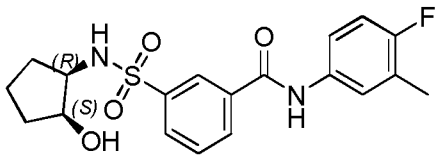
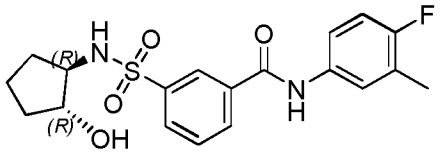
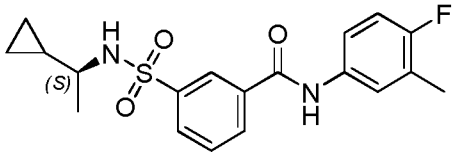
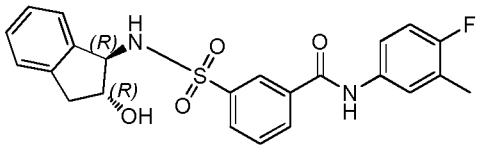
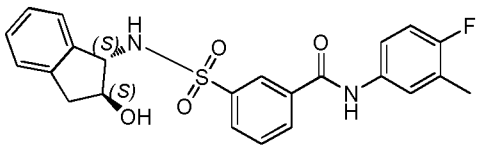
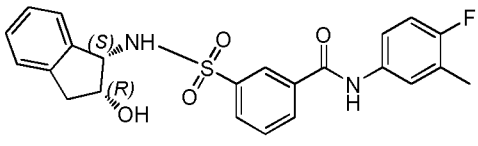
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**143**	0.91		2.66	>25
	**144**	0.13		0.24	>25
	**145**	0.22		0.27	>25
	145a	0.14		0.21	>25
	145b	0.44		0.58	>25
	145c	0.34		0.34	>25
	145d	0.40		0.64	>25
	**146**	0.45		0.42	>25
	**147**	0.26		0.15	>25

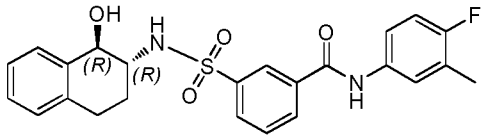
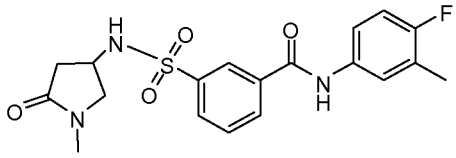
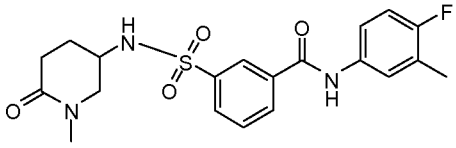
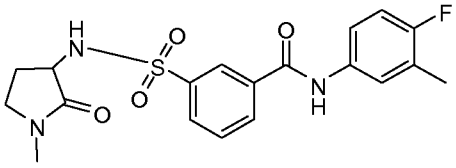
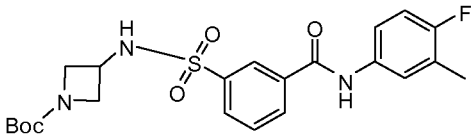
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**148**	0.90		3.11	18.2
	**149**	0.22		0.73	20.8
	**150**	0.10		0.73	>25
	**151**	0.66		2.74	>25
	**152**	<0.1		0.57	>25
	**153**	0.22		0.25	>25

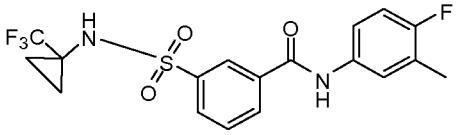
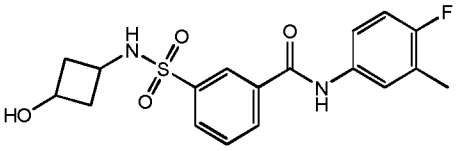
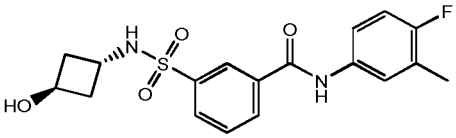
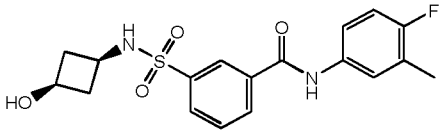
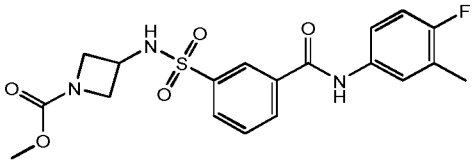
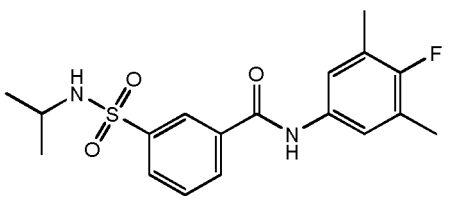
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**155**	0.36		0.81	>25
	**156**	0.19		0.21	>25
	**157**	0.13		0.23	>25
	**158**	0.15		0.50	>25
	**159**	0.15		0.30	>25
	159a	0.17		0.86	
	159b	0.16		0.23	

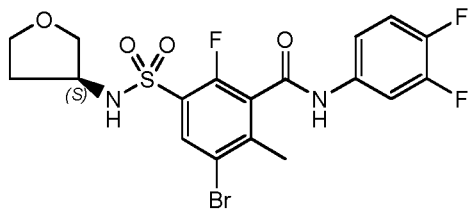
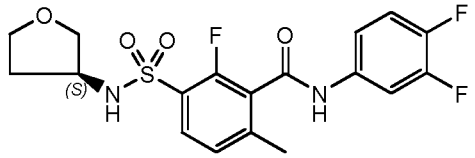
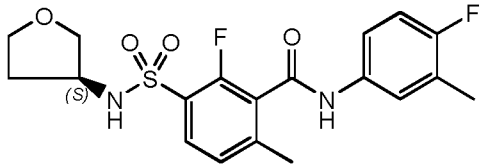
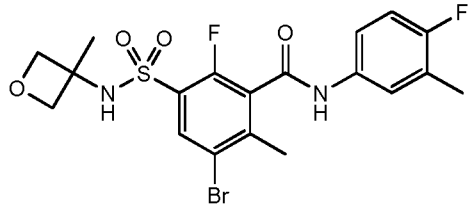
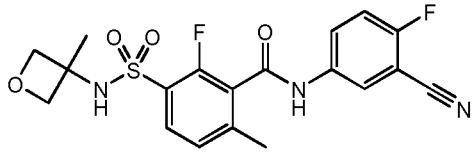
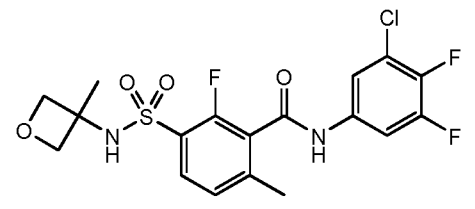
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**160**	0.20		0.69	>25
	**161**	0.20		0.35	>25
	**162**	0.17		1.26	>25
	**163**	0.53		8.53	>25
	**164**	3.71		0.97	>25
	**165**	0.71		0.36	>25

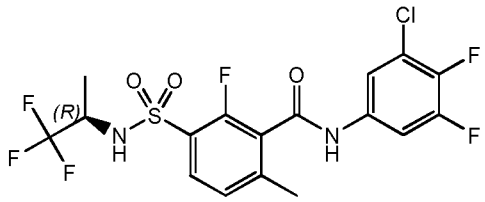
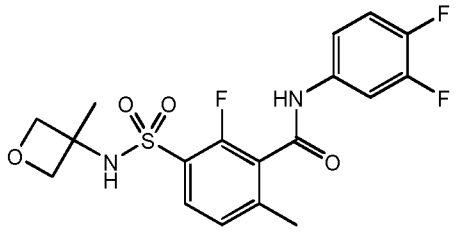
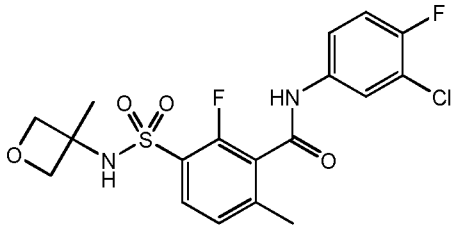
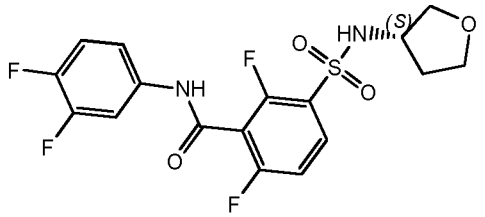
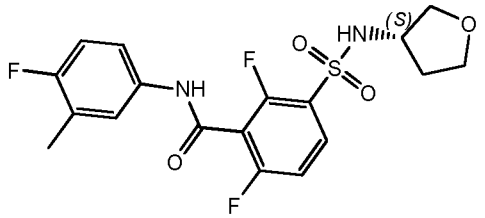
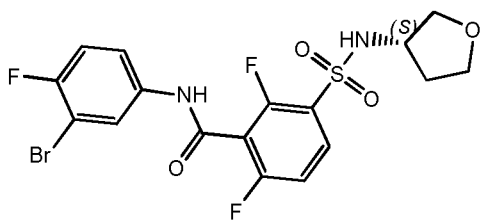
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**166**	0.19		2.39	14.6
	**167**	0.62		9.84	>25
	**168**	0.27		0.37	11.8
	**169**	0.24		1.41	14.9
	**170**	0.26		0.45	>25
	**171**	0.79		4.39	>25

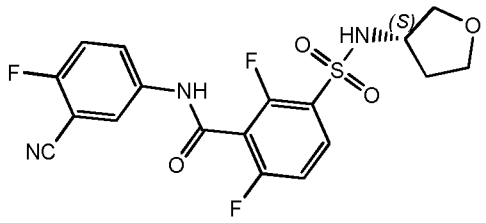
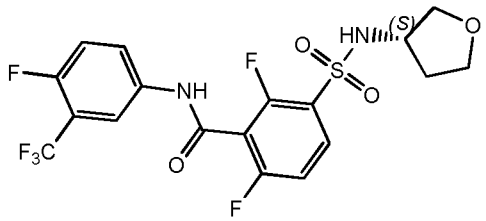
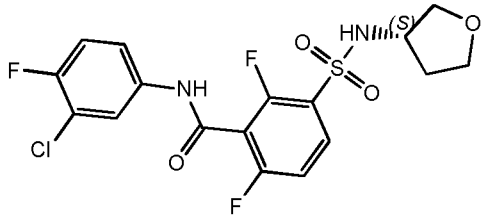
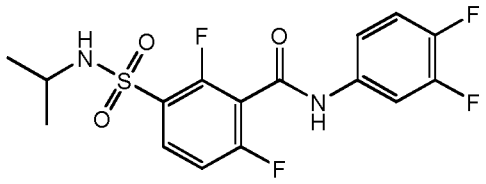
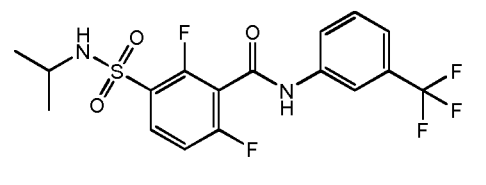
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**172**	0.26		0.61	>25
	**173**	0.37		0.36	>25
	**174**	0.47		2.84	>25
	**175**	0.23		0.15	>25
	**176**	0.62		0.56	>25
	**177**	0.77		0.72	>25

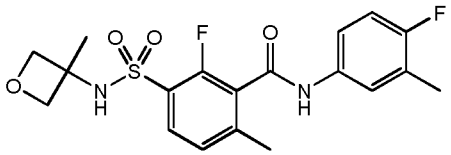
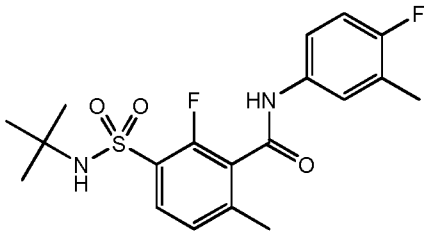
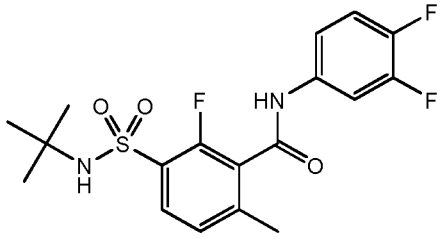
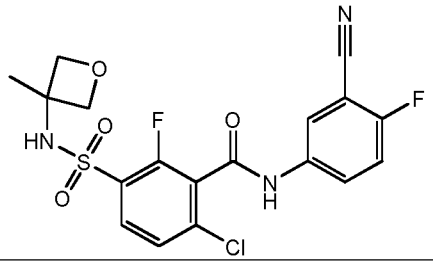
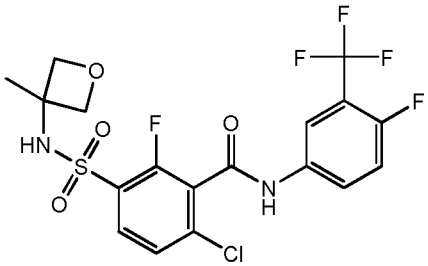
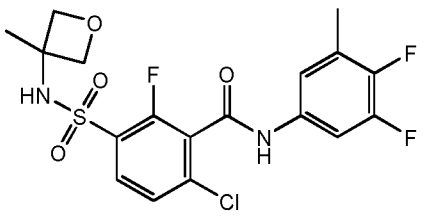
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**178**	0.75		2.54	>25
	**179**	0.21		0.44	>25
	179a	0.38		0.25	>25
	179b	1.11		1.84	>25
	**180**	0.76		1.30	>25
	**181**	2.59		2.04	>25
	**182**	0.31		0.88	>25

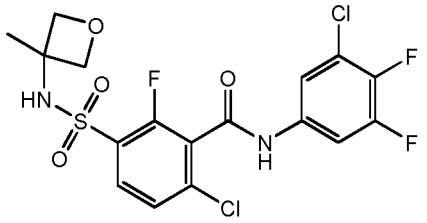
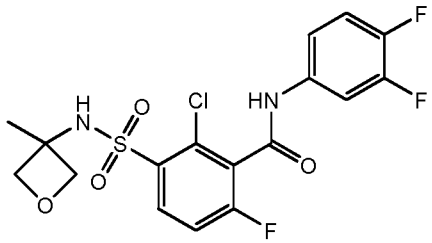
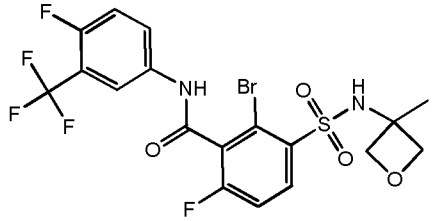
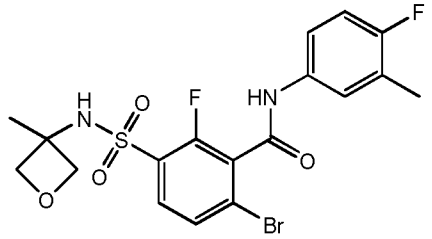
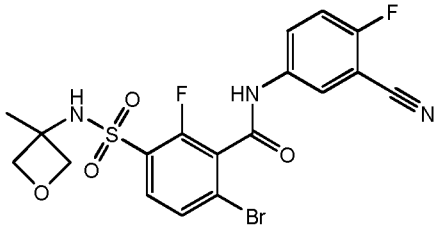
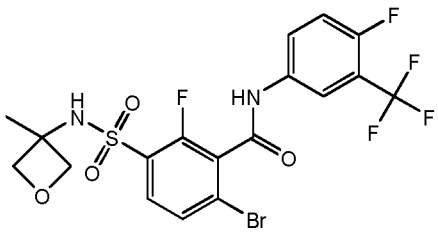
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**183**	0.08		0.84	>25
	**184**	0.15		0.40	>25
	**184a**	0.31		0.77	>25
	**184b**	0.30		0.33	>25
	**185**	0.22		0.62	>25
	**186**	0.20		1.34	>25

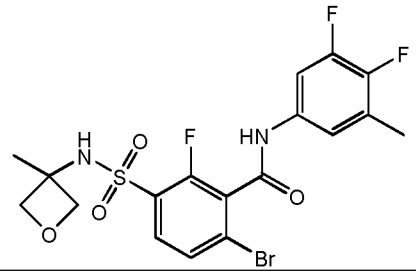
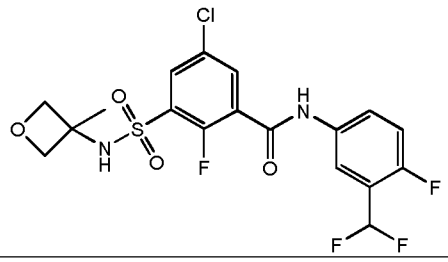
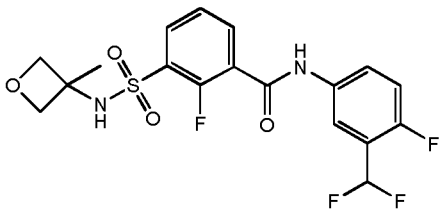
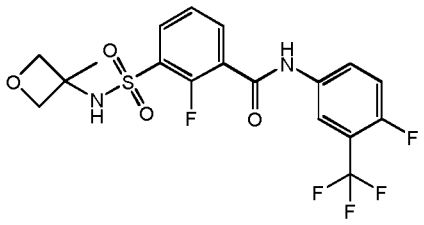
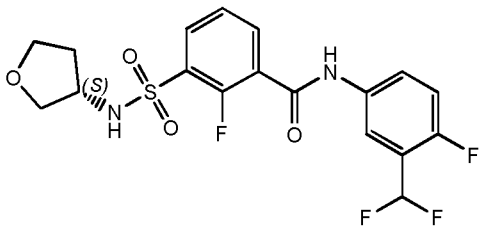
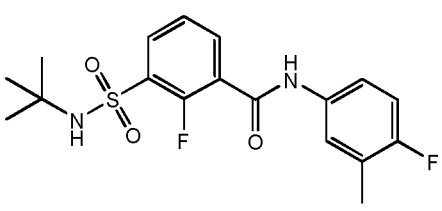
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**187**			0.95	>25
	**188**			0.24	>25
	**189**			0.35	>25
	**190**			0.27	>25
	**191**	0.33		0.36	>25
	**192**			0.19	>25

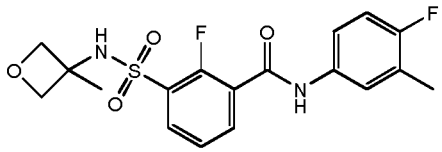
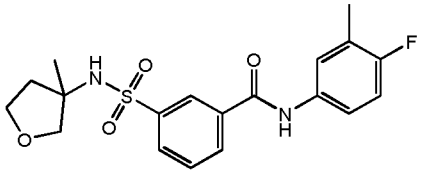
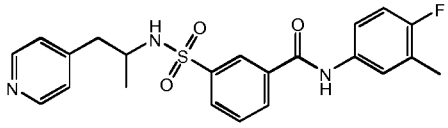
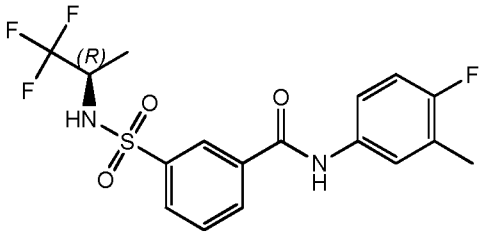
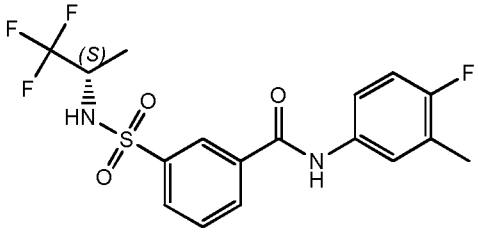
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**193**			0.10	13.5
	**194**	0.38		0.31	>25
	**195**	0.27		0.18	>25
	**196**	0.13		0.07	>25
	**197**			0.09	>25
	**198**			0.15	>25

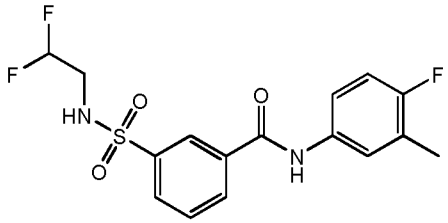
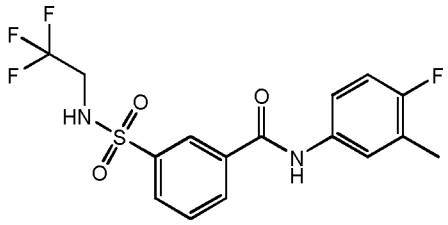
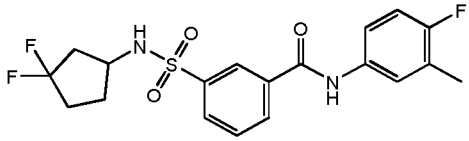
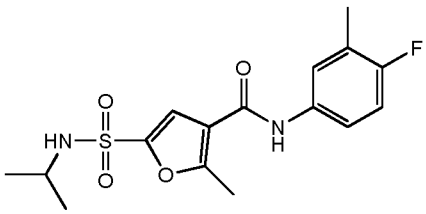
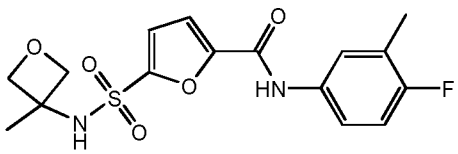
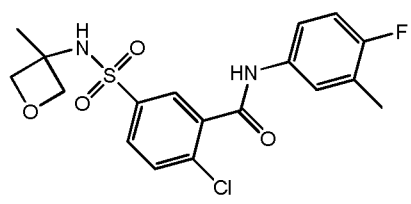
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**199**			0.43	>25
	**200**			0.45	>25
	**201**	0.06		0.06	>25
	**202**			0.11	>25
	**203**			0.24	16.7

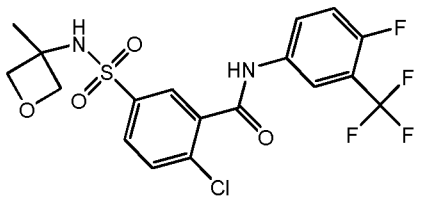
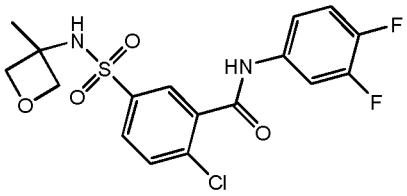
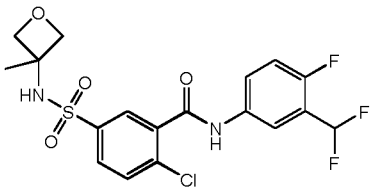
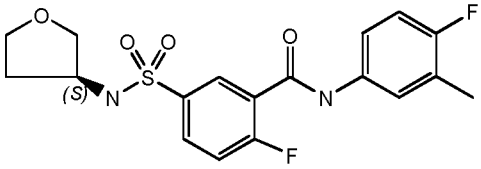
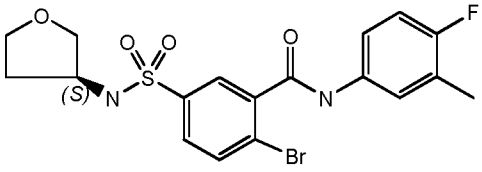
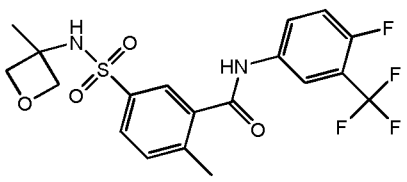
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**204**			0.09	>25
	**205**			0.35	>25
	**206**			0.64	>25
	**207**			>1	>25
	**208**			>1	>25
	**209**			0.15	>25

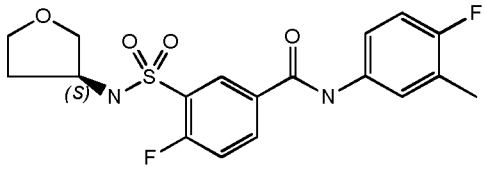
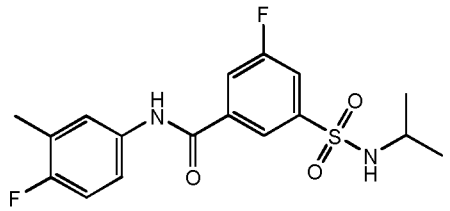
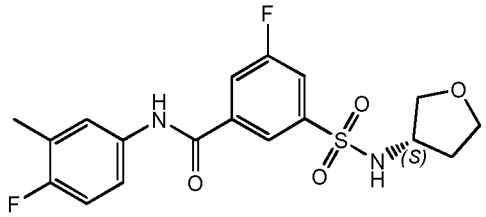
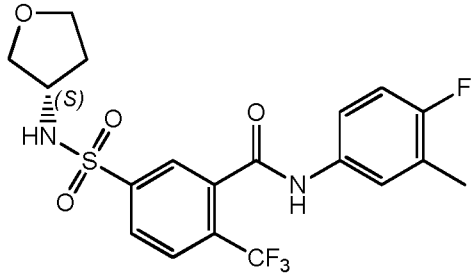
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**210**			0.46	>25
	**211**			0.65	>25
	**212**			7.3	>25
	**213**			0.28	>25
	**214**			>1	>25
	**215**			>1	>25

STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**216**			0.29	>25
	**217**	0.20		0.60	>25
	**218**	0.12		0.10	>25
	**219**			0.46	>25
	**220**	0.11		0.09	>25
	**221**			0.13	>25

STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**222**	0.05		0.10	>25
	**223**			0.21	>25
	**224**	0.16		0.76	>25
	**225**	0.09		1.34	>25
	**226**	0.27		1.9	>25

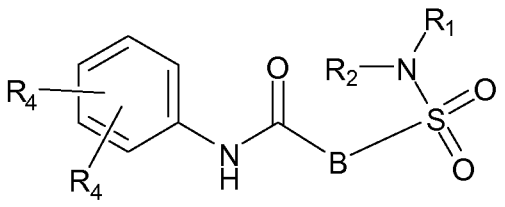
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**227**	0.16		0.71	>25
	**228**	0.17		1.19	>25
	**229**	0.20		0.49	>25
	**230**	0.73		1.52	>25
	**231**	0.21		0.32	>25
	**232**			0.31	>25

STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**233**	>1		>1	>25
	**234**	0.72		0.34	>25
	**235**	0.83		0.33	>25
	**236**	0.48		1.58	>25
	**237**	0.43		0.13	>25
	**238**	0.61		0.50	>25

STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**239**	0.48		0.53	>25
	**240**	0.40		2.86	>25
	**241**	0.38		1.79	>25
	**242**	1.91		1.80	>25

Claims

1. A compound of Formula (Ia)



(Ia)

or a stereoisomer or tautomeric form thereof, wherein:

B represents a monocyclic 5 to 6 membered aromatic ring, optionally containing one or more heteroatoms each independently selected from the group consisting of O, S and N, such 5 to 6 membered aromatic ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halo, C_1-C_3alkyl, CN, CFH_2, CF_2H and CF_3;

R_1 represents hydrogen or C_1-C_3alkyl;

R_2 represents C_1-C_6alkyl, C_1-C_3alkyl-R_5, benzyl, C(=O)-R_5, CFH_2, CF_2H, CF_3 or a 3-7 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O, S and N, such 3-7 membered saturated ring or C_1-C_6alkyl optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halo, C_1-C_4alkyloxy, oxo, C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3;

Or R_1 R_2 together with the Nitrogen to which they are attached form a 1,4-dioxa-8-azaspiro[4.5] moiety or a 5-7 membered saturated ring, optionally containing one or more additional heteroatoms each independently selected from the group consisting of O, S and N, such 5-7 membered saturated ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halo, C_1-C_4alkyloxy, oxo C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3;

Each R_4 is independently selected from hydrogen, halo, C_1-C_4alkyloxy, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H, CF_3 or a 3-5 membered saturated ring optionally containing

one or more heteroatoms each independently selected from the group consisting of O and N;

R_5 represents C_1-C_6alkyl, CFH_2, CF_2H, CF_3 or a 3-7 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O, S and N, such 3-7 membered saturated ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halo, C_1-C_4alkyloxy, oxo, C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3;

or a pharmaceutically acceptable salt or a solvate thereof.

2. The compound according to claim 1, wherein R_2 represents a 3-7 membered saturated ring, containing one or more heteroatoms each independently selected from the group consisting of O, S and N, such 3-7 membered saturated ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halo, C_1-C_4alkyloxy, C(=O)- C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3;

Or R_1 R_2 together with the Nitrogen to which they are attached form a 5-7 membered saturated ring, optionally containing one or more additional heteroatoms each independently selected from the group consisting of O, S and N, such 5-7 membered saturated ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halo, C_1 C_4alkyloxy, oxo, C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3.

3. The compound according to claim 1 or 2, wherein R_2 represents a 4-7 membered saturated ring containing carbon and one or more oxygen atoms, such 4-7 membered saturated ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halo, C_1 C_4alkyloxy, C(=O)- C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3.

4. A compound according any one of claims 1 to 3, wherein B represents phenyl or thiophene, optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halogen, C_1-C_3alkyl, CN, CFH_2, CF_2H and CF_3.

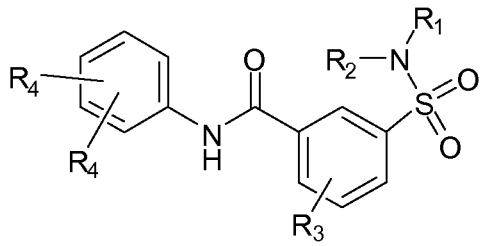
5. A compound of Formula (I) according to any one of the previous claims, wherein

R_2 represents C_1-C_3alkyl-R_6 or a 4-7 membered saturated ring consisting of carbon atoms and one or more heteroatoms each independently selected from the group consisting of O or S, such 4-7 membered saturated ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halo, C_1-C_4alkyloxy, oxo, C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3;

Each R_4 is independently selected from hydrogen, halo, C_1-C_4alkyloxy, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H, CF_3 or a 3-5 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O and N; and

R_6 represents a 4-7 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O or S, such 4-7 membered saturated ring optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halo, C_1-C_4alkyloxy, oxo, C(=O)-C_1-C_3alkyl, C_1-C_4alkyl, OH, CN, CFH_2, CF_2H and CF_3.

6. A compound according to any one of the previous claims, which is of Formula (Ib)

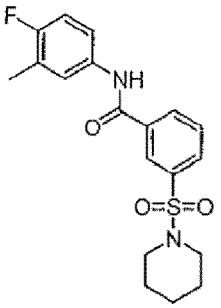


(Ib)

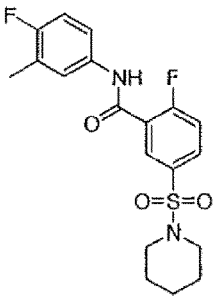
wherein R_1, R_2, R_4 are defined as in any one of the previous claims and R_3 is selected from the group comprising hydrogen, halo, C_1-C_3alkyl, CN, CFH_2, CF_2H, CF_3.

7. A compound according to any one of the previous claims, wherein at least one R_4 represents Fluor, C_1-C_3alkyl or cyclopropyl.

8. A compound according to any one of the previous claims, wherein one R_4 on the *para* position represents Fluor and the other one R_4 on the *meta* position represents methyl and such compound is not



or



.

9. A compound according to any one of the previous claims, wherein R_3 represents Fluor.

10. A compound according to any one of claims 1 to 9, wherein B represents phenyl or thiophene, optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halogen, C_1-C_3alkyl, CN, CFH_2, CF_2H and CF_3.

11. A compound according to any one of the previous claims for use in the prevention or treatment of an HBV infection in a mammal.

12. A pharmaceutical composition comprising a compound according to any of claims 1 to 10, and a pharmaceutically acceptable carrier.

13. A product containing (a) a compound of formula I as defined in any one of claims 1 to 10, and (b) another HBV inhibitor, as a combined preparation for simultaneous, separate or sequential use in the treatment of HBV infections.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/067821

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D309/14 C07D231/14 C07D333/46 C07C311/37 C07D295/26
A61K31/18 A61K31/277 A61K31/351 A61K31/4453 A61K31/381
A61P31/20 A61P1/18 A61K31/337 A61K31/341 A61K31/4164

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 C07C A61K

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, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	D. CAI ET AL: "Identification of Disubstituted Sulfonamide Compounds as Specific Inhibitors of Hepatitis B Virus Covalently Closed Circular DNA Formation", ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, vol. 56, no. 8, 1 August 2012 (2012-08-01) , pages 4277-4288, XP055059505, ISSN: 0066-4804, DOI: 10.1128/AAC.00473-12 abstract figure 3; compounds B (CCC-0346) page 4278, left-hand column, paragraph 3 - right-hand column, paragraph 3 page 4282, right-hand column, paragraph 4 - page 4283, right-hand column, paragraph 1 page 4286, right-hand column, last paragraph - page 4287, left-hand column, paragraph 1 ----- -/--	1-13

[X] Further documents are listed in the continuation of Box C.

[X] 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" document which may throw doubts on priority claim(s) or which 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
21 November 2013	28/11/2013

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	Langer, Oliver

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NAM DOO KIM ET AL: "Discovery of novel HCV polymerase inhibitors using pharmacophore-based virtual screening", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, GB, vol. 21, no. 11, 4 April 2011 (2011-04-04) , pages 3329-3334, XP028211474, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2011.04.010 [retrieved on 2011-04-09] table 1; compounds 14,15	1,2,4,6, 7,10,12
X	MAI S MABROUK: "Discovering best candidates for Hepatocellular Carcinoma (HCC) by in-silico techniques and tools", INT. J. BIOINFORMATICS RESEARCH AND APPLICATIONS, vol. 8, no. 1/2, 1 January 2012 (2012-01-01), pages 141-152, XP055059465, page 148; figures 5,6 page 151, paragraph 1 tables 3,4	1,4-6, 10-13
X	LAMBENG ET AL: "Arylsulfonamides as a new class of cannabinoid CB1 receptor ligands: Identification of a lead and initial SAR studies", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, vol. 17, no. 1, 22 December 2006 (2006-12-22), pages 272-277, XP005812156, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2006.09.049 table 3; compound 18	1,4,6, 10,12
X	ZHANG XIAOQIAN ET AL: "A potent small molecule inhibits polyglutamine aggregation in Huntington's disease neurons and suppresses neurodegeneration in vivo", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, NATIONAL ACADEMY OF SCIENCES, US, vol. 102, no. 3, 18 January 2005 (2005-01-18), pages 892-897, XP009116402, ISSN: 0027-8424, DOI: 10.1073/PNAS.0408936102 figure 2A; compound C2	1,4,6,10

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3

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2010/016310 A1 (INGRAHAM RICHARD HAROLD [US]) 21 January 2010 (2010-01-21) page 20, right-hand column; claim 5; compound 1	1,4,6, 10,12
X	WO 02/064618 A2 (MASSACHUSETTS INST TECHNOLOGY [US]; HOUSMAN DAVID E [US]) 22 August 2002 (2002-08-22) claim 2; figure 3	1,4,6,7, 9,10,12
X	US 2005/239833 A1 (KAZANTSEV ALEKSEY G [US] ET AL) 27 October 2005 (2005-10-27) claims 25,26; table 2; compounds B1,B4,B5,B6,B8,B9	1,2,4,6, 10,12
X	US 2011/009622 A1 (JITSUOKA MAKOTO [JP] ET AL) 13 January 2011 (2011-01-13) example 38 paragraph [0137] table 1	1,2,4,6, 7,10,12
X,P	WO 2013/006394 A1 (INST HEPATITIS AND VIRUS RES [US]; GUO JU-TAO [US]; XU XIAODONG [US];) 10 January 2013 (2013-01-10) cited in the application claims 1,2,4 last compound (DVR-74) on page 25 second but last compound (DVR-73) on page 25 table 6; compounds DVR-73, DVR-74 paragraph [0157]	1,2,4-7, 9-13
X,P	WO 2013/096744 A1 (NOVIRA THERAPEUTICS INC [US]) 27 June 2013 (2013-06-27) abstract claims 1,31,38 page 39; compound 042 compound 041 on page 39 is disclaimed in claim 8 page 47; compound 174 page 150; compounds 1404, 1405	1-4,6-13

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Information on patent family members

International application No
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(19)中华人民共和国国家知识产权局

(12)发明专利申请

(10)申请公布号 CN 104812743 A
(43)申请公布日 2015.07.29

(21)申请号 201380044856.2

(22)申请日 2013.08.28

(30)优先权数据
12182076.5 2012.08.28 EP
12185055.6 2012.09.19 EP
12190837.0 2012.10.31 EP
13157230.7 2013.02.28 EP
13169574.4 2013.05.28 EP

(85)PCT国际申请进入国家阶段日
2015.02.27

(86)PCT国际申请的申请数据
PCT/EP2013/067821 2013.08.28

(87)PCT国际申请的公布数据
WO2014/033170 EN 2014.03.06

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(51)Int.Cl.
C07D 309/14(2006.01)
C07D 231/14(2006.01)
C07D 333/46(2006.01)
C07C 311/37(2006.01)
C07D 295/26(2006.01)
A61K 31/18(2006.01)
A61K 31/277(2006.01)
A61K 31/351(2006.01)
A61K 31/4453(2006.01)
A61K 31/381(2006.01)
A61P 31/20(2006.01)
A61P 1/18(2006.01)
A61K 31/337(2006.01)
A61K 31/341(2006.01)
A61K 31/4164(2006.01)

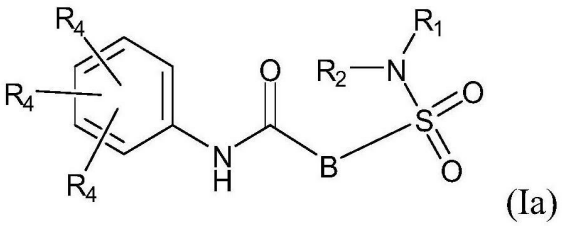
权利要求书3页 说明书154页

(54)发明名称

氨磺酰基-芳基酰胺和其作为药物用于治疗乙型肝炎的用途

(57)摘要

具有化学式(I)的HBV复制抑制剂

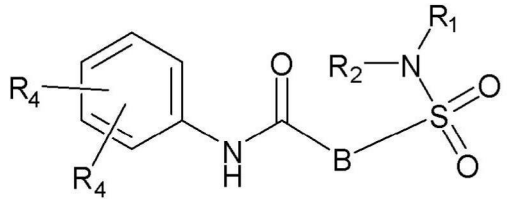


(Ia)

包括其立体化学同分异构形式,以及盐、水合物、溶剂化物,其中B、R_1、R_2和R_4具有如在此定义的含义。本发明还涉及包含这些抑制剂的药物组合物以及在HBV疗法中它们单独的或与其他HBV抑制剂组合的用途。

CN 104812743 A

1. 一种具有化学式 (Ia) 的化合物



(Ia)

或其一种立体异构体或互变异构形式，其中：

B 代表一个单环的 5 至 6 元芳族环，该芳族环可任选地包含一个或多个杂原子，这些杂原子各自独立地选自由 O、S 和 N 组成的组，这种 5 至 6 元芳族环可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_3烷基、CN、CFH_2、CF_2H 和 CF_3组成的组；

R_1代表氢或 C_1-C_3烷基；

R_2代表 C_1-C_6烷基、C_1-C_3烷基 -R_5、苄基、C(=O)-R_5、CFH_2、CF_2H、CF_3或一个 3-7 元饱和环，该饱和环可任选地包含一个或多个杂原子，这些杂原子各自独立地选自由 O、S 和 N 组成的组，这种 3-7 元饱和环或 C_1-C_6烷基可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_4烷氧基、氧代、C(=O)-C_1-C_3烷基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H 和 CF_3组成的组；

或 R_1R_2与它们附接其上的氮一起形成一个 1,4- 二氧杂 -8- 氮杂螺 [4.5] 部分、或一个 5-7 元饱和环，该饱和环可任选地包含一个或多个另外的杂原子，这些杂原子各自独立地选自由 O、S 和 N 组成的组，这种 5-7 元饱和环可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_4烷氧基、氧代 C(=O)-C_1-C_3烷基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H 和 CF_3组成的组；

每个 R_4独立地选自氢、卤素、C_1-C_4烷氧基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H、CF_3或一个 3-5 元饱和环，该饱和环可任选地包含一个或多个杂原子，这些杂原子各自独立地选自由 O 和 N 组成的组；

R_5代表 C_1-C_6烷基、CFH_2、CF_2H、CF_3或一个 3-7 元饱和环，该饱和环可任选地包含一个或多个杂原子，这些杂原子各自独立地选自由 O、S 和 N 组成的组，这种 3-7 元饱和环可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_4烷氧基、氧代、C(=O)-C_1-C_3烷基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H 和 CF_3组成的组；

或其一种药学上可接受的盐或溶剂化物。

2. 根据权利要求 1 所述的化合物，其中 R_2代表一个 3-7 元饱和环，该饱和环包含一个或多个杂原子，这些杂原子各自独立地选自由 O、S 和 N 组成的组，这种 3-7 元饱和环可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_4烷氧基、C(=O)-C_1-C_3烷基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H 和 CF_3组成的组；

或 R_1R_2与它们附接其上的氮一起形成一个 5-7 元饱和环，该饱和环可任选地包含一个或多个另外的杂原子，这些杂原子各自独立地选自由 O、S 和 N 组成的组，这种 5-7 元饱和环可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1C_4烷氧基、氧代、C(=O)-C_1-C_3烷基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H 和 CF_3组成的组。

3. 根据权利要求 1 或 2 所述的化合物，其中 R_2代表一个 4-7 元饱和环，该饱和环包含碳

和一个或多个氧原子，这种 4-7 元饱和环可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1C_4烷氧基、C(=O)-C_1-C_3烷基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H 和 CF_3组成的组。

4. 根据权利要求 1 至 3 中任一项所述的化合物，其中 B 代表苯基或噻吩，可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_3烷基、CN、CFH_2、CF_2H 和 CF_3组成的组。

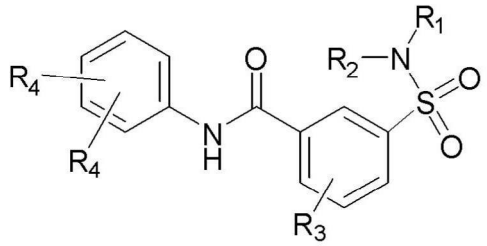
5. 根据前述权利要求中任一项所述的具有化学式 (I) 的化合物，其中

R_2代表 C_1-C_3烷基 -R_6或一个 4-7 元饱和环，该饱和环由碳原子和一个或多个杂原子组成，这些杂原子各自独立地选自由 O 或 S 组成的组，这种 4-7 元饱和环可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_4烷氧基、氧代、C(=O)-C_1-C_3烷基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H 和 CF_3组成的组；

每个 R_4独立地选自氢、卤素、C_1-C_4烷氧基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H、CF_3或一个 3-5 元饱和环，该饱和环可任选地包含一个或多个杂原子，这些杂原子各自独立地选自由 O 和 N 组成的组；并且

R_6代表一个 4-7 元饱和环，该饱和环可任选地包含一个或多个杂原子组成，这些杂原子各自独立地选自由 O 或 S 组成的组，这种 4-7 元饱和环可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_4烷氧基、氧代、C(=O)-C_1-C_3烷基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H 和 CF_3组成的组。

6. 根据前述权利要求中任何一项所述的化合物，其具有化学式 (Ib)

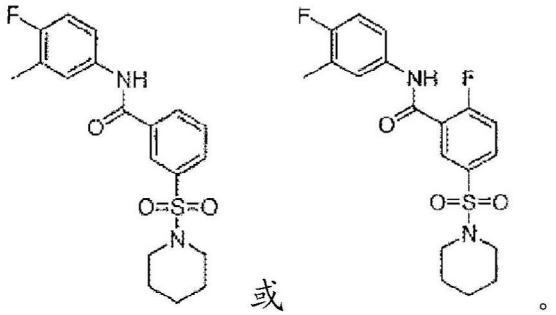


(Ib)

其中 R_1、R_2、R_4是如前述权利要求中任一项所定义的，并且 R_3选自包括以下项的组：氢、卤素、C_1-C_3烷基、CN、CFH_2、CF_2H、CF_3。

7. 根据前述权利要求中任一项所述的化合物，其中至少一个 R_4代表氟、C_1-C_3烷基或环丙基。

8. 根据前述权利要求中任何一项所述的化合物，其中一个位于对位的 R_4代表氟并且另一个位于间位的 R_4代表甲基并且这种化合物不是



或 。

9. 根据前述权利要求中任一项所述的化合物，其中 R_3代表氟。

10. 根据权利要求 1 至 9 中任一项所述的化合物，其中 B 代表苯基或噻吩，可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_3烷基、CN、CFH_2、CF_2H 和 CF_3组成的组。

11. 根据前述权利要求中任一项所述的化合物，用于在哺乳动物中预防或治疗 HBV 感染中使用。

12. 一种药物组合物，包括根据权利要求 1 至 10 中任一项所述的化合物、以及一种药学上可接受的载体。

13. 一种产品，包含 (a) 如在权利要求 1 至 10 中任一项所定义的具有化学式 I 的化合物，以及 (b) 另一种 HBV 抑制剂，作为用于在 HBV 感染的治疗中同时、分开或页序地使用的组合制剂。

氨磺酰基 - 芳基酰胺和其作为药物用于治疗乙型肝炎的用途

技术背景

[0001] 乙型肝炎病毒 (HBV) 是一种有包膜的、部分双链 DNA(dsDNA) 的、嗜肝病毒 DNA 家族 (肝病毒科 (Hepadnaviridae)) 的病毒。它的基因组包含 4 个重叠阅读框 :前核 / 核基因 ;聚合酶基因 ;L、M 和 S 基因 (它们编码三个包膜蛋白质) ;以及 X 基因。

[0002] 在感染前时,该部分双链 DNA 基因组在宿主细胞核中 (开环 DNA ;rcDNA) 转变为共价闭合环状 DNA(cccDNA) 并且该病毒 mRNA 进行转录。一旦被壳体化,该前基因组 RNA(pgRNA)(其还为核心蛋白和 Pol 编码) 作为模板用于逆转录,这种逆转录在核衣壳中再生该部分 dsDNA 基因组 (rcDNA)。

[0003] HBV 在亚洲和非洲的部分地区造成了流行病,并且它在中国是地方性的。HBV 已经在全球感染了大约 20 亿人,其中大约 3.5 亿人发展成了慢性传染病。该病毒造成了乙型肝炎疾病并且慢性传染病与肝硬化和肝癌的发展的高增加风险相关联。

[0004] 乙型肝炎病毒的传播来源于暴露于传染性的血液或体液,同时在血清中具有高效价 DNA 的慢性携带者的唾液、泪液以及尿液中检测到了病毒 DNA。

[0005] 存在一种有效的并且具有良好耐受性的疫苗,但是直接治疗的选择目前还限于干扰素以及以下的抗病毒药 ;替诺福韦、拉米夫定、阿德福韦、恩替卡韦以及替比夫定。

[0006] 此外,杂芳基二氢嘧啶 (HAPs) 在组织培养以及动物模型中被鉴别作为的一类 HBV 抑制剂 (韦伯 (Weber) 等人,《抗病毒研究》(Antiviral Res.)54 :69-78)。

[0007] WO 2013/006394(公开于 2013 年 1 月 10 日),和 WO 2013/096744(公开于 2013 年 6 月 27 日),涉及抗 HBV 活性的氨磺酰基 - 芳基酰胺。

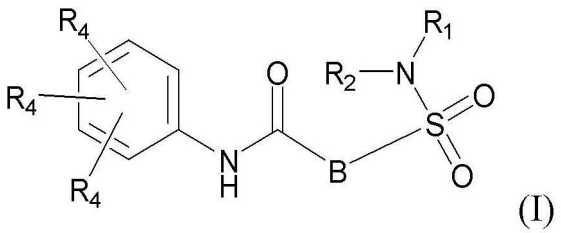
[0008] 在这些直接的 HBV 抗病毒药的问题中可能遇到的是毒性、致突变性、缺乏选择性、疗效差、生物利用度差以及合成困难。

[0009] 针对另外的 HBV 抑制剂有一种需要,该抑制剂可以克服至少一种这些不利条件或者该抑制剂具有另外的优势,例如增加的效价或者一种增加的安全窗。

[0010] 发明说明

[0011] 本发明涉及具有化学式 (I) 的化合物

[0012]



(I)

[0013] 或其一种立体异构体或互变异构形式,其中 :

[0014] B 代表一个单环的 5 至 6 元芳族环,该芳族环可任选地包含一个或多个杂原子,这些杂原子各自独立地选自由 O、S 和 N 组成的组,这种 5 至 6 元芳族环可任选地被一个或多个取代基取代,这些取代基各自独立地选自由氢、卤素、C_1-C_3烷基、CN、CFH_2、CF_2H 和 CF_3组

成的组；

[0015] R_1代表氢或 C_1-C_3烷基；

[0016] R_2代表 C_1-C_6烷基、C_1-C_6烯基、C_1-C_6烷基 -R_5、C(=O)-R_5、CFH_2、CF_2H、CF_3、一个可任选地被 OH 取代的二氢 - 茚基或者四氢萘基部分、或一个 3-7 元饱和环，该饱和环可任选地包含一个或多个杂原子，这些杂原子各自独立地选自由 O、S 和 N 组成的组，这种 3-7 元饱和环、C_1-C_6烷基 -R_5或 C_1-C_6烷基可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_4烷氧基、C_1-C_4烷氧基羰基、氧代、C(=O)-C_1-C_3烷基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H 和 CF_3组成的组；

[0017] 或 R_1和 R_2与它们附接其上的氮一起形成一个 6-10 元二环或桥环或一个 5-7 元饱和环，这种二环、桥环或饱和环部分可任选地包含一个或多个另外的杂原子，这些杂原子各自独立地选自由 O、S 和 N 组成的组，这种 5-7 元饱和环可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_4烷氧基、C_1-C_4烷氧基羰基、氧代、C(=O)-C_1-C_3烷基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H 和 CF_3组成的组；

[0018] 每个 R_4独立地选自氢、卤素、C_1-C_4烷氧基、C_1-C_4烷基、C_1-C_4烯基、OH、CN、CFH_2、CF_2H、CF_3、HC≡C 或一个 3-5 元饱和环，该饱和环可任选地包含一个或多个杂原子，这些杂原子各自独立地选自由 O 和 N 组成的组，这种 C_1-C_4烷基可任选地被 OH 取代；

[0019] R_5代表 C_1-C_6烷基、CFH_2、CF_2H、CF_3、苯基、吡啶基或一个 3-7 元饱和环，该饱和环可任选地包含一个或多个杂原子，这些杂原子各自独立地选自由 O、S 和 N 组成的组，这种 3-7 元饱和环可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_4烷氧基、C_1-C_4烷氧基羰基、氧代、C(=O)-C_1-C_3烷基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H 和 CF_3组成的组；

[0020] 或其一种药学上可接受的盐或溶剂化物。

[0021] 本发明进一步涉及一种药物组合物，该药物组合物包括一种具有化学式 (I) 的化合物，以及一种药学上可接受的载体。

[0022] 本发明还涉及具有化学式 (I) 的化合物用于作为一种药物，优选地用于在哺乳动物中在 HBV 感染的预防和治疗中使用。

[0023] 在另一方面，本发明涉及一种具有化学式 (I) 的化合物与另一种 HBV 抑制剂的组合。

[0024] 定义

[0025] 术语“C_{1-3}烷基”作为一种基团或基团的部分，是指具有化学式 C_nH_{2n+1}的烃基基团，其中 n 是范围为从 1 至 3 的数字。在 C_{1-3}烷基偶联至一种另外的基团的情况下，它是指一种化学式 C_nH_{2n}。C_{1-3}烷基基团包含 1 至 3 个碳原子，更优选 1 至 2 个碳原子。C_{1-3}烷基包括具有 1 和 3 个碳原子之间的所有线性的、或支链的烷基基团，并且因此包括例如像甲基、乙基、正丙基和异丙基。

[0026] 作为基团或基团的部分的 C_{1-4}烷基定义了具有从 1 至 4 个碳原子的直链或支链饱和烃基，例如针对 C_{1-3}烷基和丁基以及类似物定义的基团。

[0027] 作为基团或基团的部分的 C_{1-6}烷基定义了具有从 1 至 6 个碳原子的直链或支链饱和烃基，例如针对 C_{1-4}烷基和戊基、己基、2- 甲基丁基以及类似物定义的基团。

[0028] 作为基团或基团的部分的 C_{1-4}烯基定义了具有从 1 至 4 个碳原子的在任何可能

位置具有至少一个双键的直链或支链烃基。此类烯基的实例是乙烯基、丙烯基、1- 丁烯基、2- 丁烯基。作为基团或基团的部分的C_{1-6}烯基定义了具有从 1 至 6 个碳原子的具有至少一个双键的直链或支链烃基。

[0029] 作为基团或基团的一部分的术语“C_{1-3}烷基氧基”指具有式 --OR^{c}的基团，其中 R^{c}是 C_{1-3}烷基。合适的 C_{1-3}烷氧基的非限制实例包括甲基氧基 (methyloxy)(也作甲氧基 (methoxy))、乙基氧基 (ethyloxy)(也作乙氧基 (ethoxy))，丙氧基以及异丙氧基。

[0030] 术语氧代、C(＝ O)、或羰基是指一种由一个双键键合至氧原子的碳原子构成的基团。

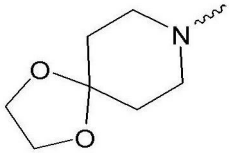
[0031] 如在此使用的，术语“3-7 元饱和环”意思是具有 3、4、5、6 或 7 个碳原子的饱和环烃，并且对于环丙基、环丁基、环戊基、环己基和环庚基是通用的。

[0032] 此类饱和环可任选地包含一个或多个杂原子，例如至少一个碳原子被杂原子取代，该杂原子选自 N、O 和 S，尤其是选自 N 和 O。实例包括氧杂环丁烷、氮杂环丁烷、四氢 -2H- 吡喃基、哌啶基、四氢呋喃基、吗啉基和吡咯烷基。优选地是具有 3 或 4 个碳原子以及 1 个氧原子的饱和环烃。实例包括氧杂环丁烷以及四氢呋喃基。

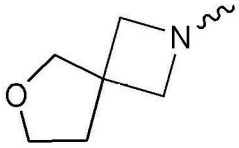
[0033] 如在此使用的，术语单环的 5 至 6 元芳族环 (“芳基”)，意思是一种具有 5 或 6 个碳原子的芳族环烃。芳基基团的优选实例是苯基。

[0034] 此类饱和环可任选地包含一个或多个杂原子，这些杂原子各自独立地选自由 O、S 和 N(“杂芳基”) 组成的组，针对本发明的目的，一种杂芳基基团需要仅仅具有一些程度的芳族特征。杂芳基基团的说明性实例包括，但不限于，吡啶基、哒嗪基、嘧啶基、吡嗪基、三嗪基、吡咯基、吡唑基、咪唑基、(1,2,3,)- 三唑基以及 (1,2,4)- 三唑基、吡嗪基、嘧啶基、四唑基、呋喃基、噻吩基、异噁唑基、噻唑基、异噁唑基、和噁唑基。一种杂芳基基团可以不被取代或被一个或多个合适的取代基取代。

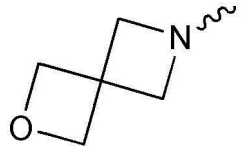
[0035] 如在此使用的，术语 6-10 元二环指示一种具有 6-7-8-9 个或者 10 个原子的饱和二环。此类饱和二环可任选地包含一个或多个杂原子，例如至少一个碳原子被杂原子取代，该杂原子选自 N、O 和 S，特别是选自 N 和 O。

[0036] 如在此使用的此类 6-10 元二环的实例是 1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸基部分，指示了具有结构式  的基团，6- 氧杂 -2- 氮杂螺 [3.4] 辛烷部分，指示了具有以下结构式的基团

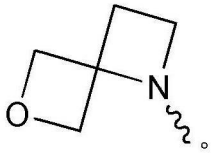
[0037]



[0038] 2- 氧杂 -6- 氮杂螺 [3.3] 庚基部分，指示了具有以下结构式的基团，

[0039]  或具有以下结构式的 6- 氧杂 -1- 氮杂螺 [3.3] 庚基部分

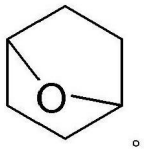
[0040]



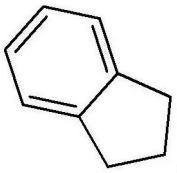
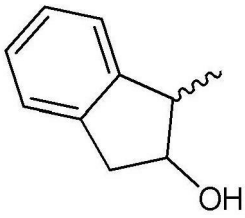
。

[0041] 如在此使用的，术语 6-10 元桥环指示一种具有 6-7-8-9 个或者 10 个原子的饱和桥环。此类饱和二环可任选地包含一个或多个杂原子，例如至少一个碳原子被杂原子取代，该杂原子选自 N、O 和 S，特别是选自 N 和 O。如在此使用的此类 6-10 元桥环的实例是由以下结构代表的 - 噁二环 [2.2.1] 庚烷

[0042]



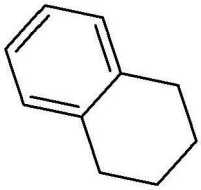
。

[0043] 如在此使用的，二氢茚基部分代表具有以下结构式的基团  此类二氢茚基部分可以可任选地被 OH 取代。如在此使用的一个实例，2- 羟基 -2,3- 二氢 -1H- 茚基部分指示了一种具有以下结构式的基团 

。

[0044] 如在此使用的，四氢萘基部分代表具有以下结构式的基团

[0045]



。

[0046] 如果没有指示，对于以上任何部分，只要它是化学稳定的，那么主结构上的附接可以位于此类部分地任何位置。

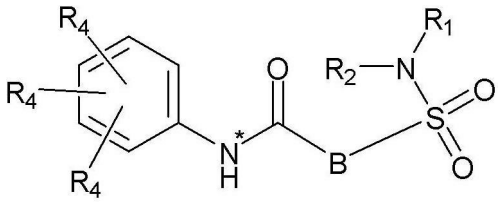
[0047] 应该注意的是不同杂环的不同异构体可以存在于如贯穿本说明使用的定义中。例如，吡咯基可以是 1H- 吡咯基或者 2H- 吡咯基。

[0048] 术语卤素 (halo) 和卤素 (halogen) 对于氟、氯、溴或碘是通用的。优选的卤素是

氟和氯。

[0049] 还应该注意的是在定义中使用的任何分子部分上的基团位置可以是在此类部分上的任何位置，只要它是化学稳定的。例如，吡啶基包括 2- 吡啶基，3- 吡啶基和 4- 吡啶基；戊基包括 1- 戊基，2- 戊基和 3- 戊基。

[0050] 在苯基上指示的位置（例如邻位、间位和 / 或对位）是相对于将该苯基连接到主结构上的键所指示的。关于 R_4 位置的一个实例，指示了相对于连接到主结构上的氮 (*) 的任何位置：

[0051] 

（化学式 (I*)

[0052] 当任一变量（例如卤素或 C_{1-4} 烷基）在任何构成中出现多于一次时，每个定义是独立的。

[0053] 为了治疗使用，具有化学式 (I) 的化合物的盐是其中平衡离子是药学上或生理学上可接受的那些。然而，例如在药学上可接受的具有化学式 (I) 的化合物的制备或纯化中，还可以发现具有非药学上可接受的平衡离子的盐的用途。所有的盐，不论是药学上可接受的还是不可接受的，均被包括在本发明的范围内。

[0054] 本发明的化合物能够形成的药学上可接受的或生理学上可耐受的加成盐形式可以使用合适的酸方便地进行制备，这些酸例如像，无机酸例如氢卤酸（诸如盐酸或氢溴酸）、硫酸、半硫酸、硝酸、磷酸以及类似酸；或者有机酸例如像，乙酸、天冬氨酸、十二烷基硫酸、庚酸、己酸、烟酸、丙酸、羟乙酸、乳酸、丙酮酸、草酸、丙二酸、琥珀酸、顺丁烯二酸、反丁烯二酸、苹果酸、酒石酸、柠檬酸、甲磺酸、乙磺酸、苯磺酸、对甲苯磺酸、环己氨基磺酸、水杨酸、对氨基水杨酸、扑酸和类似酸。

[0055] 相反地，可以通过用合适的碱的处理将所述酸加成盐形式转化为游离碱形式。

[0056] 术语“盐”还包括本发明的化合物能够形成的水合物和溶剂加成形式。这些形式的实例是例如水合物、醇化物等。

[0057] 本发明的化合物还可以它们的互变异构形式存在，例如酰胺 (-C(=O)-NH-) 基团的互变异构形式是亚氨基醇 (-C(OH)=N-)。互变异构形式，虽然没有在此处代表的结构式中明确指出，也旨在包括在本发明的范围之内。

[0058] 如在上文中使用的术语“本发明的化合物的立体化学同分异构形式”定义了由通过相同顺序的键键合的相同原子组成的但具有不可互换的不同三维结构的所有可能化合物，本发明的化合物可以具有这些特征。除非另外提到或指示，化合物的化学指定包括所述化合物可以具有的所有可能立体化学同分异构形式的混合物。所述混合物可以包含具有所述化合物的基本分子结构的所有非对映异构体和 / 或对映异构体。处于纯态的或与彼此混合的本发明的化合物的所有立体化学同分异构形式都旨在被包含在本发明的范围之内。

[0059] 在此提到的化合物和中间体的纯的立体异构形式被定义为基本上没有具有所述化合物或中间体的相同基本分子结构的其他对映异构或非对映异构形式的异构体。具体地说，术语“立体异构纯”涉及具有至少 80％立体异构超额（即，最小 90％的一种异构体以及

最大 10％的其他可能异构体）达至 100％超额（即，100％的一种异构体并且没有其他的）的化合物或中间体，更尤其是，具有 90％达至 100％立体异构超额的化合物或中间体，甚至更尤其是具有 94％达至 100％立体异构超额并且最尤其是具有 97％达至 100％立体异构超额。应当以类似的方式理解术语‘对映异构纯’和‘非对映异构纯’，但是讨论中的分别是关于混合物中的对映异构超额以及非对映异构超额。

[0060] 可以通过领域已知的程序的应用来获得本发明的化合物和中间体的纯的立体异构形式。例如，对映异构体可以通过用旋光酸或旋光碱使它们的非对映异构盐进行选择性结晶而得以彼此分离。其实例是酒石酸、二苯甲酰酒石酸 (dibenzoyltartaric acid)、二甲苯酰酒石酸 (ditoluoyltartaric acid) 以及樟脑磺酸。可替代地，可以通过使用手性固定相的层析技术分离对映异构体。所述纯的立体化学同分异构形式还可以衍生自适当的起始材料的相应的纯的立体化学同分异构形式，其条件是该反应立体定向地发生。优选地，如果一种具体的立体异构体是所希望的，所述化合物将通过制备的立体定向方法得以合成。这些方法将有利地采用对映异构纯的起始材料。

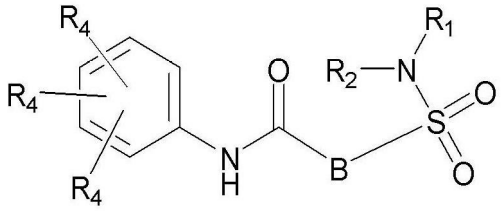
[0061] 可以通过常规方法分别地获得具有化学式 (I) 的非对映异构外消旋体。可以有利地被采用的合适的物理分离方法是例如选择性结晶和层析法（例如柱层析）。

[0062] 本发明还旨在包括在此类化合物上出现的原子的所有同位素。同位素包括具有相同原子序数但具有不同质量数的那些原子。通过大体举例并且没有限制，氢的同位素包括氚和氘。碳的同位素包括 C-13 和 C-14。

[0063] 发明详细说明

[0064] 每当在下文中使用，术语“具有化学式 (I) 的化合物”，

[0065]

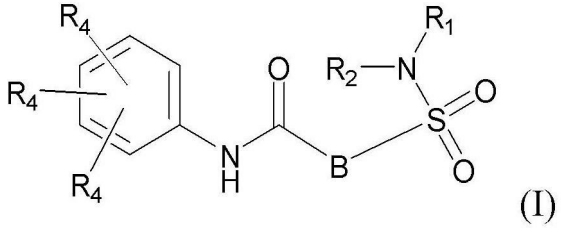


[0066] 或“本发明的化合物”或相似的术语意思是包括具有通式 (I)、(I*)、(Ia)、(Ib)、(Ic) 和 (Id) 的化合物、它们的盐、立体异构形式和外消旋混合物或任何亚组。

[0067] 在哺乳动物中用于在 HBV 感染的预防和治疗中使用的化合物作为化合物本身进行披露并且除非受限于本权利要求书而不限于这类使用。

[0068] 本发明涉及具有化学式 (I) 的化合物

[0069]



(I)

[0070] 或其一种立体异构体或互变异构形式，其中：

[0071] B 代表一个单环的 5 至 6 元芳族环，该芳族环可任选地包含一个或多个杂原子，这

些杂原子各自独立地选自由 O、S 和 N 组成的组，这种 5 至 6 元芳族环可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_3烷基、CN、CFH_2、CF_2H 和 CF_3组成的组；

[0072] R_1代表氢或 C_1-C_3烷基；

[0073] R_2代表 C_1-C_6烷基、C_1-C_6烯基、C_1-C_6烷基 -R_5、C(=O)-R_5、CFH_2、CF_2H、CF_3、一个可任选地被 OH 取代的二氢 - 茚基或者四氢萘基部分、或一个 3-7 元饱和环，该饱和环可任选地包含一个或多个杂原子，这些杂原子各自独立地选自由 O、S 和 N 组成的组，这种 3-7 元饱和环、C_1-C_6烷基 -R_5或 C_1-C_6烷基可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_4烷氧基、C_1-C_4烷氧基羰基、氧代、C(=O)-C_1-C_3烷基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H 和 CF_3组成的组；

[0074] 或 R_1和 R_2与它们附接其上的氮一起形成一个 6-10 元二环或桥环或一个 5-7 元饱和环，这种二环、桥环或饱和环部分可任选地包含一个或多个另外的杂原子，这些杂原子各自独立地选自由 O、S 和 N 组成的组，这种 5-7 元饱和环可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_4烷氧基、C_1-C_4烷氧基羰基、氧代、C(=O)-C_1-C_3烷基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H 和 CF_3组成的组；

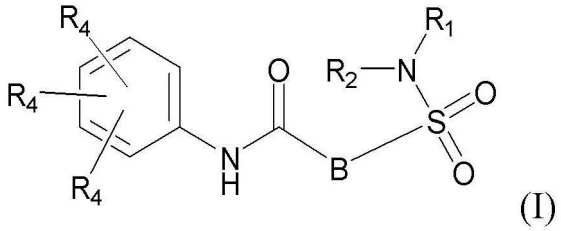
[0075] 每个 R_4独立地选自氢、卤素、C_1-C_4烷氧基、C_1-C_4烷基、C_1-C_4烯基、OH、CN、CFH_2、CF_2H、CF_3、HC≡C 或一个 3-5 元饱和环，该饱和环可任选地包含一个或多个杂原子，这些杂原子各自独立地选自由 O 和 N 组成的组，这种 C_1-C_4烷基可任选地被 OH 取代；

[0076] R_5代表 C_1-C_6烷基、CFH_2、CF_2H、CF_3、苯基、吡啶基或一个 3-7 元饱和环，该饱和环可任选地包含一个或多个杂原子，这些杂原子各自独立地选自由 O、S 和 N 组成的组，这种 3-7 元饱和环可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_4烷氧基、C_1-C_4烷氧基羰基、氧代、C(=O)-C_1-C_3烷基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H 和 CF_3组成的组；

[0077] 或其一种药学上可接受的盐或溶剂化物。

[0078] 在第一方面，本发明进一步提供了具有化学式 (I) 的化合物

[0079]



(I)

[0080] 或其一种立体异构体或互变异构形式，其中：

[0081] B 代表一个单环的 5 至 6 元芳族环，该芳族环可任选地包含一个或多个杂原子，这些杂原子各自独立地选自由 O、S 和 N 组成的组，这种 5 至 6 元芳族环可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_3烷基、CN、CFH_2、CF_2H 和 CF_3组成的组；

[0082] R_1代表氢或 C_1-C_3烷基；

[0083] R_2代表 C_1-C_6烷基、C_1-C_6烯基、C_1-C_6烷基 -R_5、C(=O)-R_5、CFH_2、CF_2H、CF_3、一个 2- 羟基 -2,3- 二氢 -1H- 茚基部分或一个 3-7 元饱和环，该饱和环可任选地包含一个或多

个杂原子，这些杂原子各自独立地选自由 O、S 和 N 组成的组，这种 3-7 元饱和环、C_1-C_6烷基 -R_5或 C_1-C_6烷基可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_4烷氧基、C_1-C_4烷氧基羰基、氧代、C(= O)-C_1-C_3烷基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H 和 CF_3组成的组；

[0084] 或 R_1和 R_2与它们附接其上的氮一起形成一个 1，4- 二氧杂 -8- 氮杂螺 [4.5] 癸基部分、一个 2- 氧杂 -6- 氮杂螺 [3.3] 庚基部分或一个 5-7 元饱和环，该饱和环可任选地包含一个或多个另外的杂原子，这些杂原子各自独立地选自由 O、S 和 N 组成的组，这种 5-7 元饱和环可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_4烷氧基、C_1-C_4烷氧基羰基、氧代、C(= O)-C_1-C_3烷基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H 和 CF_3组成的组；

[0085] 每个 R_4独立地选自氢、卤素、C_1-C_4烷氧基、C_1-C_4烷基、C_1-C_4烯基、OH、CN、CFH_2、CF_2H、CF_3、HC ≡ C 或一个 3-5 元饱和环，该饱和环可任选地包含一个或多个杂原子，这些杂原子各自独立地选自由 O 和 N 组成的组，这种 C_1-C_4烷基可任选地被 OH 取代；

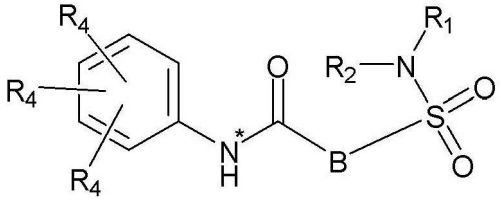
[0086] R_5代表 C_1-C_6烷基、CFH_2、CF_2H、CF_3、苯基、吡啶基或一个 3-7 元饱和环，该饱和环可任选地包含一个或多个杂原子，这些杂原子各自独立地选自由 O、S 和 N 组成的组，这种 3-7 元饱和环可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_4烷氧基、C_1-C_4烷氧基羰基、氧代、C(= O)-C_1-C_3烷基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H 和 CF_3组成的组；

[0087] 或其一种药学上可接受的盐或溶剂化物。

[0088] 在一个实施例中，至少一个 R_4代表氟，并且一个其他的 R_4选自由 C_1-C_3烷基、C_1-C_3烯基、CHF_2或环丙基组成的组。

[0089] 在一个子实施例中，一个 R_4代表氟并且一个其他的 R_4选自由甲基或 CHF_2（优选甲基）组成的组，并且其中相对于氮 (*) 所述氟的位置是在对位并且所述甲基或者 CHF_2的位置是在间位，如在以下化学式 (I*) 中指示的。

[0090]

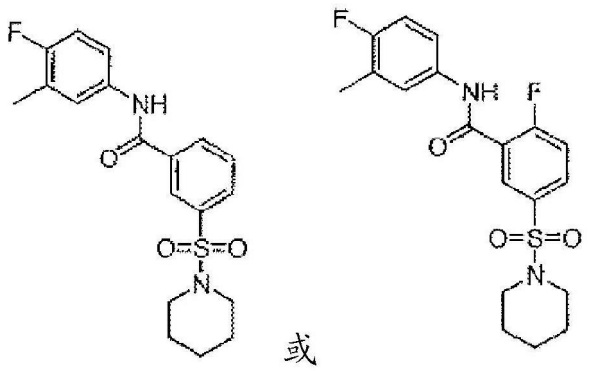


(I*)

[0091] 在又另一个实施例中，本发明提供了具有化学式 (I) 的化合物，其中至少一个 R_4代表氟，并且一个其他的 R_4选自由 C_1-C_3烷基、C_1-C_3烯基、CHF_2或环丙基组成的组；更优选地，一个 R_4代表氟，并且一个其他的 R_4选自由甲基或 CHF_2组成的组，并且其中相对于氮 (*) 所述氟的位置是在对位并且所述甲基或 CHF_2的位置是在间位，并且 R_2代表一个 4-7 元饱和环，该饱和环包含碳和一个或多个氧原子，这种 4-7 元饱和环可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_4烷氧基、C_1-C_4烷氧基羰基、C(= O)-C_1-C_3烷基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H 和 CF_3组成的组。

[0092] 在又另一个实施例中，披露了化合物，其中一个位于对位的 R_4代表氟并且另一个位于间位的 R_4代表甲基并且这种化合物不是

[0093]

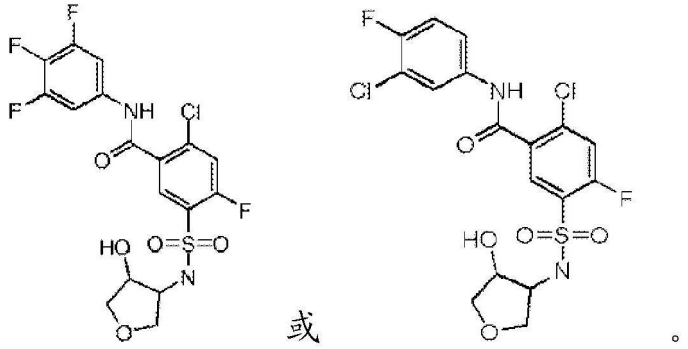


或 。

[0094] 在本发明的另一个实施例中，提供了根据化学式 (I) 的化合物，其中 R_2代表一个 4-7 元饱和环，该饱和环包含碳和一个或多个氧原子，这种 4-7 元饱和环可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_4烷氧基、C_1-C_4烷氧基羰基、C(= O)-C_1-C_3烷基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H 和 CF_3组成的组。对于这种包含碳和一个或多个氧原子的 4-7 元饱和环的优选取代基是 C_1-C_4烷基。在一个子实施例中，该饱和环是一个 4、5 或 6 元环。

[0095] 在本发明的另一个实施例中，提供了根据化学式 (I) 的化合物，其中 R_2代表一个 4-7 元饱和环，该饱和环包含碳和一个或多个氮原子，这种 4-7 元饱和环可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_4烷氧基、C_1-C_4烷氧基羰基、C(= O)-C_1-C_3烷基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H 和 CF_3组成的组。在一个另外的实施例中，R_2代表一个 4-7 元饱和环，该饱和环包含碳和一个或多个氧原子，这种 4-7 元饱和环可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_4烷氧基、C_1-C_4烷氧基羰基、C(= O)-C_1-C_3烷基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H 和 CF_3组成的组，其中这种化合物不是

[0096]



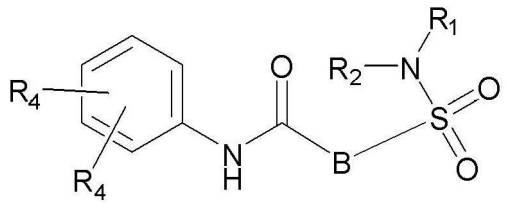
或 。

[0097] 优选地，在这种 3-7、4-7 和 5-7 元饱和环、6-10 元二环或桥环上的任何任选的取代基，C_1-C_6烷基 -R_5或 C_1-C_6烷基独立地选自由氢、氟、OH、C_1-C_3烷基和 CF_3组成的组，最优选选自由氢、C_1-C_3烷基、氟和 CF_3组成的组。

[0098] 在本发明的另一个实施例中，提供了根据化学式 (I) 的化合物，其中 B 代表苯基或噻吩，可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_3烷基、CN、CFH_2、CF_2H 和 CF_3组成的组。

[0099] 在一个子实施例中，根据本发明的化合物由化学式 (Ia) 代表

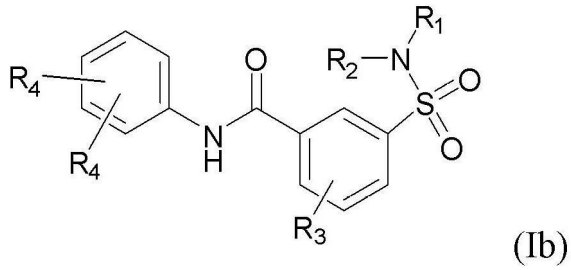
[0100]



[0101] (Ia)，其中 R_1、R_2和 R_4是如所描述的任何一个实施例中所定义的。

[0102] 在一个子实施例中，此类化合物是由化学式 (Ib) 代表

[0103]

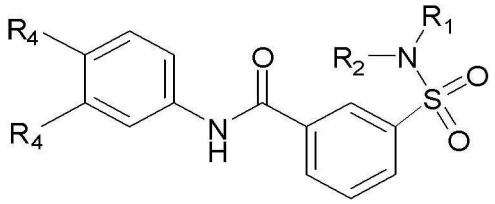


(Ib)

[0104] 其中 R_1、R_2、R_4是如所描述的任何一个实施例中所定义的，并且 R_3选自包括以下项的组：氢、卤素、C_1-C_3烷基、CN、CFH_2、CF_2H、CF_3。在一个优选的实施例中，R_3代表氟或氢，更优选氢。

[0105] 在又另一个子实施例中，化合物是由化学式 (Ic) 代表：

[0106]

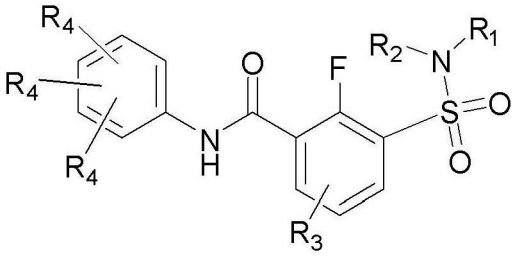


(Ic)

[0107] 其中 R_1、R_2和 R_4是如所描述的任何一个实施例中所定义的。

[0108] 在一个子实施例中，根据本发明的化合物由化学式 (Id) 代表

[0109]



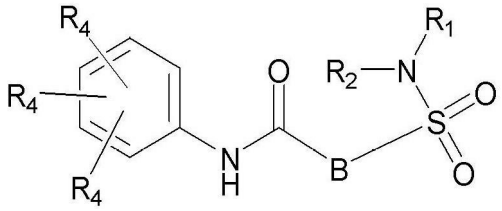
(Id)

[0110] 其中 R_1、R_2、和 R_4是如所描述的任何一个实施例中所定义的，并且 R_3选自包括以下项的组：氢、卤素、C_1-C_3烷基、CN、CFH_2、CF_2H、CF_3。

[0111] 在一个优选实施例中，根据本发明的化合物被考虑用于在哺乳动物中预防或治疗 HBV 感染中使用。

[0112] 在一个另外的方面，本发明提供了可以由化学式 (I) 代表的化合物：

[0113]



(I)

[0114] 或其一种立体异构体或互变异构形式，其中：

[0115] B 代表一个单环的 5 至 6 元芳族环，该芳族环可任选地包含一个或多个杂原子，这些杂原子各自独立地选自由 O、S 和 N 组成的组，这种 5 至 6 元芳族环可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_3烷基、CN、CFH_2、CF_2H 和 CF_3组成的组；

[0116] R_1代表氢或 C_1-C_3烷基；

[0117] R_2代表 C_1-C_6烷基、C_1-C_3烷基 -R_5、苄基、C(=O)-R_5、CFH_2、CF_2H、CF_3或一个 3-7 元饱和环，该饱和环可任选地包含一个或多个杂原子，这些杂原子各自独立地选自由 O、S 和 N 组成的组，这种 3-7 元饱和环或 C_1-C_6烷基可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_4烷氧基、氧代、C(=O)-C_1-C_3烷基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H 和 CF_3组成的组；

[0118] 或 R_1和 R_2与它们附接其上的氮一起形成一个 1,4- 二氧杂 -8- 氮杂螺 [4.5] 部分、或一个 5-7 元饱和环，该饱和环可任选地包含一个或多个另外的杂原子，这些杂原子各自独立地选自由 O、S 和 N 组成的组，这种 5-7 元饱和环可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_4烷氧基、氧代、C(=O)-C_1-C_3烷基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H 和 CF_3组成的组；

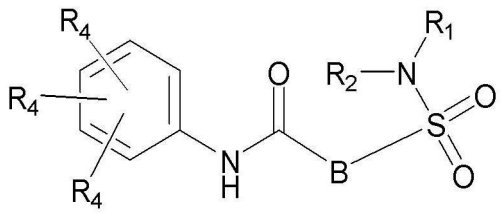
[0119] 每个 R_4独立地选自氢、卤素、C_1-C_4烷氧基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H、CF_3、HC≡C 或一个 3-5 元饱和环，该饱和环可任选地包含一个或多个杂原子，这些杂原子各自独立地选自由 O 和 N 组成的组；

[0120] R_5代表 C_1-C_6烷基、CFH_2、CF_2H、CF_3或一个 3-7 元饱和环，该饱和环可任选地包含一个或多个杂原子，这些杂原子各自独立地选自由 O、S 和 N 组成的组，这种 3-7 元饱和环可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_4烷氧基、氧代、C(=O)-C_1-C_3烷基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H 和 CF_3组成的组；

[0121] 或其一种药学上可接受的盐或溶剂化物。这些化合物尤其适合用于在哺乳动物中在预防或治疗 HBV 感染中使用。

[0122] 在又另外的方面，本发明涉及根据化学式 (I) 的化合物

[0123]



(I)

[0124] 或其一种立体异构体或互变异构形式，其中：

[0125] B 代表一个单环的 5 至 6 元芳族环，该芳族环可任选地包含一个或多个杂原子，这些杂原子各自独立地选自由 O、S 和 N 组成的组，这种 5 至 6 元芳族环可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_3烷基、CN、CFH_2、CF_2H 和 CF_3组成的组；

[0126] R_1代表氢或 C_1-C_3烷基；

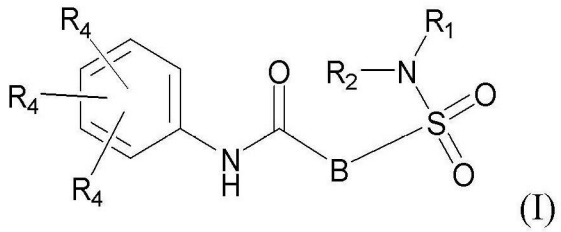
[0127] R_2代表一个 4-7 元饱和环，该饱和环由碳原子和一个或多个杂原子组成，这些杂原子各自独立地选自由 O 或 S 组成的组，这种 4-7 元饱和环可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_4烷氧基、氧代、C(＝O)-C_1-C_3烷基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H 和 CF_3组成的组；

[0128] 每个 R_4独立地选自氢、卤素、C_1-C_4烷氧基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H、CF_3、HC≡C 或一个 3-5 元饱和环，该饱和环可任选地包含一个或多个杂原子，这些杂原子各自独立地选自由 O 和 N 组成的组；

[0129] 或其一种药学上可接受的盐或溶剂化物。

[0130] 本发明另外地涉及具有化学式 (I) 的化合物

[0131]



(I)

[0132] 或其一种立体异构体或互变异构形式，或其一种药学上可接受的盐或溶剂化物

[0133] 其中：

[0134] B 代表一个单环的 5 至 6 元芳族环，该芳族环可任选地包含一个或多个杂原子，这些杂原子各自独立地选自由 O、S 和 N 组成的组，这种 5 至 6 元芳族环可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_3烷基、CN、CFH_2、CF_2H 和 CF_3组成的组；

[0135] R_1代表氢或 C_1-C_3烷基；

[0136] R_2代表 C_1-C_6烷基、C_1-C_3烷基 -R_5、苄基、C(＝O)-R_5、CFH_2、CF_2H、CF_3或一个 3-7 元饱和环，该饱和环可任选地包含一个或多个杂原子，这些杂原子各自独立地选自由 O、S 和 N 组成的组，这种 3-7 元饱和环或 C_1-C_6烷基可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_4烷氧基、氧代、C(＝O)-C_1-C_3烷基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H 和 CF_3组成的组；

[0137] 或 R_1和 R_2与它们附接其上的氮一起形成一个 1,4- 二氧杂 -8- 氮杂螺 [4.5] 部分、或一个 5-7 元饱和环，该饱和环可任选地包含一个或多个另外的杂原子，这些杂原子各自独立地选自由 O、S 和 N 组成的组，这种 5-7 元饱和环可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_4烷氧基、氧代、C(＝O)-C_1-C_3烷基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H 和 CF_3组成的组；

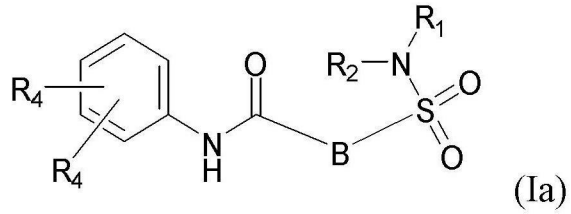
[0138] 每个 R_4独立地选自氢、卤素、C_1-C_4烷氧基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H、CF_3、HC≡C 或一个 3-5 元饱和环，该饱和环可任选地包含一个或多个杂原子，这些杂原子各自独立地

选自由 O 和 N 组成的组；

[0139] R_5代表 C_1-C_6烷基、CFH_2、CF_2H、CF_3或一个 3-7 元饱和环，该饱和环可任选地包含一个或多个杂原子，这些杂原子各自独立地选自由 O、S 和 N 组成的组，这种 3-7 元饱和环可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_4烷氧基、氧代、C(=O)-C_1-C_3烷基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H 和 CF_3组成的组；

[0140] 本发明的一个亚实施例提供了可以通过化学式 (Ia) 代表的化合物

[0141]



(Ia)

[0142] 其中 R_1、R_2、B 是如上所定义的，并且每个 R_4独立地选自氢、卤素、C_1-C_4烷氧基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H、CF_3或一个 3-5 元饱和环，该饱和环可任选地包含一个或多个杂原子，这些杂原子各自独立地选自由 O 和 N 组成的组。

[0143] 在一个实施例中，R_2代表一个 3-7 元饱和环，该饱和环包含一个或多个杂原子，这些杂原子各自独立地选自由 O、S 和 N 组成的组，这种 3-7 元饱和环可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_4烷氧基、氧代、C(=O)-C_1-C_3烷基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H 和 CF_3组成的组。

[0144] 在又另一个实施例中，R_2代表一个 4-7 元饱和环，该饱和环包含碳和一个或多个氧原子，这种 4-7 元饱和环可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_4烷氧基、C(=O)-C_1-C_3烷基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H 和 CF_3组成的组。

[0145] 在另一个实施例中，R_1和 R_2与它们附接其上的氮一起形成一个 5-7 元饱和环，该饱和环可任选地包含一个或多个另外的杂原子，这些杂原子各自独立地选自由 O、S 和 N 组成的组，这种 5-7 元饱和环可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_4烷氧基、氧代、C(=O)-C_1-C_3烷基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H 和 CF_3组成的组。

[0146] 在本发明的一个优选实施例中，B 代表苯基或噻吩，可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_3烷基、CN、CFH_2、CF_2H 和 CF_3组成的组。

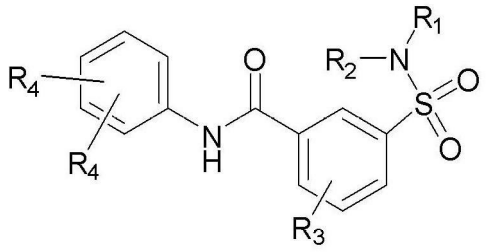
[0147] 在根据本发明的化合物的一个选择中，或在哺乳动物中用于在预防或治疗 HBV 感染中使用的化合物中，至少一个 R_4代表氟、C_1-C_3烷基、CHF_2或环丙基。

[0148] 优选地，至少一个 R_4代表甲基、异丙基或环丙基。在另一个实施例中，一个 R_4代表甲基、异丙基或环丙基并且其他的 R_4代表氟或氢。R_4的位置优选地是间位和 / 或对位（从 -N ～所指示的位置）。

[0149] 一个具体的实施例是具有化学式 (I) 的化合物，其中一个位于对位的 R_4代表氟并且另一个位于间位的 R_4代表氟或甲基（从 -N ～所指示的位置）。

[0150] 本发明的一个亚实施例提供了可以通过化学式 (Ib) 代表的化合物

[0151]

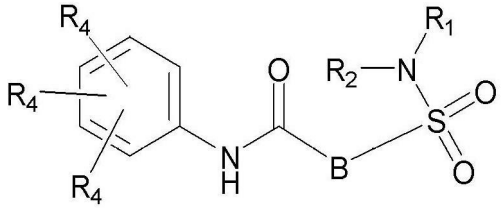


(Ib)

[0152] 其中 R_1、R_2、R_4是如上所定义的，并且 R_3选自包括以下项的组：氢、卤素、C_1-C_3烷基、CN、CFH_2、CF_2H、CF_3。在一个优选的实施例中，R_3代表氟或氢。

[0153] 本发明进一步涉及根据化学式 (I) 的化合物

[0154]



(I)

[0155] 或其一种立体异构体或互变异构形式，其中：

[0156] B 代表一个单环的 5 至 6 元芳族环，该芳族环可任选地包含一个或多个杂原子，这些杂原子各自独立地选自由 O、S 和 N 组成的组，这种 5 至 6 元芳族环可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_3烷基、CN、CFH_2、CF_2H 和 CF_3组成的组；

[0157] R_1代表氢或 C_1-C_3烷基；

[0158] R_2代表 C_1-C_3烷基 -R_6或一个 4-7 元饱和环，该饱和环由碳原子和一个或多个杂原子组成，这些杂原子各自独立地选自由 O 或 S 组成的组，这种 4-7 元饱和环可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_4烷氧基、氧代、C(=O)-C_1-C_3烷基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H 和 CF_3组成的组；

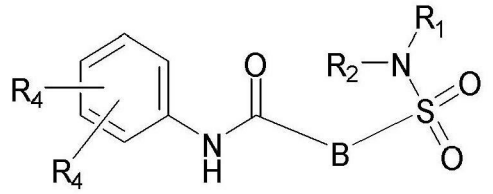
[0159] 每个 R_4独立地选自氢、卤素、C_1-C_4烷氧基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H、CF_3、HC≡C 或一个 3-5 元饱和环，该饱和环可任选地包含一个或多个杂原子，这些杂原子各自独立地选自由 O 和 N 组成的组；

[0160] R_6代表一个 4-7 元饱和环，该饱和环可任选地包含一个或多个杂原子组成，这些杂原子各自独立地选自由 O 或 S 组成的组，这种 4-7 元饱和环可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_4烷氧基、氧代、C(=O)-C_1-C_3烷基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H 和 CF_3组成的组；

[0161] 或其一种药学上可接受的盐或溶剂化物。

[0162] 本发明的一个亚实施例提供了可以通过化学式 (Ia) 代表的化合物

[0163]



(Ia)

[0164] 其中R_1、R_2、B是如上所定义的，并且每个R_4独立地选自氢、卤素、C_1-C_4烷氧基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H、CF_3或一个3-5元饱和环，该饱和环可任选地包含一个或多个杂原子，这些杂原子各自独立地选自由O和N组成的组。

[0165] 在一个实施例中，R_2代表C_1-C_3烷基-R_6或一个4-7元饱和环，该饱和环由碳原子和一个或多个杂原子组成，这些杂原子各自独立地选自由O或S组成的组，这种4-7元饱和环可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_4烷氧基、氧代、C(=O)-C_1-C_3烷基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H和CF_3组成的组。

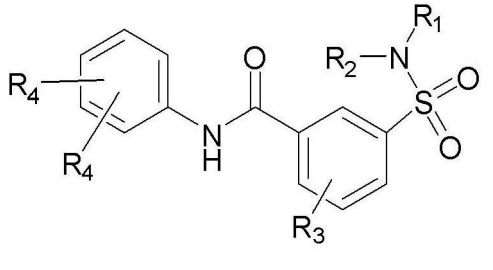
[0166] 在针对本发明的化合物的一个优选实施例中，B代表苯基或噻吩，可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_3烷基、CN、CFH_2、CF_2H和CF_3组成的组。

[0167] 在根据本发明的化合物的一个选择中，至少一个R_4代表氟、C_1-C_3烷基、CHF_2或环丙基。优选地，至少一个R_4代表甲基、异丙基或环丙基。在另一个实施例中，一个R_4代表甲基、异丙基或环丙基并且其他的R_4代表氟或氢。R_4的位置优选地是间位和/或对位。

[0168] 一个具体的实施例是具有化学式(I)的化合物，其中一个位于对位的R_4代表氟并且另一个位于间位的R_4代表氟或甲基。

[0169] 本发明化合物的一个亚实施例涉及根据化学式(Ib)的化合物

[0170]



(Ib)

[0171] 其中R_1代表氢或C_1-C_3烷基；

[0172] R_2代表C_1-C_3烷基-R_6或一个4-7元饱和环，该饱和环由碳原子和一个或多个杂原子组成，这些杂原子各自独立地选自由O或S组成的组，这种4-7元饱和环可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_4烷氧基、氧代、C(=O)-C_1-C_3烷基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H和CF_3组成的组；

[0173] 每个R_4独立地选自氢、卤素、C_1-C_4烷氧基、C_1-C_4烷基、OH、CN、CFH_2、CF_2H、CF_3或一个3-5元饱和环，该饱和环可任选地包含一个或多个杂原子，这些杂原子各自独立地选自由O和N组成的组；

[0174] R_6代表一个4-7元饱和环，该饱和环可任选地包含一个或多个杂原子组成，这些杂原子各自独立地选自由O或S组成的组，这种4-7元饱和环可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_4烷氧基、氧代、C(=O)-C_1-C_3烷基、C_1-C_4

烷基、OH、CN、CFH_2、CF_2H 和 CF_3 组成的组；

[0175] R_3 选自包括以下项的组：氢、卤素、C_1-C_3 烷基、CN、CFH_2、CF_2H、CF_3。在一个优选的实施例中，R_3 代表氟或氢。

[0176] 在一个实施例中，R_6 代表一个 4-7 元饱和环，该饱和环由碳原子和一个或多个杂原子组成，这些杂原子各自独立地选自由 O 或 S 组成的组，这种 4-7 元饱和环可任选地被一个或多个取代基取代，这些取代基各自独立地选自由氢、卤素、C_1-C_4 烷氧基、氧代、C(=O)-C_1-C_3 烷基、C_1-C_4 烷基、OH、CN、CFH_2、CF_2H 和 CF_3 组成的组。

[0177] 任何亚实施例或优选实施例的另外的组合也构思在本发明范围内。

[0178] 根据本发明的优选化合物是以下这样的化合物或其立体异构体或互变异构形式：它们具有针对选自下表 1 和 2 的化学式的化学式或参考：

[0179] 表 2

[0180]

化合物编号	化合物编号	化合物编号	化合物编号	化合物编号	化合物编号	化合物编号	化合物编号
1	65	96	123	150	177	200	227
2	66	97	124	151	178	201	228
3	67	98	125	152	179	202	229
4	68	99	126	153	180	203	230
5	69	100	127	154	181	204	231
6	70	101	128	155	182	205	232
7	71	102	129	156	183	206	233
8	72	103	130	157	184	207	234
9	73	104	131	158	184 a	208	235
10	74	105	132	159	184 b	209	236
11	76	106	133	160	185	210	237
12	77	107	134	161	186	211	238
14	79	108	135	162	187	212	239
16	81	109	136	163	188	213	240
17	82	110	137	164	189	214	241
18	83	111	138	165	190	215	242
19	84	112	139	166	191	216	243
38	85	113	140	167	192	217	
39	86	114	141	168	193	218	
42	87	115	142	169	194	219	
43	89	116	143	170	195	220	
45	90	117	144	171	196	221	
46	91	118	145	172	197	222	
48	92	119	146	173	198	223	
56	93	120	147	174	199	224	
63	94	121	148	175		225	
64	95	122	149	176		226	

[0181] 或其一种药学上可接受的盐或溶剂化物

[0182] 在一个另外的方面，本发明关注一种药物组合物，该药物组合物包括如在此指定的治疗上或预防上有效量的具有化学式 (I) 的化合物，以及药学上可接受的载体。在这种背景下，一种预防上的有效量是一种在有被感染风险的受试者中足以预防 HBV 感染的量。在这种背景下，一种治疗上的有效量是一种在已被感染的受试者中足以稳定 HBV 感染、减轻 HBV 感染、或根除 HBV 感染的量。仍然在一个另外的方面，本发明涉及制备如在此指定的药物组合物的方法，其包括紧密地将药学上可接受的载体与如在此指定的治疗上有效量的或预防上有效量的具有化学式 (I) 的化合物混合。

[0183] 因此，可以将本发明的化合物或其任何亚组配制为用于给药目的的不同的药用形式。可以引用所有通常用于全身给药药物的组合物作为合适的组合物。为了制备本发明的药用组合物，将作为活性成分的有效量的特定化合物（可任选地处于加成盐形式）与药学上可接受的载体以紧密混合进行组合，该载体可以取决于用于给药的所希望的制品形式而采取各种各样的形式。令人希望的是这些药用组合物处于特别适合用于经口服、直肠、经皮、或肠胃外注射给药的单元剂型。例如，在制备处于口服剂型的药物组合物中，可使用任何常见药物介质，在口服液体制剂（例如悬浮剂、糖浆剂、酏剂、乳液以及溶液）的情况中，例如像水，二醇类、油类、醇类以及类似物；或者在粉剂、丸剂、胶囊剂以及片剂的情况中的固体载体，例如淀粉、糖、高岭土、润滑剂、粘合剂、崩解剂以及类似物。因为它们易于给药，片剂和胶囊代表最有利的口服单位剂型，在这种情况中采用固体药物载体。对于肠胃外组合物，载体通常至少大部分包括无菌水，虽然可以包括例如帮助溶解的其他成分。可以制备例如可注射溶液，其中载体包括生理盐水溶液、葡萄糖溶液或生理盐水与葡萄糖溶液的混合物。也可以制备注射混悬液，在此情况下可以采用合适的液体载体、悬浮剂以及类似物。还包括预期在使用之前不久将其转化为液体形式制品的固体形式制品。在适用于经皮给药的组合物中，载体可任选地包括渗透增强剂和 / 或适合的润湿剂，可任选地与占较小比例的具有任何性质的适合的添加剂组合，这些添加剂不对皮肤引入显著的有毒作用。本发明的化合物还可以按溶液、混悬液或干粉形式，使用任何本领域已知的递送系统经由口腔吸入或吹入来给予。

[0184] 尤其有利的是配制处于单位剂型的前述的药用组合物，以便于给药和剂量的一致性。如在此使用的单位剂型指的是适合作为单位剂量的物理离散单位，各单位含有预定量的活性成分，该预定量的活性成分经计算与所需药物载体相结合而产生所希望的治疗效果。此类单位剂型的实例是片剂（包括刻痕片剂或包衣片剂）、胶囊、丸剂、栓剂、粉剂包、晶片、可注射的溶液或悬浮剂以及类似物、以及它们的隔离的多重体。

[0185] 具有化学式 (I) 的化合物作为 HBV 复制循环的抑制剂是有活性的并且可以用于治疗和预防 HBV 感染或与 HBV 相关的疾病。后者包括进展性肝纤维化、导致肝硬化的炎症和坏死、末期肝病、以及肝癌。

[0186] 由于它们的抗病毒特性，特别是它们抗 -HBV 特性，具有化学式 (I) 的化合物或其任何亚组在 HBV 复制循环的抑制中是有用的，具体地在感染 HBV 的温血动物的治疗中（具体地人类）以及用于 HBV 感染的预防方面是有用的。此外本发明涉及治疗被 HBV 感染或处于被 HBV 感染的风险的温血动物（具体地人类）的方法，所述方法包括给予治疗上有效量的具有化学式 (I) 的化合物。

[0187] 如在此指定的具有化学式 (I) 的化合物，可以因此被作为一种药物，具体地作为治疗或预防 HBV 感染的药物。作为药物的所述用途或治疗方法包括将有效对抗 HBV 感染相关病症的量或有效预防 HBV 感染的量全身性给药至 HBV 感染的受试者或易受 HBV 感染的受试者。

[0188] 本发明还涉及本发明的化合物在制造用于治疗或预防 HBV 感染的药剂中的用途。

[0189] 总体上，考虑的是抗病毒有效的日量将是从约 0.01mg/kg 至约 50mg/kg 体重，或从约 0.01mg/kg 至约 30mg/kg 体重。可以合适的是将所要求的剂量以在全天中的合适的间隔作为两个、三个、四个或更多个亚剂量给予。所述亚剂量可以配制为单位剂型，例如每单位

剂型含有约 1mg 至约 500mg、或约 1mg 至约 300mg、或约 1mg 至约 100mg、或约 2mg 至约 50mg 的活性成分。

[0190] 本发明还关注如在此指定的具有化学式 (I) 的化合物或其任何亚组与抗 -HBV 制剂的组合。术语“组合”还涉及一种产品或试剂盒，该产品和试剂盒包含 (a) 如以上指定的具有化学式 (I) 的化合物，以及 (b) 至少一种能够治疗 HBV 感染的其他的化合物 (在此指作为抗 -HBV 剂)，作为用于同时、分开或顺序地用于 HBV 感染治疗的组合制剂。在一个实施例中，本发明关注具有化学式 (I) 的化合物或其任何亚组与至少一种抗 -HBV 剂的组合。在一个具体实施例中，本发明关注具有化学式 (I) 的化合物或其任何亚组与至少两种抗 -HBV 剂的组合。在一个具体实施例中，本发明关注具有化学式 (I) 的化合物或其任何亚组与至少三种抗 -HBV 剂的组合。在一个具体实施例中，本发明关注具有化学式 (I) 的化合物或其任何亚组与至少四种抗 -HBV 剂的组合。

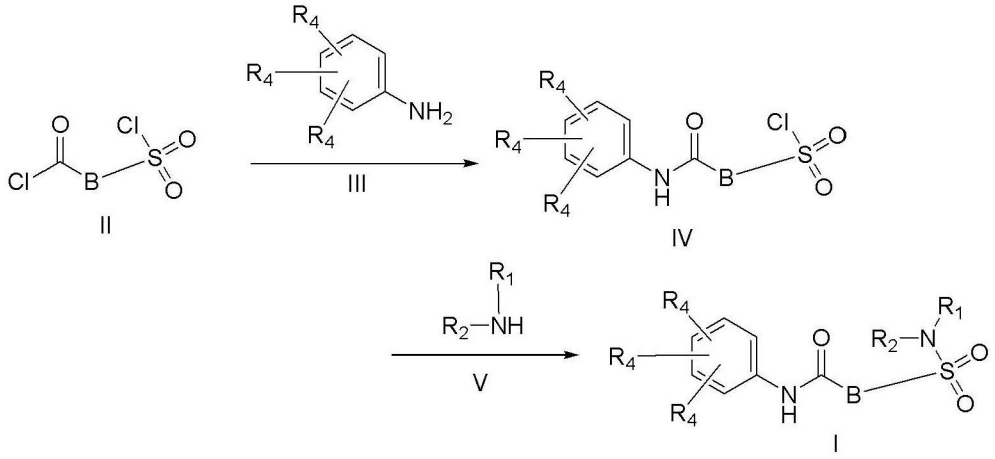
[0191] 预先已知的抗 -HBV 剂的组合 (例如干扰素 - α (IFN- α)、聚乙二醇化干扰素 - α 、3TC、阿德福韦或其组合) 以及具有化学式 (I) 的化合物或其任何亚组可以在组合疗法中用作一种药物。

[0192] 通用合成 :

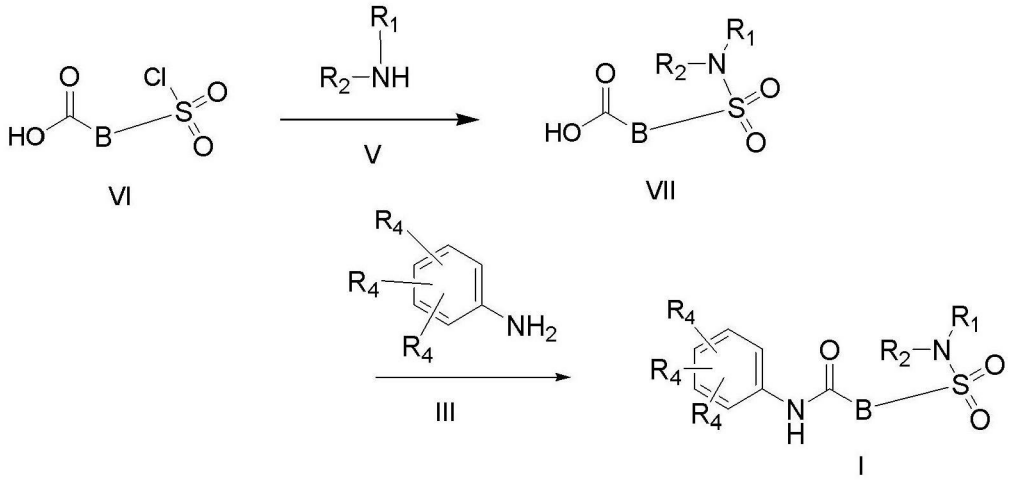
[0193] 根据化学式 (I) 的化合物可以如在通用方案 1 至 7 中所描述的进行合成。

[0194] 一种具有通式 II 的羧酸氯可以选择性地例如在有机溶剂 (像 CH_2Cl_2) 中，在有机碱 (像三乙胺或 DIPEA(N, N- 二异丙基乙胺)) 存在下与具有通式 III 的苯胺反应，或者作为另一个实例，通过将苯胺 III 添加至化合物 II 的回流甲苯溶液，产生化合物 IV。化合物 IV 中的残余的磺酰氯官能度可以进一步与具有通式 V 的胺进行反应，产生具有化学式 (I) 的化合物。可替代地，具有通式 (I) 的化合物可以如在方案 2 中所描述的获得。这次例如在有机溶剂中 (像 CH_2Cl_2) 在有机碱 (像三乙胺或 DIPEA) 的存在下，或者作为另一个实例，在 Na_2CO_3的存在下在 H_2O/THF 的混合物中，磺酰氯 VI 与具有通式 V 的胺进行反应。在一种活化试剂 (像例如 HATU) 和一种有机碱 (像三乙胺或 DIPEA) 存在下，将形成的化合物 VII 与具有通式 III 的苯胺进行偶联。

[0195]



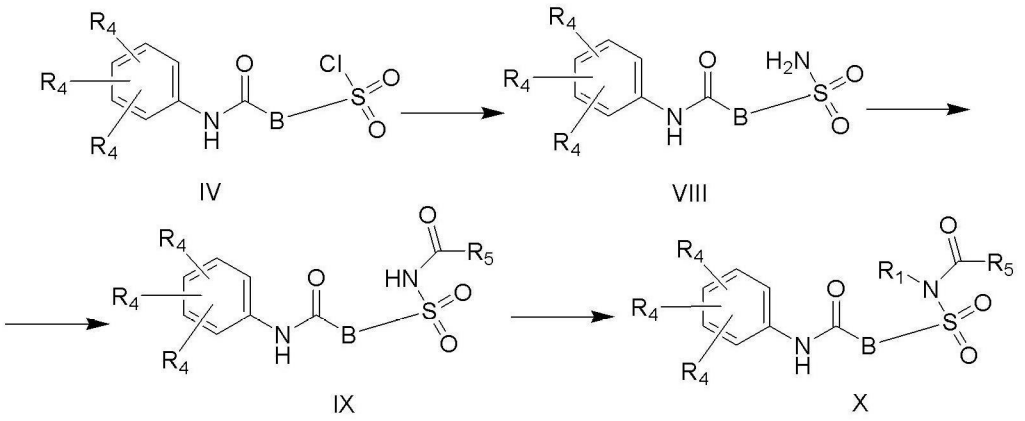
方案 1



方案 2

[0196] 具有化学式 IX 和 X 的化合物的通用合成描述在方案 3 中。中间体 IV 与氨进行反应，产生具有化学式 VIII 的化合物。在 $CHCl_3$的回流中在 SiO_2和 H_2SO_4的存在下，这个中间体可以通过与碳酰氯（例如环己烷碳酰氯）反应进一步转化为具有化学式 IX 的化合物。具有通式 IX 的化合物可以进一步转化为具有化学式 X 的化合物。在 R_1等于 Me 的情况下，这可以通过在 $MeOH/CH_2Cl_2$中 IX 与 $TMSCHN_2$反应来完成

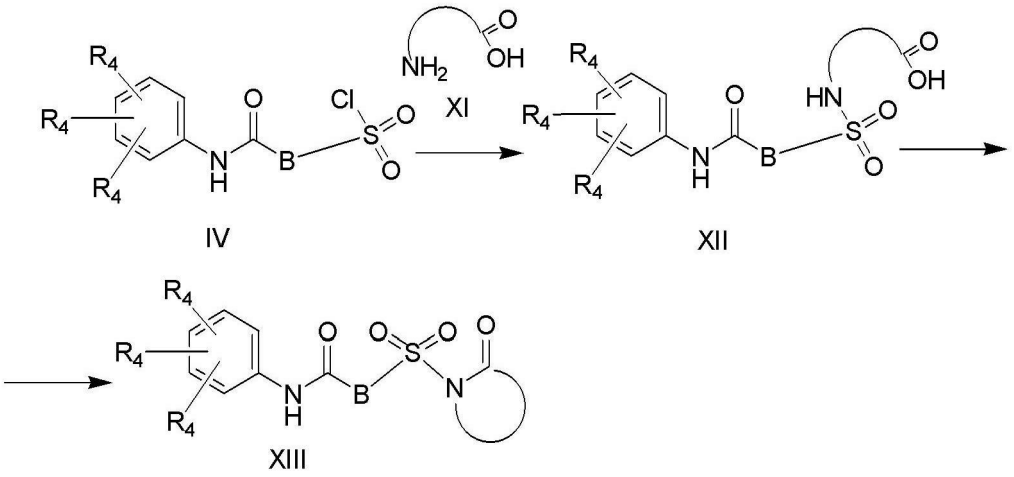
[0197]



方案 3

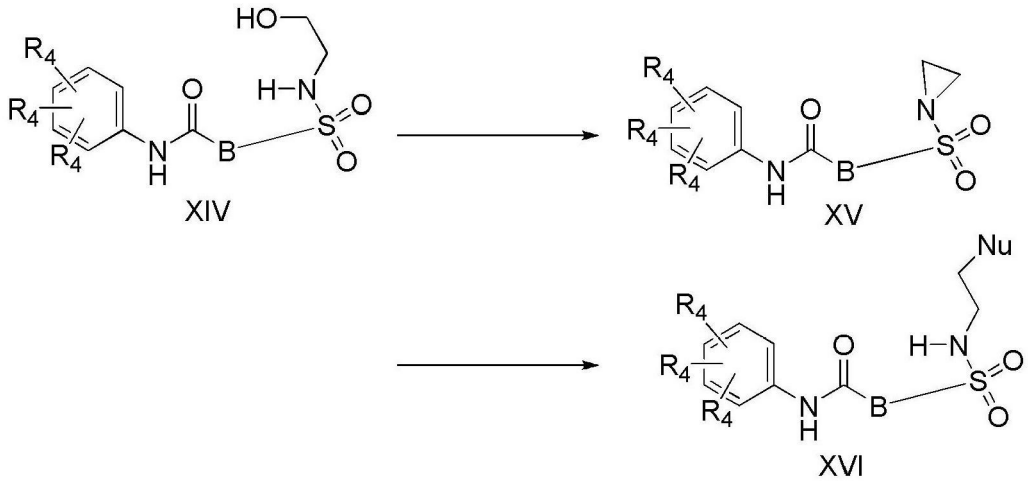
[0198] 在另一个实例中，在一种碱（像NaOH）存在下，化合物IV可以与氨基酸XI反应，产生如在方案4中描述的化合物XII。然后这个中间体XII可以可任选地环化为化合物XIII，例如通过在甲苯中将乙酸酐与KOAc进行加热，或者在碱（像三乙胺）存在下将羧酸转变为酰基氯接着环化。具有结构XI的氨基酸的合适的实例是具有5-氨基戊酸或4-氨基丁酸的衍生物

[0199]



方案 4

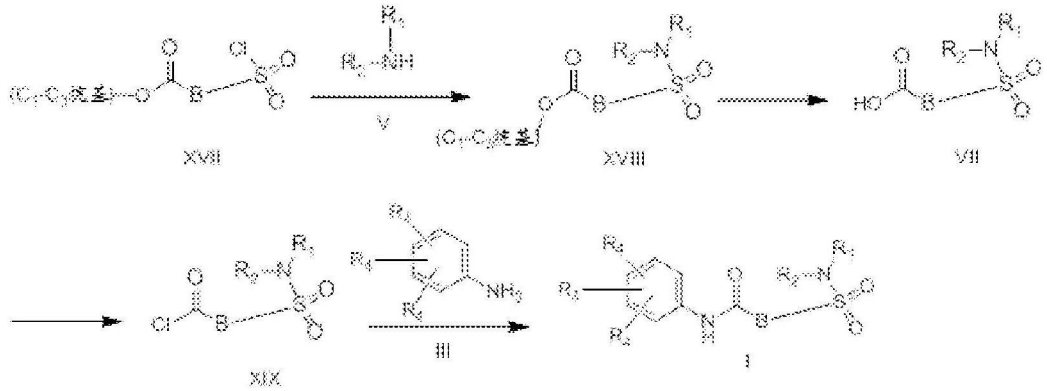
[0200]



方案 5

[0201] 具有通式 XVI 的化合物的合成途径描述在方案 5 中所。在 THF 中，通过用二氮烯 -1,2- 二羧酸二乙酯和 PPh_3进行处理，氨基乙醇衍生物 XIV（如在方案 1 中针对具有通式 (I) 的化合物所描述的制备）被转化为氮丙啶衍生物 XV。具有通式 XV 的氮丙啶与亲核体 Nu 进行反应，产生具有通式 XVI 的化合物。此类亲核体 (Nu) 的实例是，但不限于吗啉和 1- 甲基哌嗪。根据在方案 5 中描述的途径而合成的化合物的实例是化合物 116 和 117。

[0202]

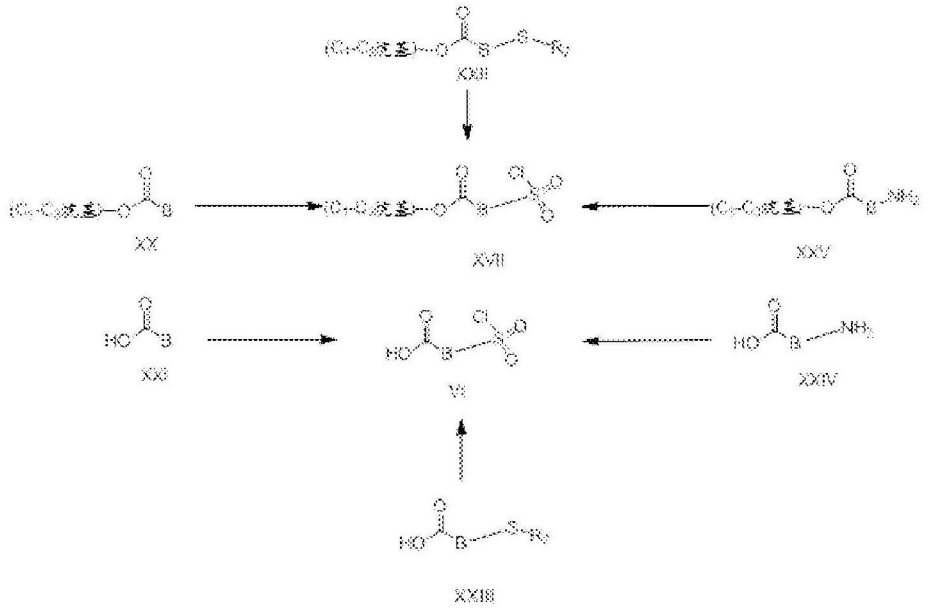


方案 6

[0203] 一种用于具有通式 VII 的化合物的合成的可替代的方法是如在方案 6 中描述的经由酯 XVII。将 XVII 与胺 V 进行反应（例如在有机溶剂（像 CH_2Cl_2或 THF）中在有机碱（像例如三乙胺或 DIPEA）存在下，接着将该酯进行水解（例如用在 THF/H_2O 中的 LiOH），接着进行酸化，产生具有通式 VII 的化合物。具有通式 VII 的化合物（经由方案 2 或方案 6 中的途径获得），可以转化为具有化学式 XIX 的酰基氯（例如通过用草酰氯或亚硫酰二氯进行处理）。然后具有通式 XIX 的化合物可以通过与具有通式 III 的苯胺进行反应转化为具有通式 (I) 的化合物。

[0204] 具有通式 VI 的化合物可以例如通过在 CH_2Cl_2中使用草酰氯进行处理转变为具有通式 II 的化合物。

[0205]



方案 7

[0206] 针对具有通式 XVII 或 VI 的化合物的可能合成途径描述于方案 7 中，并且在实验部分进一步举例说明。羧酸 XXI 或羧酸酯 XX 的氯磺化可以分别产生具有通式 VI 或 XVII 的化合物，例如通过使用氯磺酸进行处理（例如在《磷、硫以及硅和相关元素》(Phosphorus, Sulfur, and Silicon and the Related Elements)56 卷，Iss.1-4,1991 中所综述的）。可替代地，具有通式 XXV 或 XXIV 的化合物可以分别转变为具有通式 XVII 和 VI 的化合物，这是通过转变为相应的重氮盐（例如通过 $NaNO_2$/HCl)，接着将该重氮盐转变为磺酰氯（例如通过 SO_2/CuCl)（例如如在《有机方法研究 & 进展》(Organic Process Research & Development)13(5)，875-879；2009 中描述的）。可替代地，具有通式 XXII 和 XXIII 的化合物（其中 R_7 等于 H、苄基或甲基）可以分别转变为具有通式 XVII 和 VI 的化合物，例如通过在 AcOH/H_2O 中用 Cl_2 或 N- 氯代琥珀酰亚胺进行处理。

[0207] 在这个通用合成部分中由 R_4 代表的取代基是指包括本领域的普通技术人员没有额外负担下适合用于转变为根据本发明的任何 R_4 取代基的任何取代基或反应性组分。

[0208] 在以下化合物合成部分中没有特别描述的化合物可以根据以上方案 1-7 进行合成以及商购获得。

[0209] 化合物的合成：

[0210] IC-MS 方法：

[0211] 方法 A：流动相 A：H_2O(0.1％ TFA；B：CH_3CN(0.05％ TFA) 停止时间：10min；梯度时间 (min)[％ A/％ B]0.0[100/0] 至 1[100/0] 至 5[40/60] 至 7.5[40/60] 至 8.0[100/0]；流速：0.8mL/min；柱温：50℃，YMC-PACK ODS-AQ,50×2.0mm 5μm

[0212] 方法 B：流动相 A：H_2O(0.1％ TFA；B：CH_3CN(0.05％ TFA) 停止时间：10min；梯度时间 (min)[％ A/％ B]0.0[90/10] 至 0.8[90/10] 至 4.5[20/80] 至 7.5[20/80] 至 8.0[90/10]；流速：0.8mL/min；柱温：50℃，YMC-PACK ODS-AQ,50×2.0mm 5μm

[0213] 方法 C：流动相 A：H_2O(0.1％ TFA)；B：CH_3CN(0.05％ TFA) 停止时间：10min；梯度时间 (min)[％ A/％ B]0.0[90/10] 至 0.8[90/10] 至 4.5[20/80] 至 7.5[20/80]；9.5[90/10]

流速 :0.8mL/min ;柱温 :50℃,安捷伦 (Agilent)TC-C18,50×2.1mm,5μm

[0214] 方法 D :流动相 A :H_2O(0.05% $NH_3.H_2O$) ;B :CH_3CN 停止时间 :10 分钟 ;梯度时间 (min)[% A/ % B]0.0[100/0] 至 1[100/0] 至 5[40/60] 至 7.5[40/60] ;8[100/0] 流速 :0.8mL/min ;柱温 :40℃,XBridge Shield-RP18,50*2.1mm 5μm

[0215] 方法 E :流动相 A :H_2O(0.1% TFA ;B :CH_3CN(0.05% TFA) 停止时间 :10min ;后运行时间 (Post Time) :0.5min ;梯度时间 (min)[% A/% B]0[100/0] 至 1[100/0] 至 5[40/60] 至 7.5[15/85] 至 9.5[100/0] ;流速 :0.8mL/min ;柱温 :50℃,安捷伦 TC-C18,50×2.1mm,5μm

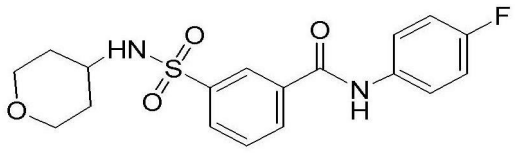
[0216] 方法 F :使用具有柱加热器 (设定在 55℃) 的 Acquity UPLC(沃特斯公司) 系统进行 LC 测量。在桥联的乙基硅氧烷 / 硅石混合体 (BEH)C18 柱 (1.7μm,2.1×50mm ;沃特斯公司 (Waters)Acquity) 上进行反相 UPLC(超高效液相层析),流速为 0.8ml/min。使用两种流动相 (在 H_2O/ 乙腈 95/5 中的 10mM 乙酸铵 ;流动相 B :乙腈) 运行梯度条件 :在 1.3 分钟内从 95% A 和 5% B 到 5% A 和 95% B,并且保持 0.3 分钟。使用 0.5μl 的注入体积。对于阳电离模式的锥孔电压是 10V,并且对于阴电离模式的锥孔电压是 20V。

[0217] 方法 G :使用具有柱加热器 (设定在 55℃) 的 Acquity UPLC(沃特斯公司) 进行 LC 测量。在 Acquity UPLC HSS T3 柱 (1.8μm,2.1×100mm ;沃特斯公司 (Waters)Acquity) 上进行反相 UPLC(超高效液相层析),流速为 0.8ml/min。使用两种流动相 (A :在 H_2O/ 乙腈 95/5 中的 10mM 乙酸铵 ;流动相 B :乙腈) 运行梯度条件 :在 2.1 分钟内从 100% A 和 0% B 到 5% A 和 95% B 并且随后在 0.9 分钟内到 0% A 和 100% B 在 0.5 分钟内到 5% A 和 95% B。使用 1μl 的注入体积。锥孔电压,对于正离子模式是 30V,而对于负离子模式是 30V。

[0218] 方法 H :在一个 Atlantis C18 柱 (3.5μm,4.6×100mm) 上,进行反相 HPLC,伴随 1.6ml/min 的流速。柱加热器设定在 45℃。采用两个流动相 (流动相 A :70% 甲醇 +30% H_2O ; 流动相 B :在 H_2O/ 甲醇 95/5 中的 0.1% 甲酸) 来运行一个梯度条件 :在 9 分针内从 100% B 到 5% B+95% A,并且保持这些条件 3 分钟。使用 10μl 的注入体积。锥孔电压,对于正离子模式是 10V,而对于负离子模式是 20V。

[0219] 化合物 21、49-55、57-62 是从奥罗拉精细化学品公司 (Aurora Fine Chemicals) 购得。

[0220]



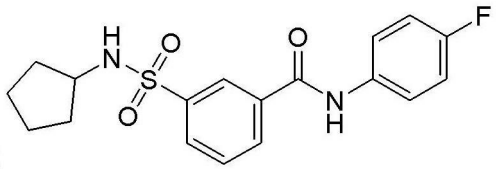
化合物 **1**

[0221] 将 3-(氯磺酰基) 苯甲酰氯 (207mg,1mmol) 溶解在二氯甲烷 (3mL) 中并且在 0℃ 将在二氯甲烷 (2mL) 中的 4- 氟苯胺 (111mg,1.0mmol) 和三乙胺 (112mg,1.0mmol) 添加到该混合物中。接着将该混合物在 20℃下搅拌 1 小时。在 0℃,向这种包含 3-(4- 氟苯基氨基甲酰基) 苯 -1- 磺酰氯的反应混合物添加三乙胺 (121mg,1.2mmol) 和 4- 氨基四氢吡喃 (88mg,0.861mmol) 于二氯甲烷 (3mL) 中的溶液。将该混合物在 20℃搅拌 1 小时。将该溶剂在真空中去除。将该残余物通过高效液相层析 (柱 :菲罗门公司 (Phenomenex)Synergi C18

150*20mm*5um.A :H_2O+0.1% TFA ;B :MeCN) 进行纯化。将该产物部分进行收集并且将该有机溶剂进行蒸发。将该部分用饱和 $NaHCO_3$进行中和。将该混合物用二氯甲烷进行萃取。将有机层用 Na_2SO_4干燥并且浓缩,产生化合物 1(85.4mg) 方法 A ;Rt :4.88min. m/z :379.2(M+H)+ 精确质量 :378.1

[0222] 接下来的化合物如化合物 1 进行类似制备,使用相应的胺代替 4- 氨基四氢吡喃 :

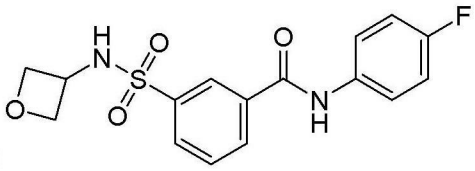
[0223]



化合物 **2**

[0224] 方法 B ;Rt :4.27min. m/z :363.1(M+H)$^+$精确质量 :362.1

[0225]



化合物 **3**

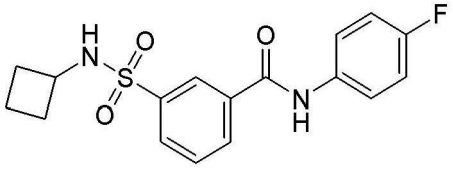
[0226] 方法 A ;Rt :4.64min. m/z :351.1(M+H)$^+$精确质量 :350.1

[0227]

化合物 **4**

[0228] 方法 A ;Rt :4.87min. m/z :365.1(M+H)$^+$精确质量 :364.1

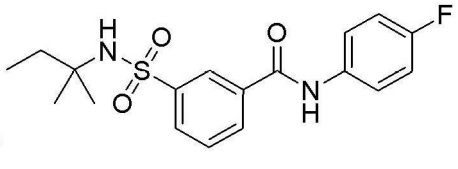
[0229]



化合物 **5**

[0230] 方法 A ;Rt :5.32min. m/z :349.1(M+H)$^+$精确质量 :348.1

[0231]

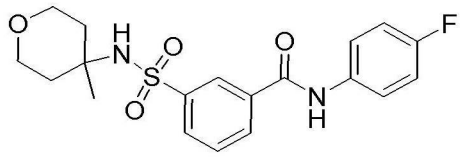


化合物 **79**

[0232] 方法 A ;Rt :5.39min. m/z :365.2(M+H)$^+$精确质量 :364.1

[0233] ^{1}H NMR(400MHz, 氯仿 -d) δ ppm 8.37(1H, t, J = 1.5Hz),8.16(1H, br.s.), 8.11(1H, dm, J = 8.0Hz),8.05(1H, dm, J = 8.0Hz),7.57-7.70(3H, m),7.08(2H, t, J = 8.7Hz),4.78(1H, s),1.55(2H, q, J = 7.5Hz),1.18(6H, s),0.84(3H, t, J = 7.5Hz)。

[0234]

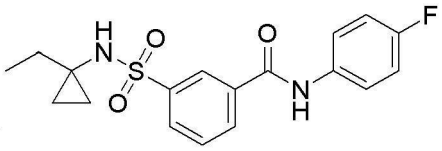


化合物 **83**

[0235] 方法 A ;Rt :4.20min. m/z :415.0(M+Na)+精确质量 :392.1 ;

[0236] 通过硅胶层析法 (梯度洗脱液 :石油醚 / 乙酸乙酯从 100/1 至 1/1) 进行纯化。^{1}H NMR(400MHz,DMSO-d_6) δ ppm 10.57(1H,br. s),8.33-8.47(1H,m),8.19(1H,dm,J = 7.5Hz),8.06(1H, dm, J = 7.5Hz),7.72-7.85(3H, m),7.66-7.73(1H, br. s),7.12-7.31(2H, m),3.42-3.58(4H,m),1.71-1.92(2H,m),1.27-1.50(2H,m),1.06(3H, s)。

[0237]

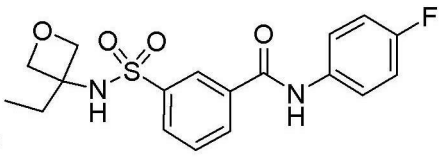


化合物 **87**

[0238] 方法 B ;Rt :3.94min. m/z :363.1(M+H)+精确质量 :362.1

[0239] 通过高效液相层析使用 RP-18(洗脱液 :在水 (0.1 % TFA) 中的 CH_3CN 从 25 到 55, v/v) 进行纯化。^{1}H NMR(400MHz, DMSO-d_6), δ ppm 0.34-0.42(m,2H),0.46-0.54(m,2H),0.75(t,J = 7.3Hz,3H),1.28(q,J = 7.3Hz,2H),7.15-7.25(m,2H)7.67-7.83(m,3H),7.97(d,J = 8.3Hz ;1H),8.14-8.25(m,2H),8.33(s,1H),10.55(s,1H)。

[0240]

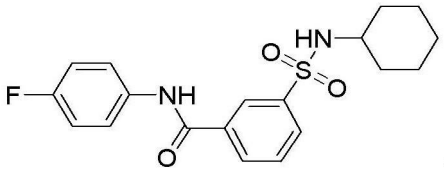


化合物 **89**

[0241] 方 法 E ;Rt :4.83min。m/z :379.1(M+H)+Exact mass :378.1 ;^{1}H NMR(400MHz, DMSO-d6), δ ppm 10.60(s,1H),8.48(br. s.,1H),8.39(s,1H),8.23(d, J = 7.8Hz,1H),8.04(d, J = 7.8Hz,1H),7.74-7.87(m,3H),7.23(t, J = 9.0Hz,2H),4.51(d, J = 6.5Hz,2H),4.20(d, J = 6.5Hz,2H),1.84(q, J = 7.3Hz,2H),0.64(t, J = 7.3Hz,3H)。如针对化合物 1 描述的类似地制备,使用 3- 乙基氧杂环丁 -3- 胺代替 4- 氨基四氢吡喃。3- 乙基氧杂环丁 -3- 胺的合成 :将 3- 乙基氧杂环丁烷 -3- 羧酸 (3.0g,23.1mmol)、DPPA(叠氮化磷酸二苯酯,7.61g,27.7mmol)、三乙胺 (3.0g,23.1mmol) 和 BnOH(2.99g,27.7mmol) 溶解在甲苯 (50mL) 中。将该混合物在 110℃搅拌过夜。将该溶剂在真空中去除。添加二氯甲烷 (50mL)。将该混合物用 1N HCl(20mL) 进行洗涤。将水层用二氯甲烷 (20ml) 萃取。将合并的有机层用盐水洗涤并且经 Na_2SO_4干燥。将该溶剂在真空中去除。将残余物通过硅胶柱层析 (洗脱液 :石油醚 / 乙酸乙酯从 100/1 至 60/40) 进行纯化,产生了 3- 乙基氧杂环丁 -3- 基氨基甲酸苄酯 (4.0g)。在 N_2下,向 3- 乙基氧杂环丁 -3- 基氨基甲酸苄酯 (2.0g,8.5mmol) 和环己 -1,4- 二烯 (1.02g,12.75mmol) 于 MeOH(20mL) 中的溶液里添加 Pd-C(10%,0.2g)。将该混合物在 H_2球形烧瓶中在 25℃搅拌 4 小时。过滤后,将滤液进行浓缩产生 3- 乙基氧杂环丁 -3- 胺 (860mg),将其照原样用于下一个反应中。

[0242] 化合物 6 的合成 :

[0243]

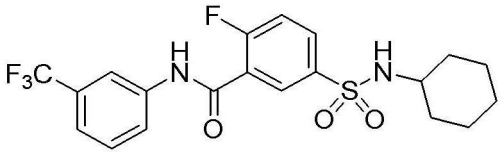


化合物 6

[0244] 在 5℃向 3-(氯磺酰基) 苯甲酸 (1g,4.53mmol) 于 CH_2Cl_2(20mL) 中的溶液相继逐滴添加环己胺 (0.899g,9.06mmol) 和三乙胺 (1.38g,13.60mmol)。将该溶液在室温下搅拌过夜。将该混合物用 1N HCl(50mL) 进行洗涤。将该有机相用 $MgSO_4$进行干燥并浓缩,产生作为白色固体 (1.2g) 的 3-(N- 环己基氨磺酰) 苯甲酸,将其不经纯化而用于下一步中。在 5℃向 3-(N- 环己基氨磺酰基) 苯甲酸 (1.2g,4.24mmol) 于 DMF(15mL) 中的溶液相继添加 4- 氟苯胺 (0.52g,4.66mmol) 和 DIPEA(1.64g,12.71mmol)。将该混合物搅拌 20 分钟然后添加 HATU(1.93g,5.08mmol)。将该溶液在室温下搅拌过夜。随后向该反应混合物中添加水性 $NaHCO_3$(50mL),接着添加添加 EtOAc(50mL)。将该有机层用 HCl(5% ;50mL) 和盐水进行洗涤。将该有机层用 $MgSO_4$进行干燥并且浓缩,产生一种残余物。将获得的残余物通过硅胶层析柱 (石油醚 : EtOAc = 2 : 1) 进行纯化,以产生作为白色固体 (850mg) 的化合物 6。方法 B ;Rt :4.50min. m/z :377.2 $(M+H)^+$精确质量 :376.1

[0245] 化合物 7 的合成

[0246]

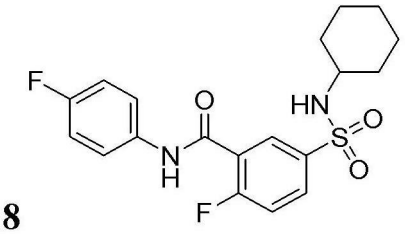


化合物 7

[0247] 在室温下向在 EtOAc(150mL) 中的 5-(氯磺酰基)-2- 氟苯甲酸 (10g,41.91mmol) 添加环己胺 (12.47g,125.72mmol)。在室温下将该反应混合物搅拌 10 分钟并且用 1N HCl(100mL) 进行洗涤。将该有机相用 $MgSO_4$进行干燥并浓缩,产生作为白色固体 (10.9g) 的 5-(N- 环己基氨磺酰基)-2- 氟苯甲酸,将其不经纯化而用于下一步中。在 5℃向 5-(N- 环己基氨磺酰基)-2- 氟苯甲酸 (1g,3.32mmol) 于 DMF(15mL) 中的溶液里相继添加 3-(三氟甲基) 苯胺 (0.54g,3.32mmol) 和 DIPEA(1.29g,9.96mmol)。将该混合物搅拌 20 分钟然后添加 HATU(1.51g,3.98mmol)。将该溶液在室温下搅拌过夜。随后向该反应混合物中添加水性 $NaHCO_3$(50mL),接着添加添加 EtOAc(50mL)。将该有机层用 HCl(5%) 和盐水进行洗涤。将有机层用 $MgSO_4$进行干燥,在真空中浓缩,并且将获得的残余物用制备型 HPLC 进行纯化,产生作为白色固体的化合物 7(902mg)。方法 B ;Rt :4.85min. m/z :445.2 $(M+H)^+$精确质量 :444.1 ; ^1H NMR(400MHz, DMSO-d_6) δ ppm10.94(1H, br. s),8.15-8.22(1H, m),8.12(1H, dd, J = 6.5,2.5Hz),8.03(1H, ddd, J = 9.0,4.5,2.5Hz),7.88-7.97(1H, m),7.83(1H, d, J = 7.5Hz),7.58-7.67(2H, m),7.46-7.54(1H, m),2.90-3.07(1H, m),1.51-1.67(4H, m),1.38-1.51(1H, m),0.96-1.27(5H, m)

[0248] 如化合物 7 制备的类似的化合物的实例,使用相应的苯胺代替 3-(三氟甲基) 苯胺 :

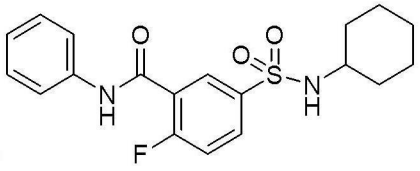
[0249]



化合物 **18**

[0250] ^{1}H NMR(400MHz, DMSO-d_6) δ ppm 10.68(1H, br. s), 8.08(1H, dd, J = 6.0, 2.5Hz), 8.01(1H, ddd, J = 8.5, 4.5, 2.5Hz), 7.83(1H, br. s), 7.70-7.77(2H, m), 7.60(1H, app. t, J = 9.0Hz), 7.18-7.27(2H, m), 2.90-3.07(1H, m), 1.53-1.67(4H, m), 1.40-1.53(1H, m), 0.96-1.25(5H, m)。方法 C ;Rt :4.21min. m/z :395.1(M+H)$^+$精确质量 :394.1

[0251]

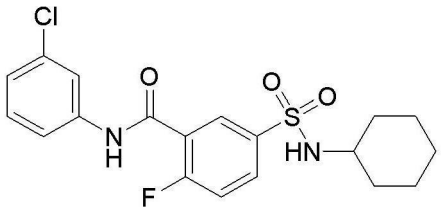


化合物 **19**

[0252] 方法 C ;Rt :4.17min. m/z :377.1(M+H)$^+$精确质量 :376.1

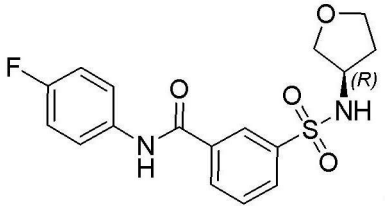
[0253]

化合物 **43**



[0254] 方法 C ;Rt :4.53min. m/z :411.1(M+H)$^+$精确质量 :410.1

[0255]

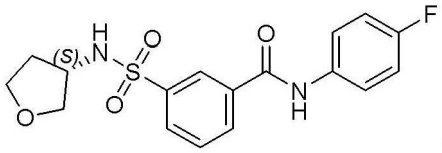


化合物 **8**

[0256] 在冰浴中,向 (R)- 四氢呋喃 -3- 胺 (0.87g,9.97mmol) 在 THF(20mL) 中的溶液里添加水性氢氧化钠 (4mL,5N),随后添加 3-(氯磺酰基) 苯甲酸 (2.2g,9.97mmol)。在 25℃搅拌 3 小时后,将该反应混合物用 H_2O(20mL) 稀释并且用 EtOAc(20mL) 进行萃取。将该水层通过 HCl(2N) 水溶液调整至 pH = 3 然后将产生的混合物用 EtOAc(3×20mL) 进行萃取。将该合并的有机层用盐水进行洗涤,用无水 $MgSO_4$进行干燥并且在真空中浓缩,产生化合物 (R)-3-(N-(四氢呋喃 -3- 基) 氨磺酰基) 苯甲酸 (900mg)。在 N_2气氛下,向化合物 (R)-3-(N-(四氢呋喃 -3- 基) 氨磺酰基) 苯甲酸 (0.80g,2.95mmol)、4- 氟苯胺 (0.39g,3.54mmol) 和 HATU(3.36g,8.85mmol) 在冰浴冷却的 CH_2Cl_2(10mL) 中的溶液里添加 DIPEA(0.57g,0.44mmol)。将产生的混合物用 CH_2Cl_2(15mL) 稀释并且用饱和水性 $NaHCO_3$(15mL) 和盐水 (10mL) 进行洗涤。在用无水 $MgSO_4$进行干燥后,将该溶剂在真

空中去除。将获得的残余物通过制备型高效液相层析使用 RP-18（洗脱液：CH_3CN 在 H_2O 中：从 40％到 80％，v/v；0.05％ TFA 作为添加物）进行纯化。收集纯的部分并且将挥发物在真空中去除。将该水层用安伯莱特 IRA-900 离子交换树脂（OH 型）调整至 PH ＝ 7，过滤并且冻干。将获得的残余物进一步通过制备型 SFC（柱：大赛璐公司 (Chiralpak) AD-3 150×4.6mm I.D.，3um 流动相：在 CO2 中 40％的甲醇 (0.05％二乙胺）流速：2.5mL/min) 进行纯化，产生化合物 8(370mg)。方法 A；Rt：4.6min. m/z：365.2(M+H)$^+$精确质量：364.1；$[\alpha]^{20}_D$＝ -13.60(c ＝ 0.11，MeOH) ^{1}H NMR(400MHz，DMSO-d_6) δ ppm10.57(1H，br. s)，8.34-8.40(1H，m)，8.18-8.27(1H，m)，8.09(1H，br. s)，7.99-8.06(1H，m)，7.74-7.84(3H，m)，7.13-7.33(2H，m)，3.64-3.83(2H，m)，3.50-3.64(2H，m)，3.35-3.39(1H，m)，1.80-1.99(1H，m)，1.51-1.68(1H，m)。

[0257]

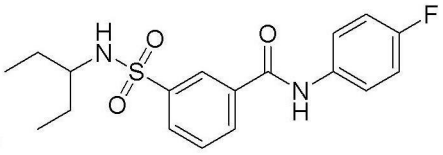


化合物 9

[0258] 向 (S)- 四氢呋喃 -3- 胺盐酸盐 (0.500g，4.41mmol) 和 NaOH(0.485g，12.138mmol) 于 H_2O(5mL) 和 THF(5mL) 中的冰冷却的混合物里分数份添加 3-（氯磺酰基）苯甲酸 (0.893g，4.406mmol)。然后在 20℃，将该反应混合物搅拌 2 小时。将产生的混合物用 H_2O(10mL) 稀释并且用乙酸乙酯 (10mL) 进行萃取。通过添加 1N HCl 将该水层的 pH 值调整至 3 并且然后将该混合物用乙酸乙酯 (3×10mL) 进行萃取。将该合并的有机层用盐水 (10mL) 进行洗涤，用无水 Na_2SO_4 进行干燥并且在减压下浓缩，产生 (S)-3-(N-（四氢呋喃 -3- 基）氨磺酰基）苯甲酸 (0.60g)。在 N_2 气氛下，向 (S)-3-(N-（四氢呋喃 -3- 基）氨磺酰基）苯甲酸 (600mg，2.212mmol)、4- 氟苯胺 (270mg，2.433mmol) 和 HATU(1.01g，2.654mmol) 于 DMF(5mL) 中的冰冷却的混合物里添加 DIPEA(1.15mL，6.636mmol)。将产生的混合物在 20℃搅拌 2 小时。将该溶剂在真空中去除。将该混合物用饱和水性柠檬酸 (10mL)、盐水进行洗涤并且用 Na_2SO_4 进行干燥。将该溶剂在真空中去除。将残余物通过硅胶柱层析（梯度洗脱液：石油醚 / 乙酸乙酯从 100/0 至 10/90) 进行纯化。收集纯的部分并且将溶剂在真空中去除。将残余物进一步通过制备型高效液相层析使用 RP-18（洗脱液：CH_3CN 在 H_2O 中：从 40％到 80％，v/v；0.06％ NH_4HCO_3 作为添加物）进行纯化。收集纯的部分并且将挥发物在真空中去除。将该水层冻干至干燥，产生化合物 9(0.48g)。方法 A；Rt：4.6min. m/z：365.2(M+H)$^+$ 精确质量：364.1；$[\alpha]^{20}_D$＝ +15.56(c 0.10，MeOH)；^{1}H NMR(400MHz，80℃，DMSO-d_6) δ ppm 10.35(1H，br. s)，8.32-8.48(1H，m)，8.15-8.32(1H，m)，8.03(1H，br. s)，7.83-7.94(1H，m)，7.68-7.83(3H，m)，7.06-7.31(2H，m)，3.70-3.87(2H，m)，3.51-3.70(2H，m)，3.32-3.48(1H，m)，1.85-2.04(1H，m)，1.59-1.78(1H，m)

[0259] 如针对化合物 8 和 9 描述的从相应的胺（代替四氢呋喃 -3 胺）类似地制备的化合物：

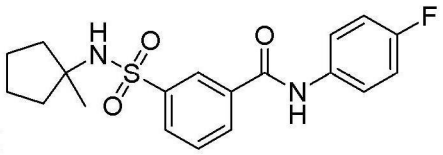
[0260]



化合物 **10**

[0261] 方法 B ;Rt :4.24min. m/z :365.2(M+H)$^+$精确质量 :364.1 ;

[0262]



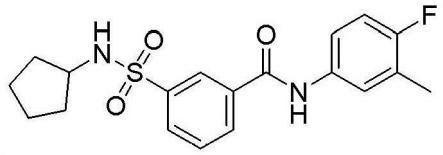
化合物 **76**

[0263] 使用 1- 甲基环戊胺代替四氢呋喃 -3- 胺,使用 Gemini 250*20mm*5um(洗脱液 : CH_3CN 在 H_2O(0.1% TFA) 中从 40% 到 70%,v/v)。方法 B ;Rt :4.24min. m/z :377.2(M+H)$^+$精确质量 :376.1 ;

[0264] 3-(N- 环戊基氨磺酰基) 苯甲酸的合成 :

[0265] 向环戊胺 (1.93g,22.66mmol) 和 NaOH(1.81g,45.32mmol) 于 H_2O(25mL) 与 THF(25mL) 中的溶液的冰冷却混合物里分部分添加 3-(氯磺酰基) 苯甲酸 (5.0g, 22.66mmol)。将反应混合物在 20℃搅拌 2 小时。将产生的混合物用 H_2O(20mL) 稀释并且用乙酸乙酯 (30mL) 进行萃取。将水层分离并且通过 4N HCl 调整至 pH = 2 并且用二氯甲烷 (3×30mL) 进行萃取。将该合并的有机层用盐水 (15mL) 进行洗涤,用无水 Na_2SO_4进行干燥并且在减压下浓缩,以产生 3-(N- 环戊基氨磺酰基) 苯甲酸 (4.5g)。

[0266]

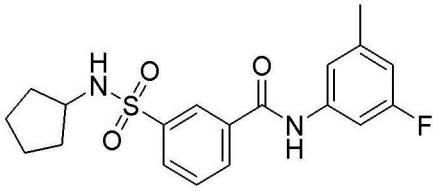


化合物 **11**

[0267] 在 N_2气氛下,向 3-(N- 环戊基氨磺酰基) 苯甲酸 (250mg,0.928mmol)、4- 氟 -3- 甲基苯胺 (116.2mg,0.928mmol)、HATU(388.2mg,1.021mmol) 于 CH_2Cl_2(15mL) 中冰冷却的混合物里添加 DIPEA(359.8mg,2.784mmol)。将产生的混合物在 20℃搅拌 16 小时。将该溶剂在真空中去除。将该混合物用饱和水性柠檬酸 (10mL)、盐水进行洗涤并且用 Na_2SO_4进行干燥。将该溶剂在真空中去除。将残余物通过硅胶柱层析 (梯度洗脱液 :石油醚 / 乙酸乙酯从 100/0 至 10/90) 进行纯化。收集纯的部分并且将溶剂在真空中去除。将残余物进一步通过制备型高效液相层析使用 RP-18(洗脱液 :CH_3CN 在 H_2O 中 :从 45% 到 75%,v/v ;0.01% HCl 作为添加物) 进行纯化。收集纯的部分并且将挥发物在真空中去除。将该水层用安伯莱特 IRA-900 离子交换树脂 (OH 型) 调整至 Ph = 7,过滤并且冻干至干燥以产生化合物 11(170.0mg)。方法 B ;Rt :4.31min. m/z :377.2(M+H)$^+$精确质量 :376.1 ; ^{1}H NMR(400MHz, DMSO-d_6) δ ppm 10.47(1H,br.s),8.33-8.35(1H,m),8.17(1H,dm,J = 8.0),7.98(1H,dm,J = 8.0),7.78(1H,d,J = 7.0Hz),7.74(1H,t,J = 8.0Hz),7.62-7.68(1H,m),7.53-7.61(1H, m),7.13(1H,t,J = 9.0Hz),3.37-3.48(1H,m),2.23(3H,d,J = 1.8Hz),1.44-1.69(4H,m), 1.12-1.45(4H,m)

[0268] 如化合物 11 从相应的苯胺 (代替 4- 氟 -3- 甲基苯胺) 起始的类似地制备 :

[0269]



化合物 **12**

[0270] ^{1}H NMR(400MHz,DMSO-d_6) δ ppm 10.60(1H,bs),8.36(1H,t,J = 1.5Hz),8.19(1H,dm,J = 7.5Hz),8.02(1H,dm,J = 7.5Hz),7.81(1H,d,J = 7.5Hz),7.78(1H,t,J = 7.5Hz),7.55(1H,dm,J = 11.0Hz),7.38-7.46(1H,m),6.82(1H,dm,J = 9.5Hz),3.41-3.54(1H,m),2.34(3H, s),1.45-1.70(4H, m),1.19-1.45(4H, m) ;方法 B ;Rt :4.41min. m/z :377.2(M+H)$^+$ 精确质量 :376.1

[0271]

化合物 **13**

[0272] 将残余物通过硅胶柱层析 (梯度洗脱液 :石油醚 / 乙酸乙酯从 100/0 至 40/60) 进行纯化。方法 B ;Rt :4.41min. m/z :377.2(M+H)$^+$精确质量 :376.1

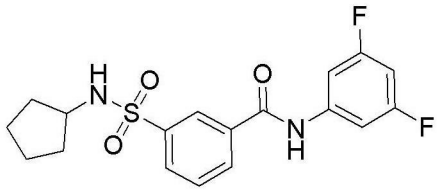
[0273]

化合物 **14**

[0274] 方法 B ;Rt :4.34min. m/z :381.2(M+H)$^+$精确质量 :380.1

[0275] ^{1}H NMR(400MHz,DMSO-d_6) δ ppm 1.20-1.44(m,4H),1.44-1.68(m,4H),3.44(sxt,J = 6.8Hz,1H),7.45(dt, J = 10.6,9.0Hz,1H),7.51-7.60(m,1H),7.77(t, J = 7.8Hz,1H),7.80(d, J = 7.2Hz,1H),7.93(ddd, J = 13.2,7.5,2.5Hz,1H),8.02(d, J = 7.8Hz,1H),8.19(d,J = 7.7Hz,1H),8.35(t,J = 1.7Hz,1H),10.70(s,1H)

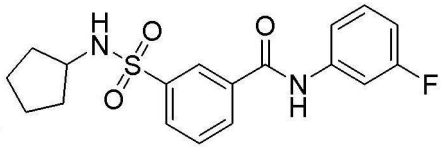
[0276]



化合物 **15**

[0277] 方法 B ;Rt :4.43min. m/z :381.2(M+H)$^+$精确质量 :380.1

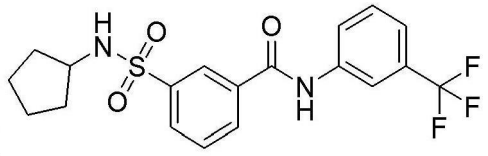
[0278]



化合物 **77**

[0279] 方法 B ;Rt :5.45min. m/z :363.2(M+H)$^+$精确质量 :362.1

[0280]



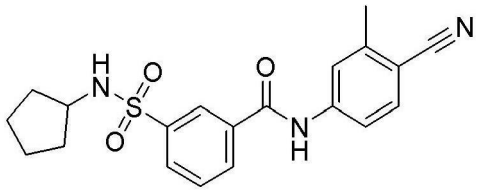
化合物 **81**

[0281] 通过制备型高效液相层析 (柱 :Phenomenex Synergi 200mm*77mm,10um ;流动相 :CH_3CN 在水 (0.1 % TFA) 中从 45 % 到 75 %,) 进行纯化。方法 A ;Rt :5.87min. m/z : 413.2(M+H)$^+$精确质量 :412.1

[0282]

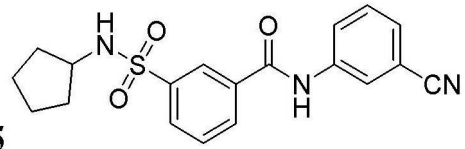
化合物 **16**

[0283]



[0284] 将 3-(N- 环戊基氨磺酰基) 苯甲酸 (500mg,1.73mmol) 在草酰二氯 (10mL) 中的溶液在 45℃搅拌 5 小时。将该溶剂在真空中去除。将粗制 3-(N- 环戊基氨磺酰基) 苯甲酰氯 (600mg) 按照这样用于下一步骤中。在 N_2气氛下,向 3-(N- 环戊基氨磺酰基) 苯甲酰氯 (600mg,1.74mmol) 和 4- 氨基 -2- 甲苯甲腈 (230mg,1.74mmol) 于 CH_2Cl_2(5mL) 中冰冷却的混合物里添加吡啶 (10mL)。将产生的混合物在 20℃搅拌 16 小时。将该溶剂在真空中去除。将残余物通过制备型高效液相层析使用 RP18(洗脱液 :CH_3CN 在 H_2O 中 :从 50 % 到 80 %, v/v ;0.05 % TFA 作为添加物) 进行纯化。收集纯的部分并且将挥发物在真空中去除。将该水层用安伯莱特 IRA-900 离子交换树脂 (OH 型) 调整至 PH = 7,过滤并且冻干产生化合物 16(250mg)。方法 B ;Rt :4.23min. m/z :384.2(M+H)$^+$精确质量 :383.1。

[0285]



化合物 **75**

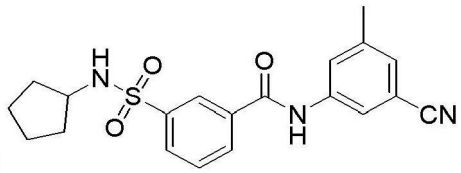
[0286] 如针对化合物 16 描述的类似地制备,使用 3- 氨基苄腈代替 4- 氨基 -2- 甲苯甲腈。方法 A ;Rt :5.24min. m/z :370.2(M+H)$^+$精确质量 :369.1。

[0287]

化合物 **80**

[0288] 如针对化合物 16 描述的类似地制备,使用 4- 氨基苄腈代替 4- 氨基 -2- 甲苯甲腈。方法 A ;Rt :5.32min. m/z :370.2(M+H)$^+$精确质量 :369.1。

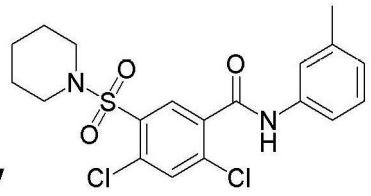
[0289]



化合物 **82**

[0290] 如针对化合物 16 描述的类似地制备，使用 3- 氨基 -5- 甲苯甲腈代替 4- 氨基 -2- 甲苯甲腈。方法 A ;Rt :5.52min. m/z :384.2(M+H)$^+$精确质量 :383.1。

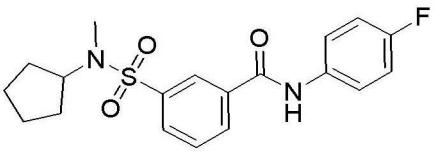
[0291]



化合物 **17**

[0292] 在 N_2气氛下，向化合物 2,4- 二氯 -5-(哌啶 -1- 基磺酰基) 苯甲酸 (1.0g, 2.96mmol)、间甲苯胺 (0.38g,3.55mmol)，和 HATU(1.69g,4.44mmol) 于冰浴冷却的 CH_2Cl_2(10mL) 中的溶液里添加 DIPEA(1.15g,8.88mmol)。将产生的混合物用 CH_2Cl_2(15mL) 稀释并且用饱和水性 $NaHCO_3$(15mL) 和盐水 (10mL) 进行洗涤，用无水 $MgSO_4$进行干燥并且将溶剂在真空中去除。将残余物通过硅胶柱层析 (梯度洗脱液 :石油醚 / 乙酸乙酯从 100/0 至 40/60) 进行纯化。收集纯的部分并且将溶剂在真空中去除，产生化合物 17(0.65g)。方法 B ;Rt :4.70min. m/z :427.1(M+H)$^+$精确质量 :426.1

[0293]

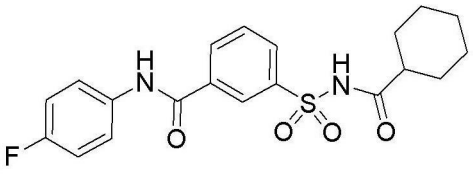


化合物 **46**

[0294] 在冰浴中，向 3-(氯磺酰基) 苯甲酸 (1.10g,4.97mmol) 于 THF(60mL) 中的溶液里添加氢氧化钠 (水性的,2mL,5N)，随后添加 N- 甲基环戊胺 (0.50g,4.97mmol)。在 25℃搅拌 3 小时后，将该反应混合物用 H_2O(50mL) 稀释并且用 EtOAc(50mL) 进行萃取。将水层通过 HCl(2N) 调整至 pH ＝ 3 并且用 EtOAc(3×50mL) 进行萃取。将该合并的有机层用盐水进行洗涤，用无水 $MgSO_4$进行干燥并且在真空中浓缩，产生 3-(N- 环戊基 -N- 甲基氨磺酰基) 苯甲酸 (0.8g)。在 N_2气氛下，向 3-(N- 环戊基 -N- 甲基氨磺酰基) 苯甲酸 (0.80g,2.82mmol)、4- 氟苯胺 (0.31g,2.82mmol) 和 HATU(1.61g,4.24mmol) 于冰浴冷却的 CH_2Cl_2(10mL) 中的溶液里添加 DIPEA(1.09g,8.47mmol)。将产生的混合物用 CH_2Cl_2(15mL) 稀释并且用饱和水性 $NaHCO_3$(15mL) 和盐水 (10mL) 进行洗涤，用无水 $MgSO_4$进行干燥并且将溶剂在真空中去除。将获得的残余物通过制备型高效液相层析使用 RP-18(洗脱液 :CH_3CN 在 H_2O 中 :从 30% 到 80%，v/v ;0.05% TFA 作为添加物) 进行纯化。收集纯的部分并且将挥发物在真空中去除。将该水层用安伯莱特 IRA-900 离子交换树脂 (OH 型) 调整至 Ph ＝ 7，过滤并且冻干至干燥，产生化合物 46(0.73g)。方法 B ;Rt :4.43min. m/z :377.2(M+H)$^+$精确质量 :376.1

[0295]

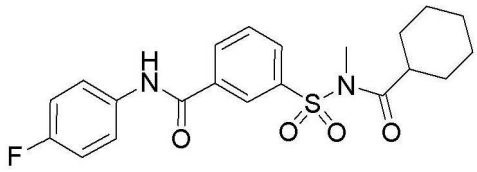
化合物 **56**



[0296] 将 4- 氟 苯 胺 (0.93g,8.366mmol) 和 DIPEA(2.91mL,16.732mmol) 溶 解 在 CH_2Cl_2(20mL) 中。在 0℃将在 CH_2Cl_2(20mL) 中的 3-(氯磺酰基) 苯甲酰氯 (2g,8.366mmol) 进行一次性添加。将该混合物在 0℃搅拌 1 小时。包含 3-(4- 氟苯基氨基甲酰基) 苯 -1- 磺酰氯的该反应混合物 (40mL) 不经进一步纯化而用于下一步骤中。在 0℃,将氨 (2.52g,18mmol,25% -28% wt) 添加到 3-(4- 氟苯基氨基甲酰基) 苯 -1- 磺酰氯 (如以上获得的,6mmol) 在 CH_2Cl_2(30mL) 中的溶液。将该混合物在 20℃搅拌 1 小时。将 1N HCl(30mL) 添加到该反应混合物中并且将该挥发物在真空中部分地去除。将形成的沉淀进行过滤并且与甲苯 (10mL) 共同蒸发,产生 N-(4- 氟苯基)-3- 氨磺酰基苯甲酰胺 (1.6g)。N-(4- 氟苯基)-3- 氨磺酰基苯甲酰胺 (1.8g,6.12mmol) 和环己烷羰酰氯 (1.79g,12.23mmol) 在氯仿 (40mL) 中的溶液连同 SiO_2(180mg) 和 H_2SO_4(0.5mL) 进行回流 1 小时。添加二氯甲烷 (20mL) 并且将该固体过滤出。将滤液用水 (10mL) 洗涤并且经 Na_2SO_4干燥。将该溶剂在真空中去除。将获得的残余物通过硅胶柱层析 (梯度洗脱液 :石油醚 / 乙酸乙酯 :从 100/0 至 70/30) 进行纯化。将获得的产物 (1.2g,纯度 95%) 用甲基叔丁基醚 (10mL) 进一步进行洗涤,产生化合物 56(500mg,纯度 99.7%)。方法 A ;Rt :5.51min. m/z :405.2(M+H)$^+$精确质量 :404.1 ; ^{1}H NMR(400MHz, DMSO-d_6) δ ppm 12.16(1H, br. s),10.62(1H, br. s),8.41(1H, t, J = 2.0Hz),8.27(1H, dm, J = 7.5Hz),8.09(1H, dm, J = 7.5Hz),7.73-7.82(3H, m),7.07-7.33(2H, m),2.11-2.31(1H, m),1.43-1.80(5H, m),0.94-1.32(5H, m)

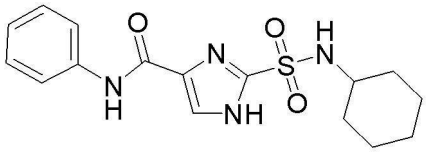
[0297]

化合物 **48**



[0298] 在 20℃,将化合物 56(600mg) 溶解在 CH_2Cl_2(6mL) 中,并且逐滴添加 MeOH(2mL) 和 $TMSCHN_2$(3.7mL,7.415mmol,在己烷中 2M)。将该混合物在 20℃下搅拌 2 小时。将该溶剂在真空中去除。将残余物通过快速柱 (梯度洗脱液 :石油醚 / 乙酸乙酯从 100/0 至 70/30) 进行纯化,产生一种残余物 (0.41g)。将获得的产物通过制备型高效液相层析使用 RP-18(洗脱液 : CH_3CN 在 H_2O 中 (0.1% TFA) :从 20% 到 50%,v/v) 进一步纯化。收集纯的部分并且将挥发物在真空中去除。将沉淀过滤并且将残留水通过冻干法进行去除,产生化合物 48(300mg)。方法 B ;Rt :4.60min. m/z :419.2(M+H)$^+$精确质量 :418.1 ; ^{1}H NMR(400MHz, DMSO-d_6) δ ppm 10.62(1H, br. s),8.40-8.45(1H, m),8.28(1H, dm, J = 7.5Hz),8.13(1H, dm, J = 7.5Hz),7.66-7.95(3H, m),7.07-7.33(2H, m),3.40(3H, s),2.73-2.92(1H, m),1.42-1.77(5H, m),0.90-1.35(5H, m)。

[0299]



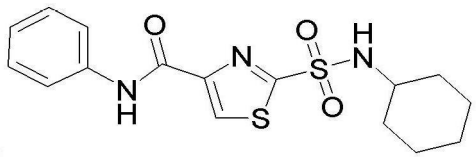
[0300]

化合物 **63**

[0301] 将乙基 2-(氯磺酰基)-1H-咪唑-4-羧酸盐 (1g,4.19mmol)、Et_3N(1.27g,12.55mmol) 和环己胺 (0.623g,6.28mmol) 于 THF(25mL) 中的混合物在室温下搅拌 15 小时。将该混合物浓缩并且通过制备型 HPLC(柱 :C18 ;流动相 A :净化水 (0.075% TFA, V/V) ;流动相 B :乙腈 ;流速 :80mL/min ;梯度 :25% -55%,30min) 进行纯化,产生呈浅黄色固体的 2-(N-环己基氨磺酰基)-1H-咪唑-4-羧酸乙酯 (0.6g)。向 2-(N-环己基氨磺酰基)-1H-咪唑-4-羧酸乙酯 (0.6g,1.99mmol) 于 EtOH-H_2O(3/1 ;20mL) 中的溶液里添加 LiOH(0.145g,6.055mmol)。将该混合物在室温下搅拌 15 小时。将该反应混合物用 HCl(2M) 进行中和,用水稀释然后将其萃取到 EtOAc,用 $MgSO_4$进行干燥,过滤并且浓缩,产生呈白色固体的 2-(N-环己基氨磺酰基)-1H-咪唑-4-羧酸 (400mg)。将 2-(N-环己基氨磺酰基)-1H-咪唑-4-羧酸 (0.3g,1.098mmol)、苯胺 (0.102g,1.098mmol)、DIPEA(0.284g,2.196mmol) 和 HATU(0.501g,1.317mmol) 在 DMF(25mL) 中的混合物在室温下搅拌 15 小时。将该混合物通过制备型 HPLC 进行纯化(柱 :YMC 150x 30mm。

[0302] 流动相 A :净化的水 (0.075% TFA, V/V) ;流动相 B :乙腈 ;流速 :30mL/min ;梯度 :40% -70%,8min) 进行纯化,产生化合物 63(218mg)。方法 B ;Rt :3.98min. m/z :349.2(M+H)$^+$精确质量 :348.1。^{1}H NMR(400MHz,甲醇 -d_4) δ ppm 1.26(s,5H)1.51-1.62(m,1H)1.65-1.80(m,4H)3.23-3.29(m,1H)7.10-7.18(m,1H)7.32-7.39(m,2H)7.67-7.74(m,2H)7.86(s,1H) ;

[0303]

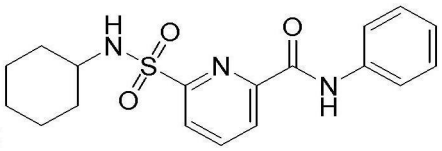


化合物 **64**

[0304] 将 2-(氯磺酰基)噻唑-4-羧酸乙酯 (3g,11.73mmol)、Et_3N(3.56g,35.2mmol) 和环己胺 (1.75g,17.65mmol) 于 THF(100mL) 中的混合物在室温下搅拌 15 小时。将该混合物浓缩并且通过制备型 HPLC 进行纯化,产生呈白色固体的 2-(N-环己基氨磺酰基)噻唑-4-羧酸乙酯 (2g)。向 2-(N-环己基氨磺酰基)噻唑-4-羧酸乙酯 (2g) 在 EtOH-THF(1/1,60mL) 中的溶液里添加 LiOH(0.451g,18.83mmol)。将该混合物在室温下搅拌 15 小时。将该反应混合物用 HCl(2M) 进行中和,用水稀释然后将其萃取到 EtOAc,用 $MgSO_4$进行干燥,过滤并且在真空中浓缩,产生呈白色固体的 2-(N-环己基氨磺酰基)噻唑-4-羧酸 (1.7g)。将 2-(N-环己基氨磺酰基)噻唑-4-羧酸 (1g)、苯胺 (0.321g,3.44mmol)、DIPEA(1.33g,10.29mmol) 和 HATU(1.57g,4.13mmol) 于 DMF(40mL) 中的混合物在室温下搅拌 15 小时。将该混合物浓缩并且通过制备型 HPLC(柱 :SYNERGI 250*50 10um ;流动相 A :净化水 (0.075% TFA,V/V) ;流动相 B :乙腈 ;流速 :80mL/min ;梯度 :35% -65%,30min) 进行纯化,

产生呈白色固体的化合物 64(895mg)。方法 B ;Rt :4.45min. m/z :366.1(M+H)$^+$精确质量 :365.1

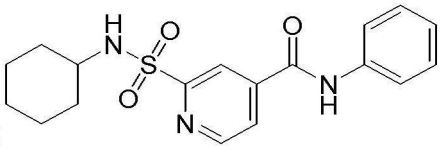
[0305]



化合物 65

[0306] 将 6- 氯 -N- 苯基吡啶酰胺 (4g,17.19mmol)、苯甲硫醇 (3.23g,25.79mmol) 和 K_2CO_3(4.75g,34.38mmol) 于 DMF 中的混合物在 80℃搅拌 18 小时。将该反应混合物用 EtOAc(150mL) 稀释,并且用盐水 (2×200mL) 进行洗涤。将有机层经 $MgSO_4$干燥,过滤并浓缩。将该残余物通过快速硅胶层析 (在石油醚中 20%的 EtOAc) 进行纯化以获得 6-(苄基硫)-N- 苯基吡啶酰胺 (2.8g)。将 N- 氯代琥珀酰亚胺 (3.42g,25.6mmol) 添加到 6-(苄基硫)-N- 苯基吡啶酰胺 (2g,6.24mmol) 于乙酸 (60mL) 和水 (40mL) 中的混合物里。将该反应混合物在室温下搅拌 3 小时。将该反应用 CH_2Cl_2(100mL) 进行稀释。用水洗涤后,将该有机层添加到环己胺 (12.4g,125mmol) 和 Et_3N(50mL) 于 CH_2Cl_2(200mL) 中的混合物里。将产生的混合物在室温下搅拌 4 小时。将该反应混合物用 NH_4Cl(饱和的)、盐水进行洗涤,用 $MgSO_4$干燥,过滤并浓缩。将获得的残余物通过制备型 HPLC(柱 :Synergi 150*30mm*5um ;流动相 A : 净化水 (0.075% TFA, V/V) ;流动相 B :乙腈 ;流速 :30mL/min ;梯度 :46% -76% (溶剂 B), 8min) 进行纯化,产生化合物 65(330mg)。方法 B ;Rt :4.46min. m/z :360.2(M+H)$^+$精确质量 :359.1。^{1}H NMR(400MHz, DMSO-d_6) δ ppm 1.00-1.31(m,5H)1.34-1.47(m,1H)1.51-1.71(m,4H)3.02-3.13(m,1H)7.15-7.21(m,1H)7.40-7.46(m,2H)7.82-7.88(m,2H)8.15(dd, J = 6.3,2.5Hz,1H)8.23-8.28(m,1H)8.29-8.36(m,2H)10.47(s,1H)

[0307]

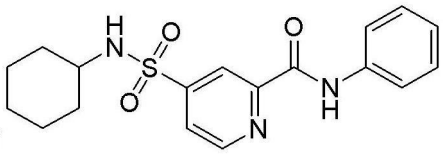


化合物 66

[0308] 将 2- 氯 -N- 苯基异烟酰胺 (2g,8.6mmol)、苯甲硫醇 (2.11g,17mmol) 和 K_2CO_3(2.35g,17mmol) 于 DMF 中的混合物在 80℃搅拌 18 小时。将该反应用水 (200mL) 稀释并且用 EtOAc(2×100mL) 进行萃取。将合并的有机层用盐水洗涤,用 $MgSO_4$干燥,过滤并浓缩。将获得的残余物通过硅胶层析法 (在石油醚中 0-20%的 EtOAc) 进行纯化以产生 2-(苄基硫)-N- 苯基异烟酰胺 (1.7g)。将 N- 氯代琥珀酰亚胺 (2.56g,19.2mmol) 添加到 2-(苄基硫)-N- 苯基异烟酰胺 (1.5g,4.68mmol) 于乙酸 (20mL) 和水 (10mL) 中的混合物里。将该反应混合物在室温下搅拌 4 小时。将该反应用 CH_2Cl_2(20mL) 进行稀释。用水洗涤后,将该有机层添加到环己胺 (4.641g,46.8mmol) 和 Et_3N(10mL,71.74mmol) 于 CH_2Cl_2(50mL) 中的混合物里。将产生的混合物在室温下搅拌 4 小时。将该反应混合物用 NH_4Cl(饱和的)、盐水进行洗涤,用 $MgSO_4$干燥,过滤并浓缩。将获得的残余物通过制备型 HPLC(柱 :C18-10um ;流动相 A :净化水 (0.075% TFA,V/V) ;流动相 B :乙腈 ;流速 :80mL/min ;梯度 :40% -70% (溶剂 B),25min) 进行纯化,产生化合物 66(250mg)。方法 B ;Rt :4.22min. m/z :360.2(M+H)$^+$精确质量 :359.1。^{1}H NMR(400MHz,DMSO-d_6) δ ppm0.96-1.08(m,1H)1.08-1.24(m,4H)1.40-1.52(m,

1H)1.53-1.67(m,4H)3.11-3.22(m,1H)7.14-7.21(m,1H)7.37-7.44(m,2H)7.78(d, J = 7.8Hz,2H)7.97(br.s,1H)8.12(dd, J = 5.0,1.5Hz,1H)8.40(s,1H)8.94(d, J = 5.0Hz, 1H)10.75(s,1H)

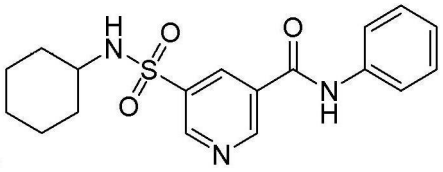
[0309]



化合物 67

[0310] 在 CO(50Psi) 气氛下,将在甲醇 (50mL) 中的 2- 氯 -N- 环己基吡啶 -4- 磺酰胺 (540mg,1.965mmol)、$PdCl_2$dppf(100mg,0.137mmol) 和 Et_3N(5.89mmol) 在 50℃搅拌 18 小时。在减压下去除该溶剂。包含 4-(N- 环己基氨磺酰基)- 吡啶甲酸甲酯的获得的残余物 (700mg) 不经进一步纯化而用于下一步骤中。将 K_2CO_3(421mg,3.05mmol) 添加到 4-(N- 环己基氨磺酰基)- 吡啶甲酸甲酯于甲醇和水中的混合物里。将该混合物在 20℃下搅拌 18 小时。将溶剂去除,将残余物用水 (50mL) 稀释并且用 EtOAc(2×50mL) 进行洗涤。然后将水层用 1M HCl 酸化至 pH = 3 并且用 EtOAc(2×50mL) 进行萃取。将合并的有机层用 $MgSO_4$进行干燥,过滤并且浓缩,产生 4-(N- 环己基氨磺酰基)- 吡啶甲酸 (380mg)。然后在室温下将 HATU(0.76g,2.0mmol) 添加到 4-(N- 环己基氨磺酰基)- 吡啶甲酸 (380mg,1.34mmol)、苯胺 (251mg,2.7mmol) 和 DIPEA(0.517g,4.0mmol) 在 DMF(50mL) 中的混合物里。将所得混合物在室温下搅拌 18 小时。将该混合物用水 (200mL) 稀释,并且用 EtOAc 进行萃取。将该有机层用盐水洗涤,用 $MgSO_4$干燥,过滤并在真空中浓缩。将获得的残余物通过硅胶层析法 (在石油醚中 10% -20%的 EtOAc) 进行纯化,产生呈白色固体 (330mg) 的化合物 67。方法 B ;Rt :4.58min. m/z :360.2$(M+H)^+$精确质量 :359.1。 ^1H NMR(300MHz, DMSO-d_6) δ ppm 0.93-1.26(m,5H)1.37-1.50(m,1H)1.50-1.69(m,4H)2.98-3.12(m,1H)7.15(t, J = 7.2Hz, 1H)7.32-7.45(m,2H)7.86-7.97(m,2H)8.03(dd, J = 5.0,1.5Hz,1H)8.25(d, J = 7.3Hz, 1H)8.47(d, J = 1.5Hz,1H)9.00(d, J = 5.0Hz,1H)10.78(s,1H)

[0311]

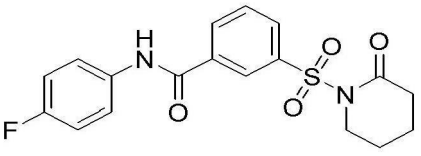


化合物 68

[0312] 在 0-5℃将亚硫酰氯 (10mL,137mmol) 逐滴添加到水 (60mL) 中。将该混合物在室温下搅拌 16 小时。添加 CuCl(40mg,0.4mmol),并且将该混合物 (混合物 A) 冷却至 -5℃。在 -5℃至 0℃,向 5- 氨基 - 烟酸于浓 HCl(35mL) 中的混合物里添加 $NaNO_2$(2.76g,40mmol) 于水 (40mL) 中的溶液 (混合物 B)。经 30 分钟将混合物 B 分部分地添加到混合物 A,温度保持在 -5℃至 0℃。在 0℃搅拌 1 小时后,将该固体通过过滤收集,用水洗涤,并且在真空中干燥,产生 5-(氯磺酰基) 烟酸 (1.05g)。将 5-(氯磺酰基) 烟酸 (1g,4.5mmol)、环己胺 (0.893g,9mmol) 和 Et_3N(1.37mmol,13.5mmol) 于 CH_2Cl_2(30mL) 中的混合物在室温下搅拌 18 小时。在减压下去除该溶剂。将残余物通过 HPLC(柱 :C1810um ;流动相 A :净化水 (0.075% TFA,V/V) ;流动相 B :乙腈 ;流速 :80mL/min ;梯度 :30% -60% (溶剂 B),30min) 进行纯化,

产生呈白色固体 (1g) 的 5-(N- 环己基氨磺酰基) 烟酸。在室温下将 HATU(2.6g,7mmol) 添加到 5-(N- 环己基氨磺酰基)- 烟酸 (1g,3.5mmol)、苯胺 (391mg,4.2mmol) 和 DIPEA(1.36g,10.5mmol) 在 DMF(50mL) 中的混合物里。将所得混合物在室温下搅拌 18 小时。将该混合物用水 (200mL) 稀释,并且用 EtOAc 进行萃取。将有机层用盐水洗涤,用 $MgSO_4$ 干燥,过滤并浓缩。将残余物通过硅胶层析法 (在石油醚中 10％ -100％的 EtOAc) 进行纯化,产生呈白色固体 (708mg) 的化合物 68。方法 B ;Rt :4.58min. m/z :360.2(M+H)$^+$ 精确质量 :359.1

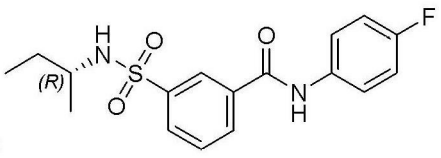
[0313]



化合物 **69**

[0314] 向 5- 氨基戊酸 (1.2g,3.44mmol) 和 1N NaOH(8mL) 于 THF(16mL) 中冰冷却的溶液里添加 3-(4- 氟苯基氨基甲酰基) 苯 -1- 磺酰氯 (0.444g,3.78mmol)。然后将反应混合物在 25℃搅拌过夜。将产生的混合物用 1N HCl(10mL) 稀释并且用乙酸乙酯 (2×30mL) 进行萃取。将该合并的有机层用盐水洗涤,用无水 Na_2SO_4 干燥,并且在减压下浓缩。将残余物通过硅胶柱层析 (梯度洗脱液 : 石油醚 : 乙酸乙酯 :从 100 : 0 至 65 : 35) 进行纯化,产生 5-(3-(4- 氟苯基氨基甲酰基) 苯磺酰氨基) 戊酸 (0.9g)。将 5-(3-(4- 氟苯基氨基甲酰基) 苯磺酰氨基) 戊酸 (400mg,0.913mmol)、乙酸酐 (0.466g,4.57mmol) 和 AcOK(1.79g,18.3mmol) 在甲苯 (25mL) 中的混合物用微波辐射在 150℃加热 30 分钟。将形成的沉淀过滤出并且将滤液在真空中浓缩。将残余物通过制备型高效液相层析 (洗脱液 :在 H_2O 中 (0.05％ HCl) 的 CH_3CN :从 0％到 35％, v/v) 进行纯化。收集纯的部分并且使用安伯莱特 IRA-900(OH) 阴离子交换树脂调整至 pH ＝ 7。将树脂过滤出并且将滤液冻干至干燥,产生化合物 69(200mg)。方法 A ;Rt :4.97min. m/z :377.2(M+H)$^+$ 精确质量 :376.1 ; ^{1}H NMR(400MHz, 氯仿 -d) δ ppm 1.78-1.87(m,2H),1.90-1.99(m,2H),2.44(t, J ＝ 6.8Hz,2H),3.95(t, J ＝ 6.0Hz,2H),7.08(t, J ＝ 8.7Hz,2H),7.55-7.70(m,3H),8.15(d, J ＝ 8.0Hz,1H),8.20(d, J ＝ 7.8Hz,1H),8.26(br. s. ,1H),8.49(s,1H)

[0315]



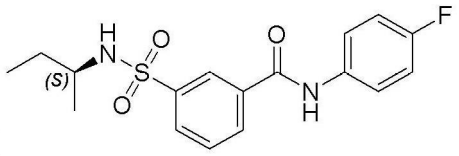
化合物 **70**

[0316] 向 (R)- 丁 -2- 胺 (0.500g,6.837mmol) 和 NaOH(0.547g,13.67mmol) 于 H_2O(15mL) 和 THF(15mL) 中冰冷却的混合物里分部分添加 3-(氯磺酰基) 苯甲酸 (1.508g,6.84mmol)。将反应混合物在 20℃搅拌 2 小时。将产生的混合物用 H_2O(15mL) 稀释并且用乙酸乙酯 (15mL) 进行萃取。将水层分离并且通过 1N HCl 调整 pH 至 3 并且用乙酸乙酯 (3×10mL) 进行萃取。将该合并的有机层用盐水 (10mL) 进行洗涤,用无水 Na_2SO_4 进行干燥并且在减压下浓缩,产生 (R)-3-(N- 仲丁基氨磺酰基) 苯甲酸 (0.73g)。

[0317] 在 N_2 气氛下,向 (R)-3-(N- 仲丁基氨磺酰基) 苯甲酸 (730mg)、4- 氟苯胺 (347mg,3.121mmol)、HATU(1.294g,3.404mmol) 于 DMF(10mL) 中冰冷却的混合物里添加 DIPEA(1.48mL,8.51mmol)。将产生的混合物在 20℃搅拌 2 小时。将该溶剂在真空中去除。

将该混合物用饱和水性柠檬酸 (10mL)、盐水进行洗涤并且用 Na_2SO_4进行干燥。将该溶剂在真空中去除。将残余物通过硅胶柱层析 (梯度洗脱液 :石油醚 / 乙酸乙酯从 100/0 至 55/45) 进行纯化。收集纯的部分并且将溶剂在真空中去除。将残余物通过 SFC 分离 (大赛璐公司 (Chiralcel)OJ,20μm ;超临界 CO_2:MeOH(0.2% 二乙胺)) 进行纯化。收集纯的部分并且将溶剂在真空中去除,产生化合物 70(300mg)。方法 A ;Rt :5.25min. m/z :351.2(M+H)$^+$精确质量 :350.1。[α]20D = -(c = 0.2,MeOH)。[α]20 D = -9.9(c 0.435w/v%,DMF) ;柱 :大赛璐公司 (Chiralpak)AD-3150×4.6mm I.D.,3um ;流动相 :在 CO_2中的甲醇 (0.05% 二乙胺) : 从 5% 到 40%,流速 :2.5mL/min ;Rt :7.58min ;^{1}H NMR(400MHz,DMSO-d_6) δ ppm 0.70(t,J = 7.4Hz,3H),0.88(d,J = 6.5Hz,3H),1.30(quin,J = 7.2Hz,2H),3.01-3.18(m,1H),7.21(t, J = 8.8Hz,2H),7.67(br.d, J = 5.5Hz,1H),7.75(t, J = 7.8Hz,1H),7.78(dd, J = 8.8, 5.1Hz,2H),8.00(d,J = 7.8Hz,1H),8.19(d,J = 7.8Hz,1H),8.36(s,1H),10.55(s,1H)。

[0318]

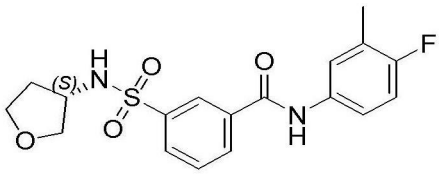


化合物 71

[0319] 如针对化合物 70 描述的类似地制备,从 (S)- 丁 -2- 胺 (代替 (R)- 丁 -2- 胺) 起始。方法 B ;Rt :4.03min. m/z :351.2(M+H)$^+$精确质量 :350.1

[0320] ([α]20 D = +(c = 0.2,MeOH).[α]20 D = +9.49(c 0.611w/v%,DMF),柱 :大赛璐公司 (Chiralpak)AD-3150×4.6mm I.D.,3um ;流动相 :在 CO_2中的甲醇 (0.05% 二乙胺) : 从 5% 到 40%,流速 :2.5mL/min ;Rt :7.73min。[α]20 589+9.49° (c 0.61w/v%,MeOH)

[0321]

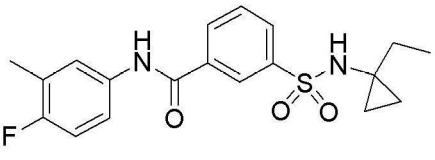


化合物 72

[0322] 将 3-(氯磺酰基) 苯甲酰氯 (1200mg,5.0mmol) 溶解在二氯甲烷 (15mL) 中。在 0℃ 将 4- 氟 -3- 甲基苯胺 (625mg,5.0mmol) 和三乙胺 (606mg,6.0mmol) 于二氯甲烷 (15mL) 中的溶液添加到该混合物中。将该混合物在 25℃ 搅拌 1 小时。该反应混合物不经进一步纯化而用于下一步中。在 0℃,将三乙胺 (606mg,6.0mmol) 和 (S)- 四氢呋喃 -3- 胺 (460.0mg, 5.3mmol) 于二氯甲烷 (15mL) 中的溶液添加到以上反应混合物里。将该混合物在 25℃ 搅拌 1 小时。将该溶剂在真空中去除。将残余物通过反相高效液相层析 (洗脱液 :在水中 (0.1% TFA) 的 CH_3CN :从 25 到 55,v/v) 进行纯化。将纯的部分进行收集并且将该有机溶剂进行蒸发。将水层用饱和水性 $NaHCO_3$中和至 pH = 7-8。将该混合物用二氯甲烷 (3×15mL) 进行萃取。将这些合并的有机层用 Na_2SO_4进行干燥并且在真空中浓缩,产生化合物 72(620mg)。方法 A ;Rt :4.88min. m/z :379.2(M+H)$^+$精确质量 :378.1。 ^{1}H NMR(400MHz, DMSO-d_6) δ ppm 1.56-1.65(m,1H),1.85-1.94(m,1H),2.22-2.28(m,3H),3.33-3.39(m,1H),3.52-3.65(m, 2H),3.65-3.73(m,1H),3.73-3.79(m,1H),7.14(t, J = 9.2Hz,1H),7.56-7.62(m,1H), 7.67(dd, J = 7.0,2.3Hz,1H),7.78(t, J = 7.8Hz,1H),8.02(d, J = 7.8Hz,1H),8.10(d, J

＝ 4.5Hz,1H),8.21(d,J ＝ 7.8Hz,1H),8.37(s,1H),10.49(s,1H)

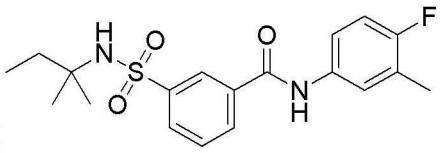
[0323]



化合物 85

[0324] 如针对化合物 72 描述的类似地制备,使用 1- 乙基环丙胺盐酸盐代替 (S)- 四氢呋喃 -3- 胺。将化合物 85 通过制备型高效液相层析使用 RP-18(洗脱液 :CH_3CN 在 H_2O 中 (0.5% NH_4HCO_3) :从 43％到 73％, v/v) 进行纯化。方法 B ;Rt :4.17min. m/z :377.1(M+H)$^+$ 精确质量 :376.1。^{1}H NMR(400MHz,DMSO-d_6) δ ppm 0.35-0.45(m,2H),0.49-0.58(m,2H),0.77(t,J ＝ 7.2Hz,3H),1.31(q,J ＝ 7.1Hz,2H),2.26(s,3H),7.15(t,J ＝ 9.3Hz,1H),7.55-7.64(m,1H)7.69(d,J ＝ 7.0Hz,1H),7.76(t,J ＝ 7.8Hz,1H),7.98(d,J ＝ 7.8Hz,1H),8.16-8.25(m,2H),8.35(s,1H),10.50(s,1H)。

[0325]



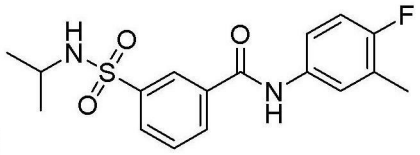
化合物 86

[0326] 如针对化合物 72 描述的类似地制备,使用 2- 甲基丁 -2- 胺盐酸盐代替 (S)- 四氢呋喃 -3- 胺。通过高效液相层析使用 RP-18(洗脱液 :CH_3CN 在水中 :从 47％到 77％, v/v) 进行纯化。方法 D ;Rt :5.97min. m/z :379.1(M+H)$^+$ 精确质量 :378.1。^{1}H NMR(400MHz,DMSO-d_6), δ ＝ 0.73(t, J ＝ 7.5Hz,3H),1.02(s,6H),1.44(q, J ＝ 7.5Hz,2H),2.23(d, J ＝ 1.0Hz,3H),7.12(t, J ＝ 9.3Hz,1H),7.52-7.61(m,2H),7.64-7.77(m,2H),8.01(d, J ＝ 7.8Hz,1H),8.14(d,J ＝ 7.8Hz,1H),8.36(s,1H).10.45(s,1H)。

[0327] 化合物 72 的替代合成法 :

[0328] 将 3-(氯磺酰基) 苯甲酰氯 (4.61g,19.28mmol) 在甲苯 (45mL) 中的混合物在温和的氮流下进行回流。将在甲苯 (15mL) 中的 4- 氟 -3- 甲基苯胺 (2.19g,17.53mmol) 逐滴添加到该回流溶液中。添加后,将该混合物另作回流 30 分钟。下一步将该混合物冷却至室温,并且逐滴添加 (S)-3- 氨基四氢呋喃甲苯磺酸酯 (5g,19.28mmol) 和二异丙基乙胺 (15mL) 于甲苯 (15mL) 和 CH_2Cl_2(10mL) 中的混合物。添加后,将该混合物在室温下搅拌 4 小时。将产生的混合物用 HCl(2×100mL,1M 水性的)、水 (2×100mL) 和 $NaHCO_3$(2×100mL, 饱和水性的) 进行洗涤。将有机层用 $MgSO_4$ 进行干燥,过滤并且在减压下进行浓缩。使用硅胶层析法 (CH_2Cl_2-MeOH 100 ： 0 到 95 ： 5) 在 CH_2Cl_2 洗脱液中将获得的残余物进行纯化,产生 3-(4- 氟 -3- 甲基苯基氨基甲酰基) 苯 -1- 磺酰氯 (1.07g),随后在去除该溶剂 (在 55℃在真空烘箱中干燥 20 小时) 后得到呈白色固体的化合物 72(2.85g)。([α]20 D ＝ -5.21(c 0.67w/v％,MeOH),方法 F ;Rt :0.88min. m/z :379.1(M+H)$^+$ 精确质量 :378.1。该化合物从 CH_2Cl_2 结晶 :DSC(以 10℃ /min 从 30℃到 300℃) :149℃。[α]20 D ＝ +3.21(c 0.65w/v％,DMF)。

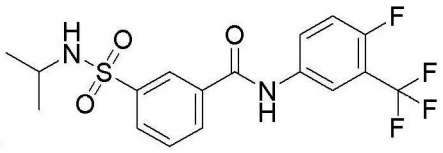
[0329]



化合物 **73**

[0330] 向 3-(氯磺酰基)苯甲酸(50.0g,226.6mmol)在乙酸乙酯(1000mL)中冰冷却的溶液里一次性添加异丙胺(67.0g,1.13mol)。将反应混合物在 25℃搅拌 3 小时。将产生的混合物用 1N HCl(500mL)稀释并且用乙酸乙酯(2×500mL)进行萃取。将该合并的有机层用盐水(400mL)进行洗涤,用无水 Na_2SO_4进行干燥并且在减压下浓缩,产生 3-(N-异丙基氨磺酰基)苯甲酸(46g)。在 N_2气氛下,向 3-(N-异丙基氨磺酰基)苯甲酸(7.0g,28.77mmol)、4-氟-3-甲基苯胺(3.6g,28.77mmol)和 DIPEA(18.6g,143.91mmol)于 CH_2Cl_2(70mL)中冰冷却的混合物里添加 HATU(12.0g,31.56mmol)。将产生的混合物在 20℃搅拌 16 小时。将该溶剂在真空中去除。将该混合物用饱和水性柠檬酸(30mL)、盐水(20mL)进行洗涤并且用 Na_2SO_4进行干燥。将该溶剂在真空中去除。将残余物通过制备型高效液相层析在 SYNERGI 250*50 10um 上(洗脱液:在 H_2O 中(0.05% TFA)的 CH_3CN:从 35%到 65%,v/v)进行纯化。收集纯的部分并且使用安伯莱特 IRA-900(OH)阴离子交换树脂调整至 pH = 7。将树脂过滤出。将滤液冻干至干燥,产生化合物 73(7.5g)。方法 B;Rt:3.44min.m/z:351.1$(M+H)^+$精确质量:350.1 ^1H NMR(400MHz,DMSO-d_6)δ ppm10.49(1H,br.s),8.36(1H,t,J = 1.5Hz),8.19(1H,ddd,J = 7.8,1.5,1.0Hz),8.01(1H,ddd,J = 7.8,1.5,1.0Hz),7.76(1H,t,J = 7.8Hz),7.68(1H,dd,J = 7.0,3.0Hz),7.75(1H,bs),7.59(1H,ddd,J = 9.0,4.5,3.0Hz),7.15(1H,t,J = 9.0Hz),3.14-3.33(1H,m),2.25(3H,d,J = 1.5Hz),0.96(6H,d,J = 6.5Hz)。

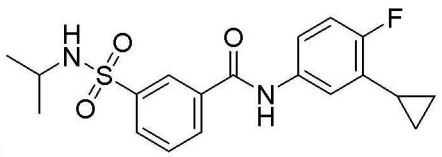
[0331]



化合物 **74**

[0332] 如针对化合物 73 描述的类似地制备,使用 4-氟-3-(三氟甲基)-苯胺代替 4-氟-3-甲基苯胺。在 HPLC Synergi 150×30mm×5u 上(洗脱液:在 H_2O 中(0.05% HCl)的 CH_3CN:从 45%到 75%,v/v)进行纯化。方法 A;Rt:5.62min.m/z:405.2$(M+H)^+$精确质量:404.1。^1H NMR(400MHz,DMSO-d_6)δ ppm 10.82(1H,s),8.39(1H,t,J = 1.5Hz),8.17-8.30(2H,m),8.07-8.17(1H,m),8.03(1H,d,J = 7.8),7.73-7.83(2H,m),7.55(1H,t,J = 10.0Hz),3.20-3.33(1H,m),0.95(6H,d,J = 6.5Hz)。

[0333]

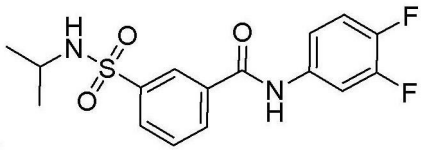


化合物 **84**

[0334] 在 N_2下在 100℃,将 N-(3-溴-4-氟苯基)-3-(N-异丙基氨磺酰基)苯甲酰胺(如针对化合物 73 描述的类似地制备,使用 3-溴-4-氟苯胺代替 4-氟-3-甲基苯胺并且经由制备型高效液相层析使用 RP-18(洗脱液:CH_3CN 在 H_2O 中(0.05% NH_4HCO_3)从 40%到 70%,

v/v) 进行纯化;700mg,1.69mmol)、环丙基硼酸 (0.22g,2.529mmol)、$Pd(PPh_3)4$(0.20g,0.169mmol) 和 Na_2CO_3(1.43g,13.49mmol) 在水 (7mL)、EtOH(7mL) 和甲苯 (7mL) 中的混合物通过微波辐射加热 40 分钟。将反应混合物通过硅藻土进行过滤。将水 (10mL) 添加到该滤液,并且将该混合物用乙酸乙酯 (2×10mL) 进行萃取。将合并的有机层用盐水洗涤并且经 Na_2SO_4干燥。将该溶剂在真空中去除。将残余物通过制备型高效液相层析使用 RP-18(洗脱液 :CH_3CN 在 H_2O 中 (0.1% TFA) :从 20%到 50%,v/v) 进行纯化。收集纯的部分并且将挥发物在真空中去除。使用饱和水性 $NaHCO_3$将该水层调整至 pH = 7 并且用乙酸乙酯 (2×20mL) 进行萃取。将合并的有机层经 Na_2SO_4干燥。将溶剂在真空中去除并且将获得的残余物进一步通过超临界流体层析 (柱 :大赛璐公司 (Chiralpak)AD-3150×4.6mm I.D.,3um 流动相 :在 CO_2中的甲醇 (0.05%二乙胺) :从 5%到 40%,流速 :2.5mL/min) 进行纯化。收集纯的部分并且将挥发物在真空中去除。将残余物在水 (5mL) 中悬浮并且冻干至干燥,产生化合物 84(35mg)。方法 B ;Rt :4.18min.m/z :377.1$(M+H)^+$精确质量 :376.1 ;^1H NMR(400MHz,氯仿 -d) δ ppm 8.34(s,1H),8.12(d, J = 8.0Hz,1H),7.97-8.07(m,2H),7.65(t, J = 8.0Hz,1H),7.36-7.46(m,1H),7.15-7.22(m,1H),7.01(t, J = 9.3Hz,1H),4.65(d, J = 7.5Hz,1H),3.44-3.58(m,1H),2.04-2.16(m,1H),1.10(d, J = 6.5Hz,6H),0.96-1.06(m,2H),0.71-0.82(m,2H)。

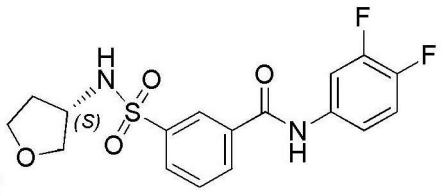
[0335]



化合物 **88**

[0336] 如针对化合物 73 描述的类似地制备,使用 3,4- 二氟苯胺代替 4- 氟 -3- 甲基苯胺。方法 E ;Rt :5.31min.m/z :355.1$(M+H)^+$精确质量 :354.1 ;^1H NMR(400MHz, DMSO-d_6) δ ppm 10.71(s,1H),8.36(t, J = 1.5Hz,1H),8.19(d, J = 7.8Hz,1H),7.98-8.08(m,1H),7.94(ddd, J = 13.2,7.5,2.4Hz,1H),7.71-7.83(m,2H),7.53-7.59(m,1H),7.42-7.51(m,1H),3.21-3.29(m,1H),0.96(d, J = 6.5Hz,6H)。

[0337]

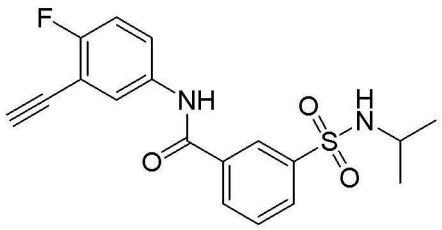


化合物 **90**

[0338] 将 3-(氯磺酰基) 苯甲酰氯 (1200mg,5.0mmol) 溶解在二氯甲烷 (15mL) 中。在 0℃将 3,4- 二氟苯胺 (650mg,5.0mmol) 和三乙胺 (606mg,6.0mmol) 于二氯甲烷 (15mL) 中的溶液添加到该混合物中。将该混合物在 25℃搅拌 1 小时。在 0℃,将三乙胺 (606mg,6.0mmol) 和 (S)- 四氢呋喃 -3- 胺 (460.0mg,5.3mmol) 于二氯甲烷 (15mL) 中的溶液添加到获得的反应混合物里。将该混合物在 25℃搅拌 1 小时。将该溶剂在真空中去除。将获得的残余物通过高效液相层析使用 RP-18(洗脱液 :CH_3CN 在水 (0.1% TFA) 中的从 30 到 60,v/v) 进行纯化。将纯的部分进行收集并且将该有机溶剂进行蒸发。将水层用饱和水性 $NaHCO_3$中和至 pH = 7-8。将该混合物用二氯甲烷 (3 x 15mL) 进行萃取。将这些合并的有机层用 Na_2SO_4进

行干燥并且在真空中浓缩，产生化合物 90(710mg)。方法 A ;Rt :4.16min. m/z :383.0(M+H)$^+$ 精确质量 :382.1 ;^{1}H NMR(400MHz, DMSO-d_6) δ ppm 1.54-1.63(m,1H),1.83-1.93(m,1H),3.32-3.38(m,1H),3.52-3.63(m,2H),3.63-3.77(m,2H),7.45(dt, J = 10.5,9.0Hz,1H),7.51-7.57(m,1H),7.78(t,J = 7.8Hz,1H),7.92(ddd,J = 13.3,7.5,2.5Hz,1H),8.02(d,J = 7.8Hz,1H),8.09(d,J = 6.5Hz,1H),8.20(d,J = 7.8Hz,1H),8.35(s,1H),10.70(s,1H)。SFC :柱 :大赛璐公司 (Chiralcel)OJ-H 250×4.6mm I.D.,5um ;流速 2.35mL/min ;流动相 :甲醇 (0.05％二乙胺) 在 CO_2中 :从 5％到 40％;Rt :5.61Min。[α]20 D = +3.21(c 0.624w/v％,DMF)

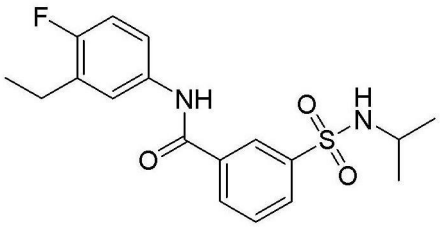
[0339]



化合物 **91**

[0340] 将 N-(3- 溴 -4- 氟苯基)-3-(N- 异丙基氨磺酰基) 苯甲酰胺 (1.5g,3.61mmol) 乙炔基三甲基硅烷 (1.77g,18.06mmol)、$Pd(PPh_3)_2Cl_2$(0.127g,0.181mmol) 和碘化亚铜 (34.4mg,0.181mmol) 溶解在二异丙胺 (10mL) 中。将该混合物在 80℃在高压灭菌锅中搅拌 24 小时。将该溶剂在真空中去除并且添加二氯甲烷 (30mL)。将该混合物用水 (20mL) 洗涤并且将该水层用二氯甲烷 (20mL) 进行萃取。将合并的有机层用盐水洗涤并且经 Na_2SO_4 干燥。将该溶剂在真空中去除。将获得的残余物通过硅胶柱层析 (洗脱液 :石油醚 / 乙酸乙酯从 100/1 至 60/40) 进行纯化，产生 N-(4- 氟 -3-((三甲基硅烷基) 乙炔基) 苯基)-3-(N- 异丙基氨磺酰基) 苯甲酰胺 (0.8g)。将 N-(4- 氟 -3-((三甲基硅烷基) 乙炔基) 苯基)-3-(N- 异丙基氨磺酰基) 苯甲酰胺 (0.8g,1.66mmol) 和 TFA(4mL) 溶解在无水 CH_2Cl_2(16mL) 中。将该混合物在 25℃搅拌过夜并且下一步在真空中浓缩。将获得的残余物通过硅胶柱层析 (梯度洗脱液 :石油醚 / 乙酸乙酯从 100/0 至 75/25) 进行纯化，产生化合物 91(220mg)。方法 A ;Rt :5.12min. m/z :361.3(M+H)$^+$精确质量 :360.1。 ^{1}H NMR(400MHz, DMSO-d_6) δ ppm 10.60(1H,s),8.35(1H,t,J = 1.5Hz),8.18(1H,d,J = 8.0Hz),8.00(1H,d,J = 8.0Hz),7.97(1H,dd,J = 6.5,3.0Hz),7.77-7.84(1H,m),7.70-7.79(2H,m),7.32(1H,t,J = 9.0Hz),4.52(1H,s)3.22-3.31(1H,m),0.94(6H,d,J = 6.5Hz)。

[0341]



化合物 **92**

[0342] 将 N-(4- 氟 -3-((三甲基硅烷基) 乙炔基) 苯基)-3-(N- 异丙基氨磺酰基) 苯甲酰胺 (0.8g,1.66mmol) 和 TFA(4mL) 溶解在无水 CH_2Cl_2(16mL) 中。将该混合物在 25℃搅拌过夜。将混合物浓缩产生了粗制 N-(3- 乙炔基 -4- 氟苯基)-3-(N- 异丙基氨磺酰基) 苯甲酰胺 (650mg)，其按照这样在下一步中使用。在 N_2气氛下，向 N-(3- 乙炔基 -4- 氟苯

基)-3-(N-异丙基氨磺酰基)苯甲酰胺(0.6g)于MeOH(20mL)中的溶液里添加Pd-C(10%,0.2g)。将该混合物在氢气氛(50psi)下在25℃搅拌4小时。在硅藻土上过滤后,将该溶剂在真空中去除并且将获得的残余物通过制备型高效液相层析在反相C-18上(洗脱液:在H_2O中(0.05% HCl)的CH_3CN:从42%到72%,v/v)进行纯化。收集纯的部分并且将挥发物在真空中去除。将该水层用安伯莱特IRA-900阴离子交换树脂(OH型)调整至PH=7,过滤并且冻干至干燥,产生化合物92(160mg)。方法B;Rt:4.13min.m/z:365.3$(M+H)^+$精确质量:364.1;^1H NMR(400MHz,DMSO-d_6)δppm 10.48(1H,s),8.35(1H,t,J=1.5Hz),8.18(1H,d,J=8.0Hz),7.99(1H,d,J=8.0Hz),7.70-7.78(2H,m),7.65-7.70(1H,m),7.57-7.65(1H,m),7.13(1H,t,J=9.0Hz),3.21-3.32(1H,m),2.62(2H,q,J=7.5Hz),1.18(3H,t,J=7.5Hz),0.94(6H,d,J=6.5Hz)。

[0343]

化合物 **93**

[0344] 向3-(氯磺酰基)苯甲酰氯(0.50g,2.09mmol)于CH_2Cl_2(10mL)中的溶液里添加DIPEA(1.35g,10.45mmol)随后缓慢添加4-氟-3-甲基苯胺(0.25g,1.99mmol)。在25℃搅拌0.5小时后,添加3-乙基氧杂环丁-3-胺(0.21g,2.09mmol)。1小时后,将产生的混合物用CH_2Cl_2(15mL)稀释,用饱和水性$NaHCO_3$(15mL)和盐水(10mL)进行洗涤,并且用无水$MgSO_4$进行干燥。将溶剂在真空中去除并且将获得的残余物通过硅胶柱层析(梯度洗脱液:石油醚/乙酸乙酯从100/0至80/20)进行纯化,产生化合物93(70mg)。方法B;Rt:3.79min.m/z:393.3$(M+H)^+$精确质量:392.1;^1H NMR(400MHz,DMSO-d_6)δppm 10.50(1H,s),8.47(1H,br.s),8.38(1H,t,J=1.5Hz),8.22(1H,d,J=8.0Hz),8.03(1H,d,J=8.0Hz),7.78(1H,t,J=8.0Hz),7.68(1H,dd,J=7.5,2.5Hz),7.56-7.64(1H,m),7.15(1H,t,J=9.0Hz),4.51(2H,d,J=6.5Hz),4.19(2H,d,J=6.5Hz),2.25(3H,d,J=1.5Hz),1.84(2H,q,J=7.0Hz),0.64(3H,t,J=7.0Hz)。

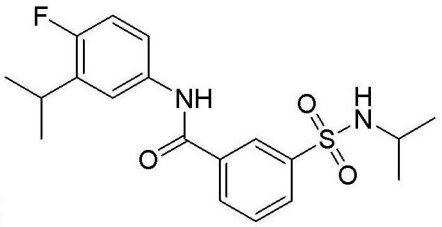
[0345]

化合物 **94**

[0346] 将3-(氯磺酰基)苯甲酰氯(1200mg,5.0mmol)溶解在二氯甲烷(15mL)中。在0℃将4-氟-3-甲基苯胺(625mg,5.0mmol)和三乙胺(606mg,6.0mmol)于二氯甲烷(15mL)中的溶液添加到该混合物中。将该混合物在25℃搅拌1小时。该反应混合物不经进一步纯化而用于下一步中(粗制,30mL)。在0℃,将三乙胺(606mg,6.0mmol)和1-甲基环丙胺(425.0mg,5.9mmol)于二氯甲烷(15mL)中的溶液添加到以上反应混合物里。将该混合物在25℃搅拌1小时。将该溶剂在真空中去除。将残余物通过反相高效液相层析(洗脱液:在水中的CH_3CN:从40%到70%,v/v)进行纯化。将纯的部分进行收集并且将该有机溶剂进行蒸发。将水层用饱和水性$NaHCO_3$中和至pH=7-8。将该混合物用二氯甲烷(3×15mL)进行

萃取。将这些合并的有机层用 Na_2SO_4 进行干燥并且在真空中浓缩，产生化合物 94(365mg)。方法 B；Rt：3.40min.m/z：363.0(M+H)$^+$精确质量：362.1；^{1}H NMR(400MHz，DMSO-d_6) δ ppm 10.49(1H,s)，8.35(1H,t，J＝1.5Hz)，8.17-8.23(2H,m)，7.99(1H,d，J＝8.0Hz)，7.76(1H,t，J＝8.0Hz)，7.68(1H,dd，J＝7.0,2.5Hz)，7.56-7.62(1H,m)，7.14(1H,t，J＝9.0Hz)，2.25(3H,d，J＝1.5Hz)，1.06(3H,s)，0.58-0.63(2H,m)，0.37-0.42(2H,m)

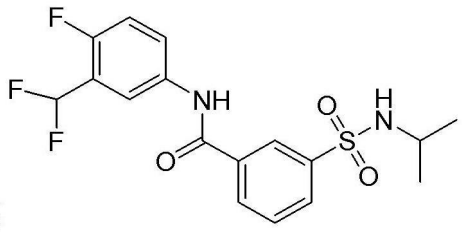
[0347]



化合物 **95**

[0348] 在 N_2 气氛下，将 N-(3-溴-4-氟苯基)-3-(N-异丙基氨磺酰基)苯甲酰胺(800mg，1.93mmol)、4,4,5,5-四甲基-2-(丙-1-烯-2-基)-1,3,2-二噁环戊硼烷(0.65g，3.85mmol)、$Pd(PPh_3)_4$(111mg，0.096mmol)和 K_2CO_3(0.53g，3.85mmol)于二噁烷(8mL)和水(2mL)中的混合物通过微波辐射在120℃加热110分钟。将该反应混合物用乙酸乙酯(20mL)稀释，并且将该催化剂过滤出。将该滤液在真空中浓缩。添加水(20mL)，并且将该水层用乙酸乙酯(2×20mL)进行萃取。将合并的有机层用盐水洗涤并且经 Na_2SO_4 干燥。将该溶剂在真空中去除并且将获得的残余物通过制备型高效液相层析在反相 C-18 上(洗脱液：在 H_2O 中(0.1% TFA)的 CH_3CN：从40%到70%，v/v)进行纯化。收集纯的部分并且将有机溶剂在真空中去除。将该水层冻干至干燥，产生 N-(4-氟-3-(丙-1-烯-2-基)苯基)-3-(N-异丙基氨磺酰基)苯甲酰胺(300mg)。在氢气氛下在25℃将 N-(4-氟-3-(丙-1-烯-2-基)苯基)-3-(N-异丙基氨磺酰基)苯甲酰胺(180mg)和 Pd/C(湿的)(20mg)在甲醇(4mL)中搅拌3小时。将混合物在硅藻土上过滤并且在真空中将滤液蒸发至干燥。将残余物通过硅胶柱层析(梯度洗脱液：石油醚/乙酸乙酯从100/0至70/30)进行纯化。将挥发物在真空中去除，产生化合物 95(175mg)。方法 B；Rt：4.33min.m/z：379.3(M+H)$^+$精确质量：378.1；

[0349]

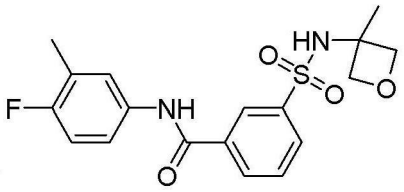


化合物 **96**

[0350] 将3-(二氟甲基)-4-氟苯胺(1.20g，7.448mmol)、3-(N-异丙基氨磺酰基)-苯甲酸(0.90g，3.699mmol)和 DIPEA(1.93mL，11.10mmol)溶解在 CH_2Cl_2(10mL)中并且在0℃添加 HATU(1.41g，3.699mmol)。将该混合物在20℃搅拌2小时。将该混合物用 CH_2Cl_2(10mL)和 H_2O(10mL)进行稀释。将有机层分离并用饱和的 $NaHCO_3$ 水溶液(10mL)和盐水(10mL)洗涤并且经 Na_2SO_4 干燥。将该溶剂在真空中去除并且将获得的残余物通过制备型高效液相层析在反相C-18上(洗脱液：在 H_2O 中(0.1‰ NH_4HCO_3)的 CH_3CN：从45%到75%，v/v)进行纯化。收集纯的部分并且将有机溶剂在真空中去除。将该水层冻干至干燥，产生化合物 96(0.885g)。方法 A；Rt：5.16min.m/z：387.3(M+H)$^+$精确质量：386.1；^{1}H NMR(400MHz，DMSO-d_6) δ ppm

10.72(1H,s),8.38(1H,t,J = 1.5Hz),8.21(1H,d,J = 8.0Hz),8.06-8.13(1H,m),8.02(1H,d,J = 8.0Hz),7.92-8.00(1H,m),7.72-7.82(2H,m),7.40(1H,t,J = 9.5Hz),7.25(1H,t,J = 55Hz),3.23-3.32(1H,m),0.95(6H,d,J = 6.5Hz)。

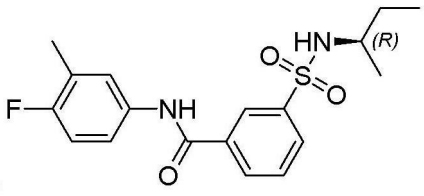
[0351]



化合物 **97**

[0352] 在室温下,将二异丙基乙胺(0.657mL,141.6mmol)和3-甲基-3-氧杂环丁胺盐酸盐(207mg,1.68mmol)于甲苯(5mL)和二氯甲烷(10mL)中的溶液逐滴添加到在甲苯(10mL)中的3-(4-氟-3-甲基苯基氨基甲酰基)苯-1-磺酰氯(500mg,1.53mmol)。2小时后,将该反应混合物用1M盐酸(2×10mL)、饱和$NaHCO_3$(2×10mL)和盐水(2×10mL)进行洗涤。将该有机层用$MgSO_4$进行干燥,过滤并且在减压下进行浓缩直至仅剩甲苯。将形成的白色沉淀进行过滤并且从二异丙醚和乙腈中再结晶。在55℃将该晶体在真空中干燥20小时,产生呈白色固体的化合物97(361mg)。方法F;Rt:0.89min.m/z:379.0$(M+H)^+$精确质量:378.1;^1H NMR(400MHz,DMSO-d_6)δppm 1.41(s,3H),2.25(d,J = 1.5Hz,3H),4.14(d,J = 6.3Hz,2H),4.56(d,J = 6.3Hz,2H),7.14(t,J = 9.0Hz,1H),7.52-7.64(m,1H),7.68(dd,J = 7.0,2.2Hz,1H),7.77(t,J = 8.0Hz,1H),7.99-8.06(m,1H),8.20(d,J = 8.0Hz,1H),8.37(t,J = 1.5Hz,1H),8.50(br.s.,1H),10.48(s,1H)。

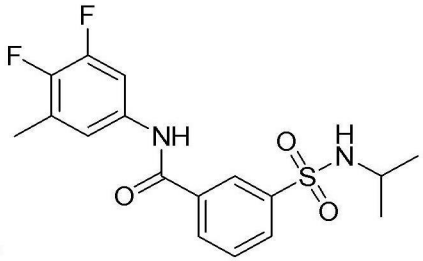
[0353]



化合物 **98**

[0354] 在室温下,将二异丙基乙胺(0.657mL,141.6mmol)和(R)-(-)-2-氨基丁烷(130mg,1.83mmol)于甲苯(5mL)和二氯甲烷(10mL)中的溶液逐滴添加到在甲苯中(10mL)的3-(4-氟-3-甲基苯基氨基甲酰基)苯-1-磺酰氯(500mg,1.53mmol)。2小时后,将该反应混合物用1M水性HCl(2×10mL)、$NaHCO_3$(2×10mL)和盐水(2×10mL)进行洗涤。将该有机层用$MgSO_4$进行干燥,过滤并且在减压下进行浓缩直至仅剩甲苯。将形成的白色沉淀过滤,再结晶(二异丙醚和乙腈)并且在55℃在真空中干燥20小时,产生呈白色固体的化合物98(257mg)。方法F;Rt:1.04min.m/z:382.1$(M+NH_4)^+$精确质量:364.1;^1H NMR(400MHz,DMSO-d_6)δppm 0.71(t,J = 7.5Hz,3H),0.88(d,J = 6.6Hz,3H),1.31(quin,J = 7.5Hz,2H),2.25(d,J = 1.8Hz,3H),3.05-3.18(m,1H),7.14(t,J = 9.0Hz,1H),7.55-7.62(m,1H),7.63-7.72(m,2H),7.75(t,J = 8.0Hz,1H),8.00(d,J = 8.0Hz,1H),8.18(d,J = 8.0Hz,1H),8.36(t,J = 1.5Hz,1H),10.46(s,1H)。

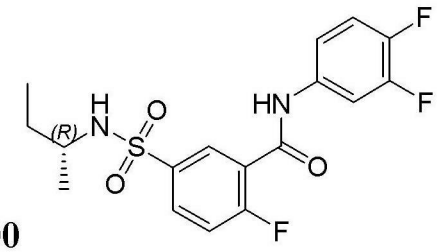
[0355]



化合物 **99**

[0356] 将 3-(N- 异丙基氨磺酰基) 苯甲酸 (2.3g,9.615mmol)、3- 溴 -4,5- 二氟苯胺 (2g,9.615mmol) 和 DIPEA(5mL) 于 CH_2Cl_2(30mL) 中的混合物冷却至 0℃并且添加 HATU(4.39g,11.538mmol)。将该混合物在 20℃下搅拌 2 小时。将该混合物用 1N HCl(30mL) 和盐水 (30mL) 进行洗涤并且用 Na_2SO_4进行干燥。将该溶剂在真空中去除。将残余物通过硅胶柱层析 (梯度洗脱液 :石油醚 / 乙酸乙酯从 100/0 至 70/30) 进行纯化,产生粗制 N-(3- 溴 -4,5- 二氟苯基)-3-(N- 异丙基氨磺酰基) 苯甲酰胺 (4g)。在 N_2气氛下,将 N-(3- 溴 -4.5- 二氟苯基)-3-(N- 异丙基氨磺酰基) 苯甲酰胺 (1g,2.308mmol)、甲基硼酸 (1g,4.616mmol)、Cs_2CO_3(2.26g,6.924mmol)、2- 二环己基膦 -2′ ,6′ - 二甲氧基联苯 (95mg,0.231mmol) 和三 (二苯亚甲基丙酮) 二钯 (0)(0.21g,0.231mmol) 于二噁烷 (15mL) 中的混合物通过微波辐射在 120℃加热 40 分钟。冷却后,将该混合物通过硅藻土进行过滤并且将滤液蒸发至干燥。将获得的残余物通过硅胶柱层析 (梯度洗脱液 :石油醚 / 乙酸乙酯从 100/0 到 70/30) 进行纯化,并且通过制备型高效液相层析使用反相 C-18(洗脱液 :在 H_2O(0.1% TFA) 中的 CH_3CN 从 38% 到 68%, v/v) 进行进一步纯化。收集纯的部分并且将挥发物的一半在真空中去除。将该混合物用安伯莱特 IRA-900(OH) 阴离子交换树脂调整至 pH = 7 并且将树脂过滤出。将该有机溶剂在真空中浓缩并且将该水层冻干至干燥。将获得的产物通过硅胶层析 (梯度洗脱液 :石油醚 / 乙酸乙酯从 100/0 至 70/30) 进一步进行纯化,产生化合物 99(190mg)。方法 A ;Rt :6.09min. m/z :369.2(M+H)$^+$精确质量 :368.1, ^{1}H NMR(400MHz, 氯仿 -d) δ ppm 8.35(1H, t, J = 1.5Hz),8.09-8.17(2H, m),8.04(1H, dt, J = 8.0,1.5Hz),7.66(1H,t,J = 8.0Hz),7.54(1H,ddd,J = 11.5,6.5,3.0Hz),7.14-7.22(1H,m),4.72(1H,d,J = 8.0Hz),3.43-3.60(1H,m),2.32(3H,d,J = 2.0Hz),1.10(6H,d,J = 6.5Hz)。

[0357]

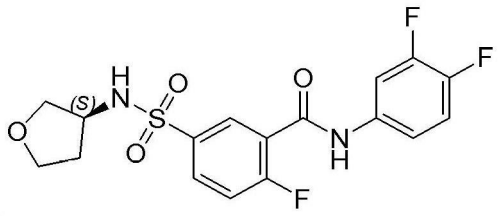


化合物 **100**

[0358] 将 5-(氯磺酰基)-2- 氟苯甲酸 (7g,29.3mmol) 溶解在二氯甲烷 (70mL) 中。添加 DMF(0.7mL),随后在 0℃逐滴添加草酰氯 (4.46g,35.16mmol)。将该混合物在 20℃搅拌 1 小时。将该混合物在真空中浓缩,并且将粗制 5-(氯磺酰基)-2- 二氟苯甲酰氯溶解在二氯甲烷 (15mL) 中。在 0℃将 3,4- 二氟苯胺 (3.6g,27.87mmol) 和 DIPEA(4.6g,35.20mmol) 于二氯甲烷 (60mL) 中的溶液添加到该混合物中。将该混合物在 25℃下搅拌 1 小时并且直接用于下一步中。在 0℃,将 (R)-(-)-2- 氨基丁烷 (2.2g,29.34mmol) 和 DIPEA(4.6g,35.20mmol)

于二氯甲烷 (60mL) 中的溶液添加到以上反应混合物里。将产生的混合物在 25℃搅拌 1 小时。将该混合物在真空中浓缩并且将获得的残余物通过反相高效液相层析 (洗脱液 :在水中 (0.1% TFA) 的 CH_3CN :从 25%到 55%, v/v) 进行纯化。将纯的部分进行收集并且将该有机溶剂进行蒸发。将该水性溶液用饱和水性 $NaHCO_3$调整至 pH = 7。将该混合物用二氯甲烷 (3×200mL) 进行萃取。将合并的有机层经 Na_2SO_4干燥并且在真空中进行浓缩。将获得的残余物在水 (10mL) 中悬浮并且将该水层冻干至干燥,产生化合物 100(4.7g)。方法 B ; Rt :4.70min. m/z :387.2 $(M+H)^+$精确质量 :386.1 :

[0359]



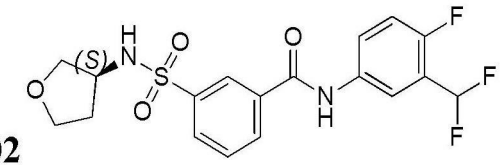
化合物 **101**

[0360] 将 (S)- 四氢呋喃 -3- 胺盐酸盐 (5.17g,42mmol) 和 NaOH(5g,126mmol) 溶解在 THF(50mL) 和 H_2O(50mL) 中。在 0℃,添加 5-(氯磺酰基)-2- 氟苯甲酸 (10g,42mmol)。将该混合物在 20℃搅拌 4 小时。将该混合物用乙酸乙酯 (3×20mL) 进行洗涤。将该水层分离,并且用 1N HCl 调整至 pH = 3。将该水层用乙酸乙酯 (3×50mL) 进行萃取。将合并的有机层用盐水洗涤并且经 Na_2SO_4干燥。将该溶剂在真空中去除,产生 (S)-2- 氟 -5-(N-(四氢呋喃 -3- 基) 氨磺酰基) 苯甲酸 (2.1g)。将 (S)-2- 氟 -5-(N-(四氢呋喃 -3- 基) 氨磺酰基) 苯甲酸 (1g,3.457mmol)、3,4- 二氟苯胺 (0.53g,4.15mmol) 和三乙胺 (0.7g,6.9mmol) 溶解在 DMF(400mL) 中并且在 0℃添加 HATU(1.57g,4.15mmol)。接着将该混合物在 20℃下搅拌 6 小时。将溶剂在真空中去除并且将获得的残余物通过硅胶层析 (洗脱液 :石油醚 : 乙酸乙酯 = 5 : 1) 进行纯化,产生化合物 101(0.8g)。方法 B ;Rt :4.15min. m/z :401.3 $(M+H)^+$ 精确质量 :400.1

[0361] 3-[[(3S)- 四氢呋喃 -3- 基] 氨磺酰基] 苯甲酸的合成 :

[0362] 将 (3S)- 四氢呋喃 -3- 胺盐酸盐 (5.6g,45.3mmol) 和 NaOH(5.2g,130mmol) 溶解在 THF(50mL) 和 H_2O(50mL) 中。在 0℃,添加 3-(氯磺酰基)- 苯甲酸 (10g,45.325mmol)。将该混合物在 20℃搅拌 4 小时。将该水层分离,并且用 1N HCl 将 pH 调整至 2。将该混合物用乙酸乙酯 (3×100mL) 进行洗涤。将合并的有机层在真空中浓缩,产生 3-[[(3S)- 四氢呋喃 -3- 基] 氨磺酰基] 苯甲酸 (11.2g)。

[0363]



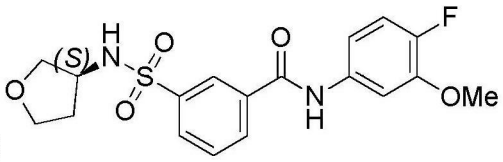
化合物 **102**

[0364] 将 (S)- 四氢呋喃 -3- 胺盐酸盐 (11.2g,90.7mmol) 和 NEt_3(50.5mL,362.6mmol) 在干 CH_2Cl_2(400mL) 中的混合物在 20℃搅拌 5 分钟。

[0365] 添加 3-(氯磺酰基) 苯甲酸 (20g,90.7mmol) 并且将该混合物在 20℃搅拌过夜。将该反应混合物用 1N HCl(100mL) 洗涤,将该水层用二氯甲烷 (2×200mL) 进行萃

取。将合并的有机层用 Na_2SO_4 进行干燥并且将该溶剂在真空中去除，产生 3-[[(3S)- 四氢呋喃 -3- 基] 氨磺酰基] 苯甲酸 (16.3g)。将 3-[[(3S)- 四氢呋喃 -3- 基] 氨磺酰基] 苯甲酸 (3g，11.058mmol)、3-(二氟甲基)-4- 氟苯胺 (2.1g，13.3mmol) 和三乙胺 (3.3g，33mmol) 溶解在 DMF(400mL) 中。在 0℃，添加 PyBrOP(132705-51-2，6.2g，13.3mmol)。将该混合物在 50℃下搅拌 12 小时。将该溶剂在真空中去除并且将获得的残余物通过反相高效液相层析 (流动相 :在水中 (0.1% TFA) 的 CH_3CN :从 30% 到 60%) 进行纯化。收集纯的部分并且通过固体 $NaHCO_3$ 中和。将该有机溶剂在真空中去除并且将形成的沉淀进行过滤，用 H_2O(5mL) 洗涤并且在高真空下干燥。将获得的残余物在水 (5mL) 中悬浮并且冻干至干燥，产生化合物 102(2.3g)。方法 A ;Rt :5.32min. m/z :415.2(M+H)$^+$ 精确质量 :414.1。^1H NMR(400MHz，DMSO-d_6) δ ppm 1.53-1.68(m,1H)1.82-1.99(m,1H)3.27-3.42(m,1H)3.51-3.90(m,4H)7.26(t，J = 55Hz,1H)7.36-7.51(m,1H)7.80(t，J = 7.8Hz,1H)7.92-8.00(m,1H)8.01-8.08(m,1H)8.08-8.15(m,2H)8.25(d，J = 7.8Hz,1H)8.40(s,1H)10.75(s,1H)。

[0366]

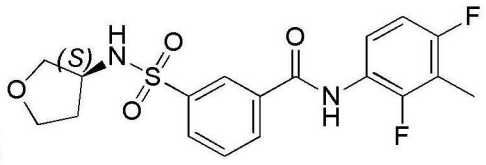


化合物 **103**

[0367] 将 3-[[(3S)- 四氢呋喃 -3- 基] 氨磺酰基] 苯甲酸 (400mg，1.47mmol) 溶解在 DMF(0.5mL) 和 CH_2Cl_2(10mL) 中。在 0℃，添加 $(COCl)_2$(223mg，1.76mmol)。将该混合物在 20℃搅拌 2 小时。将该溶剂在真空中去除并且将获得的残余物与甲苯 (2×10mL) 进行共蒸发，产生粗制 3-[[(3S)- 四氢呋喃 -3- 基] 氨磺酰基] 苯甲酰氯 (400mg)。该粗制产物不经纯化而用于下一步中。将 3-[[(3S)- 四氢呋喃 -3- 基] 氨磺酰基] 苯甲酰氯 (200mg) 溶解在二氯甲烷 (5mL) 中。在 0℃，添加 4- 氟 -3- 甲氧基 - 苯胺 (78mg，0.552mmol) 和三乙胺 (167mg，165mmol)。在 20℃将该混合物搅拌 2 小时，用 H_2O(5mL) 洗涤并且将该水层用二氯甲烷 (3×10mL) 进行萃取。将该合并的有有机层在真空中进行浓缩。将获得的残余物通过反相高效液相层析 (流动相 :在水中 (0.1% TFA) 的 CH_3CN :从 30% 到 60%) 进行纯化。收集纯的部分并且通过固体 $NaHCO_3$ 中和。将该有机溶剂在真空中去除。将获得的沉淀进行过滤，用 H_2O(5mL) 进行洗涤，并且在高真空下进行干燥。将残余物在水 (5mL) 中悬浮冻干至干燥，产生化合物 103(140mg)。方法 A ;Rt :4.98min. m/z :395.2(M+H)$^+$ 精确质量 :394.1

[0368] 如针对化合物 103 描述的类似地制备 :

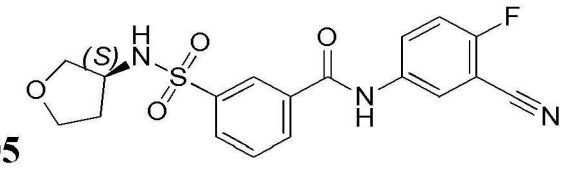
[0369]



化合物 **104**

[0370] 方法 A ;Rt :5.17min. m/z :397.3(M+H)$^+$ 精确质量 :396.1

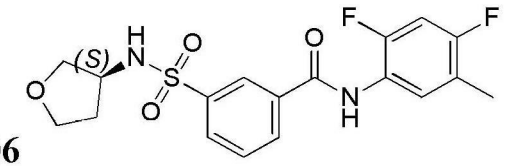
[0371]



化合物 **105**

[0372] 方法 A ;Rt :5.10min. m/z :389.1(M+H)$^+$精确质量 :390.2

[0373]

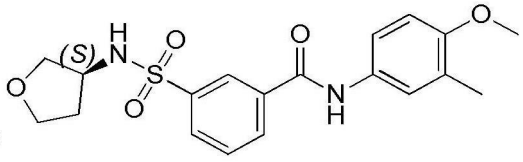


化合物 **106**

[0374] 方法 A ;Rt :5.18min. m/z :397.2(M+H)$^+$精确质量 :396.1

[0375] ^{1}H NMR(400MHz, DMSO-d_6) δ ppm 1.54-1.69(m,1H)1.82-1.98(m,1H)2.24(s,3H)3.35-3.40(m,1H)3.52-3.66(m,2H)3.66-3.83(m,2H)7.32(t,J = 10.0Hz,1H)7.49(t,J = 8.5Hz,1H)7.79(t,J = 7.8Hz,1H)8.04(d,J = 8.0Hz,1H)8.07-8.18(m,1H)8.23(d,J = 7.8Hz,1H)8.39(s,1H)10.40(br. s,1H)

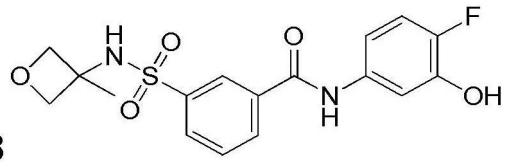
[0376]



化合物 **107**

[0377] 将 3-[[(3S)- 四氢呋喃 -3- 基] 氨磺酰基] 苯甲酸 (270mg,1.0mmol) 溶解在二氯甲烷 (5mL) 中。在 20℃,将 3- 甲基 -4- 甲氧基苯胺 (165mg,1.2mmol) 和三乙胺 (145mg,1.4mmol) 添加到该混合物中。将该混合物在 20℃搅拌 5 分钟。添加 HATU(456mg,1.2mol) 并且进一步将该混合物在 20℃搅拌 8 小时。将该溶剂在真空中去除并且将获得的残余物通过高效液相层析 (柱 :Phenomenex Synergi C18150*20mm*5um. . A :H_2O+0.1% TFA B :MeCN B 在 A 中从 30% 到 60%) 进行纯化。将该产物部分进行收集并且将该有机溶剂在真空中进行蒸发。使用饱和水性 $NaHCO_3$ 将该水层中和并且用二氯甲烷 (2×10mL) 进行萃取。将这些合并的有机层用 Na_2SO_4 进行干燥并且在真空中浓缩,产生化合物 107(135mg)。方法 A ;Rt :5.24min. m/z :391.3(M+H)$^+$精确质量 :390.1

[0378]

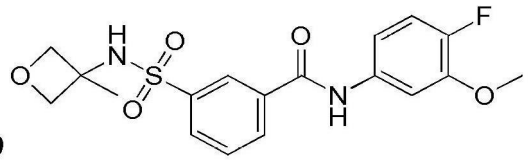


化合物 **108**

[0379] 将 5- 氨基 -2- 氟 - 苯酚 (234mg,1.84mmol) 和 3-[(3- 甲基氧杂环丁 -3- 基) 氨磺酰基] 苯甲酸 (500mg,1.84mmol) 溶解在二氯甲烷 (8mL) 中。添加 PyBrOP(132705-51-2,1030mg,2.21mmol),随后在 0℃逐滴添加 DIPEA(714mg,5.53mmol)。将该混合物在 25℃搅拌 1 小时。将该混合物用饱和水性柠檬酸 (15mL)、饱和水性 $NaHCO_3$(15mL) 和盐水进行洗涤并且用 Na_2SO_4 进行干燥。将该溶剂在真空中去除。将获得的残余物通过反相制备型高效液相层析 (流动相 :在水中 (0.05% NH_4HCO_3) 的 CH_3CN :从 29% 到 39%) 进行纯化。收集纯的部

分并且将挥发物在真空中去除。将该残余水层冻干至干燥，产生化合物 108(60mg)。方法 A ;Rt :4.47min. m/z :381.2(M+H)$^+$精确质量 :380.1

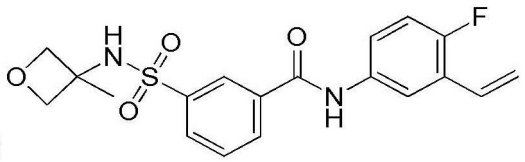
[0380]



化合物 **109**

[0381] 如针对化合物 108 描述的类似地制备，使用 4- 氟 -3- 甲氧基 - 苯胺代替 5- 氨基 -2- 氟 - 苯酚。方法 A ;Rt :5.03min. m/z :395.2(M+H)$^+$精确质量 :394.1

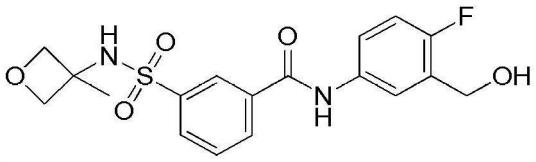
[0382]



化合物 **110**

[0383] 在 25℃将 DIPEA(2.85g,22.08mmol) 添加到 3-[(3- 甲基氧杂环丁 -3- 基) 氨磺酰基] 苯甲酸 (3.0g,11.06mmol) 和 HATU(4.20g,11.05mmol) 在 DMF(100mL) 中的溶液里。30 分钟后，将 3- 溴 -4- 氟 - 苯胺 (2.1g,11.05mmol) 添加到该溶液里。将反应混合物在 25℃搅拌过夜。将溶剂在真空中去除并且将获得的残余物通过硅胶柱层析 (梯度洗脱液 :石油醚 / 乙酸乙酯 :从 10/1 至 5/1) 进行纯化。收集纯的部分并且将溶剂在真空中去除，产生 N-(3- 溴 -4- 氟 - 苯基)-3-[(3- 甲基氧杂环丁 -3- 基) 氨磺酰基] 苯甲酰胺 (化合物 160，2.5g)。在 N_2 气氛下，将 N-(3- 溴 -4- 氟 - 苯基)-3-[(3- 甲基氧杂环丁 -3- 基) 氨磺酰基] 苯甲酰胺 (0.3g,0.68mmol)、4,4,5,5- 四甲基 -2- 乙烯基 -1,3,2- 二噁环戊硼烷 (54.2mg，0.35mmol)、$Pd(dppf)Cl_2$(50mg,0.068mmol)、KOAc(108mg,1.1mmol) 和 Na_2CO_3(100mg，0.94mmol) 于 CH_3CN(10mL) 和 H_2O(2mL) 中的混合物通过微波辐射在 130℃加热 30 分钟。将该反应混合物通过硅藻土过滤并且将滤饼用乙酸乙酯 (2×10mL) 进行洗涤。将该有机层从滤液分离，用盐水进行洗涤并且用 Na_2SO_4 进行干燥。将该溶剂在真空中去除。将获得的残余物通过反相制备型高效液相层析 (洗脱液 :在 H_2O 中 (0.05% $NH_3.H_2O$) 的 CH_3CN :从 30% 到 80%，v/v) 进行纯化。收集纯的部分并且将挥发物在真空中去除。将该水层冻干至干燥，产生化合物 110(70mg)。方法 B ;Rt :4.19min. m/z :391.3(M+H)$^+$精确质量 :390.1。

[0384]

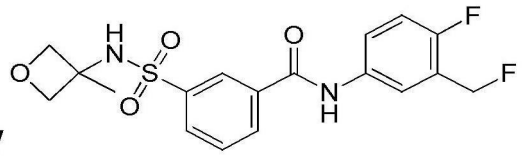


化合物 **111**

[0385] 将 3-[(3- 甲基氧杂环丁 -3- 基) 氨磺酰基] 苯甲酸 (3g,11.06mmol)、5- 氨基 -2- 氟 - 苯甲酸甲酯 (2.33g,13.2mmol) 和 DIPEA(2.84g,22mmol) 溶解在 DMF(40mL) 中。在 0℃，添加 HATU(5.02g,13.2mmol)。将该混合物在 20℃搅拌 2 小时。将溶剂在真空中去除并且将获得的残余物通过硅胶柱层析 (洗脱液 :石油醚 : 乙酸乙酯 = 3 : 1) 进行纯化，产生 2- 氟 -5-[[3-[(3- 甲基氧杂环丁 -3- 基) 氨磺酰基] 苯甲酰基] 氨基] 苯甲酸甲酯 (2.3g)。将 2- 氟 -5-[[3-[(3- 甲基氧杂环丁 -3- 基) 氨磺酰基] 苯甲酰基] 氨基] 苯

甲酸甲酯 (0.3g,0.71mmol) 溶解在 THF(5mL) 和乙醇 (5mL) 中。在 0℃,添加 $NaBH_4$(53mg,1.4mmol)。将该混合物在 20℃下搅拌 2 小时。将该溶剂在真空中去除并且将获得的残余物通过反相高效液相层析 (流动相 :在水中 (0.1% TFA) 的 CH_3CN :从 34% 到 64%) 进行纯化。收集纯的部分并且通过固体 $NaHCO_3$中和。将该有机溶剂在真空中去除。将沉淀进行过滤,用 H_2O(5mL) 进行洗涤,并且在高真空下进行干燥。将该残余物在水 (5mL) 中悬浮并且将该水层冻干至干燥,产生化合物 111(220mg)。方法 A ;Rt :4.34min. m/z :395.3(M+H)$^+$精确质量 :394.1。

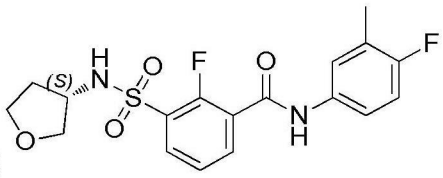
[0386]



化合物 **127**

[0387] 将 (2- 氟 -5- 硝基 - 苯基) 甲醇 (4.3g,25.1mmol) 溶解在二氯甲烷 (50mL) 中。在 -30℃,将三氟化二乙氨基硫 (4.5g,27.9mmol) 逐滴添加到该混合物中。将该混合物在 10℃搅拌 4 小时。将甲醇 (10mL) 添加到该混合物中并且将该混合物在 10℃进一步搅拌 30 分钟。将该混合物用盐水 (30mL) 洗涤并且将该水层用 CH_2Cl_2(2×30mL) 进行萃取。将这些合并的有机层用 Na_2SO_4进行干燥并且在真空中浓缩,产生 1- 氟 -2-(氟甲基)-4- 硝基 - 苯 (3.9g)。将 1- 氟 -2-(氟甲基)-4- 硝基 - 苯 (3.1g,17.9mmol)、铁 (4.0g,71.6mmol) 和甲醇 (30mL) 的混合物在 65° 搅拌 8 小时。过滤该混合物并且将滤液在真空中进行浓缩,产生 4- 氟 -3-(氟甲基) 苯胺 (1.5g)。将 3-(氯磺酰基) 苯甲酰氯 (300mg,1.2mmol) 和三乙胺 (150mg,1.5mmol) 溶解在二氯甲烷 (20mL) 中。在 0℃,将 4- 氟 -3-(氟甲基) 苯胺 (175mg,1.22mmol) 添加到该混合物中。将该混合物在 10℃搅拌 30 分钟。该混合物不经进一步纯化而用于下一步中。在 0℃,将三乙胺 (152mg,1.5mmol) 和 3- 甲基 -3- 氧杂环丁胺 (131mg,1.5mmol) 添加到以上获得的反应混合物中。将该混合物在 20℃搅拌 1 小时。将该溶剂在真空中去除并且将获得的残余物通过反相高效液相层析 (柱 :Gemini 250*20mm*5um. A :H_2O+0.1% TFA B :MeCN B 在 A 中从 27% 到 57%) 进行纯化。将该产物部分进行收集并且将该有机溶剂在真空中去除。将该部分用饱和 $NaHCO_3$进行中和。将该混合物用二氯甲烷 (3×20mL) 进行萃取并且将该合并的有机层用 Na_2SO_4进行干燥并且在真空中浓缩,产生化合物 127(91.1mg)。方法 A ;Rt :4.95min. m/z :397.3(M+H)$^+$精确质量 :396.1。^{1}H NMR(400MHz, DMSO-d_6) δ ppm 1.41(s,3H)4.14(d, J = 6.3Hz,2H)4.56(d, J = 6.3Hz,2H)5.52(d, J = 48Hz,2H)7.31(t, J = 9.4Hz,1H)7.72-7.89(m,2H)7.92-7.97(m,1H)8.03(d, J = 8.0Hz,1H)8.23(d, J = 7.8Hz,1H)8.39(s,1H)8.55(s,1H)10.67(s,1H)。

[0388]

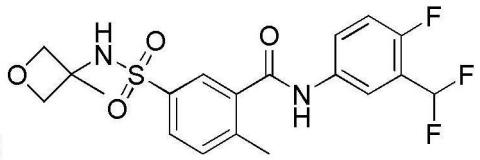


化合物 **112**

[0389] 在氢气氛下将化合物 123(255mg,0.592mmol) 和 Pd/C(50mg) 在甲醇 (25mL) 中搅拌 3 小时。将该反应混合物进行过滤,浓缩并且将获得的残余物在 50℃在真空中进行干燥,

产生呈无色树脂的化合物 112(174mg)。方法 G ;Rt :1.57min. m/z :397.1(M+H)$^+$精确质量 :396.1。^{1}H NMR(400MHz, DMSO-d_6) δ ppm 1.65-1.80(m,1H),1.91-2.04(m,1H),2.24(d, J = 1.5Hz,3H),3.43(dd, J = 9.0,4.6Hz,1H),3.55-3.79(m,3H),3.80-3.91(m,1H),7.14(t, J = 9.2Hz,1H),7.45-7.57(m,2H),7.64(dd,J = 7.0,2.4Hz,1H),7.85-8.02(m,2H),8.40(d, J = 6.8Hz,1H),10.62(s,1H)

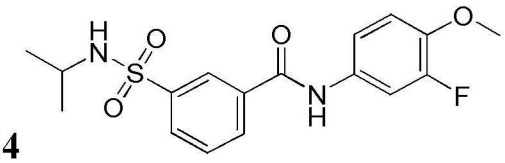
[0390]



化合物 **113**

[0391] 将 3- 甲基氧杂环丁 -3- 胺盐酸盐 (210mg,1.7mmol) 和 NaOH(204mg,5.1mmol) 溶解在 2- 甲基四氢呋喃 (5mL) 和 H_2O(5mL) 中。在 0℃,添加 5- 氯磺酰基 -2- 甲基 - 苯甲酸 (400mg,1.7mmol)。将该混合物在 20℃搅拌 4 小时。将该水层分离,并且用水性 HCl(1N) 调整至 pH = 3。将该混合物用乙酸乙酯 (3×100mL) 进行萃取。将合并的有机层在真空中浓缩,产生 2- 甲基 -5-[(3- 甲基氧杂环丁 -3- 基) 氨磺酰基] 苯甲酸 (250mg)。将 2- 甲基 -5-[(3- 甲基氧杂环丁 -3- 基) 氨磺酰基] 苯甲酸 (250mg,0.876mmol)、3-(二氟甲基)-4- 氟苯胺 (178mg,1.1mmol) 和 DIPEA(232mg,1.8mmol) 溶解在 DMF(5mL) 中。在 0℃,添加 HATU(399mg,1.05mmol)。将该混合物在 20℃搅拌 2 小时。将该溶剂在真空中去除并且将获得的残余物通过反相高效液相层析 (流动相 :在水中 (0.1% TFA) 的 CH_3CN :从 34% 到 64%) 进行纯化。收集纯的部分并且通过固体 $NaHCO_3$中和。将该有机溶剂在真空中去除并且将形成的沉淀进行过滤,用 H_2O(5mL) 洗涤并且在高真空下干燥。将该残余物在水 (5mL) 中悬浮并且将该水层冻干至干燥,产生化合物 113(220mg)。方法 A ;Rt :5.28min. m/z :429.3(M+H)$^+$精确质量 :428.1。^{1}H NMR(400MHz, DMSO-d_6) δ ppm 1.44(s,3H)2.47(s, 3H)4.15(d, J = 6.3Hz,2H)4.57(d, J = 6.0Hz,2H)7.24(t, J = 54.5Hz,1H)7.40(t, J = 9.5Hz,1H)7.56(d, J = 8.0Hz,1H)7.71-7.98(m,3H)8.09(d, J = 4.3Hz,1H)8.37(br.s., 1H)10.74(br.s.,1H)

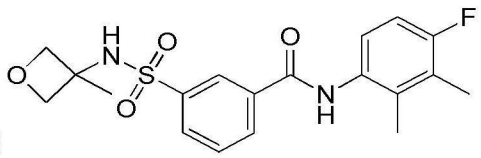
[0392]



化合物 **114**

[0393] 将 3-(异丙基氨磺酰基) 苯甲酸 (190mg,0.78mmol) 溶解在二氯甲烷 (5mL) 中。在 20℃,将 3- 氟 -4- 甲氧基苯胺 (139mg,0.94mmol) 和三乙胺 (112mg,1mmol) 添加到该混合物中。将该混合物在 20℃搅拌 5 分钟。在 20℃,将 HATU(358mg,0.94mmol) 添加到该混合物。将该混合物在 20℃搅拌 8 小时。将该溶剂在真空中去除并且将获得的残余物通过高效液相层析 (柱 :Phenomenex Synergi C18 150*20mm*5um..A :H_2O+0.1% TFA B :MeCN B 在 A 中 30% 到 60%) 进行纯化。将该产物部分进行收集并且将该有机溶剂进行蒸发。将水层用饱和水性 $NaHCO_3$中和。将该混合物用二氯甲烷 (2×10mL) 进行萃取。将这些合并的有机层用 Na_2SO_4进行干燥并且在真空中浓缩,产生化合物 114(135mg)。方法 A ;Rt :5.60min. m/z :367.2(M+H)$^+$精确质量 :366.1

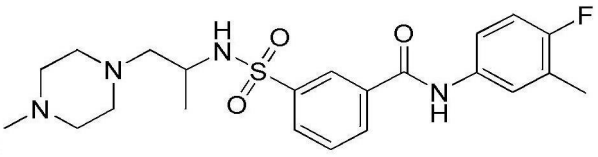
[0394]



化合物 115

[0395] 如针对化合物 127 描述的类似地制备，使用 4- 氟 -2,3- 二甲基 - 苯胺代替 4- 氟 -3-(氟甲基) 苯胺。方法 A ;Rt :4.98min. m/z :393.3(M+H)$^+$精确质量 :392.1。

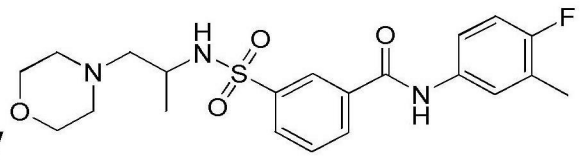
[0396]



化合物 116

[0397] 在 110℃，将 4- 氟 -3- 甲基 - 苯胺 (9.04g,72.2mmol) 逐滴添加到 3-(氯磺酰基) 苯甲酰氯 (19.0g,79.47mmol) 于甲苯 (300mL) 中的溶液里。将产生的混合物在 110℃搅拌 1 小时并且允许冷却至 20℃过夜。将沉淀进行过滤并且从干甲苯再结晶，产生 3-[(4- 氟 -3- 甲基 - 苯基) 氨基甲酰基] 苯磺酰氯 (20g)。在 0℃，将 3-[(4- 氟 -3- 甲基 - 苯基) 氨基甲酰基] 苯磺酰氯 (15g,45.77mmol) 逐滴添加到 2- 氨基丙 -1- 醇 (3.437g,45.77mmol) 和三乙胺 (6.946g) 在 THF(200mL) 中的溶液里。将产生的混合物搅拌 10 分钟然后在 2 小时内允许加温至 20℃。将该反应混合物用 1N HCl(50mL) 进行淬灭。将该混合物用二氯甲烷 (3×30mL) 进行萃取。将合并的有机层用盐水洗涤，用 $MgSO_4$干燥，过滤并在真空中浓缩。将残余物通过硅胶柱层析 (梯度洗脱液 :石油醚 / 乙酸乙酯 :从 100/1 至 50/50) 进行纯化，产生 N-(4- 氟 -3- 甲基 - 苯基)-3-[(2- 羟基 -1- 甲基 - 乙基) 氨磺酰基]- 苯甲酰胺 (15.6g)。在 -70℃在氩气下，将二氮烯 -1,2- 二羧酸二乙酯 (4.91g,28.19mmol) 逐滴添加到 N-(4- 氟 -3- 甲基 - 苯基)-3-[(2- 羟基 -1- 甲基 - 乙基) 氨磺酰基] 苯甲酰胺 (7.8g,21.29mmol) 和 PPh_3(6.14g,23.41mmol) 在 THF(500mL) 中的溶液里。将产生的混合物搅拌 1 小时然后允许加温至 20℃过夜。将该反应混合物用 1N HCl(300mL) 进行淬灭。将该混合物用二氯甲烷 (4×400mL) 进行萃取，并且将这些合并的有机层用盐水洗涤，用 $MgSO_4$干燥，过滤并在真空中浓缩。将获得的残余物通过硅胶柱层析 (梯度洗脱液 :石油醚 / 乙酸乙酯 :从 100/1 至 60/40) 进行纯化，产生 N-(4- 氟 -3- 甲基 - 苯基)-3-(2- 甲基吖丙啶 -1- 基) 磺酰基 - 苯甲酰胺 (6.5g)。将 N-(4- 氟 -3- 甲基 - 苯基)-3-(2- 甲基吖丙啶 -1- 基) 磺酰基 - 苯甲酰胺 (300mg,0.861mmol) 和 1- 甲基哌嗪 (862mg,8.61mmol) 在 1.4- 二噁烷 (3mL) 中的混合物用微波辐射在 150℃加热 30 分钟。将挥发物在真空中去除。将获得的残余物通过硅胶柱层析 (梯度洗脱液 :石油醚 / 乙酸乙酯 :从 100/1 至 1/100) 进行纯化。收集纯的部分并且将溶剂在真空中去除。将获得的残余物通过制备型高效液相层析 (柱 :Luna 150*30mm*5u，流动相 :在水中 (0.1% NH_4HCO_3) 的 CH_3CN :从 44% 到 74%) 进行纯化。收集纯的部分，在真空中浓缩并且将残余水溶液冻干至干燥，产生化合物 116(250mg)。方法 A ;Rt :4.26min. m/z :449.4(M+H)$^+$精确质量 :448.2

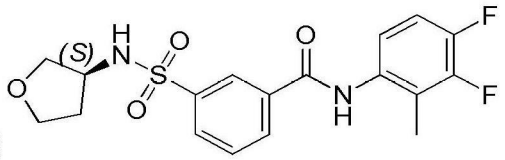
[0398]



化合物 **117**

[0399] 如针对化合物 116 描述的类似地制备，使用吗啉代替 1- 甲基哌嗪。方法 A ;Rt : 4.45min. m/z :436.3(M+H)$^+$精确质量 :435.2

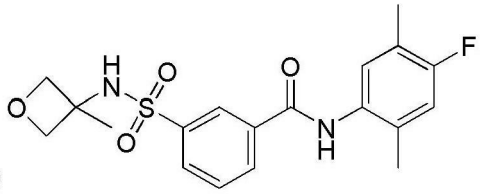
[0400]



化合物 **118**

[0401] 在 0 ℃，向 3,4- 二氟 -2- 甲基 - 苯胺 (369mg,2.6mmol)、3-[[(3S)- 四氢呋喃 -3- 基] 氨磺酰基] 苯甲酸 (700mg,2.58mmol) 和 N,N- 二异丙基乙胺 (1.35ml,7.74mmol) 于 DMF(10mL) 中的搅拌溶液里添加 Pybrop(132705-51-2,1.82g,3.9mmol)。将产生的混合物在 18℃搅拌过夜。将该混合物在真空中浓缩，添加乙酸乙酯 (15mL) 并且将该有机层用 1N HCl(15ml) 和饱和水性 $NaHCO_3$(15mL) 进行洗涤。用 Na_2SO_4进行干燥并且在真空中浓缩后，将粗制残余物通过反相制备型高效液相层析 (洗脱液 :在 H_2O 中 (0.05% $NH_3.H_2O$) 的 CH_3CN : 从 37% 到 37%,v/v) 进行纯化。收集纯的部分并且将挥发物在真空中去除。将该水层冻干至干燥，产生化合物 118(238mg)。方法 D ;Rt :5.01min. m/z :396.9(M+H)$^+$精确质量 :396.1。

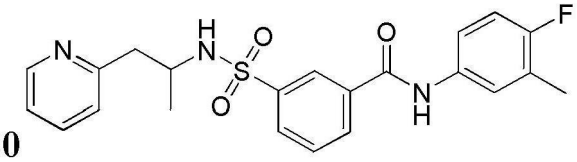
[0402]



化合物 **119**

[0403] 如针对化合物 127 描述的类似地制备，使用 4- 氟 -2,5- 二甲基 - 苯胺代替 4- 氟 -3-(氟甲基) 苯胺，并且 DIPEA 代替 NEt_3。方法 A ;Rt :5.27min. m/z :393.3(M+H)$^+$精确质量 :392.1

[0404]



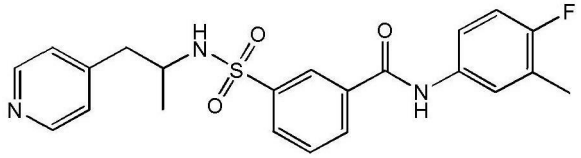
化合物 **120**

[0405] 将 1-(2- 吡啶基) 丙 -2- 胺 (207.8mg,1.53mmol) 和 DIPEA(0.532mL,3.05mmol) 的混合物溶解在 CH_2Cl_2(10mL) 中。在 0℃，将 3-[(4- 氟 -3- 甲基 - 苯基) 氨基甲酰基] 苯磺酰氯 (500mg,1.53mmol) 分部分地添加并且将该混合物在 0℃搅拌 1 小时。将该混合物用饱和柠檬酸 (10mL)、饱和水性 $NaHCO_3$(10mL)、盐水进行洗涤并且用 Na_2SO_4进行干燥。将溶剂在真空中去除并且将获得的残余物通过硅胶柱层析 (梯度洗脱液 :石油醚 / 乙酸乙酯 :从 100/1 至 1/100) 进行纯化。收集纯的部分并且将溶剂在真空中去除。将获得的固体在水 (10mL) 和乙腈 (10mL) 中悬浮并且将该溶液冻干至干燥，产生化合物 120(550mg)。方法 B ;Rt :

3.36min.m/z :428.3(M+H)$^+$精确质量 :427.1。 ^{1}H NMR(400MHz,DMSO-d_6) δ ppm 0.95(d,J = 6.5Hz,3H)2.26(d,J = 1.5Hz,3H)2.69(dd,J = 13.6,7.3Hz,1H)2.80(dd,J = 13.6,7.0Hz,1H)3.64-3.74(m,1H)7.08-7.19(m,3H)7.55-7.64(m,2H)7.64-7.71(m,2H)7.84-7.89(m,1H)7.89-7.95(m,1H)8.12-8.17(m,1H)8.25(t, J = 1.5Hz,1H)8.32-8.36(m,1H)10.45(s,1H)。

[0406]

化合物 **224**



[0407] 化合物 224 是如针对化合物 223 描述的类似地制备,使用 1-(4- 吡啶基) 丙 -2- 胺代替 1-(2- 吡啶基) 丙 -2- 胺。将化合物 224 通过制备型高效液相层析 (柱 :Luna 150*30mm*4u,流动相 :在水中 (0.05% NH_4HCO_3) 的 CH_3CN :从 40% 到 70%) 进行纯化。

[0408] 方法 A ;Rt :4.6min.m/z :428.3(M+H)$^+$精确质量 :427.1。

[0409] 5- 氯磺酰基 -2- 甲基 - 苯甲酰氯和 3-[(4- 氟 -3- 甲基 - 苯基) 氨基甲酰基]-4- 甲基 - 苯磺酰基氯的合成

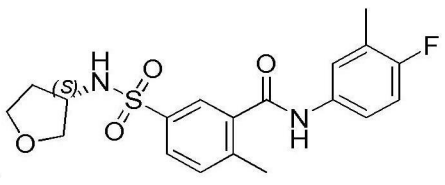
[0410] 将 5-(氯磺酰基)-2- 甲基苯甲酸 (10g,42.61mmol) 溶解在二氯甲烷 (200mL) 中。添加 N,N- 二甲基甲酰胺 (166 μL,2.13mmol) 并且将该混合物在氮气氛下在室温搅拌。

[0411] 将草酰氯 (18.3mL,213mmol) 分四部分经一小时添加。

[0412] 将产生的混合物在室温下搅拌 1 小时。将该混合物在真空中浓缩并且使用甲苯 (2×100mL) 共蒸发两次,产生呈黄色油的 5- 氯磺酰基 -2- 甲基 - 苯甲酰氯,其按照这样使用。将 5- 氯磺酰基 -2- 甲基 - 苯甲酰氯 (10.7g,42.3mmol) 溶解在甲苯 (220mL) 中并且将这个加热至回流并且在温和氮流下搅拌。

[0413] 使用注射泵 (0,8mL/min) 逐滴添加在甲苯 (80mL) 中的 4- 氟 -3- 甲基苯胺 (4.76g,38.1mmol)。将产生的混合物搅拌 30 分钟同时继续加热。然后将该混合物冷却至室温。形成了一种沉淀并且在玻璃滤器上进行收集。在 55℃将获得的固体在真空中干燥,产生呈固体的 3-[(4- 氟 -3- 甲基 - 苯基) 氨基甲酰基]-4- 甲基 - 苯磺酰氯 (10.4g),其按照这样在下一步中使用。

[0414]

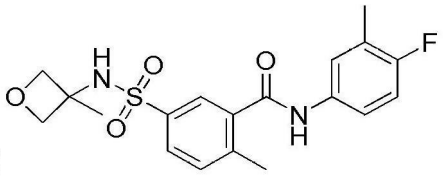


化合物 **121**

[0415] 将 (S)-3- 氨基四氢呋喃甲苯磺酸酯 (0.76g,2.93mmol) 和二异丙基乙胺 (1.26mL,7.31mmol) 于二氯甲烷 (10mL) 中的溶液逐滴添加到 3-[(4- 氟 -3- 甲基 - 苯基) 氨基甲酰基]-4- 甲基 - 苯磺酰氯 (1g,2.93mmol) 在二氯甲烷 (10mL) 中的溶液。将产生的混合物在室温下搅拌 1 小时。将该混合物用 HCl(水性 /14.6mL,14.6mmol) 进行淬灭。将各层分离并且将该水层用二氯甲烷 (2×20mL) 进行萃取。将这些合并的有机物在真空中浓缩,并且使用

硅胶柱层析（梯度洗脱液：EtOAc- 庚烷 0 ： 100 至 100 ： 0）进行纯化。在真空中将所希望的部分进行浓缩，并且在 55℃在真空中干燥，产生呈亮白色固体的化合物 121。方法 F；Rt：0.90min. m/z：393.2(M+H)$^+$精确质量：392.1。^{1}H NMR(400MHz，DMSO-d_6) δ ppm 1.58-1.69(m，1H)，1.85-1.98(m，1H)，2.24(d，J ＝ 1.3Hz，3H)，2.45(s，3H)，3.38(dd，J ＝ 8.8，4.4Hz，1H)，3.53-3.65(m，2H)，3.66-3.76(m，2H)，7.13(t，J ＝ 9.2Hz，1H)，7.46-7.59(m，2H)，7.66(dd，J ＝ 7.0，2.2Hz，1H)，7.75-7.87(m，2H)，7.96(br. s.，1H)，10.46(s，1H)。

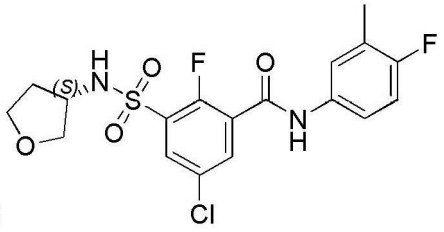
[0416]



化合物 **122**

[0417] 将 3- 甲基 -3- 氧杂环丁胺盐酸盐 (0.4g，3.22mmol) 和二异丙基乙胺 (1.26mL，7.31mmol) 在二氯甲烷 (10mL) 中的溶液逐滴添加到 3-[(4- 氟 -3- 甲基 - 苯基）氨基甲酰基]-4- 甲基 - 苯磺酰氯 (1g，2.93mmol) 于二氯甲烷 (10mL) 中的溶液里。将产生的混合物在室温下搅拌 1 小时。将该混合物用 HCl（水性 /14.63mL，14.63mmol）进行淬灭。将各层分离并且将该水层用二氯甲烷 (2×20mL) 进行萃取。将这些合并的有机层在真空中浓缩，并且使用柱层析（梯度洗脱液：EtOAc- 庚烷 0 ： 100 至 100 ： 0）进行纯化。在真空中将所希望的部分进行浓缩，并且在 55℃在真空烘箱中干燥，产生呈亮白色固体的化合物 122。方法 F；Rt：0.90min. m/z：410.2(M+NH_4)$^+$精确质量：392.1。 ^{1}H NMR(400MHz，DMSO-d_6) δ ppm 1.43(s，3H)，2.19-2.29(m，3H)，2.44(s，3H)，4.14(d，J ＝ 6.4Hz，2H)，4.56(d，J ＝ 6.2Hz，2H)，7.13(t，J ＝ 9.1Hz，1H)，7.42-7.57(m，2H)，7.59-7.71(m，1H)，7.74-7.90(m，2H)，8.36(s，1H)，10.46(s，1H)。

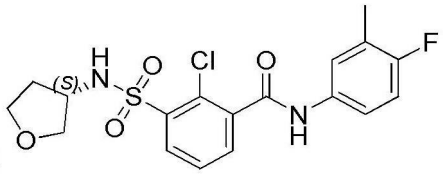
[0418]



化合物 **123**

[0419] 化合物 123(828mg) 是如针对化合物 121 描述的类似地从以下物质制备：5- 氯 -3- 氯磺酰基 -2- 氟 - 苯甲酸（从 Enamine 公司 EN300-35191 商购）起始经由 5- 氯 -3- 氯磺酰基 -2- 氟 - 苯甲酰氯 (^{1}H NMR(400MHz，氯仿 -d) δ ppm 8.23(dd，J ＝ 5.4，2.8Hz，1H)，8.37(dd，J ＝ 5.5，2.6Hz，1H))。硅胶柱层析（梯度洗脱液：EtOAc- 庚烷 10 ： 90 至 100 ： 0）后，通过将 H_2O 添加到化合物 123 的热 iPrOH 溶液来使化合物 123 进行再结晶，产生呈白色固体的化合物 123(3152mg)。方法 G；Rt：1.81min. m/z：431.0(M+H)$^+$精确质量：430.1。^{1}H NMR(400MHz，DMSO-d_6) δ ppm 1.65-1.79(m，1H)，1.93-2.06(m，1H)，2.25(d，J ＝ 1.8Hz，3H)，3.44(dd，J ＝ 9.0，4.4Hz，1H)，3.62(td，J ＝ 8.0，5.9Hz，1H)，3.69(dd，J ＝ 8.9，6.3Hz，1H)，3.71-3.79(m，1H)，3.84-3.98(m，1H)，7.15(t，J ＝ 9.1Hz，1H)，7.45-7.55(m，1H)，7.61(dd，J ＝ 6.9，2.3Hz，1H)，7.91(dd，J ＝ 5.7，2.6Hz，1H)，8.07(dd，J ＝ 5.2，2.8Hz，1H)，8.57(d，J ＝ 6.8Hz，1H)，10.68(s，1H)

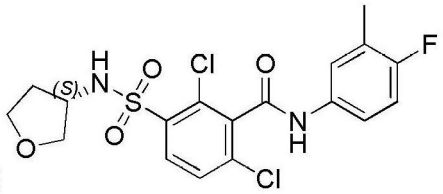
[0420]



化合物 **124**

[0421] 在氢气氛下将化合物 125(167mg,0.371mmol) 和 Pd/C(25mg) 在甲醇 (19mL) 中搅拌 80 分钟。将反应混合物进行过滤并且浓缩。将获得的残余物通过制备型 SFC(固定相 :大赛璐公司 (Chiralpak)Diacel AD 30×250mm 流动相 :CO_2, 含有 0.2% $iPrNH_2$的 MeOH), 收集所希望的部分, 蒸发, 溶解在 MeOH 中并且再次蒸发, 产生化合物 124(67mg)。方法 G ;Rt :1.61min. m/z :430.0(M+NH_4)$^+$精确质量 :412.1。 ^{1}H NMR(400MHz, DMSO-d_6) δ ppm 1.68-1.83(m,1H),1.89-2.03(m,1H),2.24(d, J = 1.5Hz,3H),3.45(dd, J = 8.9,4.7Hz, 1H),3.56-3.69(m,2H),63.70-3.86(m,2H),7.14(t, J = 9.1Hz,1H),7.45-7.55(m,1H), 7.60-7.69(m,2H),7.82(dd, J = 7.6,1.7Hz,1H),8.09(dd, J = 7.8,1.7Hz,1H),8.34(s, 1H),10.62(s,1H)

[0422]

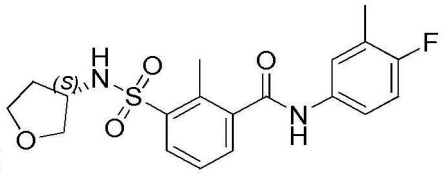


化合物 **125**

[0423] 化合物 125 是如针对化合物 126 描述的类似地制备, 从 2,6- 二氯 -3- 氯磺酰基 - 苯甲酸 (代替 3- 氯磺酰基 -2- 甲基 - 苯甲酸) 起始。方法 G ;Rt :1.77min. m/z : 464.0(M+NH_4)$^+$精确质量 :446.0。

[0424] ^{1}H NMR(400MHz, 氯仿 -d) δ ppm 1.75-1.86(m,1H),2.04-2.16(m,1H),2.30(d, J = 1.8Hz,3H),3.57-3.65(m,1H),3.66-3.76(m,2H),3.82-3.95(m,2H),5.45(d,J = 7.5Hz, 1H),7.01(t, J = 8.9Hz,1H),7.30-7.38(m,1H),7.47-7.56(m,2H),7.83(s,1H),8.05(d, J = 8.6Hz,1H)。

[0425]



化合物 **126**

[0426] 将 3- 氯磺酰基 -2- 甲基 - 苯甲酸 (从 Enamine 公司 EN300-109516 商购 ;508.4mg, 2.17mmol) 溶解在二氯甲烷 (50mL) 中。添加 DMF(1 滴) 和草酰氯 (1375mg,10.83mmol) 并且将该混合物在惰性气氛下搅拌 4 小时。将该反应混合物浓缩, 产生呈黄色油的 3- 氯磺酰基 -2- 甲基 - 苯甲酰氯 (554mg), 其按照这样在下一步中使用。^{1}H NMR(400MHz, 氯仿 -d) δ ppm 2.92-3.01(m,3H),7.60(t, J = 7.9Hz,1H),8.27-8.41(m,2H)。将溶解在二氯甲烷 (10mL) 中的 4- 氟 -3- 甲基苯胺 (227mg,1.98mmol) 经 5 分钟逐滴添加到 3- 氯磺酰基 -2- 甲基 - 苯甲酰氯 (550mg,2.17mmol) 在甲苯 (50mL) 中在回流下的溶液里。将该反应混合物

回流 30 分钟并且下一步在冰浴中冷却。添加 (S)-3- 氨基四氢呋喃甲苯磺酸酯 (564mg, 2.17mmol) 和 DIPEA(0.85ml,4.94mmol) 溶解在二氯甲烷 (10mL) 中的溶液,并且将获得的混合物搅拌 30 分钟。将产生的混合物用 HCl(2×100mL/1M 水性的)、水 (2×100mL) 和 $NaHCO_3$(2×100mL/ 饱和水性的) 进行洗涤。将该有机层经 $MgSO_4$干燥,过滤并在真空下浓缩。将获得的残余物使用硅胶柱层析 (CH_2Cl_2-MeOH 100 ： 0 至 90 ： 10) 进行纯化并且通过施用一个梯度 (在庚烷中 10％至 100％的 EtOAc) 进行再纯化。将产物部分进行浓缩并且在真空中在 50℃干燥过夜,产生呈无色油的化合物 126(16.6mg)。方法 G ;Rt :1.65min. m/z :393.1(M+H)$^+$精确质量 :392.1。 ^{1}H NMR(400MHz, 氯仿 -d) δ ppm 1.73-1.87(m,1H), 2.06-2.20(m,1H),2.30(d, J = 1.8Hz,3H),2.69(s,3H),3.54-3.63(m,1H),3.65-3.78(m, 2H),3.83-3.97(m,2H),4.99(d,J = 8.1Hz,1H),7.01(t,J = 8.9Hz,1H),7.31-7.44(m,2H), 7.51(dd,J = 6.7,2.5Hz,1H),7.58-7.69(m,2H),8.06(dd,J = 8.0,1.2Hz,1H)

[0427] 程序 S1 :将 3-[(4- 氟 -3- 甲基 - 苯基) 氨基甲酰基] 苯磺酰氯 (0.50g,1.52mmol, 1 当量) 于甲苯 (10mL) 中的溶液添加到包含胺 (1.1 当量) 的烧瓶中。添加 DIPEA(657 μL, 3.81mmol,2.5 当量) 并且将该反应混合物搅拌 1 小时。接下来向该反应混合物中添加 1M HCl(5mL)。

[0428] 程序 S2 :用 3-[(4- 氟 -3- 甲基 - 苯基) 氨基甲酰基] 苯磺酰氯 (250mg, 0.76mmol) 和胺 (1.1 当量) 来填装试管并且添加 CH_2Cl_2(5mL)。将该溶液进行搅拌,添加 DIPEA(329 μL,1.9mmol,2.5 当量) 并将该混合物进一步搅拌 30 分钟。然后添加 HCl(1M 当量 /5mL) 并且将混合物另外搅拌 5 分钟。

[0429] 程序 S3 :向 3-[(4- 氟 -3- 甲基 - 苯基) 氨基甲酰基] 苯磺酰氯 (0.50g,1.52mmol, 1 当量) 和 DIPEA(657 μL,3.81mmol,2.5 当量) 在 CH_2Cl_2(10mL) 中的溶液里添加胺 (1.1 当量)。将反应混合物搅拌 1 小时。接下来向该反应混合物中添加 1M HCl(5mL)。

[0430] 程序 S4 :将溶解在 CH_2Cl_2(5mL) 中的 3-[(4- 氟 -3- 甲基 - 苯基) 氨基甲酰基] 苯磺酰氯 (250mg,0.76mmol) 和 DIPEA(329 μL,1.9mmol,2.5 当量) 添加到包含胺 (1.1 当量) 的试管中。将反应混合物搅拌 3 小时。添加 1M HCl(5mL)。

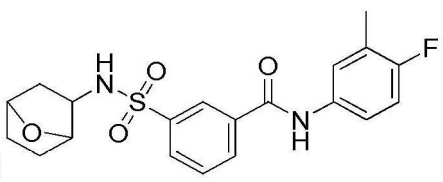
[0431] 加工 (Workup)W1 :形成了一种沉淀。将该沉淀过滤出,用二异丙醚漂洗并在真空烘箱中在 55℃进行干燥。

[0432] 加工 W2 :分离有机层并在真空中浓缩。将获得的残余物通过硅胶柱层析使用庚烷到 EtOAc 梯度作为洗脱液进行纯化。

[0433] 加工 W3 :将各层分离并且将该有机层加载到硅胶柱上用于纯化 (伴随梯度洗脱液 :CH_2Cl_2- 甲醇 100 ： 0 至 97 ： 3)。

[0434] 加工 W4 :将该有机层进行分离并且加载到硅胶柱上。将混合物使用从庚烷到 EtOAc 的梯度洗脱液进行纯化。

[0435]

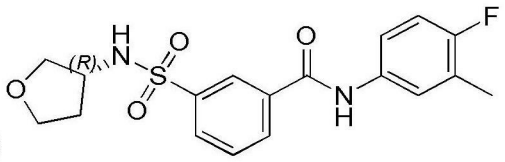


化合物 **128**

[0436] 合成遵循程序 S4,用 7- 噁二环 [2.2.1] 庚 -2- 胺

[0437] 作为胺，加工 W4。方法 F；Rt：0.94min. m/z：422.1 $(M+NH_4)^+$ 精确质量：404.1。^1H NMR(400MHz,DMSO-d_6) δ ppm 1.22-1.48(m,5H),1.68(dd,J＝12.5,7.9Hz,1H),2.25(d,J＝1.8Hz,3H),3.25-3.29(m,1H),4.14(d, J ＝ 4.8Hz,1H),4.44(t, J ＝ 4.8Hz,1H),7.14(t, J ＝ 9.2Hz,1H),7.54-7.63(m,1H),7.68(dd,J ＝ 7.2,2.3Hz,1H),7.74-7.80(m,1H),7.86(d, J ＝ 6.8Hz,1H),7.98-8.03(m,1H),8.20(dt, J ＝ 7.8,1.4Hz,1H),8.35(t, J ＝ 1.5Hz,1H),10.46(s,1H)。

[0438]

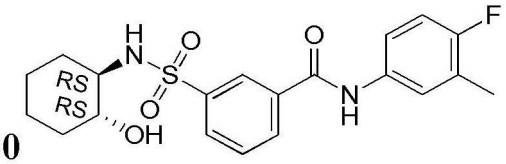


化合物 129

[0439] 合成遵循程序 S3，用 R-(+)-3- 氨基四氢呋喃甲苯 -4- 磺酸盐作为胺，加工 W2。

[0440] 方 法 F；Rt：0.89min. m/z：396.1 $(M+NH_4)^+$ 精 确 质 量：378.1。^1H NMR(400MHz, DMSO-d_6)ppm 1.56-1.65(m,1H),1.85-1.94(m,1H),2.25(d, J ＝ 1.8Hz,3H),3.36(dd, J ＝ 9.0,4.4Hz,1H),3.52-3.65(m,2H),3.65-3.73(m,1H),3.73-3.79(m,1H),7.14(t, J ＝ 9.2Hz,1H),7.56-7.62(m,1H),7.67(dd, J ＝ 7.0,2.3Hz,1H),7.78(t, J ＝ 7.8Hz,1H),7.99-8.05(m,1H),8.08(bs,1H),8.20-8.23(m,1H),8.37(t, J ＝ 1.7Hz,1H),10.47(s,1H),[α]20 D ＝ +5.8(c 0.61w/v%,MeOH)

[0441]

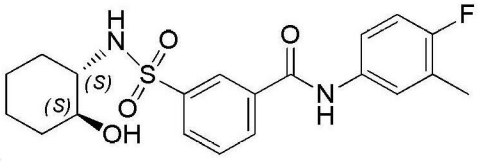


化合物 130

[0442] 方法 F；Rt：0.95min. m/z：424.2 $(M+NH_4)^+$ 精确质量：406.1。

[0443] 合成遵循程序 S3，用外消旋反式 -2- 氨基环己醇盐酸盐作为胺，加工 W2。

[0444]



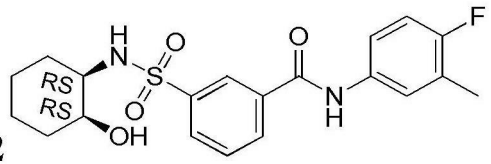
化合物 131

[0445] 合成遵循程序 S3，用 (1S,2S)- 反式 -2- 氨基环己醇盐酸盐作为胺，加工 W2。

[0446] 方法 F；Rt：0.95min. m/z：424.2 $(M+NH_4)^+$ 精确质量：406.1。

[0447] ^1H NMR(400MHz, DMSO-d_6) δ ppm 1.01-1.23(m,4H),1.41-1.58(m,2H),1.59-1.70(m,1H),1.71-1.83(m,1H),2.25(d, J ＝ 1.3Hz,3H),2.77-2.90(m,1H),3.15-3.27(m,1H),4.50(d, J ＝ 4.6Hz,1H),7.14(t, J ＝ 9.2Hz,1H),7.54-7.64(m,2H),7.64-7.69(m,1H),7.72(t, J ＝ 7.9Hz,1H),8.04(d, J ＝ 7.7Hz,1H),8.16(d, J ＝ 7.9Hz,1H),8.39(s,1H),10.43(s,1H)

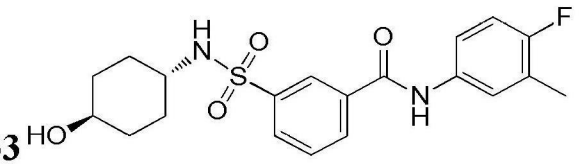
[0448]



化合物 **132**

[0449] 合成遵循程序 S3,用外消旋顺式 -2- 氨基环己醇盐酸盐作为胺,加工 W2。方法 F ;Rt :0.96min. m/z :424.1(M+NH_4)$^+$精 确 质 量 :406.1。H NMR(400MHz, DMSO-d_6) δ ppm 1.01-1.26(m,4H),1.26-1.36(m,1H),1.38-1.62(m,3H),2.25(d, J = 1.8Hz,3H),3.03-3.14(m,1H),3.57(br. s.,1H),4.52(d, J = 4.2Hz,1H),7.14(t, J = 9.1Hz,1H),7.46(d, J = 7.9Hz,1H),7.56-7.62(m,1H),7.68(dd, J = 7.0,2.6Hz,1H),7.73(t, J = 7.8Hz,1H),8.05(dt, J = 8.1,1.2Hz,1H),8.14-8.19(m,1H),8.39(t, J = 1.7Hz,1H),10.43(s,1H)

[0450]



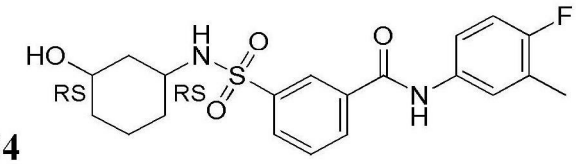
化合物 **133**

[0451] 合成遵循程序 S3,用反式 -4- 氨基环己醇盐酸盐作为胺,加工 W2。

[0452] 方法 F ;Rt :0.84min. m/z :424.2(M+NH_4)$^+$精确质量 :406.1。

[0453] ^{1}H NMR(400MHz, DMSO-d_6) δ ppm 1.01-1.31(m,4H),1.57(d, J = 10.3Hz,2H),1.69(d, J = 12.5Hz,2H),2.25(d, J = 1.8Hz,3H),2.84-3.01(m,1H),3.22-3.29(m,1H),4.46(d, J = 4.4Hz,1H),7.14(t, J = 9.1Hz,1H),7.53-7.64(m,1H),7.68(dd, J = 7.0,2.2Hz,1H),7.72-7.79(m,2H),7.95-8.04(m,1H),8.18(dt, J = 7.7,1.3Hz,1H),8.36(t, J = 1.7Hz,1H),10.46(s,1H)

[0454]



化合物 **134**

[0455] 方法 F ;Rt :0.89min. m/z :424.2(M+NH_4)$^+$精确质量 :406.1。

[0456] 合成遵循程序 S3,用 3- 氨基 - 环己醇作为胺,加工 W2。

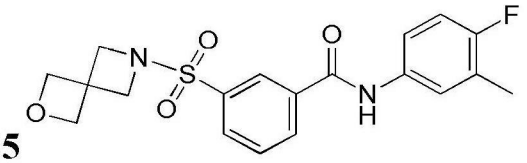
[0457] 化合物 134 以它的异构体进行分离,通过制备型 SFC(固定相 :大赛璐公司 (Chiralpak)Diacel IC 20×250mm,流动相 :CO_2,含有 0.4% iPrNH_2的 iPrOH),收集所希望的部分,蒸发,溶解在 MeOH 中并且再次蒸发,产生 134a、134b、134c、134d。SFC 柱 :ID-H 250mm×4.6mm 流速 :3ml/min 流动相 :25% iPrOH(包含 0.2% iPrNH_2) 保持 18.0min。

[0458] 温度 :30℃ ;Rt :134a(10.0min)、134b(11.1min)、134c(13.6min)、134d(14.7min)。顺式 :对映异构体 134a 和 134b N-(4- 氟 -3- 甲基 - 苯基)-3-[[(1R,3S)-3- 羟基环己基] 氨磺酰基] 苯甲酰胺或 N-(4- 氟 -3- 甲基 - 苯基)-3-[[(1S,3R)-3- 羟基环己基] 氨磺酰基] 苯甲酰胺。^{1}H NMR(400MHz, DMSO-d_6) δ ppm 0.84-1.14(m,4H),1.48-1.60(m,2H),1.60-1.72(m,1H),1.72-1.82(m,1H),2.26(d, J = 1.8Hz,3H),2.93-3.07(m,1H),3.20-3.30(m,1H),4.58(d, J = 4.6Hz,1H),7.14(t, J = 9.1Hz,1H),7.55-7.64(m,1H),

7.69(dd,J＝7.0,2.2Hz,1H),7.76(t,J＝7.8Hz,1H),7.83(br.s.,1H),7.96-8.06(m,1H),8.13-8.24(m,1H),8.38(t,J＝1.7Hz,1H),10.47(s,1H)

[0459] 反式:对映异构体134c和134d N-(4-氟-3-甲基-苯基)-3-[[(1R,3R)-3-羟基环己基]氨磺酰基]苯甲酰胺或N-(4-氟-3-甲基-苯基)-3-[[(1S,3S)-3-羟基环己基]氨磺酰基]苯甲酰胺 ^{1}H NMR(400MHz,DMSO-d_6) δ ppm 1.08-1.20(m,1H),1.25-1.42(m,4H),1.42-1.58(m,3H),2.25(d,J＝1.8Hz,3H),3.36-3.45(m,1H),3.71-3.89(m,1H),4.38(d,J＝3.5Hz,1H),7.14(t,J＝9.1Hz,1H),7.51(br.s.,1H),7.56-7.63(m,1H),7.69(dd,J＝7.2,2.3Hz,1H),7.73-7.78(m,1H),7.97-8.05(m,1H),8.19(dt,J＝7.9,1.2Hz,1H),8.37(t,J＝1.7Hz,1H),10.47(br.s.,1H)

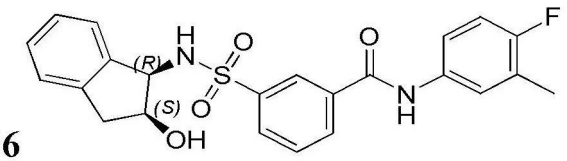
[0460]



化合物 135

[0461] 合成遵循程序S3,用2-氧杂-6-氮杂螺[3.3]庚烷作为胺,加工W2。方法F;Rt:0.91min.m/z:389.1(M-H)$^-$精确质量:390.1。 ^{1}H NMR(400MHz,DMSO-d_6) δ ppm 2.26(d,J＝1.8Hz,3H),3.95(s,4H),4.44(s,4H),7.15(t,J＝9.2Hz,1H),7.57-7.65(m,1H),7.68(dd,J＝7.0,2.4Hz,1H),7.85(t,J＝7.8Hz,1H),8.01(dt,J＝8.0,1.3Hz,1H),8.28-8.38(m,2H),10.51(s,1H)。

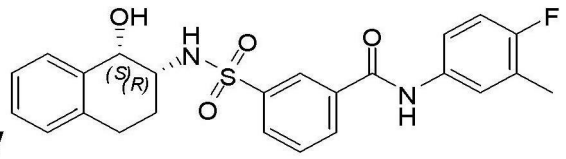
[0462]



化合物 136

[0463] 合成遵循程序S1,用(1R,2S)-(+)-顺式-1-氨基茚满-2-醇作为胺,加工W1。方法G;Rt:1.79min.m/z:439.0(M-H)$^-$精确质量:440.1。 ^{1}H NMR(400MHz,DMSO-d_6) δ ppm 2.25(d,J＝1.8Hz,3H),2.72(d,J＝15.0Hz,1H),2.93(dd,J＝16.1,4.6Hz,1H),4.15(qd,J＝4.7,1.8Hz,1H),4.69(dd,J＝8.7,4.7Hz,1H),4.96(d,J＝4.4Hz,1H),6.87(d,J＝7.3Hz,1H),7.04-7.10(m,1H),7.10-7.21(m,3H),7.55-7.64(m,1H),7.68(dd,J＝7.0,2.4Hz,1H),7.77(t,J＝7.8Hz,1H),7.93(d,J＝9.0Hz,1H),8.15(dt,J＝8.1,1.2Hz,1H),8.21(dd,J＝7.7,1.5Hz,1H),8.48(t,J＝1.7Hz,1H),10.44(s,1H)

[0464]

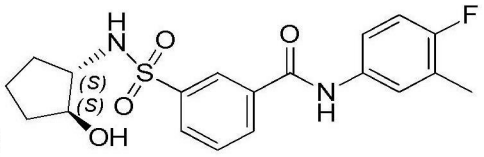


化合物 137

[0465] 合成遵循程序S4,用(1S,2R)-2-氨基萘满-1-醇盐酸盐作为胺,加工W4。方法F;Rt:1.03min.m/z:472.2(M+NH_4)$^+$精确质量:454.1。H NMR(400MHz,DMSO-d_6) δ ppm 1.35-1.46(m,1H),1.96(qd,J＝11.8,6.2Hz,1H),2.25(d,J＝1.5Hz,3H),2.62(ddd,J＝17.2,10.9,6.3Hz,1H),2.70-2.82(m,1H),3.34-3.45(m,1H),4.39(br.s.,1H),5.29(d,J

= 5.7Hz,1H),7.04(d,J = 6.8Hz,1H),7.09-7.24(m,4H),7.55-7.63(m,1H),7.62-7.70(m,2H),7.75(t, J = 7.8Hz,1H),8.06-8.13(m,1H),8.19(d, J = 8.1Hz,1H),8.43(t, J = 1.5Hz,1H),10.44(s,1H),[α]20D :+66° (c 0.55w/v%,DMF)。DSC(以 10℃ /min 从 30℃到 300℃):170℃。

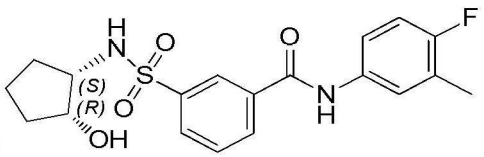
[0466]



化合物 **138**

[0467] 合成遵循程序 S1,用反式 -(1S,2S)-2- 氨基环戊醇盐酸盐作为胺,加工 W1。方法 F ;Rt :0.88min. m/z :410.4(M+NH_4)$^+$精确质量 :392.1。 ^{1}H NMR(400MHz, DMSO-d_6) δ ppm 1.16-1.29(m,1H),1.29-1.40(m,1H),1.50(quin, J = 7.4Hz,2H),1.61-1.78(m,2H),2.25(d, J = 1.8Hz,3H),3.16-3.26(m,1H),3.74-3.82(m,1H),4.67(d, J = 4.4Hz,1H),7.14(t, J = 9.2Hz,1H),7.55-7.63(m,1H),7.65-7.72(m,2H),7.75(t, J = 7.8Hz,1H),7.98-8.04(m,1H),8.18(dt,J = 7.9,1.3Hz,1H),8.36(t,J = 1.7Hz,1H),10.45(s,1H)

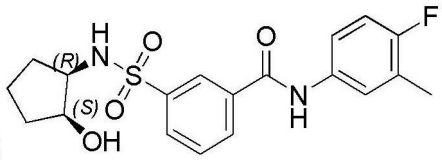
[0468]



化合物 **139**

[0469] 合成遵循程序 S1,用顺式 -(1R,2S)-2- 氨基环戊醇盐酸盐作为胺,加工 W1。方法 F ;Rt :0.92min. m/z :410.1(M+NH_4)$^+$精确质量 :392.1。 ^{1}H NMR(400MHz, DMSO-d_6) δ ppm 1.25-1.51(m,4H),1.51-1.67(m,2H),2.25(d, J = 1.5Hz,3H),3.21-3.28(m,1H),3.72-3.79(m,1H),4.63(d, J = 4.0Hz,1H),7.14(t, J = 9.2Hz,1H),7.42(d, J = 8.1Hz,1H),7.55-7.63(m,1H),7.68(dd, J = 7.3,2.4Hz,1H),7.73(t, J = 7.8Hz,1H),8.06(dt, J = 8.1,1.2Hz,1H),8.17(d,J = 8.1Hz,1H),8.40(t,J = 1.5Hz,1H),10.43(s,1H)

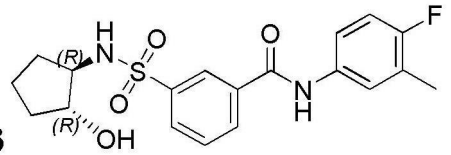
[0470]



化合物 **172**

[0471] 合成遵循程序 S2,用顺式 -(1S,2R)-2- 氨基环戊醇盐酸盐作为胺。将形成的沉淀在玻璃滤器上收集并且用 CH_2Cl_2(2×5mL) 进行漂洗。将沉淀进一步使用硅胶柱层析(梯度洗脱液 :EtOAc- 庚烷 0 : 100 至 100 : 0) 进行纯化。在真空中在 55℃进行干燥产生呈亮白色粉末的化合物 172。方法 G ;Rt :1.65min. m/z :392.9(M+H)$^+$精确质量 :392.1。DSC(以 10℃ /min 从 30℃到 300℃):145℃。

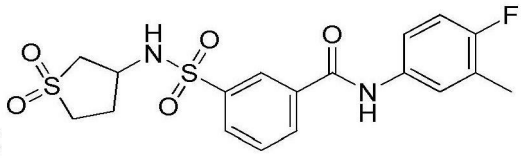
[0472]



化合物 **173**

[0473] 合成遵循程序 S4(反应时间= 20 小时而非 3 小时)用反式 -(1R,2R)-2- 氨基环戊醇作为胺,加工 W4。方法 F ;Rt :0.87min. m/z :410.1(M+NH_4)$^+$精确质量 :392.1。

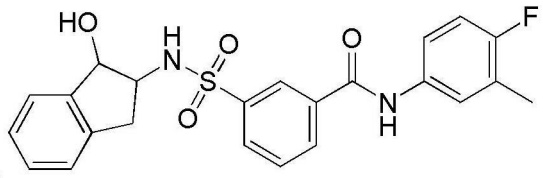
[0474]



化合物 **140**

[0475] 合成遵循程序 S1,用 1,1- 二氧四氢噻吩 -3- 胺盐酸盐作为胺,加工 W1。方法 F ;Rt :0.85min. m/z :444.2(M+NH_4)$^+$精 确 质 量 :426.1。 ^{1}H NMR(400MHz, DMSO-d_6) δ ppm 1.90-2.04(m,1H),2.16-2.24(m,1H),2.25(d, J = 1.8Hz,3H),2.81(dd, J = 13.4,7.0Hz, 1H),3.08(ddd, J = 13.1,9.1,7.5Hz,1H),3.15-3.26(m,2H),3.94-4.06(m,1H),7.15(t, J = 9.2Hz,1H),7.55-7.63(m,1H),7.68(dd, J = 7.2,2.3Hz,1H),7.79(t, J = 7.8Hz,1H), 8.01-8.07(m,1H),8.23(dt,J = 7.7,1.3Hz,1H),8.38(t,J = 1.7Hz,1H),8.40(br. s.,1H), 10.48(s,1H)

[0476]



化合物 **141**

[0477] 合成遵循程序 S4,用 2- 氨基茚满 -1- 醇盐酸盐作为胺,加工 W4。方法 F ;Rt : 0.98 和 1.01min. m/z :458.1(M+NH_4)$^+$精确质量 :440.1。化合物 141 以它的异构体进行分离,通过制备型 SFC(固定相 :Chiralcel Diacel OD 20×250mm,流动相 :CO_2,含有 0.2% iPrNH_2的 MeOH),收集所希望的部分,蒸发,溶解在 MeOH 中并且再次蒸发。SFC,柱 : OD-H(Diacel)250mm×4.6mm

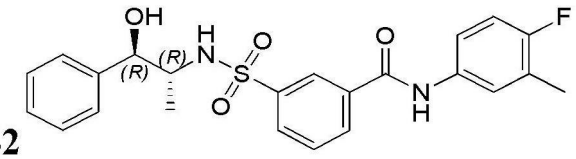
[0478] 流速 :5mL/min,流动相 :30% MeOH(包含 0.2% iPrNH_2) 保持 4.00min,直至 1min 内达到 50% 并且在 50% 保持 2.00min 温度 :40℃。Rt :141a(1.8min)、141b(2.1min)、141c(2.5min)、141d(2.7min)。

[0479] 141a、141c :N-(4- 氟 -3- 甲基 - 苯基)-3-[[(1S,2S)-1- 羟基茚满 -2- 基] 氨磺酰基] 苯甲酰胺或 N-(4- 氟 -3- 甲基 - 苯基)-3-[[(1R,2R)-1- 羟基茚满 -2- 基] 氨磺酰基] 苯甲酰胺。^{1}H NMR(400MHz, DMSO-d_6) δ ppm 2.25(d, J = 1.5Hz,3H),2.43-2.55(m, 1H),2.83(dd, J = 15.7,7.8Hz,1H),3.59-3.70(m,1H),4.83(d, J = 6.8Hz,1H),5.58(br. s.,1H),7.03-7.27(m,5H),7.56-7.65(m,1H),7.68(dd, J = 7.0,2.4Hz,1H),7.78(t, J = 7.8Hz,1H),8.05-8.11(m,1H),8.16(br.s.,1H),8.22(d, J = 8.1Hz,1H),8.43(t, J = 1.7Hz,1H),10.47(br.s.,1H) 方法 F ;Rt :0.98m/z :458.3(M+NH_4)$^+$精确质量 :440.1。

[0480] 141b、141d :N-(4- 氟 -3- 甲基 - 苯基)-3-[[(1R,2S)-1- 羟基茚满 -2- 基] 氨磺酰基] 苯甲酰胺或 N-(4- 氟 -3- 甲基 - 苯基)-3-[[(1S,2R)-1- 羟基茚满 -2- 基] 氨磺

酰基]苯甲酰胺。^{1}H NMR(600MHz,丙酮 ETONE-d_6,-14℃)δ ppm 2.25(d,J = 1.9Hz,3H),2.80-2.90(m,2H),3.94-3.99(m,1H),4.72(d,J = 5.3Hz,1H),4.87(d,J = 3.8Hz,1H),6.96(d,J = 5.0Hz,1H),7.08(t,J = 9.2Hz,1H),7.14-7.19(m,2H),7.21(td,J = 7.3,1.2Hz,1H),7.29(d,J = 7.3Hz,1H),7.65-7.70(m,1H),7.74(dt,J = 6.8,3.1Hz,1H),7.79(t,J = 7.8Hz,1H),8.19(ddd,J = 7.8,1.8,1.1Hz,1H),8.27(ddt,J = 7.8,1.8,0.9,0.9Hz,1H),8.54(q,J = 1.6Hz,1H),10.09(s,1H) 方法 F;Rt:1.00m/z:458.2$(M+NH_4)^+$精确质量:440.1。

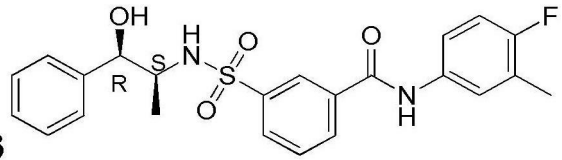
[0481]



化合物 142

[0482] 合成遵循程序 S4,用(1R,2R)-2-氨基-1-苯基-丙-1-醇作为胺,加工 W4。方法 F;Rt:1.00min.m/z:460.1$(M+NH_4)^+$精确质量:442.1。H NMR(400MHz,DMSO-d_6)δ ppm 0.76(d,J = 6.8Hz,3H),2.25(d,J = 1.3Hz,3H),3.37-3.46(m,1H),4.56(d,J = 4.6Hz,1H),5.41(br.s.,1H),7.14(t,J = 9.2Hz,1H),7.18-7.23(m,1H),7.23-7.32(m,4H),7.49(br.s.,1H),7.56-7.64(m,1H),7.64-7.72(m,2H),7.88-7.96(m,1H),8.15(d,J = 7.9Hz,1H),8.31(t,J = 1.5Hz,1H),10.42(s,1H)。

[0483]

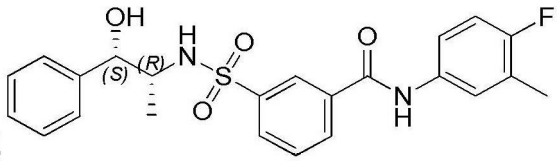


化合物 143

[0484] 合成遵循程序 S1,用(1R,2S)-(-)-苯丙醇胺作为胺,加工 W1。

[0485] 方法 F;Rt:1.01min.m/z:460.1$(M+NH_4)^+$精确质量:442.1。^{1}H NMR(400MHz,DMSO-d_6)δ ppm 0.79(d,J = 6.8Hz,3H),2.25(d,J = 1.8Hz,3H),3.33-3.37(m,1H),4.48(t,J = 4.6Hz,1H),5.42(d,J = 4.6Hz,1H),7.10-7.27(m,6H),7.55-7.63(m,1H),7.64-7.71(m,2H),7.78(d,J = 8.4Hz,1H),7.91(dt,J = 8.2,1.2Hz,1H),8.12-8.18(m,1H),8.30(t,J = 1.7Hz,1H),10.42(s,1H)

[0486]

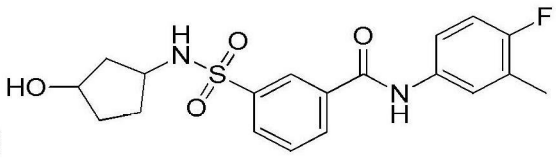


化合物 144

[0487] 合成遵循程序 S1,用(1S,2R)-(+)-苯丙醇胺作为胺,加工 W1。方法 F;Rt:1.01min.m/z:460.2$(M+NH_4)^+$精确质量:442.1。

[0488] ^{1}H NMR(400MHz,DMSO-d_6)δ ppm 0.79(d,J = 6.8Hz,3H),2.25(d,J = 1.8Hz,3H),3.32-3.38(m,1H),4.48(t,J = 4.6Hz,1H),5.42(d,J = 4.8Hz,1H),7.10-7.27(m,6H),7.56-7.63(m,1H),7.65-7.71(m,2H),7.78(d,J = 8.4Hz,1H),7.89-7.94(m,1H),8.15(dt,J = 7.8,1.3Hz,1H),8.30(t,J = 1.7Hz,1H),10.42(s,1H)

[0489]



化合物 **145**

[0490] 合成遵循程序 S4，用 3- 氨基环戊醇作为胺，完成后，将该反应混合物直接加载到硅胶柱上用于纯化（使用庚烷到 EtOAc 的梯度），产生化合物 145 为 (83(145a、145b) :17(145c :145d)) 的非对映异构体的混合物。方法 F ;Rt :0.82 和 0.86min. m/z :410.2(M+NH_4)$^+$精确质量 :392.1。化合物 145 以它的异构体进行分离，通过制备型 SFC（固定相 :大赛璐公司 (Chiralcel)Diacel AD 30x 250mm，流动相 :CO_2，含有 0.4% $iPrNH_2$的 MeOH)，收集所希望的部分，蒸发，溶解在 MeOH 中并且再次蒸发，产生化合物 145a(238mg) 和 145b(236mg) 以及化合物 145c 和 145d 的混合物。145c 和 145d 的混合物进一步通过制备型 SFC（固定相 :大赛璐公司 (Chiralpak)Diacel AD 30x250mm，流动相 :CO_2，含有 0.4% $iPrNH_2$的 EtOH) 进行分离，收集所希望的部分，蒸发，溶解在 MeOH 中并且再次蒸发，产生 145c(29mg) 和 145d(27mg)。145a 和 145b :N-(4- 氟 -3- 甲基 - 苯基)-3-[[(1R,3s)-3- 羟基环戊基] 氨磺酰基] 苯甲酰胺或 N-(4- 氟 -3- 甲基 - 苯基)-3-[[(1S,3R)-3- 羟基环戊基] 氨磺酰基] 苯甲酰胺。

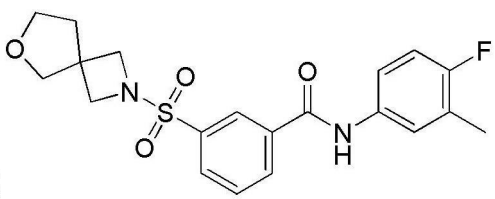
[0491] 方法 F ;Rt :0.85min. m/z :410.2(M+NH_4)$^+$精确质量 :392.1。

[0492] ^{1}H NMR(400MHz, DMSO-d_6) δ ppm 1.21(ddd, J = 13.3,7.8,6.1Hz,1H), 1.36-1.64(m,4H),1.84-1.95(m,1H),2.25(d, J = 1.1Hz,3H),3.37-3.47(m,1H), 3.85-3.96(m,1H),4.25-5.00(1H, br.s),7.14(t, J = 9.2Hz,1H),7.35-7.75(1H, br.s), 7.54-7.63(m,1H),7.68(dd, J = 7.0,2.2Hz,1H),7.75(t, J = 7.8Hz,1H),8.01(d, J = 7.9Hz,1H),8.19(d,J = 7.7Hz,1H),8.36(s,1H),10.46(br.s.,1H)

[0493] 145c 和 145d :N-(4- 氟 -3- 甲基 - 苯基)-3-[[(1S,3S)-3- 羟基环戊基] 氨磺酰基] 苯甲酰胺或 N-(4- 氟 -3- 甲基 - 苯基)-3-[[(1R,3R)-3- 羟基环戊基] 氨磺酰基] 苯甲酰胺。方法 F ;Rt :0.82min. m/z :410.2(M+NH_4)$^+$精确质量 :392.1。

[0494] ^{1}H NMR(400MHz, DMSO-d_6) δ ppm 1.17-1.35(m,2H),1.41(ddd, J = 13.4,8.0, 5.7Hz,1H),1.56(ddd, J = 13.2,7.3,2.6Hz,1H),1.69-1.83(m,2H),2.25(d, J = 1.8Hz, 3H),3.59-3.72(m,1H),3.99-4.09(m,1H),4.43(d,J = 3.5Hz,1H),7.14(t,J = 9.2Hz,1H), 7.55-7.63(m,1H),7.68(dd, J = 7.0,2.2Hz,1H),7.73-7.84(m,2H),7.96-8.02(m,1H), 8.20(dt, J = 7.9,1.2Hz,1H),8.36(t, J = 1.7Hz,1H),10.48(br.s.,1H)145a :[α]20 D : +5.2° (c 0.56w/v%, DMF) ;145b :[α]20 D :-5.4° (c 0.60w/v%, DMF) ;145c :[α]20 D :-3.5° (c 0.46w/v%,DMF) ;145d :[α]20 D :+2.5° (c 0.44w/v%,DMF)

[0495]

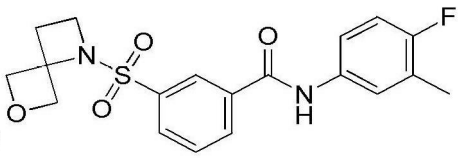


化合物 **146**

[0496] 合成遵循程序 S2，用 6- 氧杂 -2- 氮杂螺 [3.4] 辛烷草酸盐作为胺，完成后，将该

反应混合物直接加载到硅胶柱上用于纯化（使用庚烷到EtOAc的梯度），产生化合物146。方法F；Rt：0.93min.m/z：422.3$(M+NH_4)^+$精确质量：404.1。^1H NMR(400MHz，DMSO-d_6)ppm 1.81(t，J = 6.9Hz,2H)，2.26(d，J = 1.8Hz,3H)，3.46(s,2H)，3.57(t，J = 6.9Hz,2H)，3.72-3.80(m,4H)，7.15(t，J = 9.1Hz,1H)，7.58-7.64(m,1H)，7.69(dd，J = 7.0,2.2Hz，1H)，7.87(t，J = 7.8Hz,1H)，8.04(dt，J = 8.0,1.3Hz,1H)，8.32-8.41(m,2H)，10.53(s，1H)。

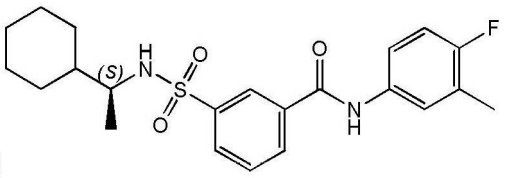
[0497]



化合物 **147**

[0498] 合成遵循程序S2，用6-氧杂-1-氮杂螺[3.3]庚烷作为胺，完成后，将该反应混合物直接加载到硅胶柱上用于纯化（使用庚烷到EtOAc的梯度），产生化合物147。方法F；Rt：0.92min.m/z：408.2$(M+NH_4)^+$精确质量：390.1。^1H NMR(400MHz，DMSO-d_6) δ ppm 2.25(d，J = 1.8Hz,3H)，2.53(t，J = 7.3Hz,2H)，3.73(t，J = 7.4Hz,2H)，4.53(d，J = 7.9Hz,2H)，5.01(d，J = 7.9Hz,2H)，7.15(t，J = 9.1Hz,1H)，7.56-7.64(m,1H)，7.68(dd，J = 7.0,2.2Hz,1H)，7.82(t，J = 7.8Hz,1H)，8.05-8.11(m,1H)，8.29(dt，J = 7.8,1.3Hz，1H)，8.40(t，J = 1.7Hz,1H)，10.51(s,1H)

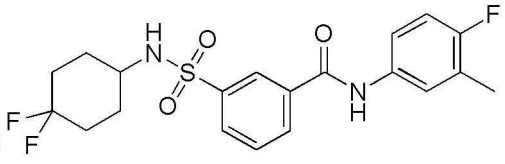
[0499]



化合物 **148**

[0500] 合成遵循程序S4，用(S)-(+)-1-环己基乙胺作为胺，加工W4。方法F；Rt：1.23min.m/z：436.2$(M+NH_4)^+$精确质量：418.2

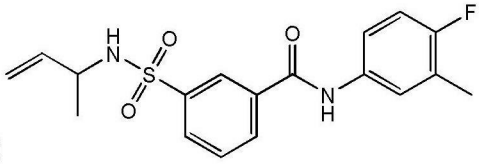
[0501]



化合物 **149**

[0502] 合成遵循程序S4，用4,4-二氟环己胺作为胺，加工W4。方法F；Rt：1.06min.m/z：444.5$(M+NH_4)^+$精确质量：426.1。

[0503]

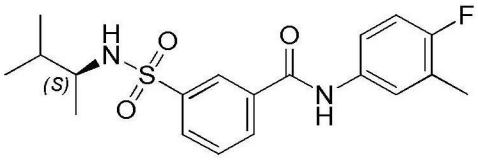


化合物 **150**

[0504] 合成遵循程序S4，用3-丁烯-2-胺盐酸盐作为胺，加工W4。方法F；Rt：1.01min.m/z：380.3$(M+NH_4)^+$精确质量：362.1。^1H NMR(400MHz，DMSO-d_6) δ ppm 1.03(d，J = 6.8Hz，3H)，2.25(d，J = 1.8Hz,3H)，3.74-3.87(m,1H)，4.87(dt，J = 10.5,1.4Hz,1H)，5.00(dt，

J = 17.3,1.4Hz,1H),5.61(ddd,J = 17.3,10.5,6.1Hz,1H),7.14(t,J = 9.2Hz,1H),7.55-7.63(m,1H),7.68(dd,J = 7.2,2.3Hz,1H),7.74(t,J = 7.8Hz,1H),7.93(d,J = 7.9Hz,1H),7.96-8.01(m,1H),8.18(dt,J = 7.7,1.3Hz,1H),8.35(t,J = 1.7Hz,1H),10.45(s,1H)。

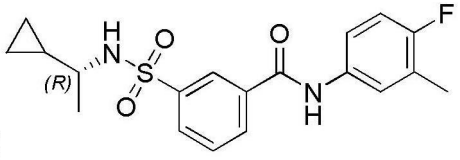
[0505]



化合物 **151**

[0506] 合成遵循程序 S4(搅拌 20 小时而非 3 小时)用 (S)-(+)-2- 氨基 -3- 甲基丁烷作为胺,加工 W4。方法 F ;Rt :1.11min. m/z :396.2 $(M+NH_4)^+$ 精确质量 :378.1。^1H NMR(400MHz,氯 仿 -d) δ ppm 0.81(d,J = 6.8Hz,6H),0.95(d,J = 6.8Hz,3H),1.57-1.67(m,1H),2.28(d,J = 1.8,3H),3.13-3.28(m,1H),4.85(d,J = 8.6Hz,1H),6.98(t,J = 9.0Hz,1H),7.36-7.46(m,1H),7.49-7.57(m,1H),7.61(t,J = 7.8Hz,1H),8.00(dt,J = 7.9,1.5Hz,1H),8.12(dt,J = 7.9,1.5Hz,1H),8.25(s,1H),8.39(t,J = 1.9Hz,1H)。

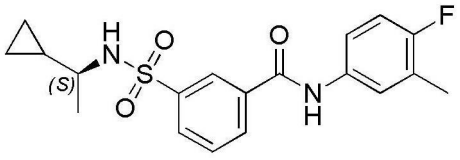
[0507]



化合物 **152**

[0508] 合成遵循程序 S4(搅拌 20 小时而非 3 小时)用 (1R)-1- 环丙基乙胺作为胺,加工 W4。^1H NMR(400MHz,氯仿 -d) δ ppm-0.05-0.05(m,1H),0.09-0.16(m,1H),0.20-0.36(m,1H),0.38-0.51(m,1H),0.69-0.81(m,1H),1.13(d,J = 6.6Hz,3H),2.27(d,J = 1.8Hz,3H),2.63-2.85(m,1H),5.10(d,J = 6.8Hz,1H),6.98(t,J = 8.9Hz,1H),7.37-7.45(m,1H),7.52(dd,J = 6.6,2.4Hz,1H),7.60(t,J = 7.8Hz,1H),7.98-8.02(m,1H),8.08-8.13(m,1H),8.25(s,1H),8.38(t,J = 1.7Hz,1H)。方法 F ;Rt :1.07min. m/z :394.2 $(M+NH_4)^+$ 精确质量 :376.1。

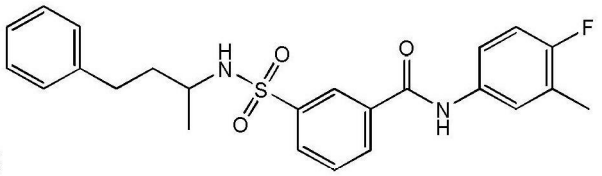
[0509]



化合物 **174**

[0510] 合成遵循程序 S4(搅拌 20 小时而非 3 小时)用 (1R)-1- 环丙基乙胺作为胺,加工 W4。将获得的残余物从二异丙醚 / 乙腈中进行再结晶。收集该沉淀并且在真空中在 55℃进行干燥,产生化合物 174。^1H NMR(400MHz,DMSO-d_6) δ ppm-0.11--0.01(m,1H),0.07-0.23(m,2H),0.29-0.38(m,1H),0.70-0.82(m,1H),0.99(d,J = 6.6Hz,3H),2.21-2.30(m,3H),2.66(quin,J = 6.8Hz,1H),7.14(t,J = 9.1Hz,1H),7.56-7.64(m,1H),7.68(dd,J = 7.0,2.4Hz,1H),7.75(t,J = 7.8Hz,1H),7.85(br. s.,1H),7.93-8.07(m,1H),8.18(d,J = 7.9Hz,1H),8.37(t,J = 1.7Hz,1H),10.46(br. s.,1H)

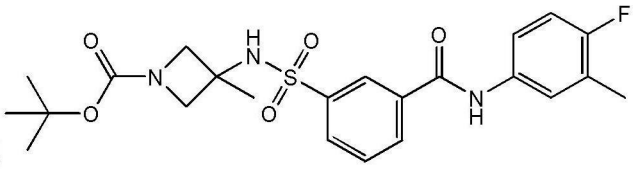
[0511]



化合物 **153**

[0512] 合成遵循程序 S4(搅拌 20 小时而非 3 小时) 用 3- 氨基 -1- 苯基丁烷作为胺,加工 W4。方法 F ;Rt :1.19min. m/z :458.2(M+NH_4)$^+$精确质量 :440.2。^{1}H NMR(400MHz,氯仿 -d) δ ppm 1.06(d, J = 6.6Hz,3H),1.62-1.76(m,2H),2.25(d, J = 1.8Hz,3H),2.44-2.64(m,2H),3.30-3.43(m,1H),5.05(d, J = 8.4Hz,1H),6.96(t, J = 8.9Hz,1H),7.00-7.04(m,2H),7.09-7.17(m,1H),7.17-7.25(m,2H),7.36-7.42(m,1H),7.50(dd, J = 6.8,2.4Hz,1H),7.57(t, J = 7.8Hz,1H),7.95(m, J = 7.8,1H),8.10(m, J = 7.8Hz,1H),8.25(s,1H),8.37(t, J = 1.5Hz,1H)

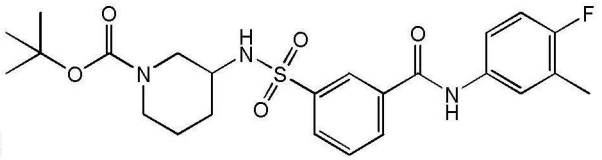
[0513]



化合物 **154**

[0514] 将溶解在 CH_2Cl_2(15mL) 中的 3-[(4- 氟 -3- 甲基 - 苯基) 氨基甲酰基] 苯磺酰氯 (500mg,1.53mmol) 和 DIPEA(657 μL,3.8mmol,2.5 当量) 添加到包含 3- 氨基 -1-Boc-3- 甲基 - 氮杂环丁烷 (1.1 当量) 的试管中。将反应混合物搅拌 20 小时。添加 1M HCl(5mL) 并且将该混合物搅拌 5 分钟。将该有机层进行分离并且加载到硅胶柱上。将该混合物使用从庚烷到 EtOAc 的梯度洗脱液进行纯化,产生化合物 154(721mg)。方法 F ;Rt :1.11min. m/z :478.2(M+H)$^+$精确质量 :477.2。

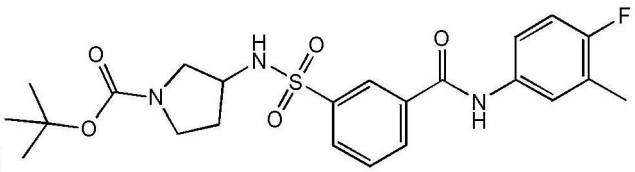
[0515]



化合物 **155**

[0516] 如针对化合物 154 描述地制备,使用 1-Boc-3- 氨基哌啶代替 3- 氨基 -1-Boc-3- 甲基 - 氮杂环丁烷。方法 F ;Rt :1.13min. m/z :492.1(M+H)$^+$精确质量 :491.2。

[0517]

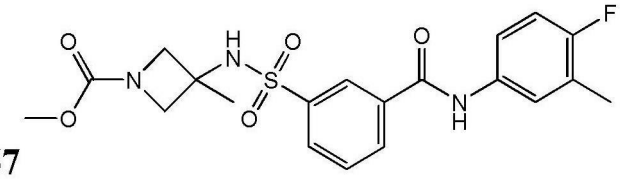


化合物 **156**

[0518] 如针对化合物 154 描述地制备,使用 (+/-)-3- 氨基 -1-N-Boc- 吡咯烷代替 3- 氨基 -1-Boc-3- 甲基 - 氮杂环丁烷。方法 F ;Rt :1.08min. m/z :478.2(M+H)$^+$精确质量 :477.2 ^{1}H NMR(400MHz,氯仿 -d) δ ppm 1.36(s,9H),1.71-1.92(m,1H),1.92-2.15(m,1H),2.28(d, J = 1.8Hz,3H),3.10-3.24(m,1H),3.24-3.44(m,3H),3.81-3.94(m,1H),5.50-6.00(m,1H),6.98(t, J = 9.0Hz,1H),7.40-7.48(m,1H),7.52-7.71(m,2H),7.93-8.03(m,1H),

8.04-8.17(m,1H),8.31(br.s.,1H),8.45-8.88(m,1H)。

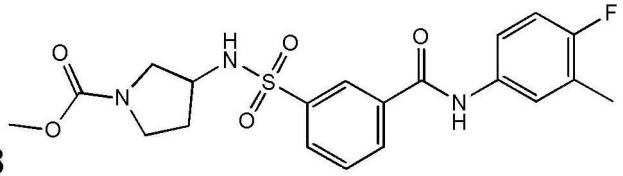
[0519]



化合物 **157**

[0520] 将化合物 154(721mg,1.51mmol) 溶解在 CH_2Cl_2(10mL) 中并添加 HCl(6M 于 iPrOH 中,2.5mL)。将该混合物搅拌过夜并且将该挥发物在真空中去除,产生呈白色固体的 N-(4- 氟 -3- 甲基 - 苯基)-3-[(3- 甲基氮杂环丁 -3- 基) 氨磺酰基] 苯甲酰胺盐酸盐 (0.57g)。向在 CH_2Cl_2(10mL) 中的 N-(4- 氟 -3- 甲基 - 苯基)-3-[(3- 甲基氮杂环丁 -3- 基) 氨磺酰基] 苯甲酰胺盐酸盐 (150mg) 添加 DIPEA(263μL,1.5mmol) 和氯甲酸甲酯 (44μL,0.57mmol)。将该混合物在温和氮流下在 55℃浓缩直至仅剩 2mL。将此残余物使用硅胶柱层析 (梯度洗脱液 :EtOAc- 庚烷 0 ： 100 至 100 ： 0) 进行纯化。在减压下将所希望的部分进行浓缩并且将获得的产物在真空烘箱中在 55℃进行干燥,产生呈亮白色粉末的化合物 157(74.2mg)。方法 F ;Rt :0.93min.m/z :436.1(M+H)$^+$精确质量 :435.1。^{1}H NMR(400MHz, DMSO-d_6) δ ppm1.36(s,3H),2.25(d, J = 1.5Hz,3H),3.52(s,3H),3.56-3.68(m,2H),3.83-3.93(m,2H),7.14(t, J = 9.2Hz,1H),7.57-7.62(m,1H),7.68(dd, J = 6.8,2.4Hz,1H),7.77(t,J = 7.9Hz,1H),8.01(m,J = 7.9Hz,1H),8.21(m,J = 7.9Hz,1H),8.37(t,J = 1.5Hz,1H),8.48(bs,1H),10.49(s,1H)

[0521]



化合物 **158**

[0522] 如针对化合物 157 描述的类似地制备,从化合物 156(代替化合物 154) 起始,经由中间体 N-(4- 氟 -3- 甲基 - 苯基)-3-(吡咯烷 -3- 基氨磺酰基) 苯甲酰胺盐酸盐。方法 F ;Rt :0.91min.m/z :436.2(M+H)$^+$精确质量 :435.1。^{1}H NMR(400MHz, DMSO-d_6) δ ppm 1.61-1.77(m,1H),1.80-1.98(m 1H),2.25(d, J = 1.5Hz,3H),3.00-3.12(m,1H),3.14-3.27(m,1H),3.26-3.39(m,2H),3.50-3.58(m,3H),3.67-3.76(m,1H),7.14(t, J = 9.2Hz,1H),7.57-7.63(m,1H),7.68(dd, J = 7.2,2.3Hz,1H),7.78(t, J = 7.8Hz,1H),7.97-8.04(m,1H),8.04-8.18(m,1H),8.18-8.25(m,1H),8.37(t, J = 1.5Hz,1H),10.48(s,1H)

[0523]

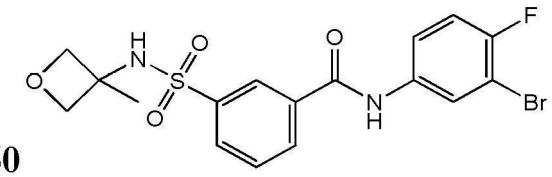
化合物 **159**

[0524] 如针对化合物 157 描述的类似地制备,从化合物 155(代替化合物 154) 起始,经由中间体 N-(4- 氟 -3- 甲基 - 苯基)-3-(3- 哌啶基氨磺酰基) 苯甲酰胺盐酸盐。方法 F ;Rt :

0.96min.m/z :467.1(M+NH_4)$^+$精确质量 :449.1。将外消旋化合物 159 进行分离,通过制备型 SFC(固定相 :大赛璐公司 (Chiralpak)Diacel IC 20 x 250mm 流动相 :CO_2,含有 0.2% iPrNH_2的 MeOH),收集所希望的部分,蒸发,溶解在甲醇中并且再次蒸发,产生化合物 159a 和 159b。

[0525] 柱 :ID-H(大赛璐公司 (Daicel))250mm x 4.6mm ; 流速 :3mL/min ; 流动相 :20 % EtOH(包含 0.2 % iPrNH_2) 保持 15.00min ; 温度 :30 ℃ ;Rt ;9.6min(159a), Rt ; 11.0min(159b)

[0526]

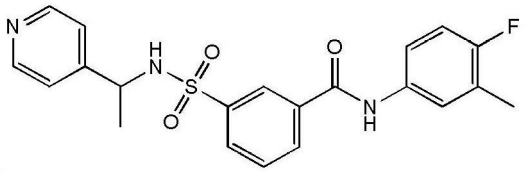


化合物 160

[0527] 方法 B ;Rt :4min.m/z :443.1(M+H)$^+$精确质量 :442.0

[0528] ^{1}H NMR(400MHz, DMSO-d_6) δ ppm 1.41(s,3H)4.14(d, J = 6.3Hz,2H)4.56(d, J = 6.0Hz,2H)7.42(t, J = 8.8Hz,1H)7.74-7.82(m,2H)8.04(s,1H)8.15-8.24(m,2H)8.37(t, J = 1.5Hz,1H)8.54(br.s,1H)10.67(br.s,1H)。

[0529]

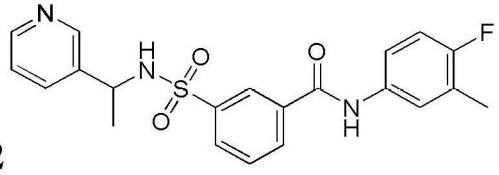


化合物 161

[0530] 将 1- 吡啶 -4- 基 - 乙胺 (220mg,1.8mmol) 和 3-[(4- 氟 -3- 甲基 - 苯基) 氨基甲酰基] 苯磺酰氯 (500mg,1.53mmol) 溶解在 CH_2Cl_2(10mL) 中。在 0℃添加 DIPEA(6.2mmol) 并且将该混合物在 25℃搅拌 4 小时。将该混合物用水 (20mL) 洗涤并且将该水层用 CH_2Cl_2(3×20mL) 进行萃取。将合并的有机层用盐水洗涤并且经 Na_2SO_4干燥。将该溶剂在真空中去除并且将获得的残余物通过反相高效液相层析 (流动相 :在水中 (0.1% TFA) 的 CH_3CN :从 30% 到 60%) 进行纯化。

[0531] 收集纯的部分并且通过固体 $NaHCO_3$中和。将该有机溶剂在真空中去除并且将形成的沉淀进行过滤,用 H_2O(5mL) 洗涤并且在高真空下干燥。将获得的残余物在水 (5mL) 中悬浮并且将该水层冻干至干燥,产生化合物 161(410mg)。方法 A ;Rt :4.34min. m/z :414.3(M+H)$^+$精确质量 :413.1。 ^{1}H NMR(400MHz, DMSO-d_6) δ ppm 1.23(d, J = 7.0Hz, 3H)2.26(d, J = 1.5Hz,3H)4.34-4.50(m,1H)7.15(t, J = 9.3Hz,1H)7.20-7.24(m, 2H)7.56-7.66(m,2H)7.68(dd, J = 7.0,2.3Hz,1H)7.86(m, J = 7.8Hz,1H)8.13(m, J = 7.8Hz,1H)8.26(t, J = 1.3Hz,1H)8.32-8.39(m,2H)8.55(d, J = 8.3Hz,1H)10.41(s,1H)。

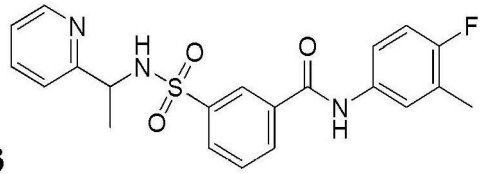
[0532]



化合物 162

[0533] 如针对化合物 161 描述的类似地制备，使用 1-(3- 吡啶基）乙胺代替 1- 吡啶 -4- 基 - 乙胺。方法 D ;Rt :5.16min. m/z :414.3(M+H)$^+$精确质量 :413.1。

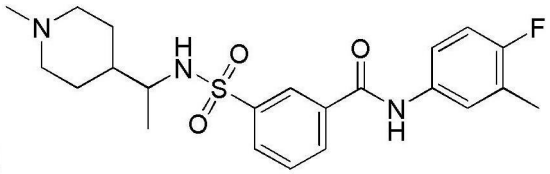
[0534]



化合物 **163**

[0535] 如针对化合物 161 描述的类似地制备，使用 1-(2- 吡啶基）乙胺代替 1- 吡啶 -4- 基 - 乙胺。方法 A ;Rt :4.60min. m/z :414.3(M+H)$^+$精确质量 :413.1。

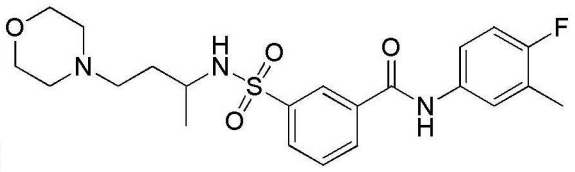
[0536]



化合物 **164**

[0537] 如针对化合物 161 描述的类似地制备，使用 1-(1- 甲基 -4- 哌啶基）乙胺代替 1- 吡啶 -4- 基 - 乙胺。方法 B ;Rt :3.35min. m/z :434.4(M+H)$^+$精确质量 :433.2。

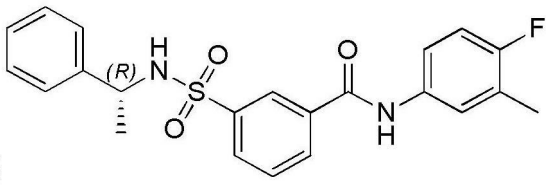
[0538]



化合物 **165**

[0539] 如针对化合物 161 描述的类似地制备，使用 4- 吗啉代丁 -2- 胺代替 1- 吡啶 -4- 基 - 乙胺。方法 B ;Rt :3.33min. m/z :450.3(M+H)$^+$精确质量 :449.2。

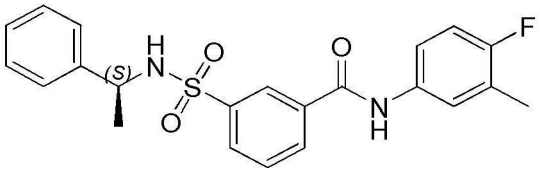
[0540]



化合物 **166**

[0541] 如针对化合物 161 描述的类似地制备，使用 (R)-1- 苯基乙胺代替 1- 吡啶 -4- 基 - 乙胺。将不纯的化合物通过制备型高效液相层析（柱 :Luna150*30mm*5u，流动相 :在水中 (0.1% NH_4HCO_3) 的 CH_3CN :从 40% 到 70%，流速 :35ml/min) 进行纯化。方法 B ; Rt :4.45min. m/z :413.3(M+H)$^+$精确质量 :412.1。[α]20 D :+55° (c 0.12w/v，甲醇）。

[0542]

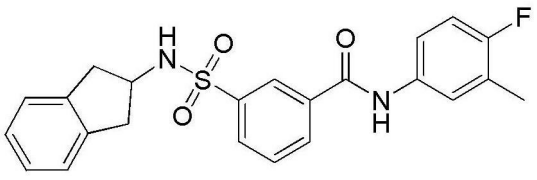


化合物 **167**

[0543] 如针对化合物 166 描述的类似地制备，使用 (S)-1- 苯基乙胺代替 (R)-1- 苯基乙胺。方法 B ;Rt :4.45min. m/z :413.3(M+H)$^+$精确质量 :412.1。[α]20 D :-57° (c 0.12w/

v,甲醇)。

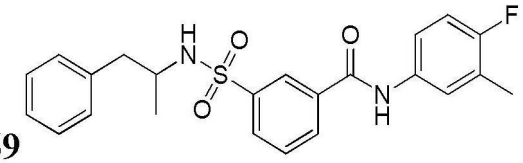
[0544]



化合物 168

[0545] 合成遵循程序 S4(反应时间为 20 小时而非 3 小时)用 2- 氨基茚满作为胺,加工 W4。将获得的残余物从二异丙醚 / 乙腈中进行再结晶,产生化合物 168。方法 F ;Rt :1.14min.m/z :442.2(M+NH_4)$^+$精确质量 :424.1。 ^{1}H NMR(400MHz, DMSO-d_6) δ ppm 2.25(d, J = 1.8Hz,3H),2.72(dd,J = 15.6,7.0Hz,2H),2.96(dd,J = 15.8,7.5Hz,2H),3.95(quin,J = 7.3Hz,1H),7.08-7.17(m,5H),7.57-7.63(m,1H),7.68(dd,J = 6.9,2.3Hz,1H),7.79(t, J = 7.8Hz,1H),8.03-8.12(m,1H),8.13-8.28(m,2H),8.41(t, J = 1.7Hz,1H),10.49(br. s.,1H)

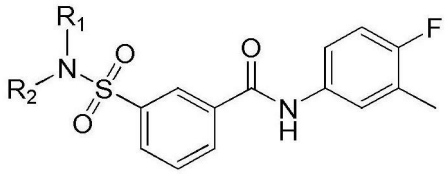
[0546]



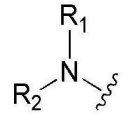
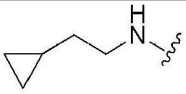
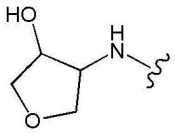
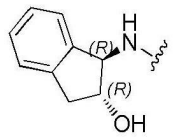
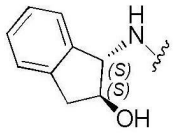
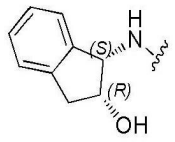
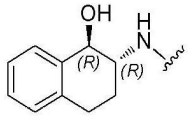
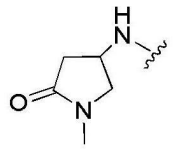
化合物 169

[0547] 如针对化合物 166 描述的类似地制备,使用 1- 苯基丙 -2- 胺代替 (R)-1- 苯基乙胺。方法 B ;Rt :4.60min.m/z :427.3(M+H)$^+$精确质量 :426.1。

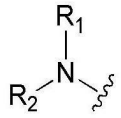
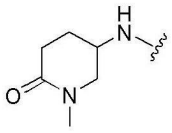
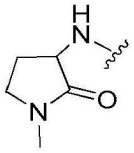
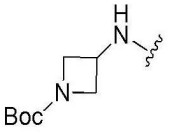
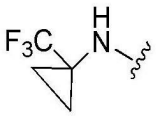
[0548]



[0549]

#		使用的胺	合成/加工程序	LC-MS方法	Rt（min.）	$[M+NH_4]^+$ 或 $[M+H]^+$	精确质量
170		2-环丙基乙胺	S4/W4	H	8.63	377.1	376.1
171		4-氨基四氢呋喃-3-醇	S4/W4	F	0.79	412.1	394.1
175		(1R,2R)-1-氨基-2,3-二氢-1H-茚-2-醇	S4*/W4	F	0.97	458.1	440.1
176		(1S,2S)-1-氨基-2,3-二氢-1H-茚-2-醇	S4*/W4	F	1.01	458.1	440.1
177		(1S,2R)-(-)-顺式-1-氨基-2-茚醇	S4*/W4	F	0.97	458.4	440.1
178		(1R,2R)-2-氨基萘满-1-醇盐酸盐	S4*/W4	F	1.01	472.2	454.1
179		4-氨基-1-甲基-吡咯烷-2-酮	S4*/W4	F	0.81	406.1	405.1

[0550]

#		使用的胺	合成/加工程序	LC-MS 方法	Rt（min.）	$[M+NH_4]^+$ 或 $[M+H]^+$	精确质量
180		5-氨基-1-甲基-哌啶-2-酮	S4*/W4	F	0.81	420.2	419.1
181		3-氨基-1-甲基吡咯烷-2-酮	S4/W4	F	0.84	423.1	405.1
182		3-氨基-1-N-boc-氮杂环丁烷	S4*/W4	F	1.06	481.2	463.2
183		1-(三氟甲基)环丙胺	S4*/W4	F	1.03	434.1	416.1

[0551] S4 * :反应时间为 20 小时而非 3 小时

[0552] 化合物 175。^{1}H NMR(400MHz,DMSO-d_6) δ ppm 2.25(d,J = 1.5Hz,3H),2.62(dd,J = 15.7,6.5Hz,1H),3.07(dd,J = 15.7,6.7Hz,1H),4.11(quin,J = 6.2Hz,1H),4.50(dd,J = 7.9,6.2Hz,1H),5.14(d,J = 5.7Hz,1H),6.92(d,J = 7.5Hz,1H),7.06-7.24(m,4H),7.55-7.65(m,1H),7.69(dd,J = 7.0,2.4Hz,1H),7.77(t,J = 7.8Hz,1H),8.05-8.15(m,1H),8.19-8.26(m,1H),8.31(d,J = 8.4Hz,1H),8.47(t,J = 1.7Hz,1H),10.45(s,1H)

[0553] 化合物 178。^{1}H NMR(400MHz,DMSO-d_6) δ ppm 1.51-1.72(m,1H),1.86-1.99(m,1H),2.22-2.31(m,3H),2.60-2.74(m,1H),2.74-2.85(m,1H),3.26-3.41(m,1H),4.38(t,J = 6.2Hz,1H),5.32-5.39(m,1H),6.96-7.09(m,1H),7.11-7.21(m,3H),7.28-7.37(m,1H),7.51-7.65(m,1H),7.69(dd,J = 7.0,2.4Hz,1H),7.72-7.82(m,2H),8.05-8.12(m,1H),8.17-8.24(m,1H),8.43(t,J = 1.7Hz,1H),10.48(s,1H)

[0554] 化合物 179。^{1}H NMR(400MHz,DMSO-d_6) δ ppm 1.99(dd,J = 5.1,16.7Hz,1H),2.25(d,J = 1.8Hz,3H),2.35(dd,J = 8.4,16.7Hz,1H),2.66(s,3H),3.10(dd,J = 10.1,4.6Hz,1H),3.47(dd,J = 10.3,7.3Hz,1H),3.80-3.92(m,1H),7.14(t,J = 9.2Hz,1H),7.53-7.63(m,1H),7.68(dd,J = 7.0,2.2Hz,1H),7.74-7.86(m,1H),7.97-8.08(m,1H),8.15-8.32(m,2H),8.37(s,1H),10.48(s,1H)。外消旋化合物 179 以对映异构体 179a 和

179b 通过制备型 SFC(固定相:大赛璐公司 (Chiralpak)Diacel AD 30 x 250mm),流动相:CO_2,含有 0.4% $iPrNH_2$的 iPrOH) 进行分离。将收集的部分在真空中进行浓缩,产生化合物 179a 和 179b。柱:AD-H(diacel)250mm x 4.6mm;流速:5mL/min;流动相:30% iPrOH(包含 0.2% $iPrNH_2$) 保持 4.00min,直至 1min 内达到 50%并且在 50%保持 2.00min;温度:40℃。Rt:2.2min(179a);2.9min(179b)。179a:+6.1° (589nm, c 0.6225w/v %, MeOH,20℃)。179b:-6.1° (589nm,c 0.506w/v%,MeOH,20℃)。

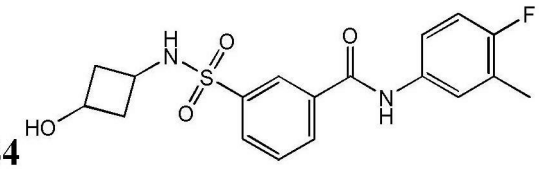
[0555] 化合物 180。^1H NMR(400MHz, DMSO-d_6) δ ppm 1.55-1.79(m,2H),2.01-2.36(m,5H),2.68(s,3H),3.06(dd, J = 12.3,6.8Hz,1H),3.25-3.30(m,1H),3.46-3.58(m,1H),7.14(t, J = 9.1Hz,1H),7.52-7.63(m,1H),7.64-7.71(m,1H),7.78(t, J = 7.8Hz,1H),8.01-8.09(m,1H),8.11-8.27(m,2H),8.39(t, J = 1.7Hz,1H),10.47(s,1H)

[0556] 化合物 181。^1H NMR(400MHz, DMSO-d_6) δ ppm 1.59(dq, J = 12.4,9.3Hz,1H),1.93-2.16(m,1H),2.25(d, J = 1.5Hz,3H),2.69(s,3H),3.06-3.24(m,2H),4.00(t, J = 9.1Hz,1H),7.14(t, J = 9.2Hz,1H),7.54-7.64(m,1H),7.65-7.71(m,1H),7.74(t, J = 7.8Hz,1H),7.99-8.09(m,1H),8.25(br.s,1H),8.11-8.20(m,1H),8.44(t, J = 1.7Hz,1H),10.42(s,1H)。

[0557] 化合物 182。^1H NMR(400MHz, DMSO-d_6) δ ppm 1.12-1.52(m,9H),2.26(d, J = 1.3Hz,3H),3.40-3.60(m 2H),3.80-4.00(m,2H),4.02-4.19(m,1H),7.15(t, J = 9.2Hz,1H),7.57-7.66(m,1H),7.70(dd, J = 7.0,2.2Hz,1H),7.80(t, J = 7.8Hz,1H),8.01(m, J = 8.1Hz,1H),8.26(m, J = 7.9Hz,1H),8.38(t, J = 1.0Hz,1H),8.51(d, J = 8.4Hz,1H),10.50(s,1H)。

[0558] 化合物183。^1H NMR(400MHz,氯仿-d) δ ppm 1.19-1.43(m,4H),2.28(d,J = 1.8Hz,3H),5.74(br.s.,1H),6.99(t,J = 8.8Hz,1H),7.37(m,J = 8.4,3.7Hz,1H),7.45-7.54(m,1H),7.64(t,J = 7.8Hz,1H),7.88(br.s.,1H),8.03(m,J = 8.1Hz,1H),8.10(m,J = 7.9Hz,1H),8.29-8.38(m,1H)

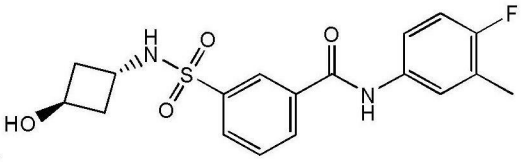
[0559]



化合物 **184**

[0560] 合成遵循程序 S4,用 3- 氨基环丁醇作为胺,1 小时反应时间而非 3 小时,加工 W4。方法 F;Rt:0.81min. m/z:396.2(M+NH_4)$^+$精确质量:378.1。SFC:柱:Diacel AD-H(250mm x 4.6mm);流速:5mL/min;流动相:30% MeOH(包含 0.2% $iPrNH_2$) 保持 4.00min,直至 1min 内达到 50%并且在 50%保持 2.00min;温度:40℃;Rt:184a(2.5min),184b(3.4min)。化合物 184 的非对映异构混合物以非对映异构体 (制备型 SFC(固定相:大赛璐公司 (Chiralpak) Diacel AD 30 x 250mm),流动相:CO_2,含有 0.4% $iPrNH_2$的 MeOH) 进行分离。将这些获得的部分在减压下进行浓缩并在真空中在 55℃干燥,产生化合物 184a 和 184b。

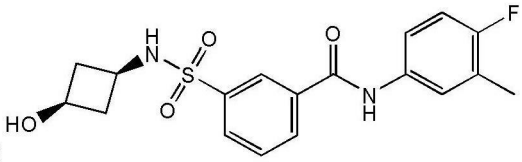
[0561]



化合物 **184a**

[0562] ^{1}H NMR(600MHz,DMSO-d_6) δ ppm 1.84-1.91(m,2H),1.92-1.98(m,2H),2.25(d,J＝1.8Hz,3H),3.77(quin,J＝6.9Hz,1H),4.10-4.14(m,1H),4.93(d,J＝4.9Hz,1H),7.14(t,J＝9.2Hz,1H),7.59(ddd,J＝8.8,4.6,2.7Hz,1H),7.68(dd,J＝7.1,2.7Hz,1H),7.76(t,J＝7.8Hz,1H),7.96(ddd,J＝7.8,1.9,1.1Hz,1H),8.06(br.s.,1H),8.20(dt,J＝7.8,1.5Hz,1H),8.33(t,J＝1.8Hz,1H),10.49(br.s.,1H)。

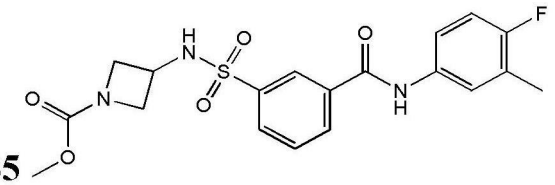
[0563]



化合物 **184b**

[0564] ^{1}H NMR(600MHz,DMSO-d_6) δ ppm 1.54-1.60(m,2H),2.19-2.24(m,2H),2.25(d,J＝1.8Hz,3H),3.09-3.19(m,1H),3.62-3.68(m,1H),5.00(d,J＝5.6Hz,1H),7.14(t,J＝9.2Hz,1H),7.59(ddd,J＝8.5,4.5,2.8Hz,1H),7.68(dd,J＝7.0,2.2Hz,1H),7.75(t,J＝7.8Hz,1H),7.97(ddd,J＝7.8,1.9,1.0Hz,1H),8.02(br.s.,1H),8.19(ddd,J＝7.8,1.8,1.1Hz,1H),8.34(t,J＝1.6Hz,1H),10.48(s,1H)

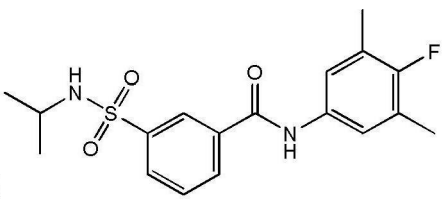
[0565]



化合物 **185**

[0566] 如针对化合物 157 描述的类似地制备,从化合物 182(代替化合物 154) 起始,经由中间体 3-(氮杂环丁 -3- 基氨磺酰基)-N-(,4- 氟 -3- 甲基 - 苯基) 苯甲酰胺盐酸盐。方法 F ;Rt :0.89min. m/z :439.2(M+NH_4)$^+$精确质量 :421.1。 ^{1}H NMR(400MHz, DMSO-d_6) δ ppm 2.25(d,J＝1.8Hz,3H),3.45-3.60(m,5H),3.85-4.05(m,2H),4.07-4.17(m,1H),7.15(t,J＝9.1Hz,1H),7.53-7.64(m,1H),7.65-7.71(m,1H),7.78(t,J＝7.8Hz,1H),7.94-8.03(m,1H),8.23(m,J＝7.9Hz,1H),8.33(t,J＝1.7Hz,1H),8.44-8.63(br.s,1H),10.49(s,1H)。

[0567]



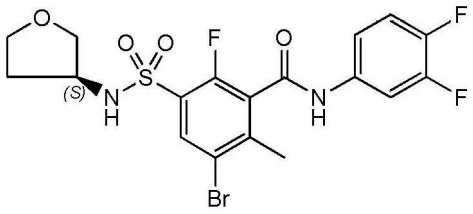
化合物 **186**

[0568] 在室温下在氮气氛下将 3-(异丙基氨磺酰基) 苯甲酸 (250mg,1.03mmol)、4- 氟 -3,5- 二甲基 - 苯胺 (157mg,1.13mmol) 和 DIPEA(398mg,3.08mmol) 在乙腈 (10mL) 中混合。添加 HATU(430mg,1.13mmol) 并将该混合物搅拌过夜。添加 EtOAc(100mL) 并将该混合物用 1M HCl、饱和 $NaHCO_3$和盐水进行洗涤。用 $MgSO_4$进行干燥并且在真空中蒸发

至干燥后，将获得的残余物从 MeOH(10mL) 中进行结晶以提供一种白色固体 (216mg)。方法 F ;Rt :1.04min. m/z :382.2(M+NH_4)$^+$精确质量 :364.1。 ^{1}H NMR(400MHz, DMSO-d_6) δ ppm 0.96(d, J = 6.6Hz,6H),2.23(d, J = 2.0Hz,6H),3.23-3.29(m,1H),7.48(d, J = 6.6Hz, 2H),7.66-7.80(m,2H),7.95-8.04(m,1H),8.18(d,J = 7.9Hz,1H),8.35(t,J = 1.7Hz,1H), 10.37(s,1H)。

[0569]

化合物 **187**



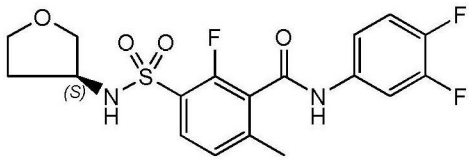
[0570] 将 2- 氟 -6- 甲基苯甲酸 (10g,0.0649mol) 在 HOAc(300mL) 中的溶液在包含少量冰的水浴上进行搅拌。在大约 15℃，逐滴添加 HNO_3(65％,32.7mL)。添加后，缓慢加入 H_2O(30mL)。添加后，逐滴加入 Br_2(3.7mL)。将硝酸银 (14.33g,0.0844mol) 在 H_2O(100mL) 中的溶液经 30 分钟的时间逐滴添加。添加后，将该反应混合物在室温下搅拌 3 小时 30 分钟。将反应混合物倾倒进 H_2O(850mL) 中，并且添加 EtOAc(300mL)。将该混合物强力搅拌 5 分钟。上面两液体层均从残余物中轻轻倒出。将分离的水层与该残余物进行合并，并用 EtOAc 萃取。上面两液体层均从该残余物中轻轻倒出。将分离的水层与该残余物进行合并，并再次用 EtOAc 萃取。将这些有机层进行合并，用饱和 NaCl 进行洗涤并用 Na_2SO_4进行干燥，过滤出，蒸发并与甲苯进行共蒸发。将获得的固体残余物在少量二异丙醚中进行搅拌，过滤出，用二异丙醚进行洗涤，产生 3- 溴 -6- 氟 -2- 甲基 - 苯甲酸 (4g)。将滤液进行蒸发。将该残余物在庚烷中搅拌，过滤出，用庚烷 (3x) 进行洗涤并在 50℃在真空中干燥，产生溴 -6- 氟 -2- 甲基 - 苯甲酸和 2- 氟 -6- 甲基苯甲酸的混合物 (12g,1/0.4 比例)。将 3- 溴 -6- 氟 -2- 甲基 - 苯甲酸 (4g,0.0172mol) 分部分地添加到正在进行搅拌的氯磺酸 (25mL) 中。将产生的溶液在 115℃搅拌 2 小时，在室温下保留过夜并接下来在 115℃再搅拌 3 小时。允许反应混合物达到室温并逐滴添加至压碎的冰 (150g) 和 H_2O(50mL) 的正在进行搅拌的混合物中。将该产物用 EtOAc(2x) 进行萃取。将这些合并的有机层用盐水进行洗涤，用 Na_2SO_4进行干燥，过滤出并蒸发，产生包含 5- 溴 -3- 氯磺酰基 -2- 氟 -6- 甲基 - 苯甲酸粗制混合物 (4.4g) (Na_2CO_3,1.407g,0.0133mol)，溶解在水 (25mL) 中。添加 (S)-3- 氨基四氢呋喃 (2.312g, 0.0265mol) 在 THF(20mL) 中的溶液并将该反应混合物在冰浴上冷却至 0℃。在 0℃，逐滴添加粗制 5- 溴 -3- 氯磺酰基 -2- 氟 -6- 甲基 - 苯甲酸 (4.4g) 在 THF(30mL) 中的溶液。添加后，将该反应混合物在 0℃搅拌 1 小时，并在室温下搅拌 2 小时。将该混合物浓缩直至剩余～ 35mL，然后放置保持 70 小时。将固体过滤出并用 H_2O(2x) 进行洗涤。用 Et_2O 洗涤该滤液。将分离的水层用 1N HCl(30mL) 进行酸化并将该产物用 2-MeTHF 进行萃取。将分离的水层进一步酸化直至 pH ～ 2 并用 2-MeTHF 进行萃取。将该有机层用盐水进行洗涤，用 Na_2SO_4 进行干燥并过滤，产生粗制 5- 溴 -2- 氟 -6- 甲基 -3-[[(3S)- 四氢呋喃 -3- 基] 氨磺酰基] 苯甲酸 (6.5g)。在 N2 气氛下，向粗制 5- 溴 -2- 氟 -6- 甲基 -3-[[(3S)- 四氢呋喃 -3- 基] 氨磺酰基] 苯甲酸 (1.3g) 在 CH_3CN(30mL) 中的正在进行搅拌的溶液里相继添加三乙胺

(1.42mL,0.0102mol)、3,4- 二氟苯胺 (0.446mL,4.42mmol) 和 HATU(1.55g,4.08mmol)。将该反应混合物在室温下搅拌 16 小时。将挥发物进行蒸发并将获得的残余物通过硅胶层析 (庚烷 -EtOAc 100/0 至 0/100) 进行纯化,产生化合物 187(0.45g)。不纯的部分进一步通过制备型 HPLC(固定相 :RP XBridge Prep C18 OBD-10μm,30x 150mm,流动相 :在水中的 0.25% NH_4HCO_3溶液,CH_3CN) 进行纯化,产生更多的化合物 187(0.048g)

[0571] 方法 F ;Rt :1.06min. m/z :491.0(M-H)⁻精确质量 :492.0。^{1}H NMR(400MHz,DMSO-d_6) δ ppm 1.66-1.76(m,1H),1.94-2.05(m,1H),2.41(s,3H),3.43(dd, J = 8.9,4.5Hz,1H),3.58-3.65(m,1H),3.68(dd, J = 8.9,6.3Hz,1H),3.71-3.78(m,1H),3.83-3.92(m,1H),7.36-7.42(m,1H),7.43-7.52(m,1H),7.85(ddd, J = 12.8,7.5,2.4Hz,1H),8.02(d, J = 6.8Hz,1H),8.55(s,1H),11.09(s,1H)

[0572]

化合物 **188**



[0573] 将化合物 187(0.45g,0.912mmol) 溶解在 MeOH(20mL) 和 THF(30mL) 中。向产生的溶液里添加三乙胺 (0.254mL,1.82mmol) 并将该混合物在氢气氛下在室温下与 10% Pd/C(0.2g) 进行搅拌。3 小时后,将催化剂在硅藻土上过滤出,并用 MeOH(3x) 和 THF(1x) 进行洗涤。将挥发物在真空中去除并将获得的残余物溶解在热 MeOH(10mL) 中并添加热 H_2O(10mL)。体积浓缩至～ 15mL 并放置保持 1 小时。将沉淀的产物过滤出,用 H_2O(3x) 洗涤并在 50℃在真空中进行干燥,产生化合物 188(245mg)。方法 F ;Rt :0.93min. m/z :413.2(M-H)⁻精确质量 :414.1。^{19}F NMR(377MHz, DMSO-d_6) δ ppm-143.7--143.2(m,1F), -137.1--136.5(m,1F), -114.8(d, J = 7.9Hz,1F)。^{1}H NMR(400MHz, DMSO-d_6) δ ppm 1.66-1.77(m,1H),1.91-2.03(m,1H),2.39(s,3H),3.43(dd, J = 9.0,4.6Hz,1H),3.57-3.70(m,2H),3.70-3.77, (m,1H),3.78-3.86(m,1H),7.35(d, J = 8.1Hz,1H),7.39-7.52(m,2H),7.79(t, J = 7.8Hz,1H),7.87(ddd, J = 12.9,7.5,2.1Hz,1H),8.32(br. s.,1H),11.00(s,1H)。

[0574]

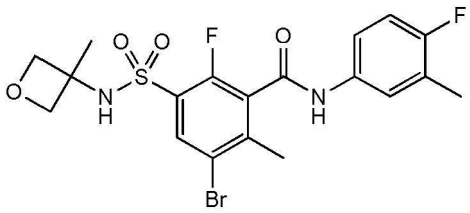
化合物 **189**

[0575] 化合物 189 是如针对化合物 188 描述的类似地制备,使用 4- 氟 -3- 甲基苯胺代替 3,4- 二氟苯胺。方法 F ;Rt :0.94min. m/z :409.2(M-H)⁻精确质量 :410.1。^{19}F NMR(377MHz, DMSO-d_6) δ ppm-122.40(dtd, J = 9.3,4.6,4.6,2.1Hz,1F), -114.96(d, J = 7.2Hz,1F)。^{1}H NMR(400MHz, DMSO-d_6) δ ppm 1.67-1.77(m,1H),1.92-2.03(m,1H),2.24(d, J = 1.5Hz, 3H),2.38(s,3H),3.43(dd, J = 8.8,4.6Hz,1H),3.58-3.64(m,1H),3.65-3.70(m,1H),

3.70-3.77(m,1H),3.78-3.86(m,1H),7.14(dd,J = 9.1Hz,1H),7.34(d,J = 8.1Hz,1H),7.45-7.53(m,1H),7.63(dd,J = 7.0,2.4Hz,1H),7.77(dd,J = 7.9Hz,1H),8.30(br.s.,1H),10.72(s,1H)。差式扫描量热法(从30℃到300℃,10℃/min):峰值在157.0℃

[0576]

化合物 **190**



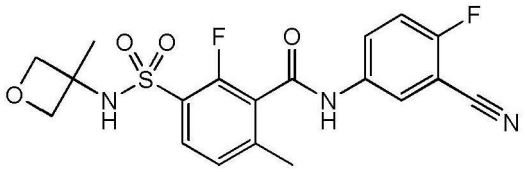
[0577] 将 Na_2CO_3(1.60g,0.0151mol)溶解在水中(25mL)。添加3-甲基氧杂环丁-3-胺(2.63g,0.0302mol)在THF(20mL)中的溶液并将该反应混合物在冰浴上冷却至0℃。在0℃,逐滴添加粗制5-溴-3-氯磺酰基-2-氟-6-甲基-苯甲酸(5g)在THF(30mL)中的溶液。添加后,将该反应混合物在0℃强力搅拌30分钟,并在室温下搅拌2小时。将这些有机挥发物蒸发,并将剩余的～30mL用 Et_2O(50mL)进行洗涤。将分离的水层用1N HCl(40mL)进行酸化并将该产物用2-MeTHF(2x)进行萃取。将这些合并的有机层用盐水进行洗涤,用 Na_2SO_4进行干燥,过滤出,蒸发并与 CH_3CN 进行共蒸发,产生了粗制5-溴-2-氟-6-甲基-3-[(3-甲基氧杂环丁-3-基)氨磺酰基]苯甲酸(3.6g)。在 N_2气氛下,向粗制5-溴-2-氟-6-甲基-3-[(3-甲基氧杂环丁-3-基)氨磺酰基]苯甲酸(0.72g,0.00188mol)在 CH_3CN(15mL)中的溶液里相继添加 NEt_3(0.786mL,0.00565mol)、4-氟-3-甲基苯胺(0.313g,0.00245mol)和HATU(0.86g,0.00226mol)。将该反应混合物在室温下搅拌20小时。添加更多的4-氟-3-甲基苯胺(0.1g)和HATU(0.3g)并且该反应继续20小时。将挥发物进行蒸发。将残余物通过硅胶层析(庚烷-EtOAc 100/0至0/100)进行纯化。将所希望的部分进行合并并且蒸发。将该残余物在二异丙醚中进行搅拌,过滤出,用二异丙醚(3x)进行洗涤,并在50℃干燥,产生化合物190(0.38g)。m/z:486.9 $(M-H)^-$ 精确质量:488.0。^{19}F NMR(377MHz,DMSO-d_6) δ ppm -122.15--121.89(m,1F),-116.05(d,J = 6.4Hz,1F)。^1H NMR(400MHz,DMSO-d_6) δ ppm 1.47(s,3H),2.25(d,J = 1.5Hz,3H),2.40(s,3H),4.22(d,J = 6.6Hz,2H),4.62(d,J = 6.4Hz,2H),7.16(dd,J = 9.2Hz,1H),7.44-7.51(m,1H),7.61(dd,J = 6.9,2.3Hz,1H),8.01(d,J = 6.8Hz,1H),8.86(br.s.,1H),10.81(s,1H)

[0578] 2-氟-6-甲基-3-[(3-甲基氧杂环丁-3-基)氨磺酰基]苯甲酸的合成

[0579] 在氢气氛下在室温,将5-溴-2-氟-6-甲基-3-[(3-甲基氧杂环丁-3-基)氨磺酰基]苯甲酸(0.9g)和三乙胺(0.98mL,7.1mmol)在MeOH(30mL)中的溶液与Pd/C 10%(0.1g)进行搅拌。在计算量的氢被吸收后,将催化剂过滤出。将该滤液在真空中浓缩,并与 CH_3CN 进行共蒸发。按照这样使用获得的包含2-氟-6-甲基-3-[(3-甲基氧杂环丁-3-基)氨磺酰基]苯甲酸的残余物。方法F;Rt:0.38min.m/z:302.0 $(M-H)^-$ 精确质量:303.1

[0580]

化合物 **191**



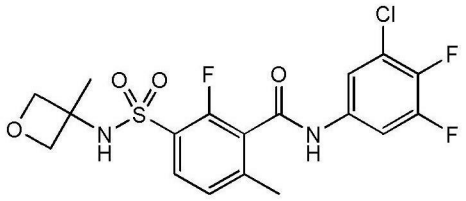
[0581] 在 N2 气氛下，将三乙胺 (0.206mL,0.00149mol) 添加到正在进行搅拌的 2- 氟 -6- 甲基 -3-[(3- 甲基氧杂环丁 -3- 基）氨磺酰基] 苯甲酸 (0.15g,0.000495mol) 和 CH_3CN(10mL) 的混合物中。向产生的溶液里添加 HATU(0.207g,0.545mmol)。搅拌 5 分钟后，添加 5- 氨基 -2- 氟苯甲腈 (79.9mg,0.569mmol)，并将该反应混合物在室温下搅拌 20 小时。接着该反应在 50℃继续 4 小时。将挥发物进行蒸发并将获得的残余物溶解在 CH_2Cl_2(2.5mL) 中并通过硅胶层析 (庚烷 -EtOAc 100/0 至 0/100) 进行纯化，随后通过使用 CH_2Cl_2-MeOH 100/0 至 98/2 作为洗脱液进行再纯化。将所希望的部分进行合并并且蒸发，并且与 EtOAc 进行共蒸发。将该残余物在 50℃在真空中进一步干燥，产生化合物 191(63mg)。方法 F；Rt :0.88min. m/z :420.1(M-H)$^-$ 精确质量 :421.1。^{1}H NMR(400MHz, DMSO-d_6)d ppm 1.46(s, 3H),2.40(s,3H),4.19(d, J = 6.6Hz,2H),4.62(d, J = 6.2Hz,2H),7.36(d, J = 8.1Hz, 1H),7.58(t, J = 9.1Hz,1H),7.80(t, J = 7.9Hz,1H),7.96(ddd, J = 9.1,4.8,2.8Hz, 1H),8.22(dd, J = 5.7,2.6Hz,1H),8.64(s,1H),11.16(s,1H)。^{19}F NMR(377MHz, DMSO-d_6) δ ppm-115.10(d, J = 7.9Hz,1F),-113.61(dt, J = 8.9,5.2Hz,1F)。

[0582] 3- 氯 -4,5- 二氟 - 苯胺的合成

[0583] 在 50℃将 3- 氯 -4,5- 二氟苯甲酸 (从 astatech 公司商购，25.5g,0.132mol) 溶解在叔丁醇中 (200mL)。添加 Et_3N(20.2mL,0.146mol)。缓慢添加叠氮化磷酸二苯酯 (30.0mL, 0.139mol)，并将该反应混合物搅拌并回流 18 小时。将挥发物进行蒸发，并与 EtOAc 进行共蒸发。将该残余物在 Et_2O(300mL)/ 饱和 $NaHCO_3$(300mL)/H_2O(50mL) 中搅拌 15 分钟。将该分离的有机层用 $MgSO_4$ 进行干燥，过滤出并且进行蒸发。将该固体残余物在二异丙醚中 (20mL) 进行搅拌，过滤出，用二异丙醚 (3x) 进行洗涤并在 50℃进行干燥，产生 N-(3- 氯 -4,5- 二氟 - 苯基) 氨基甲酸叔丁酯 (8.5g)。将该滤液在真空中浓缩。将该残余物在 CH_2Cl_2(20mL)+ 庚烷 (20mL) 中进行搅拌，过滤出，并用 CH_2Cl_2- 庚烷 1/1(2x) 和庚烷 (2x) 进行洗涤，并在 50℃在真空中干燥，产生更多的 N-(3- 氯 -4,5- 二氟 - 苯基) 氨基甲酸叔丁酯，11.8g，将 N-(3- 氯 -4,5- 二氟 - 苯基) 氨基甲酸叔丁酯 (8.5g,0.0322mol) 分部分添加到正在进行搅拌的 HCl(40mL,0.16mol,4M 在二噁烷中) 里。将该混合物在室温下搅拌 2 小时，然后放置保持 65 小时。再继续搅拌 2 小时。将形成的沉淀过滤出，用二噁烷 (4x) 进行洗涤，并在 50℃在真空中进行干燥，产生 3- 氯 -4,5- 二氟 - 苯胺盐酸盐 (5.95g)。将 3- 氯 -4,5- 二氟 - 苯胺盐酸盐 (1g,0.005mol)、NaOH(1M 在 H_2O 中，10mL,0.01mol) 和甲苯 (15mL) 的混合物在室温下搅拌 1 小时。将该分离的有机层用 $MgSO_4$ 进行干燥，过滤出并且进行蒸发。按照这样使用获得的 3- 氯 -4,5- 二氟 - 苯胺 (0.81g)。

[0584]

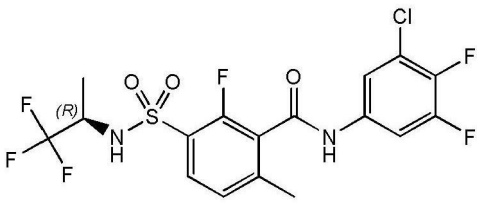
化合物 **192**



[0585] 化合物 192 是如针对化合物 191 描述的类似地制备，使用 3- 氯 -4,5- 二氟 - 苯胺盐酸盐代替 5- 氨基 -2- 氟苯甲腈。^{19}F NMR(377MHz，DMSO-d_6)d ppm-144.93(br.s.，1F)，-134.02--133.17(m,1F)，-115.09(d,J = 7.9Hz,1F)。^{1}H NMR(400MHz,DMSO-d_6) δ ppm 1.45(s,3H)，2.38(s,3H)，4.18(d，J = 6.4Hz,2H)，4.61(d，J = 6.2Hz,2H)，7.35(d，J = 8.1Hz,1H)，7.71-7.83(m,3H)，8.64(br.s.,1H)，11.14(br.s.,1H)。方法 F ;Rt :1.05min. m/z :447.1(M-H)$^-$精确质量 :448.0。

[0586]

化合物 **193**

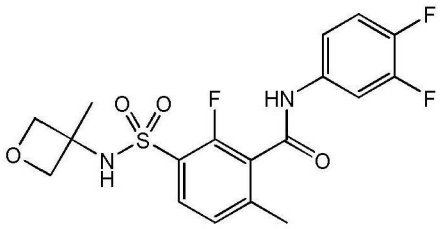


[0587] 将草酰氯 (12.3mL,0.143mol) 逐滴添加到 5- 溴 -3- 氯磺酰基 -2- 氟 -6- 甲基 - 苯甲酸 (9.5g) 和 DMF(0.111mL) 在 CH_2Cl_2(100mL) 中的正在进行搅拌的溶液里。添加后，将该反应混合物在室温下搅拌 2 小时 30 分钟。将该挥发物在真空中去除，并与甲苯进行共蒸发。按照这样使用获得的包含 5- 溴 -3- 氯磺酰基 -2- 氟 -6- 甲基 - 苯甲酰氯的残余物。在 N2 流下，将 5- 溴 -3- 氯磺酰基 -2- 氟 -6- 甲基 - 苯甲酰氯 (1.75g) 在甲苯 (20mL) 中的溶液在回流下搅拌。逐滴添加 3- 氯 -4,5- 二氟苯胺 (0.818g,0.005mol) 在甲苯 (10mL) 中的溶液。添加后，将该反应混合物回流 45 分钟，然后允许达到室温，并放置保持 18 小时。将沉淀 (0.51g) 过滤出，用甲苯 (2x) 进行洗涤，并在 50℃在真空中干燥。在 N_2气氛下，将 (R)-1,1,1- 三氟 -2- 丙胺 (0.181g,0.0016mol) 溶解在 CH_3CN(5mL) 中。添加 5- 溴 -3-[(3- 氯 -4,5- 二氟 - 苯基) 氨基甲酰基]-2- 氟 -4- 甲基 - 苯磺酰氯 (0.51g)，然后是 DIPEA(0.461mL,0.00267mol)。将该混合物在 80℃在密封管中搅拌 20 小时。允许该反应混合物达到室温并放置保持 2 小时。将该混合物进行过滤并将滤液蒸发。将该残余物溶解在 CH_2Cl_2(2mL) 中，并通过硅胶层析 (庚烷 -EtOAc 100/0 至 0/100) 进行纯化。将包含所希望的化合物的部分进行合并并蒸发，并且与 EtOH 进行共蒸发，产生粗制 5- 溴 -N-(3- 氯 -4,5- 二氟 - 苯基)-2- 氟 -6- 甲基 -3-[[(1R)-2,2,2- 三氟 -1- 甲基 - 乙基] 氨磺酰基] 苯甲酰胺 (0.12g)。向 5- 溴 -N-(3- 氯 -4,5- 二氟 - 苯基)-2- 氟 -6- 甲基 -3-[[(1R)-2,2,2- 三氟 -1- 甲基 - 乙基] 氨磺酰基] 苯甲酰胺 (0.1g) 在 EtOH(11mL) 中的溶液里添加 H_2O(3.5mL)、然后是 K_2CO_3 水性饱和溶液 (1.25mL) 并且接下来是四 (三苯基膦) 合钯 (0)(26.1mg,0.023mmol)。将该混合物通过微波辐射在 150℃搅拌 45 分钟。将该反应混合物与类似反应混合物 (从 20mg 5- 溴 -N-(3- 氯 -4,5- 二氟 - 苯基)-2- 氟 -6- 甲基 -3-[[(1R)-2,2,2- 三氟 -1- 甲基 - 乙

基]氨磺酰基]苯甲酰胺起始)合并并允许达到室温并放置保持15分钟。将该上层通过分液漏斗的手段进行分离,并进行蒸发。将获得的残余物通过硅胶层析(庚烷-EtOAc 100/0至0/100,还有CH_2Cl_2-MeOH 100/0至98/2)进行纯化,接下来通过制备型HPLC(固定相:RP Vydac Denali C18-10μm,200g,5cm),流动相:在水中的0.25% NH_4HCO_3溶液,CH_3CN)进行分离,产生化合物193(11.4mg)。方法F;Rt:1.17min.m/z:473.0$(M-H)^-$精确质量:474.0。^1H NMR(400MHz,DMSO-d_6)δppm 1.17(d,J=6.8Hz,3H),2.38(s,3H),4.00-4.15(m,1H),7.35(d,J=8.4Hz,1H),7.71-7.78(m,2H),7.82(t,J=7.8Hz,1H),9.00(br.s.,1H),11.13(s,1H)。^{19}F NMR(377MHz,DMSO-d_6)d ppm-145.3至-144.5(m,1F),-134.4至-132.8(m,1F),-114.9(br.s.,1F),-76.0(d,J=7.2Hz,3F)。

[0588]

化合物 **194**

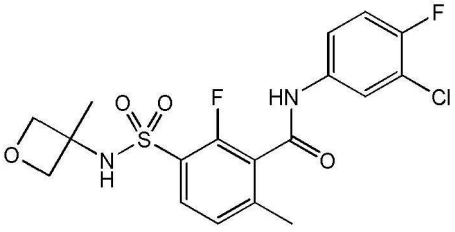


[0589] 将2-氟-6-甲基-3-[(3-甲基氧杂环丁-3-基)氨磺酰基]苯甲酸(0.15g,0.473mmol)溶解在DMF(5mL)中,并将三乙胺(0.2mL)和HATU(233mg,0.61mmol)添加到该反应混合物中。将该反应混合物搅拌10分钟并添加3,4-二氟苯胺(123mg,0.945mmol)。将该反应混合物在室温下搅拌42小时。将该反应混合物倾倒在冰水中(50mL)。将该混合物用Me-THF(3x 20mL)进行萃取。将合并的有机萃取物用盐水洗涤,进行干燥(Na_2SO_4)并且进行浓缩。将该残余物使用硅胶柱层析(在庚烷中的乙酸乙酯从0到100%以及在二氯甲烷中的甲醇从0到2%)进行纯化,产生呈白色粉末的化合物194(79mg),其在真空烘箱中干燥过夜。

[0590] 方法F;Rt:0.94min.m/z:413.2$(M-H)^-$精确质量:414.1。^1H NMR(400MHz,DMSO-d_6)δppm 1.45(s,3H),2.39(s,3H),4.18(d,J=6.6Hz,2H),4.62(d,J=6.2Hz,2H),7.35(d,J=8.1Hz,1H),7.39-7.51(m,2H),7.79(t,J=7.8Hz,1H),7.87(ddd,J=12.9,7.4,2.0Hz,1H),8.64(br.s.,1H),11.00(s,1H)

[0591]

化合物 **195**



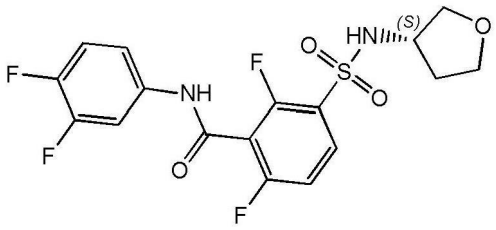
[0592] 化合物195(98mg)是如针对化合物194描述的类似地制备,使用3-氯-4-氟苯胺代替3,4-二氟苯胺。方法F;Rt:0.99min.m/z:429.1$(M-H^-)^-$精确质量:430.1。^1H NMR(400MHz,DMSO-d_6)δppm 1.45(s,3H),2.39(s,3H),4.18(d,J=6.4Hz,2H),4.62(d,

J = 6.2Hz,2H),7.35(d, J = 8.1Hz,1H),7.45(t, J = 9.0Hz,1H),7.60(ddd, J = 9.0, 4.3,2.5Hz,1H),7.79(t, J = 7.9Hz,1H),8.02(dd, J = 6.8,2.6Hz,1H),8.63(br.s.,1H), 10.99(s,1H)

[0593]

化合物 196

[0594]

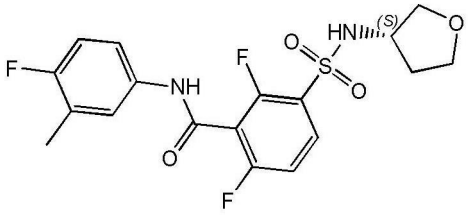


[0595] 将碳酸钠 (2.07g,19.48mmol) 溶解在蒸馏水 (30mL) 中。立即向此添加 (S)-3- 氨基四氢呋喃 (3.4g,38.97mmol) 随后是 THF(30mL)。将获得的溶液进行搅拌并在冰浴中冷却。将 3-(氯磺酰基)-2,6- 二氟苯甲酸 (5g,19.48mmol) 溶解在 THF(40mL) 中并将此逐滴添加到正在进行搅拌的溶液中。将产生的混合物搅拌 30 分钟同时继续冷却。然后将该混合物在室温下搅拌 3 小时。将该混合物在真空中进行浓缩直至仅剩余水。添加水 (20mL) 并将该混合物用 HCl(1M/ 水性 ;40mL) 进行酸化。将此用 Me-THF(3x 50mL) 进行萃取。将这些合并的有机物用盐水 (50mL) 进行洗涤,用 Na_2SO_4进行干燥,过滤并在真空中浓缩以产生呈黄色粉末的 2,6- 二氟 -3-[[(3S)- 四氢呋喃 -3- 基] 氨磺酰基] 苯甲酸 (5.9g)。方法 F, Rt :0.33min. m/z :306.0(M-H)$^-$精确质量 :307.0。将 2,6- 二氟 -3-[[(3S)- 四氢呋喃 -3- 基] 氨磺酰基] 苯甲酸 (1g,2.99mmol) 溶解在 N, N- 二甲基甲酰胺 (5mL) 中。添加 HATU(1.42g,3.74mmol) 随后是二异丙基乙胺 (1.55mL,8.98mmol)。将产生的混合物在室温下搅拌 30 分钟。然后添加 3,4- 二氟苯胺 (0.77g,5.99mmol)。将产生的混合物搅拌 24 小时并且接下来倾倒入水 (50mL) 中并用 Me-THF(3x 50mL) 进行萃取。将这些合并的有机物用盐水洗涤,用 Na_2SO_4干燥,过滤并在真空中浓缩。将获得的残余物通过硅胶柱层析使用梯度洗脱液 (从庚烷至 EtOAc(100 : 0 至 0 : 100)) 进行纯化。在真空中将所希望的部分进行浓缩,并且在 55℃在真空烘箱中干燥 24 小时,产生化合物 196。方法 F ;Rt :0.92min. m/z :417.1(M-H)$^-$精确质量 :418.1。 ^{1}H NMR(400MHz, DMSO-d_6) δ ppm 1.64-1.79(m,1H), 1.92-2.07(m,1H),3.43(dd, J = 9.0,4.6Hz,1H),3.56-3.79(m,3H),3.80-3.92(m,1H), 7.32-7.43(m,1H),7.44-7.54(m,2H),7.84(ddd, J = 12.7,7.4,2.5Hz,1H),8.01(rd, J = 8.6,6.2Hz,1H),8.49(br.s.,1H),11.21(br.s.,1H)

[0596] 化合物 197 至 201 是如针对化合物 196 描述地制备,使用相应的苯胺代替 3,4- 二氟苯胺 :

[0597]

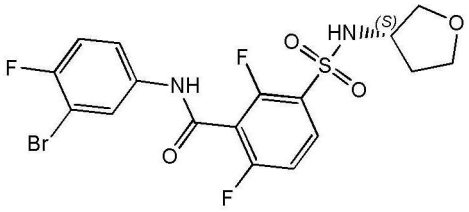
化合物 **197**



[0598] 使用 4- 氟 -3- 甲基苯胺作为苯胺。^{1}H NMR(400MHz,DMSO-d_6) δ ppm 1.64-1.76(m,1H),1.91-2.05(m,1H),2.25(d, J = 1.8Hz,3H),3.42(dd, J = 8.9,4.7Hz,1H),3.56-3.78(m,3H),3.79-3.88(m,1H),7.16(t, J = 9.1Hz,1H),7.41-7.51(m,2H),7.60(dd, J = 7.0,2.2Hz,1H),7.97(td,J = 8.6,6.2Hz,1H),8.49(br.s,1H),10.93(s,1H)。方法 F,Rt :0.93min.m/z :413.2(M-H)- 精确质量 :414.1。

[0599]

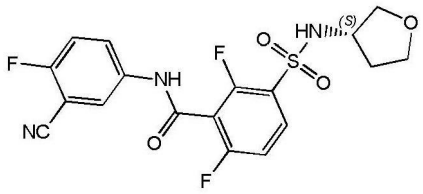
化合物 **198**



[0600] 使用 3- 溴 -4- 氟苯胺作为苯胺。方法 G,Rt :1.74min.m/z :478.8(M-H)$^-$精确质量 :480.0。^{1}H NMR(400MHz,DMSO-d_6) δ ppm 1.67-1.77(m,1H),1.93-2.05(m,1H),3.43(dd, J = 9.0,4.6Hz,1H),3.57-3.78(m,3H),3.80-3.89(m,1H),7.43(t,J = 8.7Hz,1H),7.49(m, J = 8.7,8.7Hz,1H),7.61(ddd, J = 9.0,4.4,2.6Hz,1H),8.00(td, J = 8.6,6.2Hz,1H),8.11(dd,J = 6.3,2.5Hz,1H),8.49(br.s.,1H),11.19(br.s.,1H)

[0601]

化合物 **199**

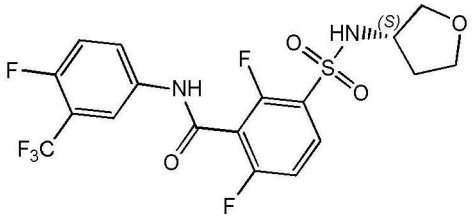


[0602] 使用 5- 氨基 -2- 氟苯甲腈作为苯胺

[0603] 方法 G,Rt :1.56min.m/z :423.9(M-H)$^-$精确质量 :425.1。^{1}H NMR(400MHz,DMSO-d_6) δ ppm 1.65-1.80(m,1H),1.94-2.06(m,1H),3.43(dd, J = 9.0,4.6Hz,1H),3.57-3.78(m,3H),3.80-3.91(m,1H),7.49(t, J = 8.5Hz,1H),7.59(t, J = 9.1Hz,1H),7.94(ddd, J = 9.2,4.8,2.6Hz,1H),8.02(td,J = 8.6,6.2Hz,1H),8.19(dd,J = 5.7,2.9Hz,1H),8.50(br.s.,1H),11.37(br.s.,1H)。

[0604]

化合物 **200**

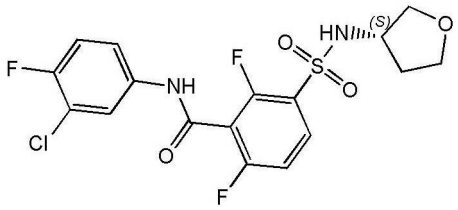


[0605] 使用 4- 氟 -3-(三氟甲基) 苯胺作为苯胺

[0606] 方法 F,Rt :1.02min.m/z :467.1(M-H)- 精确质量 :468.1。^{1}H NMR(400MHz,DMSO-d_6) δ ppm 1.72(ddt, J = 12.6,7.2,5.6,5.6Hz,1H),1.93-2.08(m,1H),3.43(dd, J = 9.0,4.6Hz,1H),3.58-3.79(m,3H),3.80-3.91(m,1H),7.49(t, J = 8.4Hz,1H),7.58(t, J = 9.7Hz,1H),7.93(s,1H),8.02(td, J = 8.6,6.2Hz,1H),8.16(dd, J = 6.4,2.6Hz,1H),8.50(br.s.,1H),11.35(br.s.,1H)

[0607]

化合物 **201**



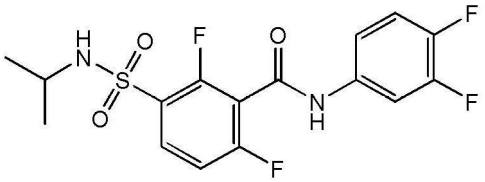
[0608] 使用 3- 氯 -4- 氟苯胺作为苯胺。

[0609] 方法 F,Rt :0.97min.m/z :433.1(M-H)- 精确质量 :434.0。^{1}H NMR(400MHz,DMSO-d_6) δ ppm 1.72(ddt, J = 12.5,7.2,5.6,5.6Hz,1H),1.92-2.12(m,1H),3.43(dd, J = 8.8,4.6Hz,1H),3.55-3.79(m,3H),3.80-3.91(m,1H),7.35-7.52(m,2H),7.53-7.67(m,1H),7.90-8.12(m,2H),8.49(br.s.,1H),11.20(br.s.,1H)

[0610] 化合物 202 和 203 是如针对化合物 196 描述的类似地制备,使用异丙胺代替 (S)-3- 氨基四氢呋喃并且针对化合物 203,使用 3-(三氟甲基) 苯胺代替 3,4- 二氟苯胺。

[0611]

化合物 **202**

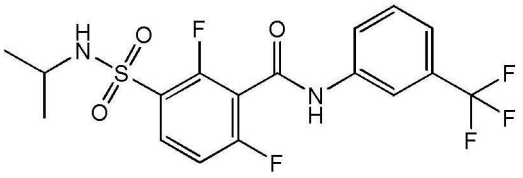


[0612] 方法 G ;Rt :1.80min.m/z :388.9(M-H)- 精确质量 :390.1。

[0613] ^{1}H NMR(400MHz, DMSO-d_6) δ ppm 1.03(d, J = 6.6Hz,8H),3.34-3.46(m,1H),7.36-7.53(m,3H),7.84(ddd, J = 12.7,7.4,2.5Hz,1H),8.00(td, J = 8.6,6.2Hz,1H),8.09(br.s.,1H),11.20(br.s.,1H)

[0614]

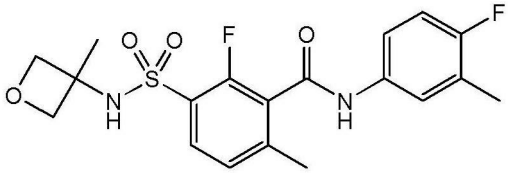
化合物 **203**



[0615] 方法G ;Rt :1.82min. m/z :421.1(M-H)-精确质量 :422.1。^{1}H NMR(400MHz,DMSO-d_6) δ ppm 1.04(d, J = 6.6Hz,6H),3.34-3.46(m,1H),7.47(t, J = 8.6Hz,1H),7.54(d, J = 7.9Hz,1H),7.65(t,J = 7.9Hz,1H),7.87(d,J = 8.4Hz,1H),8.01(td,J = 8.6,6.2Hz,1H),8.11(d,J = 7.5Hz,1H),8.15(s,1H),11.32(s,1H)。

[0616]

化合物 **204**

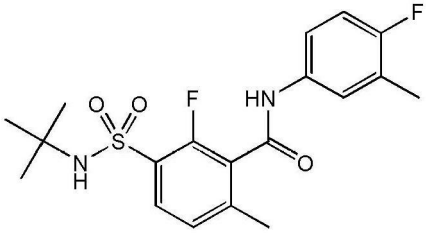


[0617] 化合物 204(0.19g) 的制备是从化合物 190(0.34g) 起始的,类似于如针对化合物 187 至化合物 188 的转变的描述。化合物 204 从 Et_2O 中结晶,过滤出,用 3x Et_2O 进行洗涤并在 50℃在真空中进行干燥。

[0618] 方法F ;Rt :0.94min. m/z :409.1(M-H)$^-$精确质量 :410.1。^{1}H NMR(400MHz,DMSO-d_6) δ ppm 1.46(s,3H),2.24(d,J = 1.8Hz,3H),2.38(s,3H),4.18(d,J = 6.6Hz,2H),4.62(d, J = 6.2Hz,2H),7.14(dd, J = 9.1Hz,1H),7.33(d, J = 8.1Hz,1H),7.45-7.53(m,1H),7.63(dd,J = 7.0,2.2Hz,1H),7.77(t,J = 7.9Hz,1H),8.61(br. s. ,1H),10.72(s,1H)。

[0619]

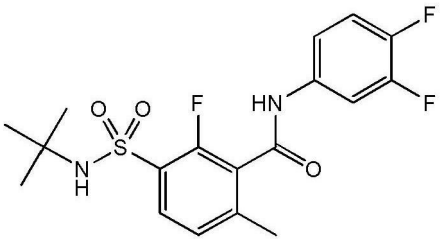
化合物 **205**



[0620] 3-(叔丁基氨磺酰基)-2-氟-6-甲基-苯甲酸是如针对2-氟-6-甲基-3-[(3-甲基氧杂环丁-3-基)氨磺酰基]苯甲酸描述的类似地制备,使用叔丁胺代替 3-甲基氧杂环丁-3-胺。化合物 205 是如针对化合物 194 描述的类似地制备,使用 4-氟-3-甲基苯胺代替 3,4-二氟苯胺并从 3-(叔丁基氨磺酰基)-2-氟-6-甲基-苯甲酸(代替 2-氟-6-甲基-3-[(3-甲基氧杂环丁-3-基)氨磺酰基]苯甲酸)起始。方法F ;Rt :1.08min. m/z :395.2(M-H)$^-$精确质量 :396.1。 ^{1}H NMR(400MHz, DMSO-d_6) δ ppm 1.16(s,9H),2.24(d, J = 1.8Hz,3H),2.37(s,3H),7.14(t, J = 9.2Hz,1H),7.30(d, J = 8.1Hz,1H),7.50(ddd, J = 9.0,4.7,2.3Hz,1H),7.64(dd,J = 6.9,2.3Hz,1H),7.73-7.84(m,2H),10.70(br. s,1H)。

[0621]

化合物 **206**



[0622] 化合物 206 是如针对化合物 194 描述的类似地制备，从 3-（叔丁基氨磺酰基）-2- 氟 -6- 甲基 - 苯甲酸（代替 2- 氟 -6- 甲基 -3-[(3- 甲基氧杂环丁 -3- 基）氨磺酰基]苯甲酸）起始。方法 F；Rt：1.08min. m/z：399.1(M-H)⁻精确质量：400.1。^{1}H NMR(400MHz, DMSO-d_6) δ ppm 1.16(s,9H),2.31(s,3H),7.32(d, J = 8.1Hz,1H),7.40-7.51(m,2H), 7.76-7.82(m,2H),7.88(ddd, J = 13.0,7.5,2.4Hz,1H),10.97(br. s.,1H)

[0623] 6- 氯 -2- 氟 -3-[(3- 甲基氧杂环丁 -3- 基）氨磺酰基]苯甲酸和 2- 氯 -6- 氟 -3-[(3- 甲基氧杂环丁 -3- 基）氨磺酰基]苯甲酸的合成

[0624] 用氯磺酸 (10mL,150.44mmol) 对 2- 氯 -6- 氟苯甲酸 (2g,11.46mmol) 进行处理并将此加热至 100℃并搅拌 5 小时。将产生的混合物冷却至室温并逐滴添加至冰水 (1 升）。然后用二氯甲烷 (2x 500mL) 对其进行萃取。将这些合并的有机物用 Na_2SO_4进行干燥，过滤并在真空中浓缩以产生呈浅黄色粉末的 2- 氯 -3- 氯磺酰基 -6- 氟 - 苯甲酸和 6- 氯 -3- 氯磺酰基 -2- 氟 - 苯甲酸 (3.1 克）的同分异构混合物，其按照这样使用。方法 F，Rt：0.47min 和 0.49min m/z：270.9(M-H)- 精确质量：271.9。将碳酸钠 (1.21g,11.4mmol) 溶解在蒸馏水 (22mL) 中。立即向此添加 3- 甲基 -3- 氧杂环丁胺 (1.19g,13.68mmol) 随后是 THF(20mL)。将获得的溶液进行搅拌并在冰浴中冷却。将 2- 氯 -3- 氯磺酰基 -6- 氟 - 苯甲酸和 6- 氯 -3- 氯磺酰基 -2- 氟 - 苯甲酸 (3.1g,11.4mmol) 的同分异构混合物溶解在 THF(30mL) 中并将此逐滴添加到正在进行搅拌的溶液中。将产生的混合物搅拌 30 分钟同时继续冷却。然后将该混合物在室温下搅拌 3 小时。将该混合物在真空中进行浓缩直至仅剩余水。

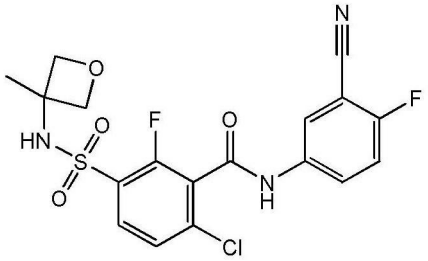
[0625] 然后添加水 (20mL) 并将该混合物用 HCl(46mL,1M/ 水性）进行酸化。将此用 Me-THF(3X 50mL) 进行萃取。将合并的有机物经 Na_2SO_4干燥、过滤并且在真空中进行浓缩。将残余物进行纯化，并将异构体使用制备型 HPLC（固定相：Uptisphere C18 ODB-10μm, 200g,5cm，流动相：在水中的 0.25％ NH_4HCO_3溶液，MeOH) 进行分离，产生呈白色粉末的 6- 氯 -2- 氟 -3-[(3- 甲基氧杂环丁 -3- 基）氨磺酰基] 苯甲酸。方法 G，Rt：0.40min. m/z：322.0(M-H)⁻精确质量：323.0。1H NMR(400MHz，DMSO-d)ppm 1.42(s,3H),4.15(d, J = 6.6Hz,2H),4.61(d, J = 5.9Hz,13H),7.29(dd, J = 8.5,0.8Hz,1H),7.36-7.73(m,5H)。

[0626] 以及呈白色粉末的 2- 氯 -6- 氟 -3-[(3- 甲基氧杂环丁 -3- 基）氨磺酰基] 苯甲酸。方法 G，Rt：0.34min. m/z：321.9(M-H)⁻精确质量：323.0

[0627] 化合物 207 至 210 是如针对化合物 196 描述的类似地制备，使用 6- 氯 -2- 氟 -3-[(3- 甲基氧杂环丁 -3- 基）氨磺酰基]苯甲酸代替 2,6- 二氟 -3-[[(3S)- 四氢呋喃 -3- 基] 氨磺酰基] 苯甲酸并且相应的苯胺代替 3,4- 二氟苯胺。

[0628]

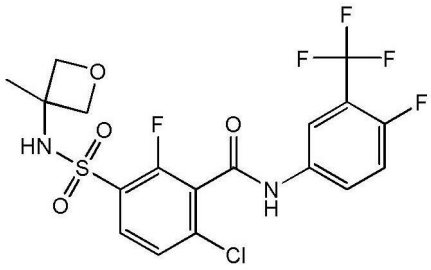
化合物 **207**



[0629] 使用 5- 氨基 -2- 氟苯甲腈作为苯胺。方法 F ;Rt :0.92min. m/z :440.0(M-H)⁻精确质量 :441.0。^{1}H NMR(400MHz, DMSO-d_6) δ ppm 1.46(s,2H),4.21(d, J = 6.4Hz,2H),4.61(d, J = 6.2Hz,2H),7.59(t, J = 9.1Hz,1H),7.66(d, J = 8.8Hz,1H),7.89-7.99(m,2H),8.18(dd, J = 5.6,2.8Hz,1H),8.93(br. s,1H),11.37(br. s.,1H)

[0630]

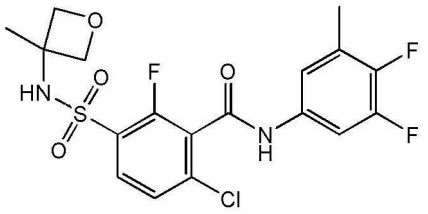
化合物 **208**



[0631] 使用 4- 氟 -3-(三氟甲基) 苯胺作为苯胺。方法 F ;Rt :1.06min. m/z :483(M-H)⁻精确质量 :484.0。^{1}H NMR(400MHz, DMSO-d_6) δ ppm 1.46(s,2H),4.20(d, J = 6.2Hz,2H),4.61(d,J = 6.2Hz,2H),7.58(t,J = 9.9Hz,1H),7.66(d,J = 8.6Hz,1H),7.94(m,J = 8.1,8.1Hz,2H),8.07-8.25(m,1H),8.91(br. s,1H),11.34(br. s.,1H)

[0632]

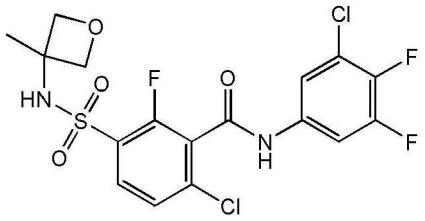
化合物 **209**



[0633] 使用 3,4- 二氟 -5- 甲基 - 苯胺作为苯胺。方法 F ;Rt :1.03min. m/z :447.1(M-H)⁻精确质量 :448.1。^{1}H NMR(400MHz, DMSO-d_6) δ ppm1.45(s,3H),2.30(d, J = 2.0Hz,3H),4.20(d, J = 6.4Hz,2H),4.61(d, J = 6.2Hz,2H),7.32(m, J = 5.9Hz,1H),7.54-7.69(m,2H),7.91(t, J = 8.3Hz,1H),8.92(br. s,1H),11.09(br. s,1H)

[0634]

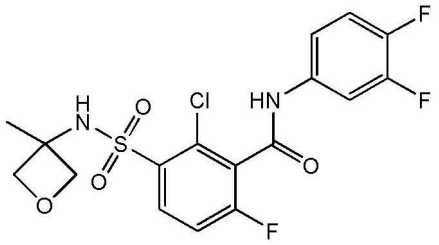
化合物 **210**



[0635] 使用 3- 氯 -4,5- 二氟 - 苯胺盐酸盐作为苯胺。方法 F ;Rt :1.07min. m/z :467.0(M-H)⁻精确质量 :468.0。^{1}H NMR(400MHz, DMSO-d_6) δ ppm1.45(s,3H),4.20(d, J = 6.6Hz,2H),4.60(d, J = 6.2Hz,2H),7.64(d, J = 8.6Hz,1H),7.67-7.79(m,2H),7.93(t, J = 8.1Hz,1H),9.08(br. s,1H),11.34(br. s.,1H)

[0636]

化合物 **211**

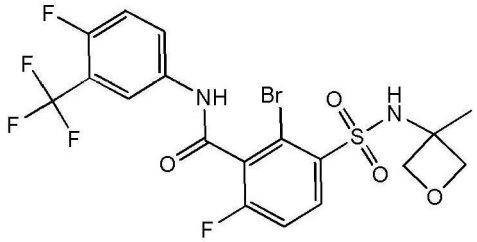


[0637] 化合物 211 是如针对化合物 196 描述的类似地制备,使用 2- 氯 -6- 氟 -3-[(3- 甲基氧杂环丁 -3- 基) 氨磺酰基] 苯甲酸代替 2,6- 二氟 -3-[[(3S)- 四氢呋喃 -3- 基] 氨磺酰基] 苯甲酸。方法 F ;Rt :0.94min. m/z :433.1(M-H)⁻精确质量 :434.0。^{1}H NMR(400MHz,DMSO-d_6) δ ppm 1.46(s,3H),4.20(d,J = 6.6Hz,2H),4.62(d,J = 6.4Hz,2H),7.30-7.43(m,1H),7.43-7.54(m,1H),7.61(t, J = 8.6Hz,1H),7.84(ddd, J = 12.7,7.4,2.3Hz,1H),8.17(dd,J = 9.0,5.9Hz,1H),8.75(br. s,1H),11.18(br. s,1H)。

[0638] 2- 溴 -6- 氟 -3-[(3- 甲基氧杂环丁 -3- 基) 氨磺酰基] 苯甲酸和 6- 溴 -2- 氟 -3-[(3- 甲基氧杂环丁 -3- 基) 氨磺酰基] 苯甲酸是如针对 2- 氯 -6- 氟 -3-[(3- 甲基氧杂环丁 -3- 基) 氨磺酰基] 苯甲酸和 6- 氯 -2- 氟 -3-[(3- 甲基氧杂环丁 -3- 基) 氨磺酰基] 苯甲酸描述的类似地制备,从 2- 溴 -6- 氟苯甲酸 (代替 2- 氯 -6- 氟苯甲酸) 起始。

[0639]

化合物 **212**



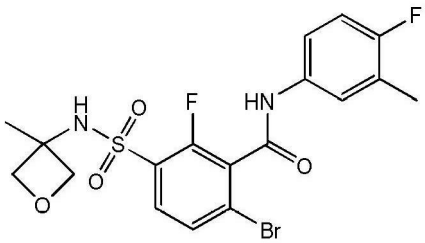
[0640] 化合物 212 是如针对化合物 196 描述的类似地制备,使用 2- 溴 -6- 氟 -3-[(3- 甲基氧杂环丁 -3- 基) 氨磺酰基] 苯甲酸代替 2,6- 二氟 -3-[[(3S)- 四氢呋喃 -3- 基] 氨磺酰

基]苯甲酸并且4-氟-3-(三氟甲基)苯胺代替3,4-二氟苯胺。^{1}H NMR(400MHz,DMSO-d_6) δ ppm 1.48(s,3H),4.20(d,J = 6.6Hz,2H),4.64(d,J = 6.2Hz,2H),7.57(t,J = 9.7Hz,1H),7.65(t,J = 8.6Hz,1H),7.93(dt,J = 8.4,3.7Hz,1H),8.08-8.31(m,2H),8.70(br.s.,1H),11.29(br.s.,1H)。

[0641] 化合物213至216是如针对化合物196描述的类似地制备,使用6-溴-2-氟-3-[(3-甲基氧杂环丁-3-基)氨磺酰基]苯甲酸代替2,6-二氟-3-[[(3S)-四氢呋喃-3-基]氨磺酰基]苯甲酸并且相应的苯胺代替3,4-二氟苯胺。

[0642]

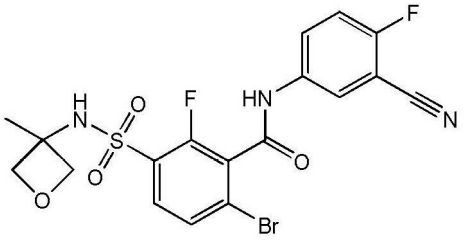
化合物 **213**



[0643] 使用4-氟-3-甲基苯胺作为苯胺。方法F,Rt :0.99min.m/z :473.0(M-H)-精确质量 :474.0。^{1}H NMR(400MHz,DMSO-d_6) δ ppm 1.46(s,3H),2.25(d,J = 1.5Hz,3H),4.20(d,J = 6.4Hz,2H),4.62(d,J = 6.2Hz,2H),7.16(t,J = 9.1Hz,1H),7.42-7.52(m,1H),7.60(dd,J = 7.0,2.4Hz,1H),7.68-7.93(m,2H),8.65(br.s,1H),10.82(br.s,1H)。

[0644]

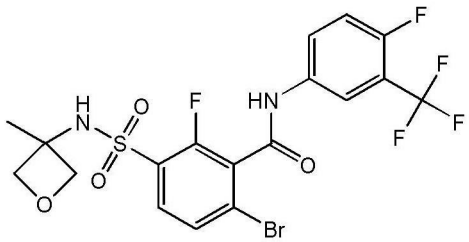
化合物 **214**



[0645] 使用5-氨基-2-氟苯甲腈作为苯胺。方法F ;Rt :0.92min.m/z :484.0(M-H)$^-$精确质量 :485.0。^{1}H NMR(400MHz, DMSO-d_6) δ ppm 1.39-1.55(m,3H),4.20(d, J = 6.6Hz,2H),4.61(d, J = 6.4Hz,2H),7.59(t, J = 9.1Hz,1H),7.77-7.89(m,2H),7.95(ddd, J = 9.2,4.8,2.8Hz,1H),8.18(dd,J = 5.7,2.6Hz,1H),8.90(br.s,1H),11.34(br.s.,1H)。

[0646]

化合物 **215**

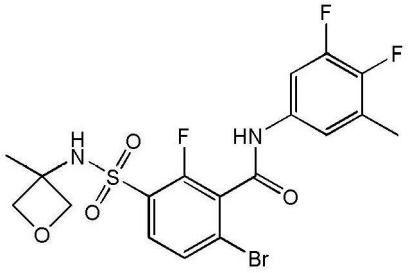


[0647] 使用4-氟-3-(三氟甲基)苯胺作为苯胺。方法F,Rt :1.07min.m/z :

527.0(M-H)⁻精 确 质 量 :528.0。 ^{1}H NMR(400MHz, DMSO-d_6) δ ppm1.46(s,3H),4.20(d, J = 6.6Hz,2H),4.61(d, J = 6.2Hz,2H),7.58(t, J = 9.8Hz,1H),7.74-7.89(m,2H), 7.90-7.98(m,1H),8.16(dd,J = 6.3,2.5Hz,1H),8.84(br.s,1H),11.31(br.s.,1H)。

[0648]

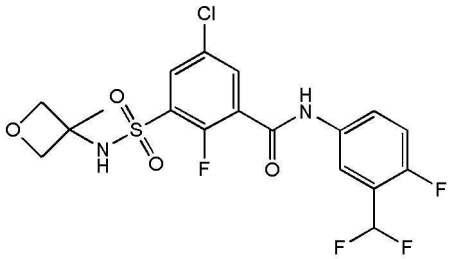
化合物 **216**



[0649] 使用3,4-二氟-5-甲基-苯胺作为苯胺。方法F ;Rt :1.03min.m/z :491.0(M-H)⁻精确 质 量 :492.0。 ^{1}H NMR(400MHz, DMSO-d_6) δ ppm1.46(s,3H),2.30(d, J = 1.8Hz,3H), 4.20(d, J = 6.6Hz,2H),4.61(d, J = 6.4Hz,2H),7.32(m, J = 5.7Hz,1H),7.61(ddd, J = 12.3,6.9,2.6Hz,1H),7.72-7.89(m,2H),8.86(br.s.,1H),11.07(br.s,1H)。

[0650]

化合物 **217**



[0651] 将3-(二氟甲基)-4-氟-苯胺(1.02mL,8.58mmol)在干甲苯(10mL)中的溶液逐滴添加到(经15分钟)5-氯-3-氯磺酰基-2-氟-苯甲酰氯(2500mg,8.576mmol)在干甲苯(100mL)中的回流溶液里。添加后,将该反应混合物在回流下搅拌1小时。在氮气氛下在搅拌的同时将该反应混合物冷却至室温。使用包含5-氯-3-[[3-(三氟甲基)-4-氟-苯基]氨基甲酰基]-2-氟-苯磺酰氯的棕色溶液而不经进一步纯化。在室温下,将3-甲基-3-氧杂环丁胺(580mg,6.66mmol)逐滴添加至上述溶液里。然后将 Et_3N(2.10mL 15.14mmol)逐滴添加至该反应混合物中并在室温下将该反应混合物搅拌45分钟。将溶剂进行蒸发,并且将残余物吸收在EtOAc中。将HCl(0.5N,30mL)添加到该反应混合物中并将各层进行分离。将该有机层再次用NaOH(0.5N,30mL)进行洗涤。

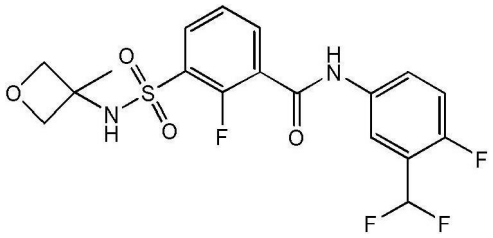
[0652] 将该有机层用 $MgSO_4$进行干燥并蒸发。将获得的残余物通过硅胶柱层析(洗脱液 :CH_2Cl_2:MeOH 100 :0- > 95 :5)进行纯化,产生化合物217(1.8g)。 ^{1}H NMR(360MHz, DMSO-d_6) δ ppm 1.45(s,3H)4.23(d, J = 6.2Hz,2H)4.63(d, J = 6.2Hz,2H)7.27(t, J = 54.3Hz,1H)7.43(t,J = 9.7Hz,1H)7.83(dt,J = 8.1,4.0Hz,1H)7.95(dd,J = 5.9,2.6Hz, 1H)8.04(dd,J = 6.0,2.4Hz,1H)8.13(dd,J = 5.3,2.7Hz,1H)8.98(s,1H)10.98(s,1H)

[0653] 方法F ;Rt :1.03min.m/z :465.1(M-H)⁻精确质量 :466.0。

[0654]

化合物 **218**

[0655]

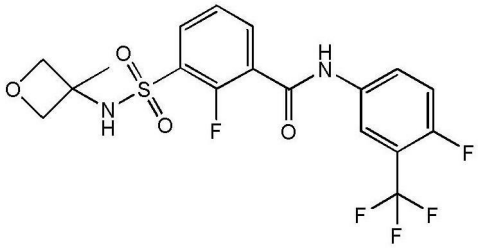


[0656] 在氮气氛下在室温下，将 Pd/C(10％)(716mg) 悬浮在化合物 217(345mg，0.673mmol) 和 Et_3N(0.467mL) 于 MeOH(100mL) 中的溶液里。接下来在室温下在氢气氛下将该反应混合物进行搅拌直至等量的氢被吸收。将该反应混合物在硅藻土上进行过滤并将溶剂蒸发。将获得的残余物通过硅胶柱层析 (CH_2Cl_2:MeOH 100 :0- ＞ 95 :5) 进行纯化，产生呈白色固体的化合物 218(206mg)，在真空中在 50℃进行干燥。

[0657] ^1H NMR(360MHz，DMSO-d_6) δ ppm 1.44(s,3H)4.19(d，J ＝ 6.6Hz,2H)4.63(d，J ＝ 6.2Hz,2H)7.26(t,J ＝ 54.3Hz,1H)7.42(t,J ＝ 9.5Hz,1H)7.52(t,J ＝ 7.7Hz,1H)7.86(dd，J ＝ 8.1,3.7Hz,1H)7.93-8.01(m,2H)8.06(dd，J ＝ 6.4,2.4Hz,1H)8.77(s,1H)10.92(s,1H)。方法 F ;Rt :0.92min. m/z :431.1(M-H)⁻精确质量 :432.1。

[0658]

化合物 **219**



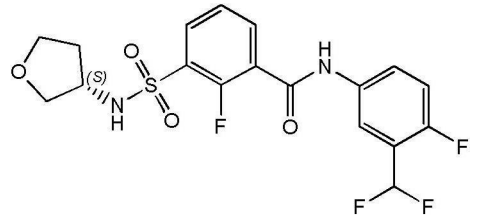
[0659] 化合物 219(828mg) 是如针对化合物 217 和 218 描述的类似地制备。使用 4- 氟 -3-(三氟甲基) 苯胺代替 3-(二氟甲基)-4- 氟 - 苯胺。方法 F ;Rt :1.00min. m/z :449.1(M-H)⁻精确质量 :450.1。

[0660] ^1H NMR(360MHz，DMSO-d_6) δ ppm 1.44(s,3H)4.19(d，J ＝ 5.9Hz,2H)4.62(d，J ＝ 6.2Hz,2H)7.53(t，J ＝ 7.9Hz,1H)7.57(t，J ＝ 9.9Hz,1H)7.94-8.02(m,3H)8.20(dd，J ＝ 6.4,2.7Hz,1H)8.78(s,1H)11.02(s,1H)。

[0661]

化合物 **220**

[0662]

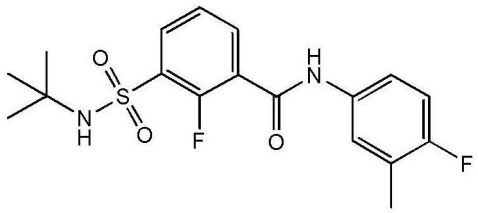


[0663] 化合物 220 是如针对化合物 217 和 218 描述的类似地制备，使用 (S)-3- 氨基

四氢呋喃代替 3- 甲基 -3- 氧杂环丁胺。方法 F ;Rt :0.90min. m/z :431.1(M-H)⁻精确质量 :432.1。^{1}H NMR(360MHz, DMSO-d_6) δ ppm 1.66-1.77(m,1H)1.91-2.03(m,1H)3.43(dd, J = 8.8,4.8Hz,1H)3.57-3.70(m,2H)3.70-3.78(m,1H)3.79-3.90(m,1H)7.26(t, J = 54.2Hz,1H)7.42(t,J = 9.5Hz,1H)7.53(t,J = 7.7Hz,1H)7.81-7.88(m,1H)7.94-8.00(m, 2H)8.07(dd,J = 6.4,2.4Hz,1H)8.45(d,J = 6.6Hz,1H)10.92(s,1H)。

[0664]

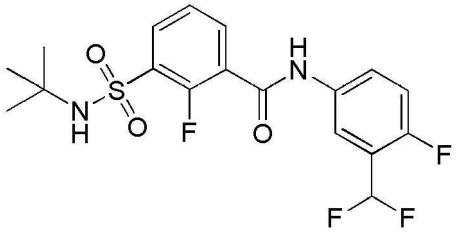
化合物 **221**



[0665] 化合物 221 是如针对化合物 217 和 218 描述的类似地制备,使用 2- 甲基丙 -2- 胺代替 3- 甲基 -3- 氧杂环丁胺,并且 4- 氟 -3- 甲基 - 苯胺代替 3-(二氟甲基)-4- 氟 - 苯胺。方法 F ;Rt :1.06min. m/z :381.2(M-H)⁻精确质量 :382.1。1H NMR(360MHz, DMSO-d_6) δ ppm 1.15(s,9H)2.24(d, J = 1.5Hz,3H)7.15(t, J = 9.1Hz,1H)7.47(t, J = 7.7Hz, 1H)7.43-7.55(m,1H)7.65(dd, J = 7.0,2.6Hz,1H)7.87(ddd, J = 7.8,6.1,1.8Hz, 1H)7.93(s,1H)7.90-7.99(m,1H)10.63(s,1H)。

[0666]

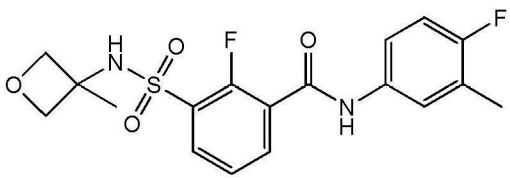
化合物 **243**



[0667] 化合物 243 是如针对化合物 217 和 218 描述的类似地制备,使用叔丁胺代替 3- 甲基 -3- 氧杂环丁胺。方法 G, Rt :1.76min. m/z :417.1(M-H)⁻精确质量 :418.1。^{1}H NMR(360MHz, DMSO-d_6) δ ppm 1.15(s,9H)7.41(t, J = 9.7Hz,1H)7.26(t, J = 54.5Hz, 1H)7.49(t,J = 7.7Hz,1H)7.85(ddd,J = 8.6,4.4,3.1Hz,1H)7.88-8.01(m,3H)8.08(dd,J = 6.2,2.6Hz,1H)10.90(s,1H)。

[0668]

化合物 **222**

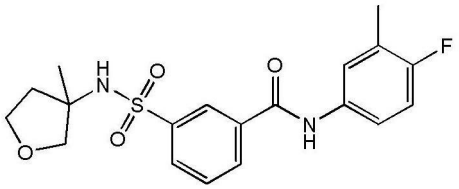


[0669] 化合物 222 是如针对化合物 221 描述的类似地制备,使用 3- 甲基 -3- 氧杂环丁胺代替 2- 甲基丙 -2- 胺。方法 F ;Rt :0.91min. m/z :395.1(M-H)⁻精确质量 :396.1。

^{1}H NMR(360MHz, DMSO-d_6) δ ppm 1.44(s,3H)2.24(d, J = 1.5Hz,3H)4.19(d, J = 6.6Hz, 2H)4.62(d, J = 6.2Hz,2H)7.15(t, J = 9.3Hz,1H)7.46-7.55(m,2H)7.63(dd, J = 7.0, 2.6Hz,1H)7.88-7.99(m,2H)8.75(s,1H)10.65(s,1H)。

[0670]

化合物 **223**

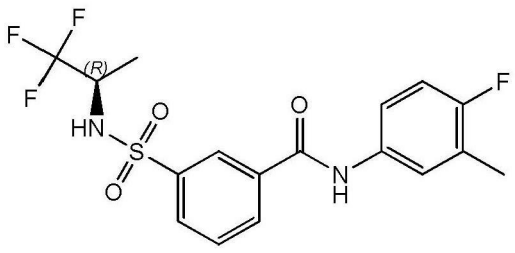


[0671] 在室温下,将3-甲基氧戊环-3-胺盐酸盐(165.9mg,1.21mmol)添加到3-[(4-氟-3-甲基-苯基)氨基甲酰基]苯磺酰氯(499mg,1.096mmol)在干CH_2Cl_2(20mL)中的溶液里。然后将Et_3N(381μL)逐滴添加至该反应混合物中并在室温下将该反应混合物搅拌1小时。将该反应混合物用EtOAc(250mL)稀释。

[0672] 添加HCl 0.5N(50mL)并将各层进行分离。将该有机层再次用NaOH 0.5N(30mL)进行洗涤。将该有机层用$MgSO_4$进行干燥并蒸发。将获得的残余物通过硅胶柱层析(CH_2Cl_2:MeOH 100:0-＞95:5)以及通过制备型HPLC(固定相:RP XBridge Prep C18OBD-10μm, 30x 150mm),流动相:在水中的0.25%NH_4HCO_3溶液,MeOH)进行纯化,在真空中在50℃干燥后产生呈白色固体的化合物223(257mg)。方法F;Rt:0.93min.m/z:391.2(M-H)$^-$精确质量:392.1。^{1}H NMR(360MHz,DMSO-d_6)ppm 1.17(s,3H)1.72(dt,J＝12.8,7.7Hz,1H)2.14(ddd,J＝12.8,7.1,6.0Hz,1H)2.25(d,J＝1.8Hz,3H)3.30-3.40(m,1H)3.61-3.77(m,3H)7.15(t, J = 9.3Hz,1H)7.55-7.64(m,1H)7.69(dd, J = 7.0,2.2Hz,1H)7.75(t, J = 7.9Hz, 1H)8.04(d, J = 8.0Hz,1H)8.10(br.s.,1H)8.18(dt, J = 7.7,1.3Hz,1H)8.39(t, J = 1.6Hz,1H)10.49(br.s.,1H)。

[0673]

化合物 **225**



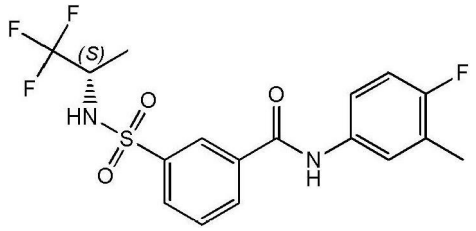
[0674] 将3-[(4-氟-3-甲基-苯基)氨基甲酰基]苯磺酰氯(0.5g,1.53mmol)和(R)-1,1,1-三氟-2-丙胺(0.38g,3.36mmol)溶解在二氯甲烷(10mL)中。然后添加二异丙基乙胺(0.66mL,3.81mmol)并将产生的混合物搅拌两小时。然后添加1M HCl(5mL)并将该有机层进行分离,加载到硅上并使用梯度洗脱液(从庚烷至EtOAc(100 : 0至0 : 100))使其经历硅胶柱层析。在真空中将所希望的部分进行浓缩,并且在55℃在真空烘箱中干燥24小时,产生呈白色粉末的化合物225(233mg)。方法F;Rt:1.05min.m/z:403.1(M-H)$^-$精确质量:404.1。^{1}H NMR(400MHz, DMSO-d_6) δ ppm 1.01(d, J＝6.8Hz,3H),2.25(d, J＝1.8Hz,3H), 4.06-4.22(m,1H),7.15(t, J = 9.2Hz,1H),7.51-7.63(m,1H),7.67(dd, J = 7.2,2.3Hz,

1H),7.78(t,J = 7.8Hz,1H),8.00-8.10(m,1H),8.16-8.28(m,1H),8.40(t,J = 1.7Hz,1H),8.66(br.s.,1H),10.46(s,1H)。

[0675]

化合物 **226**

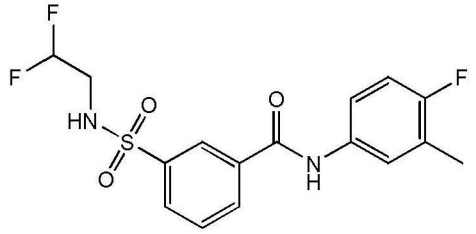
[0676]



[0677] 化合物226(416mg)是如针对化合物225描述地制备,使用(S)-1,1,1-三氟-2-丙胺代替(R)-1,1,1-三氟-2-丙胺。方法F;Rt:1.05min.m/z:403.1$(M-H)^-$精确质量:404.1。

[0678]

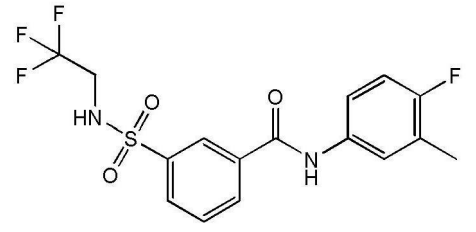
化合物 **227**



[0679] 化合物227(444mg)是如描述于合成程序S3(使用2,2-二氟乙胺作为胺),加工W4相类似地制备。方法F;Rt:0.93min.m/z:371.1$(M-H)^-$精确质量:372.1。^{1}H NMR(400MHz,DMSO-d_6)δppm 2.25(d,J = 1.8Hz,3H),3.26(td,J = 15.8,3.7Hz,2H),6.00(tt,J = 55.2,3.5Hz,1H),7.14(t,J = 9.0Hz,1H),7.52-7.62(m,1H),7.63-7.70(m,1H),7.77(t,J = 7.9Hz,1H),7.96-8.06(m,1H),8.14-8.25(m,1H),8.30-8.45(m,2H),10.46(s,1H)

[0680]

化合物 **228**



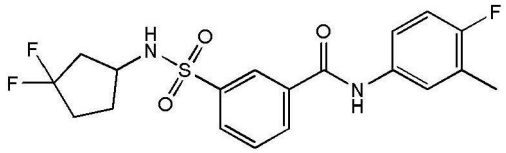
[0681] 化合物228(238mg)是如描述于合成程序S3(使用2,2-二氟乙胺作为胺),加工W4相类似地制备,随后是制备型HPLC(SunFire Prep C18 OBD-10μm,30x 150mm)。流动相(在水中的0.25% NH_4HCO_3溶液,MeOH)。方法F;Rt:0.97min.m/z:389.1$(M-H)^-$精确质量:390.1。

[0682] ^{1}H NMR(400MHz,DMSO-d_6)δppm 2.25(d,J = 1.8Hz,3H),3.74(q,J = 9.5Hz,2H),7.15(t,J = 9.2Hz,1H),7.48-7.62(m,1H),7.64-7.71(m,1H),7.77(t,J = 7.8Hz,1H),7.94-8.10(m,1H),8.20(m,J = 8.1Hz,1H),8.37(t,J = 1.7Hz,1H),8.49-9.15(bs,1H),

10.45(s,1H)

[0683]

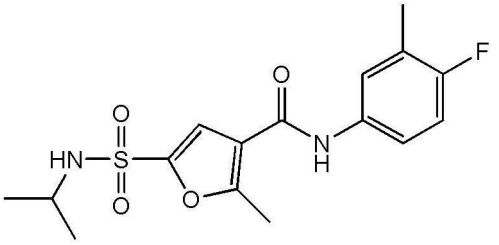
化合物 **229**



[0684] 化合物 243(239mg) 是与合成程序 S2(使用 3,3- 二氟 - 环戊胺为胺),加工 W4 相类似地制备。方法 F ;Rt :1.03min. m/z :411.2(M-H)⁻精确质量 :412.1。 ^{1}H NMR(400MHz, DMSO-d_6) δ ppm 1.50-1.165(m,1H),1.81-2.04(m,3H),2.04-2.23(m,2H),2.25(s,3H),3.63-3.76(m,1H),7.14(t, J = 9.1Hz,1H),7.59(dt, J = 8.1,3.9Hz,1H),7.65-7.72(m,1H),7.78(t,J = 7.8Hz,1H),8.02(d,J = 7.9Hz,1H),8.14(d,J = 6.8Hz,1H),8.22(d,J = 7.7Hz,1H),8.37(s,1H),10.47(s,1H)。

[0685]

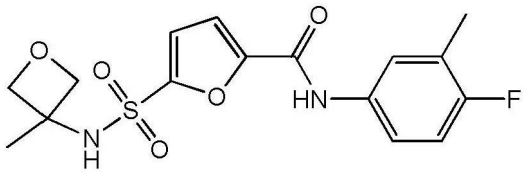
化合物 **230**



[0686] 将 2- 甲基 -3- 糠酸 (4.2g,32.6mmol) 溶解在 CH_2Cl_2(100mL) 中并用冰浴冷却至 -5℃。然后以 0.250mL/min 的速度逐滴添加氯磺酸 (10.85mL,163.2mmol)。允许该反应混合物加温至室温并且搅拌过夜。将该反应混合物在冰上进行淬灭并用 2-MeTHF 进行萃取。将有机层用盐水进行洗涤,用 $MgSO_4$进行干燥并蒸发至干燥以产生粗制的呈棕色油的 5- 氯磺酰基 -2- 甲基 - 呋喃 -3- 羧酸 (420mg)。将 5- 氯磺酰基 -2- 甲基 - 呋喃 -3- 羧酸 (420mg) 溶解在 CH_2Cl_2(10mL) 中。添加胡宁氏碱 (0.64mL,3.74mmol) 和异丙胺 (0.478mL,5.61mmol) 并且将该反应混合物在室温下搅拌过夜。将挥发物在减压下去除并将残余物按照这样在下一步中使用。将以上残余物溶解在 CH_2Cl_2(20mL) 中,添加 4- 氟 -3- 甲基苯胺 (228mg,1.82mmol)、HATU(830mg,2.18mmol) 和 N, N- 二异丙基乙胺 (0.94mL,5.46mmol) 并将该反应混合物搅拌 30 分钟。将挥发物在减压下去除并将残余物在硅上使用庚烷至 EtOAc 的梯度进行纯化,产生呈白色粉末的化合物 230(174mg)。方法 F ;Rt :1.00min. m/z : 353.1(M-H)⁻精确质量 :354.1。 ^{1}H NMR(400MHz, DMSO-d_6) δ ppm 1.03(d, J = 6.4Hz,6H),2.23(s,3H),2.64(s,3H),3.35-3.43(m,1H),7.11(t, J = 9.2Hz,1H),7.53(dd, J = 7.9,4.0Hz,1H),7.59-7.69(m,1H),7.72(s,1H),8.06(d, J = 5.5Hz,1H),9.87(s,1H)。

[0687]

化合物 **231**

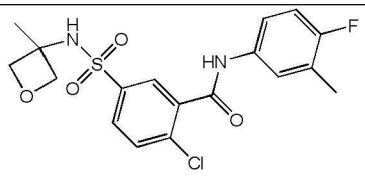
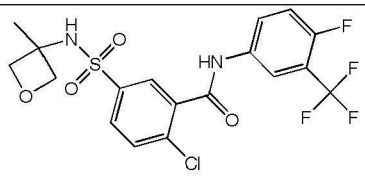
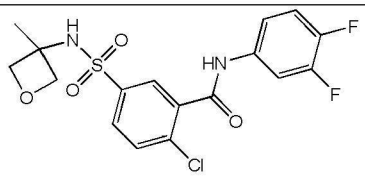


[0688] 将溶解在 CH_2Cl_2(2mL) 中的 3- 甲基 -3- 氧杂环丁胺盐酸盐 (302.6mg,2.45mmol) 和胡宁氏碱 (1.15mL,6.68mmol) 添加到甲基 5-(氯磺酰基)-2- 糠酸盐 (赛默飞世尔科技公司 (thermo scientific),500mg,2.23mmol) 在 CH_2Cl_2(10mL) 中的溶液里。将该反应混合物在室温下搅拌过夜。将挥发物在减压下去除并将获得的残余物按照这样使用。

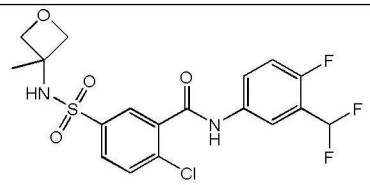
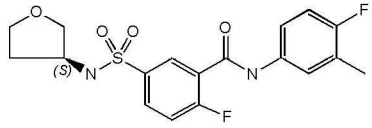
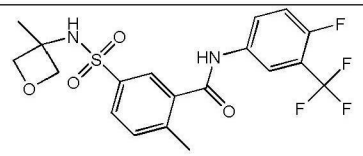
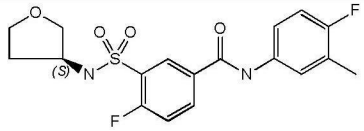
[0689] 将该残余物溶解在 THF(10mL) 中。将溶解在 H_2O(1mL) 中的 LiOH(60.2mg,2.514mmol) 添加至该反应混合物,添加 MeOH(1mL) 并将此在室温下搅拌过夜。将挥发物在减压下去除并将残余物溶解在水 (25mL) 中。添加 1M HCl(2.5mL) 然后添加 2-MeTHF(50mL)。将该水层去除并将该有机层用盐水 (50mL) 进行洗涤。将该有机层用 $MgSO_4$进行干燥,过滤并且蒸发至干燥,产生一种油,其按照这样在下一步中使用。将该油和 HATU(573mg,1.51mmol) 在 CH_2Cl_2(5mL) 中搅拌,并添加 4- 氟 -3- 甲基苯胺 (157.3mg,1.26mmol) 和 N,N- 二异丙基乙胺 (0.65mL,3.77mmol)。将该反应混合物在室温下搅拌过夜。将该挥发物在减压下去除并将残余物在硅上使用庚烷至 EtOAc 的梯度进行纯化,接下来通过制备型 HPLC(固定相 :RP Vydac Denali C18-10μm,200g,5cm),流动相 :在水中的 0.25% NH_4HCO_3 溶液,CH_3CN) 进行纯化,将所希望的部分收集,蒸发,溶解在 MeOH 中并再次蒸发。这部分在 MeOH(4mL) 中进行研磨,过滤并在烘箱中进行干燥,产生呈白色固体的化合物 231(305mg)。方法 F, Rt :0.89min. m/z :367.1(M-H)- 精确质量 :368.1。^1H NMR(400MHz, DMSO-d_6) δ ppm 1.53(s,3H),2.24(d, J = 1.8Hz,3H),4.21(d, J = 6.6Hz,2H),4.61(d, J = 6.2Hz,2H),7.14(t, J = 9.2Hz,1H),7.26(d, J = 3.7Hz,1H),7.50(d, J = 3.7Hz,1H),7.51-7.57(m,1H),7.60(dd, J = 7.0,2.4Hz,1H),8.92(s,1H),10.34(s,1H)。

[0690] 化合物 232 至 239 的制备是通过将一种苯胺缓慢添加至 3- 氯磺酰基苯甲酰氯衍生物的回流甲苯溶液中,接着是如以上所述的在一种碱 (像 NEt_3或 DIPEA) 的存在下与一种胺进行反应。

[0691]

	结构	**苯胺**	**胺**	**3-氯磺酰基苯甲酰氯衍生物**
232		4-氟-3-甲基苯胺	3-甲基-3-氧杂环丁烷胺	2-氯-5-(氯磺酰基)苯甲酰氯
233		4-氟-3-(三氟甲基)苯胺	3-甲基-3-氧杂环丁烷胺	2-氯-5-(氯磺酰基)苯甲酰氯
234		3,4-二氟苯胺	3-甲基-3-氧杂环丁烷胺	2-氯-5-(氯磺酰基)苯甲酰氯

[0692]

	结构	苯胺	胺	3-氯磺酰基苯甲酰氯衍生物
235		3-(二氟甲基)-4-氟-苯胺	3-甲基-3-氧杂环丁烷胺	2-氯-5-(氯磺酰基)苯甲酰氯
236		4-氟-3-甲基苯胺	(*S*)-3-氨基四氢呋喃甲苯磺酸盐	5-氯磺酰基-2-氟-苯甲酰氯
237		4-氟-3-甲基苯胺	(*S*)-3-氨基四氢呋喃甲苯磺酸盐	2-溴-5-氯磺酰基-苯甲酰氯
238		4-氟-3-(三氟甲基)苯胺	3-甲基-3-氧杂环丁烷胺	5-氯磺酰基-2-甲基-苯甲酰氯
239		4-氟-3-甲基苯胺	(S)-四氢呋喃-3-胺盐酸盐	3-氯磺酰基-4-氟-苯甲酰氯

化合物	LC方法	Rt（min）	m/z $(M-H)^-$	精确质量
232	G	1.67	410.8	412.1
233	G	1.83	464.9	466.0
234	G	1.68	414.9	416.0
235	G	1.69	446.9	448.1
236	F	0.90	395.1	396.1
237	F	0.93	457.1	458.0

[0693]

	结构	苯胺	胺	3-氯磺酰基苯甲酰氯衍生物
238	F	1.03	445.1	446.1
239	G	1.64	394.9	396.1

[0694]

化合物	^{1}H-NMR
232	^{1}H NMR (360MHz , DMSO-d_6) δ ppm 10.67 (s, 1 H), 8.57 (s, 1 H), 7.96 - 7.88 (m, 2 H), 7.84 - 7.79 (m, 1 H), 7.62 (dd, J = 2.6, 7.0 Hz, 1 H), 7.54 - 7.46 (m, 1 H), 7.15 (t, J = 9.1 Hz, 1 H), 4.56 (d, J = 6.2 Hz, 2 H), 4.17 (d, J = 6.2 Hz, 2 H), 2.24 (d, J = 1.8 Hz, 3 H), 1.43 (s, 3 H)
233	^{1}H NMR (360MHz , DMSO-d_6) δ ppm 1.44 (s, 3 H) 4.18 (d, J=6.6 Hz, 2 H) 4.57 (d, J=6.0Hz, 2 H) 7.57 (t, J=9.9 Hz, 1 H) 7.85 (d, J=8.4 Hz, 1 H) 7.91 - 7.98 (m, 2 H) 8.02 (d, J=2.2 Hz, 1 H) 8.20 (dd, J=6.2, 2.6 Hz, 1 H) 8.58 (s, 1 H) 11.06 (s, 1H)
234	^{1}H NMR (360 MHz, 氯仿-d) δ ppm 1.64 (s, 3 H) 4.37 (d, J=6.5Hz, 2 H) 4.66 (d, J=6.5 Hz, 2 H) 5.74 (s, 1 H) 7.09 - 7.24 (m, 2 H) 7.59 (d, J=8.2 Hz, 1 H) 7.70 (ddd, J=11.8, 7.0, 2.4 Hz, 1 H) 7.88 (dd, J=8.4, 2.2 Hz, 1 H) 8.19 (d, J=2.2 Hz, 1 H) 8.30 (s, 1 H)
235	^{1}H NMR (360MHz , DMSO-d_6) δ ppm 1.44 (s, 3 H) 4.18 (d, J=6.2 Hz, 2 H) 4.57 (d, J=6.2 Hz, 2 H) 7.26 (t, J=54.2 Hz, 1 H) 7.36 - 7.46 (m, 1 H) 7.84 (d, J=8.4 Hz, 2 H) 7.91 (d, J=2.2 Hz, 1 H) 8.00 (d, J=2.2 Hz, 1 H) 8.03 - 8.10 (m, 1 H) 8.58 (s, 1 H) 10.95 (s, 1 H)
236	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.57 - 1.70 (m, 1 H), 1.87 - 2.04 (m, 1 H), 2.25 (d, J=1.0 Hz, 3 H), 3.38 (m, 1 H), 3.54 - 3.81 (m, 4 H), 7.15 (t, J=9.1 Hz, 1 H), 7.47 - 7.56 (m, 1 H), 7.57 - 7.72 (m, 2 H), 7.95-8.20

[0695]

化合物	^{1}H-NMR
	(ddd, J=8.6, 4.6, 2.4 Hz, 1 H), 8.06 - 8.19 (m, 2 H), 10.60 (s, 1 H)
237	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.60 - 1.70 (m, 1 H), 1.89 - 2.00 (m, 1 H), 2.24 (d, J=1.6 Hz, 3 H), 3.38 (dd, J=8.9, 4.4 Hz, 1 H), 3.55-3.62 (m, 1 H), 3.63 - 3.67 (m, 1 H), 3.68-3.72 (m, 1 H), 3.73 - 3.80 (m, 1 H), 7.14 (t, J=9.3 Hz, 1 H), 7.49 (ddd, J=8.9, 4.4, 2.8 Hz, 1 H), 7.63 (dd, J=6.9, 2.4 Hz, 1 H), 7.80 (dd, J=8.3, 2.2 Hz, 1 H), 7.89 (d, J=2.4 Hz, 1 H), 7.97 (d, J=8.5 Hz, 1 H), 8.12 (br. s., 1 H), 10.63 (s, 1 H)
238	^{1}H NMR (360MHz , DMSO-d_6) δ ppm 1.42 (s, 3 H) 2.46 (s, 3 H) 4.14 (d, J=6.2 Hz, 2 H) 4.56 (d, J=6.2 Hz, 2 H) 7.51 - 7.59 (m, 2 H) 7.84 (dd, J=8.1, 1.8 Hz, 1 H) 7.89 (d, J=1.8 Hz, 1 H) 7.95 - 8.02 (m, 1 H) 8.24 (dd, J=6.6, 2.6 Hz, 1 H) 8.42 (s, 1 H) 10.87 (s, 1 H)
239	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.65 - 1.74 (m, 1 H), 1.90 - 2.00 (m, 1 H), 2.25 (d, J=1.5 Hz, 3 H), 3.41 (dd, J=8.9, 4.7 Hz, 1 H), 3.57 - 3.77 (m, 3 H), 3.83 - 3.91 (m, 1 H), 7.14 (dd, J=9.2 Hz, 1 H), 7.54 - 7.61 (m, 1 H), 7.61 - 7.69 (m, 2 H), 8.29 (ddd, J=8.5, 4.6, 2.3 Hz, 1 H), 8.40 (dd, J=7.0, 2.2 Hz, 1 H), 8.44 (br. s., 1 H), 10.47 (s, 1 H)

[0696] 差式扫描量热法（从 30℃到 300℃，10℃ /min）：

[0697] 化合物 232：峰值在 169.6℃

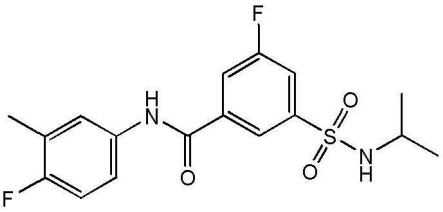
[0698] 旋光度：

[0699] 化合物 236：$[\alpha]_D^{20}$ = - 5.83 (c 0.67 w/v %, MeOH)。

[0700]

化合物 **240**

[0701]



[0702] 将 $SOCl_2$(20.1mL,277.2mmol) 缓慢添加到冷却至 5℃的水 (125mL) 中,温度保持在 4℃至 7℃ (添加历经 1.5 小时)。

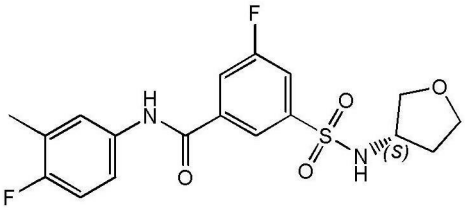
[0703] 然后将该溶液保持搅拌过夜同时允许温度缓慢达到室温。然后将氯化亚铜 (I) (76.6mg,0.774mmol) 添加至该溶液并将其冷却至 -10℃ (干冰 / 丙酮浴),(产生溶液 A)。在另一个冷却至 0℃的烧瓶中,将 HCl(在 H_2O 中 37%,65mL) 逐滴添加至 3- 氨基 -5- 氟苯甲酸 (10g,64.46mmol),保持温度低于 20℃。将此浆料冷却至 -10℃ (干冰 / 丙酮浴) 并将亚硝酸钠 (4.803g,69.62mmol) 在 H_2O(20mL) 中的溶液缓慢 (1 滴 /5 秒) 添加至该浆料,保持温度低于 -5℃。

[0704] 添加后,在冷却回至 -15℃之前 (溶液 B),允许该橙色混合物加温至 -2℃持续 5 分钟。然后将溶液 B 分部分地 (塑料移液管) 添加至溶液 A,冷却至 -10℃。添加后 (～ 30min),将该反应混合物在 0℃搅拌 2 小时。将产生的橙色固体过滤并用水 (2x 25mL) 进行漂洗,产生呈橙色固体的 3- 氯磺酰基 -5- 氟 - 苯甲酸 (在 35℃在真空中干燥)。将 Et_3N(1.22mL,8.8mmol) 缓慢添加至 3- 氯磺酰基 -5- 氟 - 苯甲酸 (525mg,2.2mmol) 在干 CH_2Cl_2(10mL) 中的溶液里。然后在室温下将异丙胺 (198μL,2.42mmol) 逐滴添加至该反应混合物中。将该反应混合物在室温下搅拌 30min。将棕色的反应混合物用 CH_2Cl_2和水进行稀释。添加 HCl 1N 至 pH 2。分离层,并且将水层用 CH_2Cl_2萃取两次。将有机层用 $MgSO_4$干燥,进行过滤,并且进行蒸发,产生呈橙色固体的 3- 氟 -5-(异丙基氨磺酰基) 苯甲酸,将其照原样不经进一步纯化使用。在室温下,将 HATU(356.7mg,0.94mmol) 添加至粗制的 3- 氟 -5-(异丙基氨磺酰基) 苯甲酸 (190mg)、4- 氟 -3- 甲基苯胺 (78.3mg,0.625mmol) 和 N,N- 二异丙基乙胺 (326.8μL,1.88mmol) 于 CH_2Cl_2(30mL) 中的溶液里。将该混合物在室温下搅拌 1 小时。将该反应混合物用 CH_2Cl_2进行稀释,用 HCl 0.5N 进行洗涤,在硅藻土 NT3(Extrelut NT3) 上进行过滤并蒸发。将获得的残余物通过在硅胶柱层析 (Grace Resolv12g,洗脱液 :CH_2Cl_2 : MeOH 100 : 0- > 95 : 5) 进行纯化,产生呈白色固体的化合物 240(136mg),在真空中在 50℃进行干燥。

[0705] 方法 G,Rt :1.87min.m/z :366.9(M-H)$^-$精确质量 :368.1。^{1}H NMR(360MHz,DMSO-d_6) δ ppm 0.97(d,J = 6.2Hz,6H)2.25(d,J = 1.5Hz,3H)3.30-3.39(m,1H),7.16(t,J = 9.3Hz,1H)7.55-7.62(m,1H)7.67(dd,J = 7.1,2.4Hz,1H)7.83(dt,J = 8.0,1.9Hz,1H)7.88(d,J = 7.0Hz,1H)8.08(dt,J = 9.3,1.7Hz,1H)8.22(s,1H)10.52(s,1H)。

[0706]

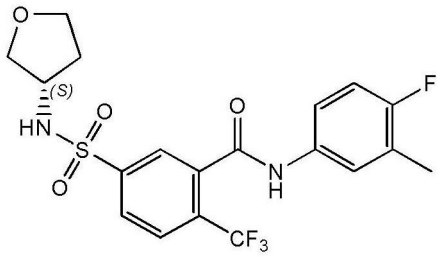
化合物 **241**



[0707] 化合物 241 是如针对化合物 240 描述的类似地制备，使用 (S)-3- 氨基四氢呋喃甲苯磺酸酯代替异丙胺。方法 G，Rt :1.70min.m/z :394.9(M-H)⁻精确质量 :396.1。^{1}H NMR(360MHz，DMSO-d_6)d ppm 1.55-1.67(m,1H)1.93(dq，J ＝ 12.8,7.4Hz,1H)2.25(d，J ＝ 1.8Hz,3H)3.37(dd，J ＝ 9.0,4.2Hz,1H)3.55-3.75(m,3H)3.75-3.85(m,1H)7.16(t，J ＝ 9.1Hz,1H)7.56-7.62(m,1H)7.67(dd，J ＝ 7.3,2.6Hz,1H)7.82-7.88(m,1H)8.08-8.13(m,1H)8.20-8.25(m,2H)10.53(s,1H)。

[0708]

化合物 **242**



[0709] 将化合物 237(400mg,0.87mmol) 溶解在 DMF(2.5mL) 和 N- 甲基吡咯烷 (0.12mL) 的混合物 (包含碘化亚铜 (I)(45.43mg,0.24mmol) 和 2,2- 二氟 -2- 氟磺酰基乙酸甲酯 (0.21g,1.09mmol)) 中。

[0710] 将产生的混合物在室温下搅拌 2 小时。添加额外量的 2,2- 二氟 -2- 氟磺酰基乙酸甲酯 (0.21g,1.09mmol) 并将该混合物在 60℃搅拌 1 小时。将该混合物在 60℃搅拌 18 小时。将饱和氯化铵溶液 (10mL) 添加至该反应混合物。然后将此用 EtOAc(3x 15mL) 进行萃取。将合并的萃取物经 Na_2SO_4干燥、过滤并且在真空中进行浓缩。将获得的残余物使用硅柱层析 (梯度洗脱液：乙酸乙酯：庚烷从 0 至 100％) 进行纯化。将所有希望的部分进行合并并在减压下浓缩然后在 50℃在真空烘箱中干燥过夜，产生呈白色粉末的化合物 242(314mg)。方法 G，Rt :1.73min.m/z :445.0(M-H)⁻精确质量 :446.1。

[0711] 生物学实例——具有化学式 (I) 的化合物的抗 -HBV 活性

[0712] 该抗 -HBV 活性使用稳定的转染细胞系 HepG2.2.15 进行测量。此细胞系描述为分泌相对一致的高水平的 HBV 病毒颗粒，该病毒颗粒已经显示出在黑猩猩中引发急性和慢性感染以及疾病。

[0713] 对于抗病毒性，使用在 96 孔板中的一式两份的连续稀释的化合物将测定细胞在三天内处理两次。处理后 6 天，通过从分泌的病毒粒子中纯化的 HBV DNA 定量 (使用实时 PCR 和 HBV 特异引物集和探针) 对该抗病毒活性进行确定。

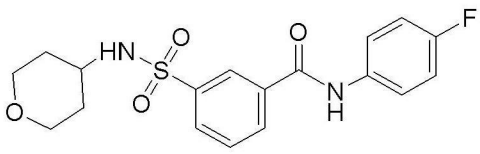
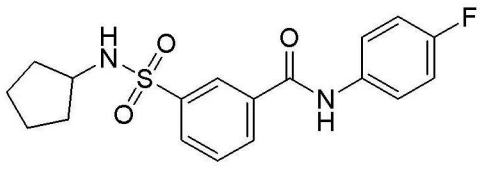
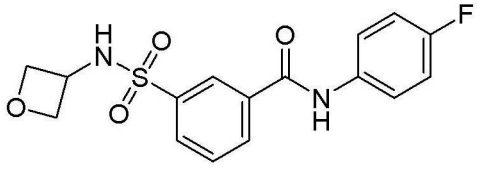
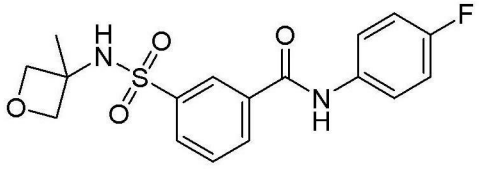
[0714] 在 HepG2 细胞中使用 CellTiter-Blue(细胞滴定 - 蓝) 对这些化合物的细胞毒性进行检测 (孵育期和剂量范围与在 HepG2.2.15 测定中一样)。

[0715] 还使用了 HepG2.117 细胞系（一种稳定的、可诱导的 HBV 生产细胞系）测量了抗 HBV 活性，该细胞系在缺乏强力霉素下复制 HBV(Tet-off 系统)。对于抗病毒测定，诱导 HBV 复制，接下来使用在 96 孔板中一式两份的连续稀释地化合物进行处理。处理后 3 天，通过细胞内 HBV DNA 定量（使用实时 PCR 和 HBV 特异引物集和探针）对该抗病毒活性进行确定。

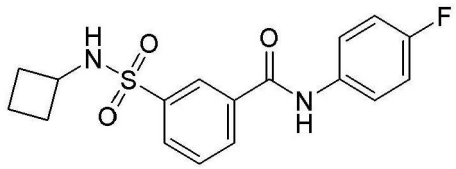
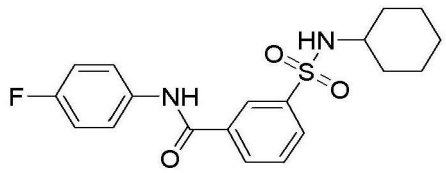
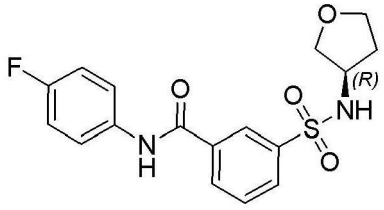
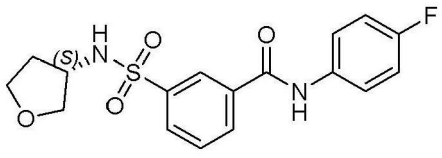
[0716] 使用 HepG2 细胞对这些化合物的细胞毒性进行检测，在这些化合物存在下孵育 4 天。使用刃天青测定对细胞活力进行评估。结果在表 1 中显示。

[0717] 表 1

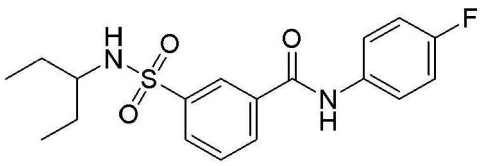
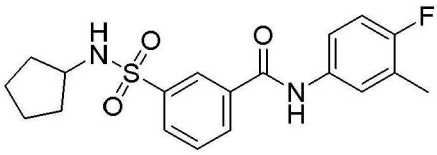
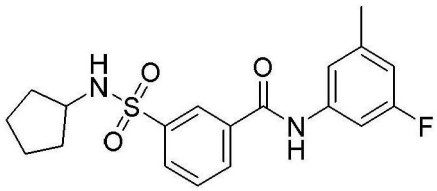
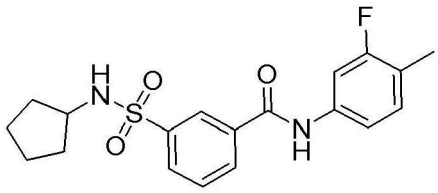
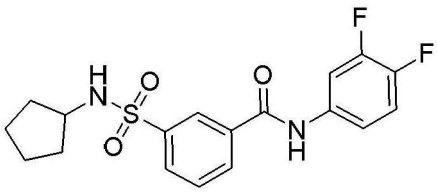
[0718]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	1	0.93		1.67	> 100
	2	0.47		0.56	32.7
	3	2.10		3.05	> 100
	4	0.96		0.93	> 100

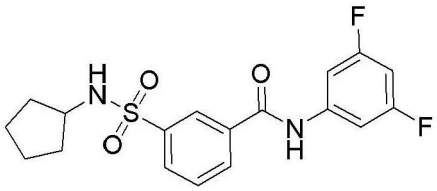
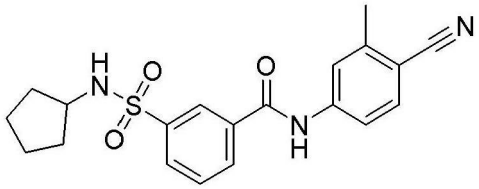
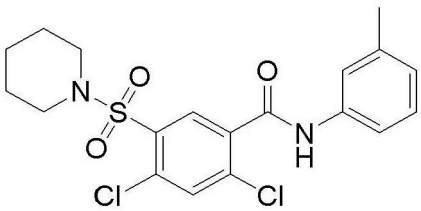
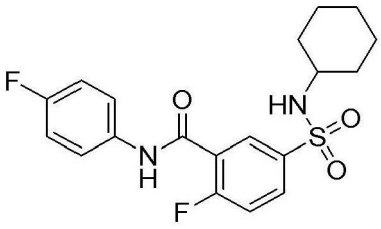
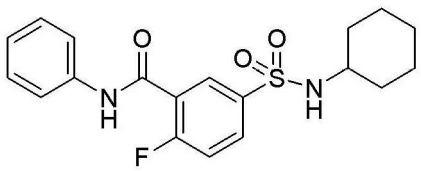
[0719]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**5**	0.83		0.90	57.7
	**6**			0.58	> 25
	**7**	0.66	-	0.56	11.4
	**8**	1.18		2.03	> 100
	**9**	0.54		1.36	> 100

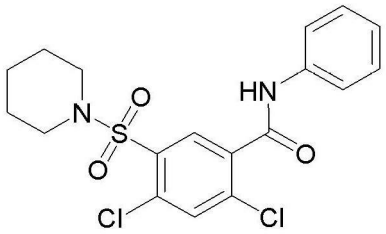
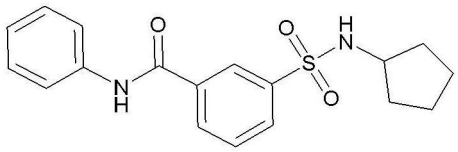
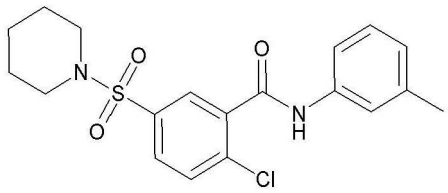
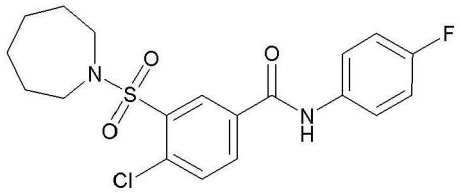
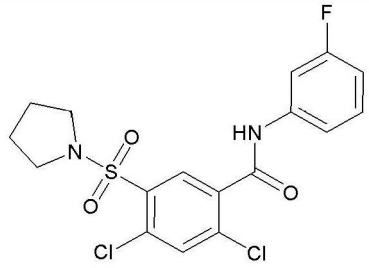
[0720]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**10**	0.75		3.63	40.3
	**11**	0.10		0.42	19.6
	**12**	0.11		1.51	13.3
	**13**	1.99		15.31	13.8
	**14**	0.09		0.36	11.7

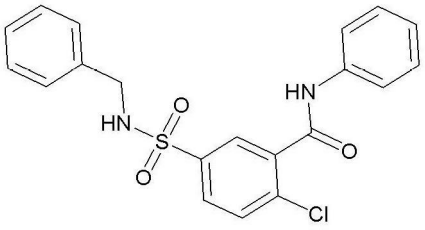
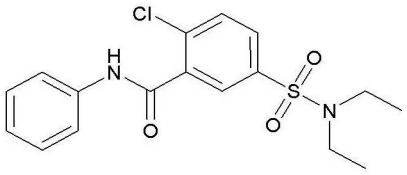
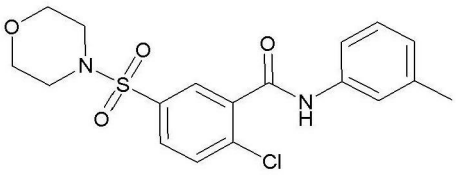
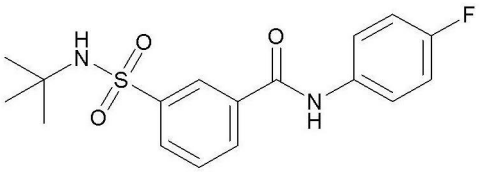
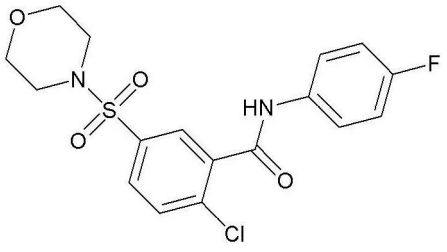
[0721]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**15**	0.28		0.78	10.1
	**16**	1.21		2.8	10.3
	**17**	0.56		2.65	> 100
	**18**	0.78	51.6	1.30	> 50
	**19**	0.66	42.5	0.60	> 25

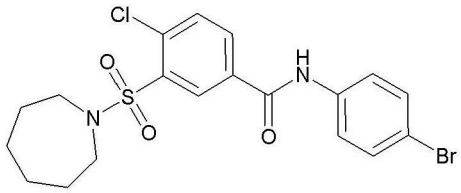
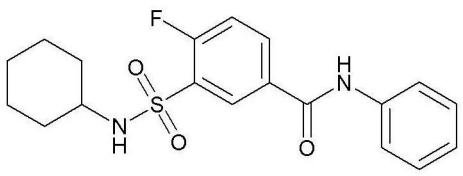
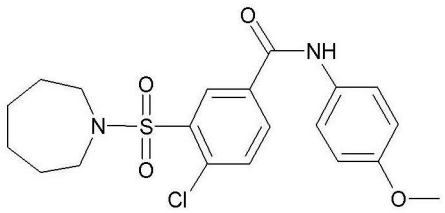
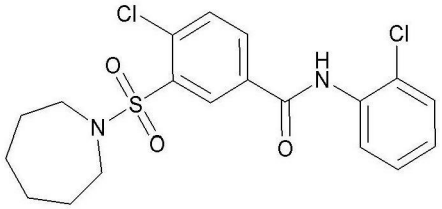
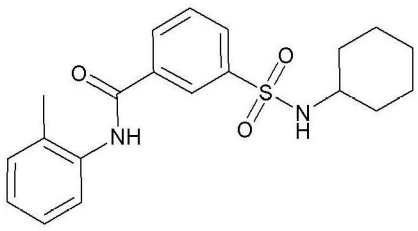
[0722]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**20**	0.50	> 25	1.00	79.6
	**21**	0.60	27.2	0.76	41.1
	**22**	0.52	> 25		
	**23**	0.66	17.0	1.30	19.6
	**24**	0.79	> 25		

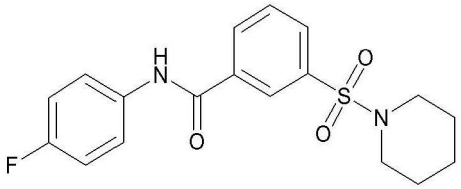
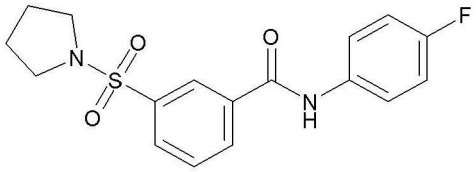
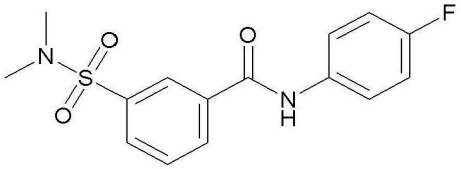
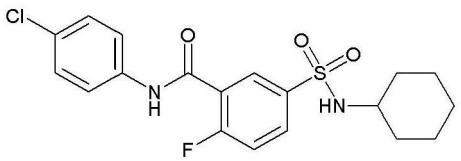
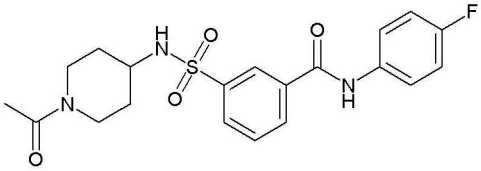
[0723]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**25**	0.80	> 25	1.02	> 6.25
	**26**	1.04	> 25		
	**27**	1.13	> 25		
	**28**	1.24		2.28	52.5
	**29**	1.39	> 25		

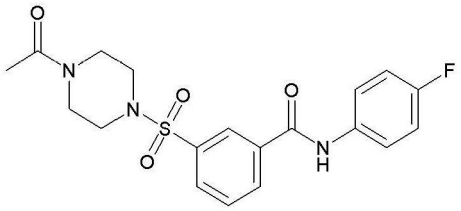
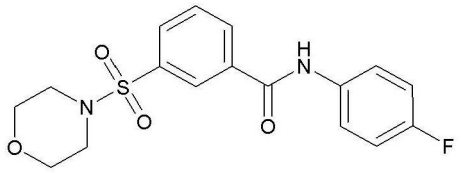
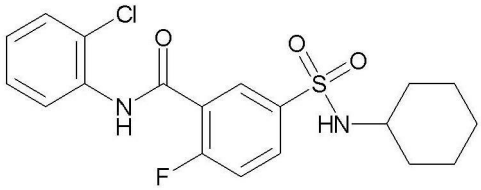
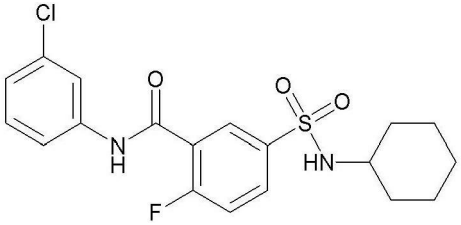
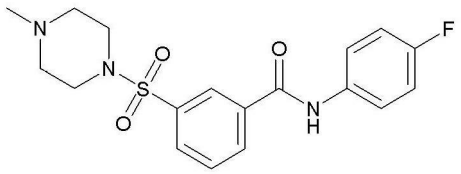
[0724]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**30**	1.67	> 25		
	**31**	2.23	16.4		
	**32**	2.59	9.9	4.58	> 25
	**33**	3.56	> 25		
	**34**	4.18	> 25		

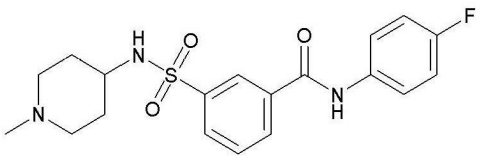
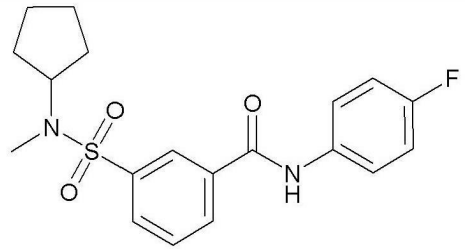
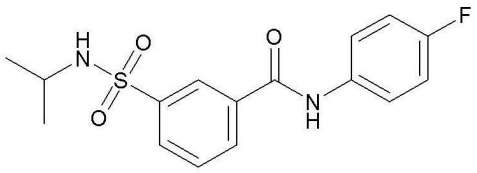
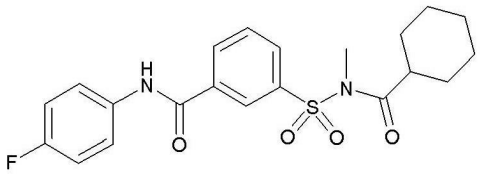
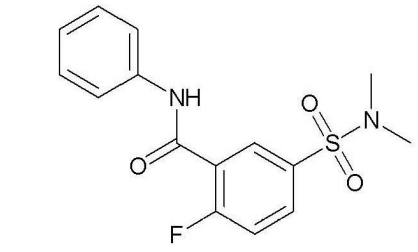
[0725]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**35**	4.50		2.70	70.4
	**36**	4.53		3.03	97.0
	**37**	5.02		2.99	> 100
	**38**	< 6.25	18.4	15.54	22.10
	**39**	6.77		4.68	> 100

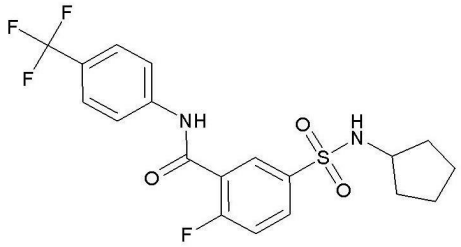
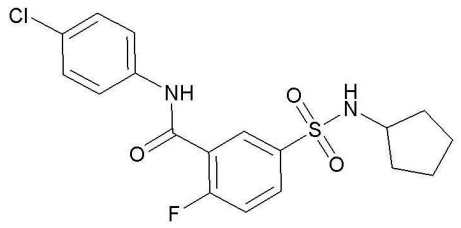
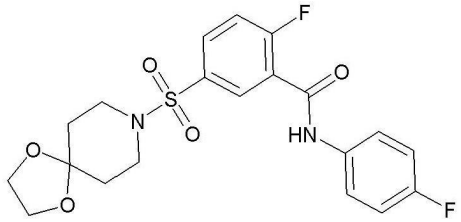
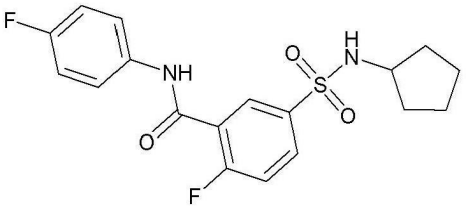
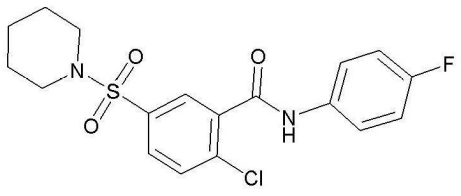
[0726]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**40**	7.10		6.29	> 100
	**41**	8.49	-	10.95	> 100
	**42**	11.64	37.2	> 25	
	**43**	15.13	36.3	> 25	> 25
	**44**	26.49		11.08	> 100

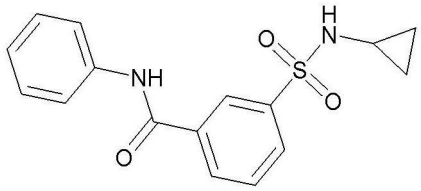
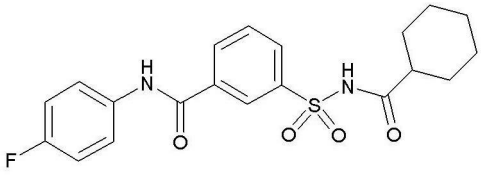
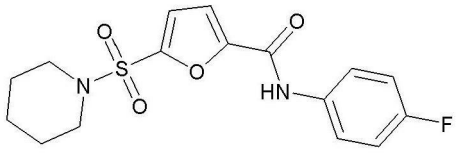
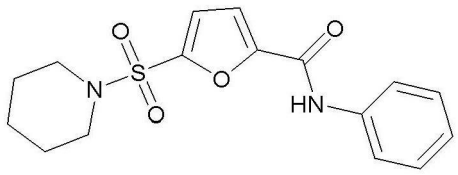
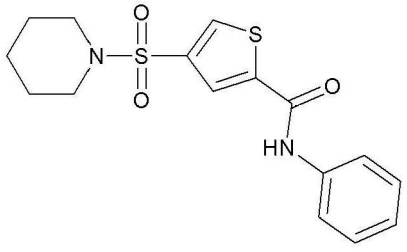
[0727]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**45**	59.33		16.03	> 100
	**46**	2.61		11.09	23.8
	**47**	0.74		0.96	57.5
	**48**	2.92		1.88	97.2
	**49**	13.4		9.15	> 100

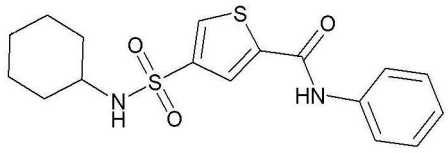
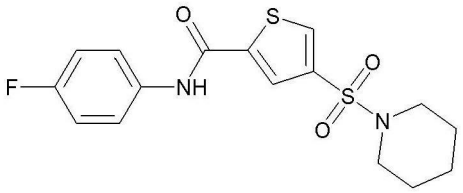
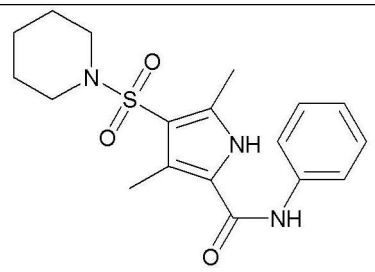
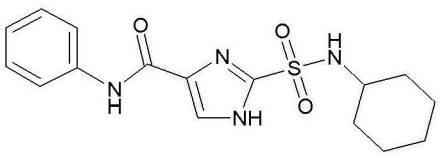
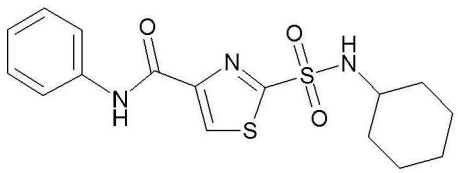
[0728]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**50**	45.9		15.80	11.3
	**51**	3.98		9.44	20.8
	**52**	1.94		2.44	> 50
	**53**	0.36		0.44	> 50
	**54**	1.63		1.55	> 50

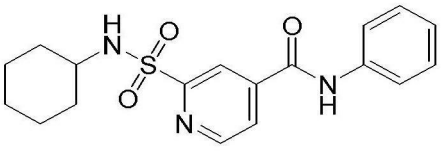
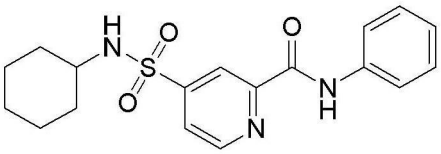
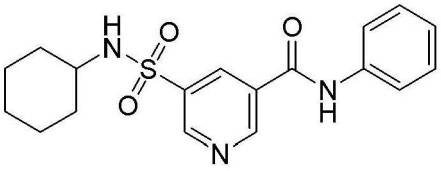
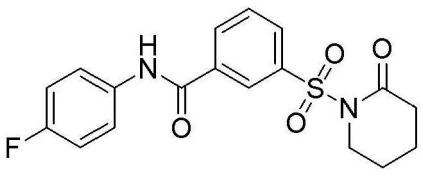
[0729]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**55**	3.06		3.26	> 100
	**56**	1.64		5.45	> 100
	**57**	15.53		12.74	52.1
	**58**	14.62		19.94	62.5
	**59**	12.79		19.27	46.7

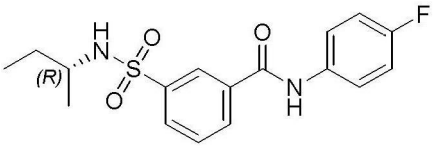
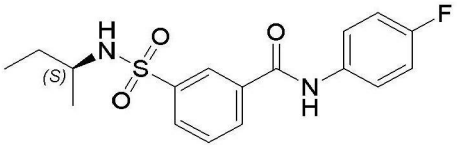
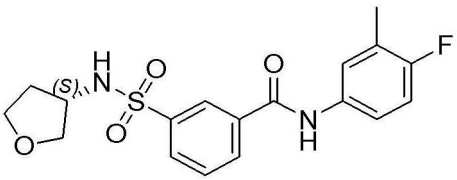
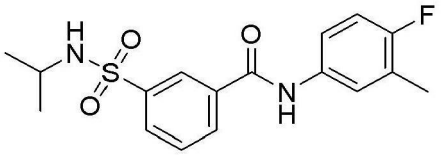
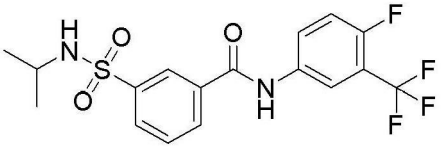
[0730]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**60**	0.85		0.67	29.1
	**61**	7.07		15.44	35.7
	**62**	7.06		10.07	> 50
	**63**	9.94		21.12	> 100
	**64**			7.83	> 25

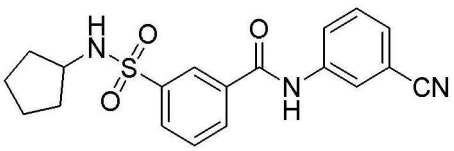
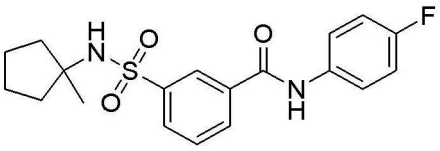
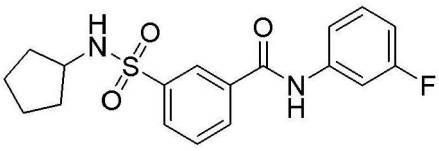
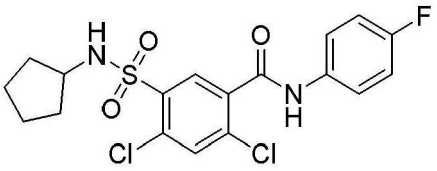
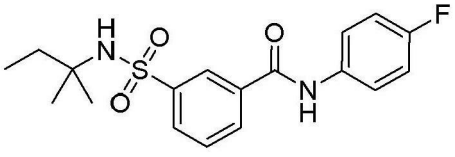
[0731]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**65**	10.76		>25	35.3
	**66**	4.27		14.49	> 100
	**67**	11.10		18.55	> 100
	**68**	18.60		> 25	68.0
	**69**	3.90		10.38	> 25

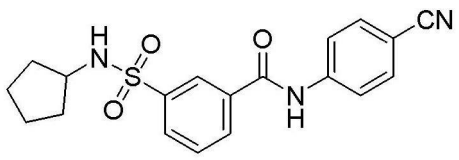
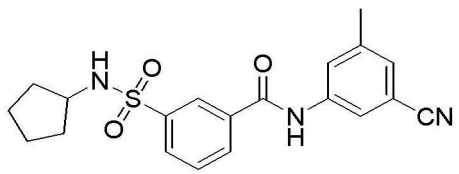
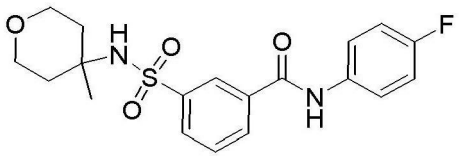
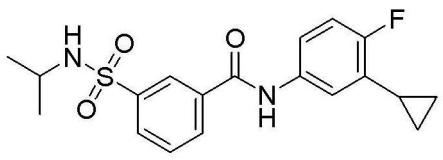
[0732]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**70**	0.34		0.89	> 25
	**71**	0.75		8.63	> 25
	**72**	0.12		0.37	> 25
	**73**	0.073		0.15	> 25
	**74**	0.64		0.53	> 25

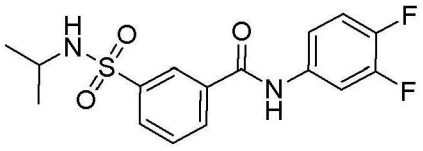
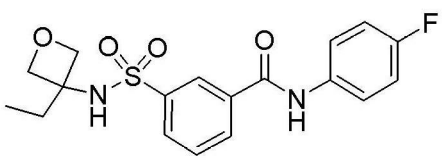
[0733]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**75**	0.39		0.82	> 25
	**76**	0.72		2.5	> 25
	**77**	0.27		0.43	> 25
	**78**	0.90		0.65	> 25
	**79**	0.96		1.69	> 25

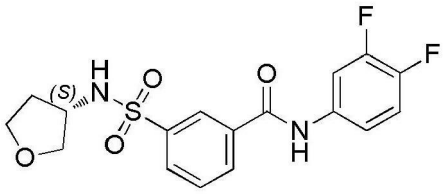
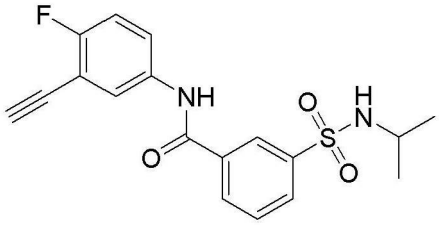
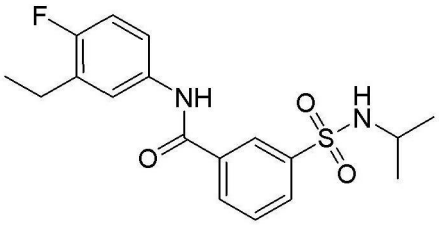
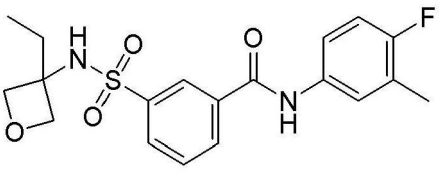
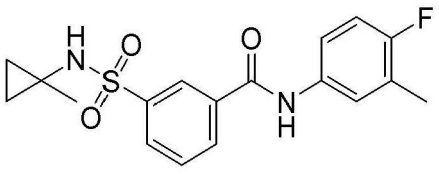
[0734]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**80**	8.4		17.9	> 25
	**81**	0.24		0.81	15.3
	**82**	1.20		3.13	> 25
	**83**	1.04		1.23	> 25
	**84**	0.32		0.91	> 25

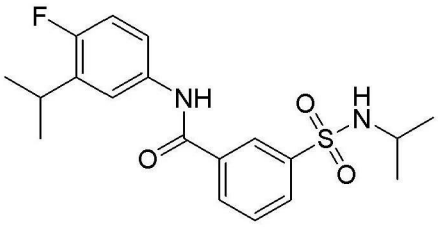
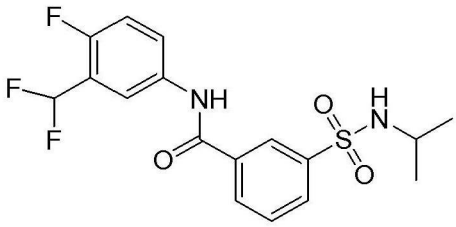
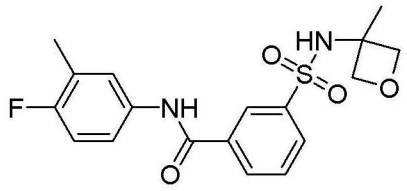
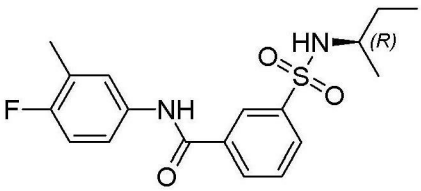
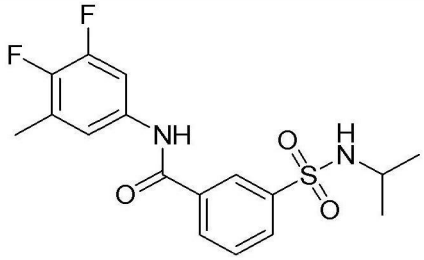
[0735]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**85**	0.05		0.38	> 25
	**86**	0.14		0.11	> 25
	**87**	0.41		0.89	> 25
	**88**	0.21		0.40	> 25
	**89**	0.54		0.72	> 25

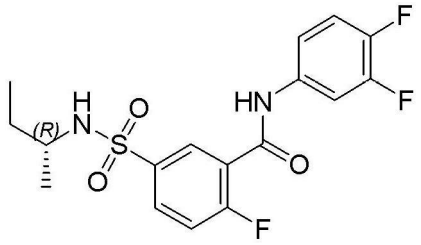
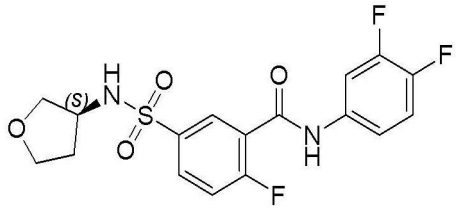
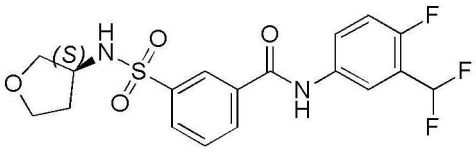
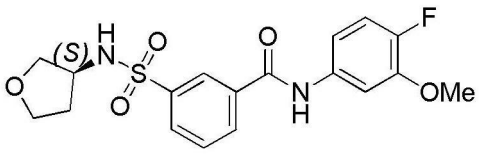
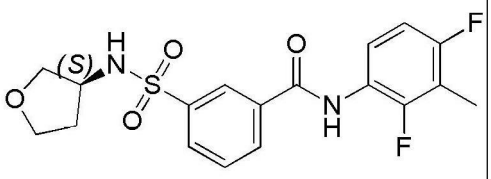
[0736]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**90**	0.38		0.51	> 25
	**91**	0.53		0.77	> 25
	**92**	0.31		2.59	> 25
	**93**	0.07		0.22	> 25
	**94**	0.15		0.23	> 25

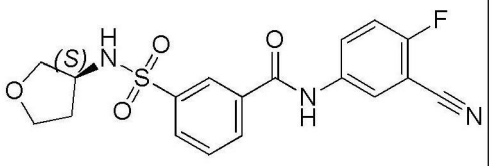
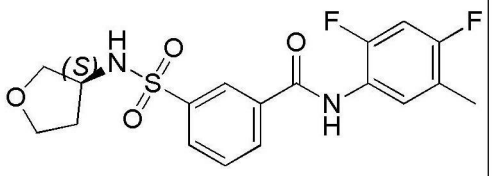
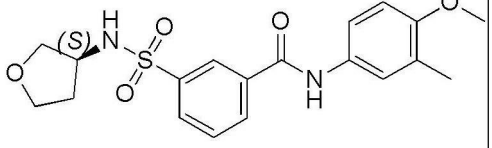
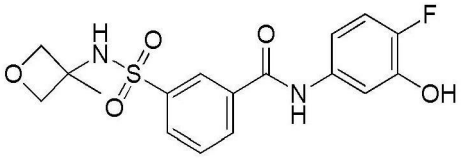
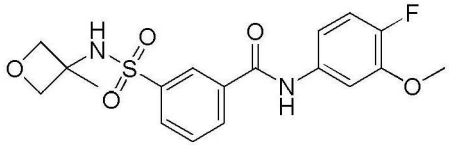
[0737]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**95**	1.4		2.79	> 25
	**96**	0.10		0.29	> 25
	**97**	0.12		0.37	> 25
	**98**	0.10		0.31	> 25
	**99**	0.09		0.46	> 25

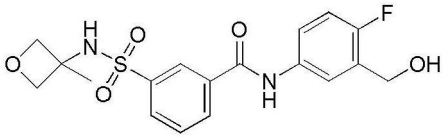
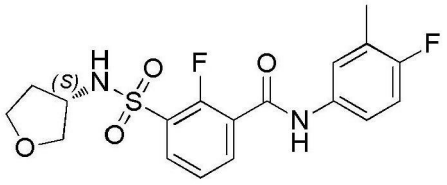
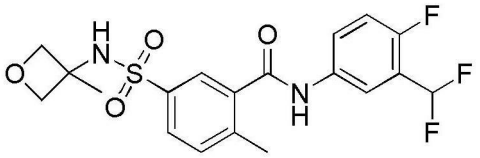
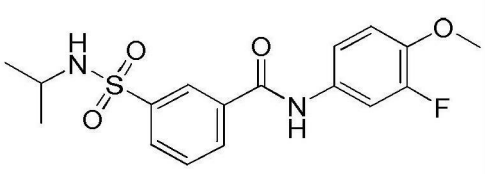
[0738]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**100**	0.13		0.43	> 25
	**101**	0.43		1.51	> 25
	**102**	0.18		0.33	> 25
	**103**	2.33		2.66	> 25
	**104**	0.29		0.78	> 25

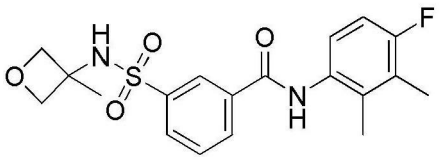
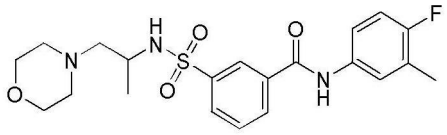
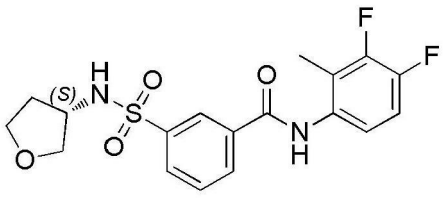
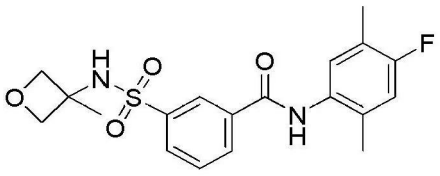
[0739]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**105**	0.81		0.98	> 25
	**106**	2.22		3.30	> 25
	**107**	7.82		13.82	> 25
	**108**	7.20		9.27	> 25
	**109**	1.23		2.53	> 25

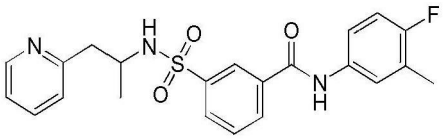
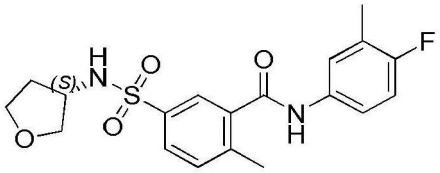
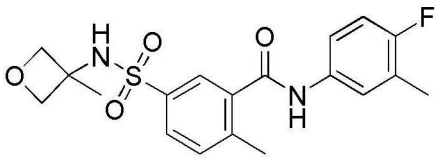
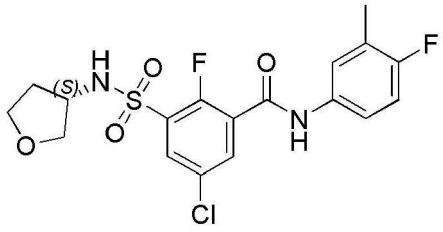
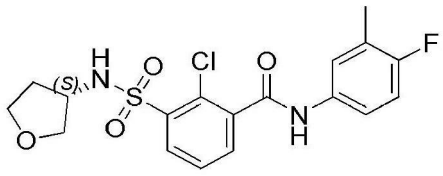
[0740]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**110**	0.66		0.85	> 25
	**111**	4.48		1.48	> 25
	**112**	0.03		0.14	> 25
	**113**	0.15		0.18	> 25
	**114**	1.35		3.15	> 25

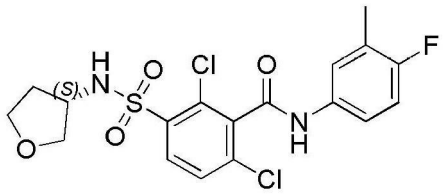
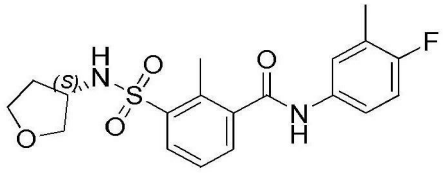
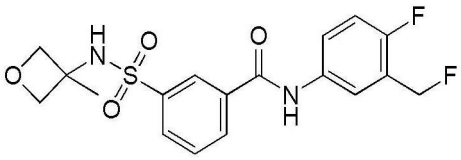
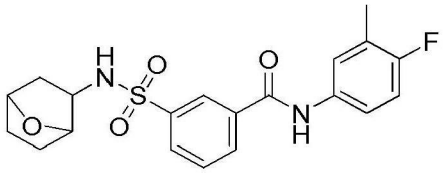
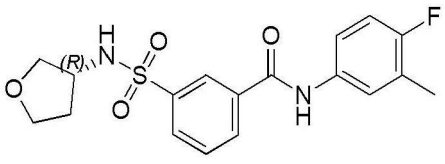
[0741]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**115**	2.74		1.65	> 25
	**116**	1.94		0.90	> 25
	**117**	0.88		0.50	> 25
	**118**	3.63		1.91	> 25
	**119**	3.06		1.91	> 25

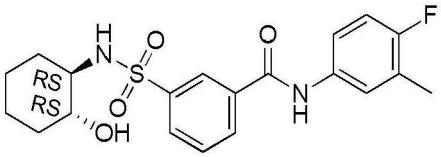
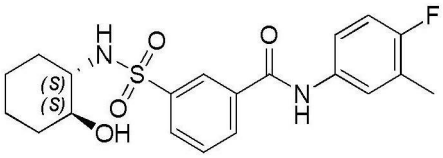
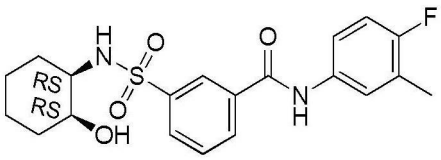
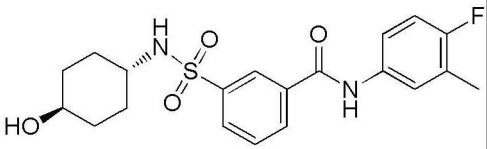
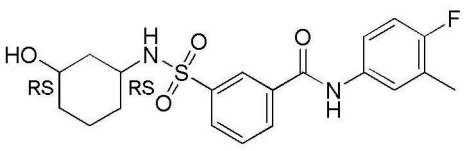
[0742]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**120**	0.53		0.51	> 25
	**121**	0.16		0.13	> 25
	**122**	0.13		0.18	> 25
	**123**	0.15		0.3	> 25
	**124**	0.33		0.68	> 25

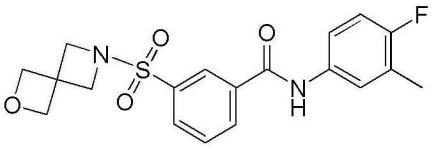
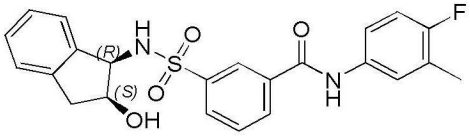
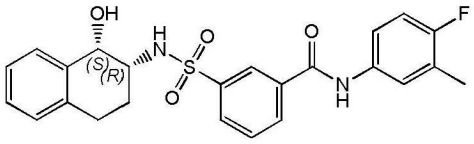
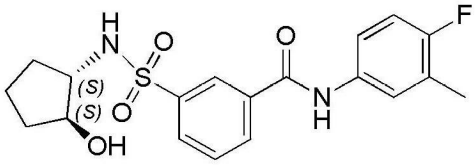
[0743]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**125**	1.44		1.15	> 25
	**126**	1.38		0.89	> 25
	**127**	0.23		0.58	> 25
	**128**	0.23		0.54	> 25
	**129**	0.35		0.78	> 25

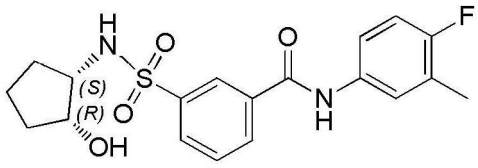
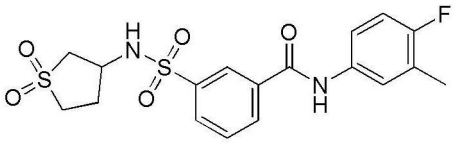
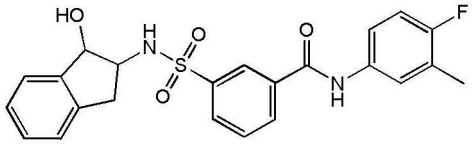
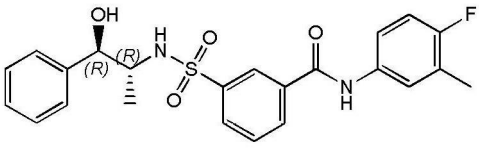
[0744]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**130**	0.88		1.03	> 25
	**131**	2.63		1.74	> 25
	**132**	0.59		0.73	> 25
	**133**	0.60		1.69	> 25
	**134**	0.18		0.57	> 25
	134a	0.66		0.72	

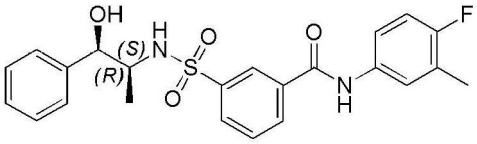
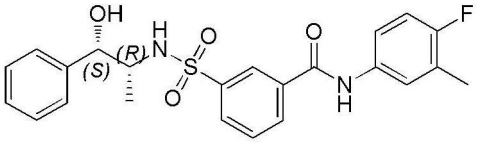
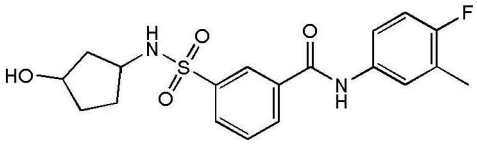
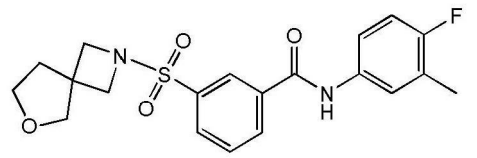
[0745]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	134b	0.57		0.20	
	134c	0.49		0.38	
	134d	0.25		1.22	
	**135**	0.56		0.36	> 25
	**136**	0.47		0.81	> 25
	**137**	0.66		0.92	23.7
	**138**	1.28		2.27	> 25

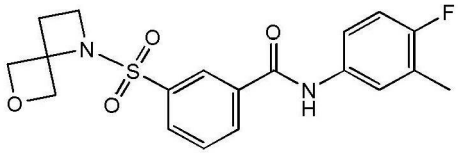
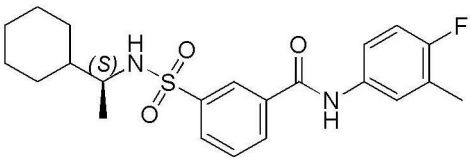
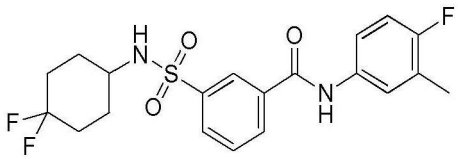
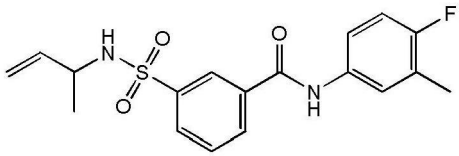
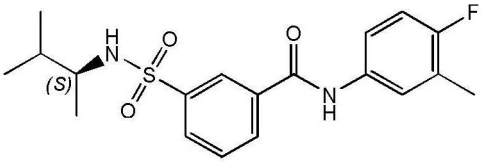
[0746]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**139**	1.00		1.75	> 25
	**140**	1.10		1.12	> 25
	**141**	0.36		0.60	> 25
	141a	0.70		1.65	> 25
	141b	0.27		0.23	> 25
	141c	0.17		0.29	> 25
	141d	0.56		1.14	> 25
	**142**	0.14		0.56	> 25

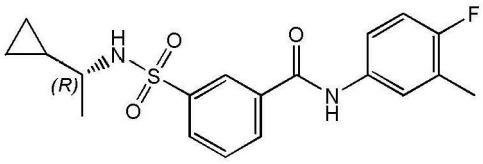
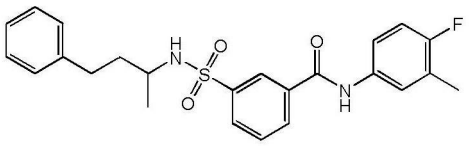
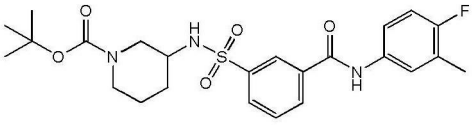
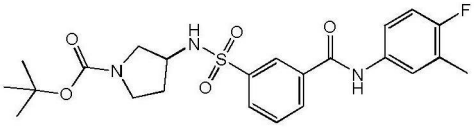
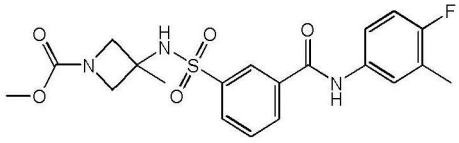
[0747]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**143**	0.91		2.66	> 25
	**144**	0.13		0.24	> 25
	**145**	0.22		0.27	> 25
	145a	0.14		0.21	> 25
	145b	0.44		0.58	> 25
	145c	0.34		0.34	> 25
	145d	0.40		0.64	> 25
	**146**	0.45		0.42	> 25

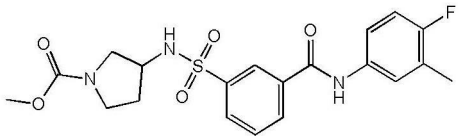
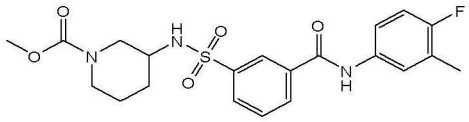
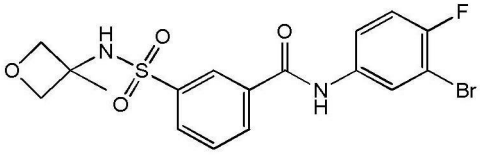
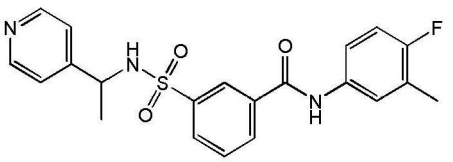
[0748]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**147**	0.26		0.15	> 25
	**148**	0.90		3.11	18.2
	**149**	0.22		0.73	20.8
	**150**	0.10		0.73	> 25
	**151**	0.66		2.74	> 25

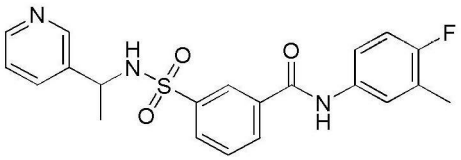
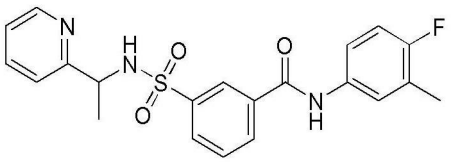
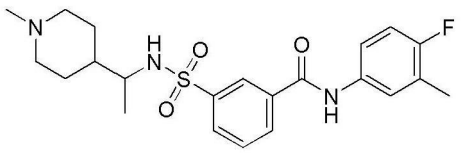
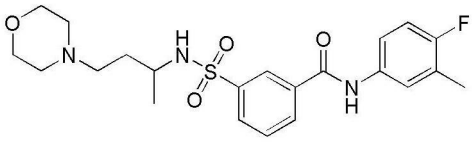
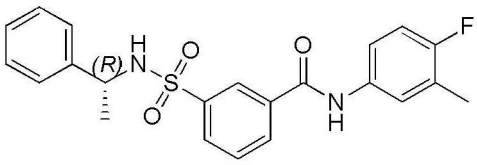
[0749]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**152**	< 0.1		0.57	> 25
	**153**	0.22		0.25	> 25
	**155**	0.36		0.81	> 25
	**156**	0.19		0.21	> 25
	**157**	0.13		0.23	> 25

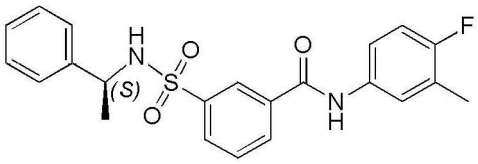
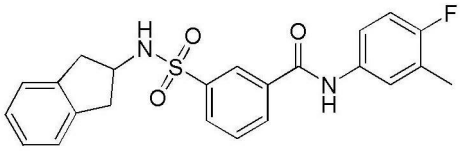
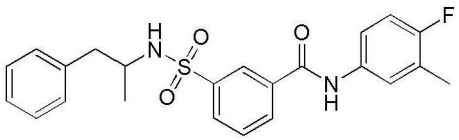
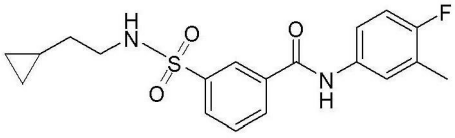
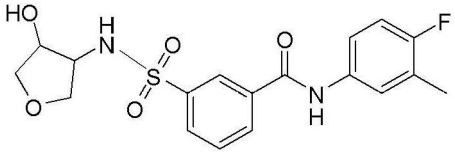
[0750]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**158**	0.15		0.50	> 25
	**159**	0.15		0.30	> 25
	159a	0.17		0.86	
	159b	0.16		0.23	
	**160**	0.20		0.69	> 25
	**161**	0.20		0.35	> 25

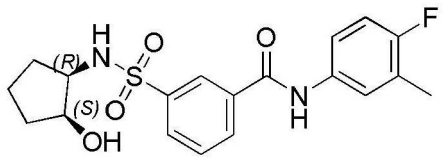
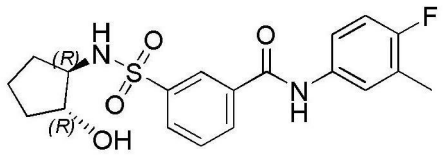
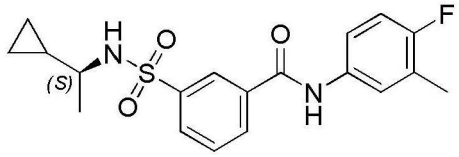
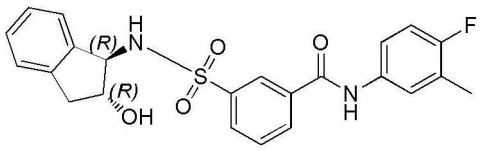
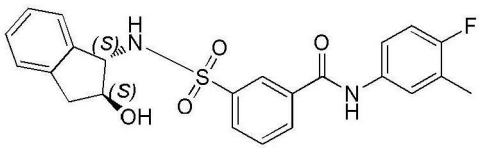
[0751]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**162**	0.17		1.26	> 25
	**163**	0.53		8.53	> 25
	**164**	3.71		0.97	> 25
	**165**	0.71		0.36	> 25
	**166**	0.19		2.39	14.6

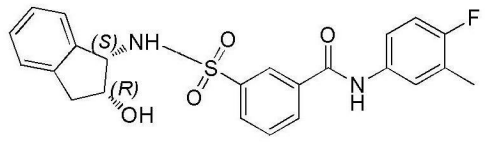
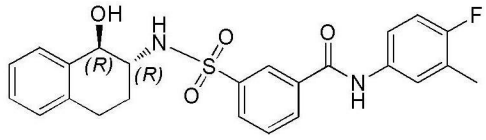
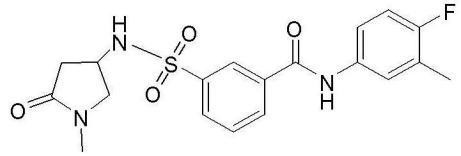
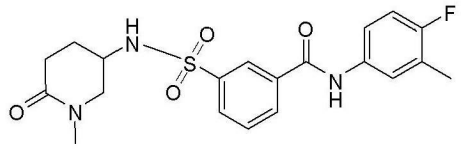
[0752]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**167**	0.62		9.84	> 25
	**168**	0.27		0.37	11.8
	**169**	0.24		1.41	14.9
	**170**	0.26		0.45	> 25
	**171**	0.79		4.39	> 25

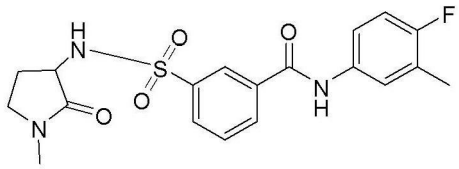
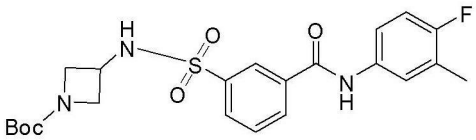
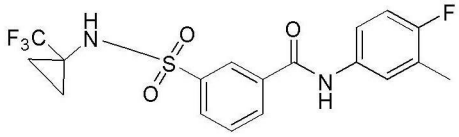
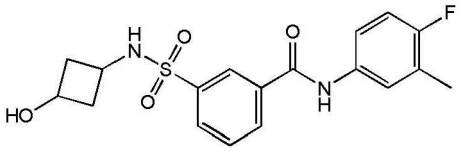
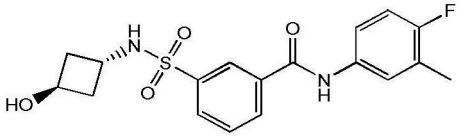
[0753]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**172**	0.26		0.61	> 25
	**173**	0.37		0.36	> 25
	**174**	0.47		2.84	> 25
	**175**	0.23		0.15	> 25
	**176**	0.62		0.56	> 25

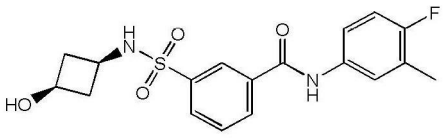
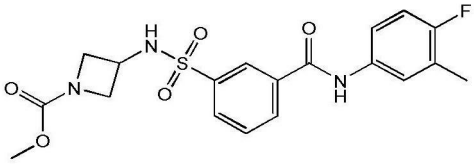
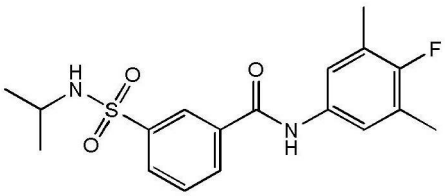
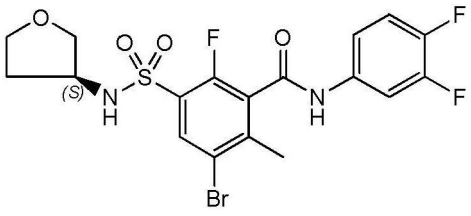
[0754]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**177**	0.77		0.72	> 25
	**178**	0.75		2.54	> 25
	**179**	0.21		0.44	> 25
	179a	0.38		0.25	> 25
	179b	1.11		1.84	> 25
	**180**	0.76		1.30	> 25

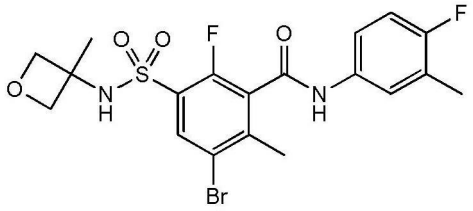
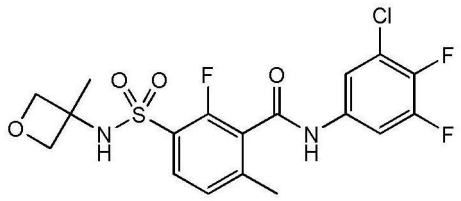
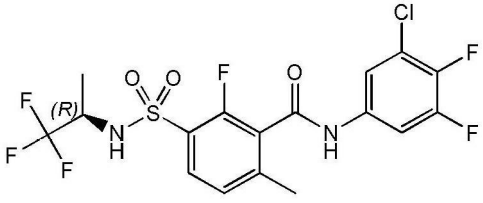
[0755]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**181**	2.59		2.04	> 25
	**182**	0.31		0.88	> 25
	**183**	0.08		0.84	> 25
	**184**	0.15		0.40	> 25
	**184a**	0.31		0.77	> 25

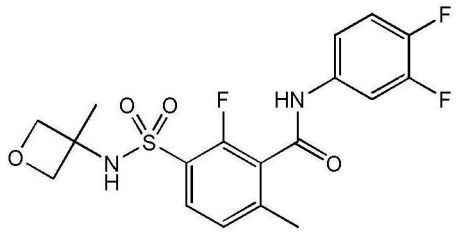
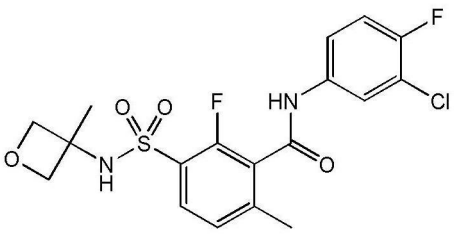
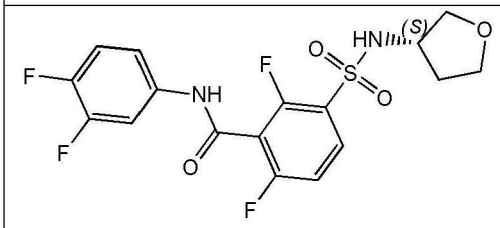
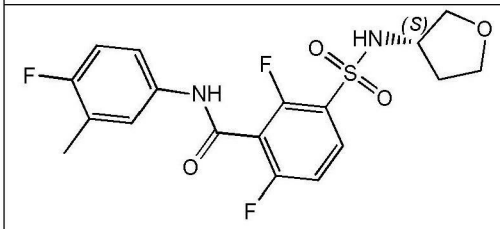
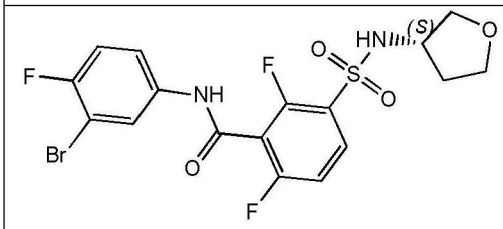
[0756]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**184b**	0.30		0.33	> 25
	**185**	0.22		0.62	> 25
	**186**	0.20		1.34	> 25
	**187**			0.95	> 25
	**188**			0.24	> 25

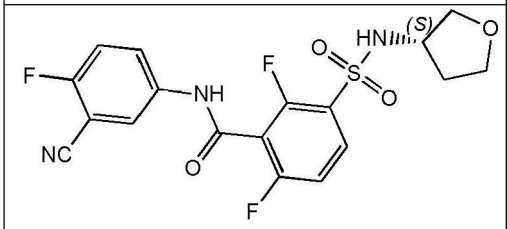
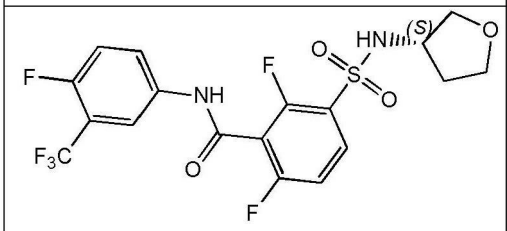
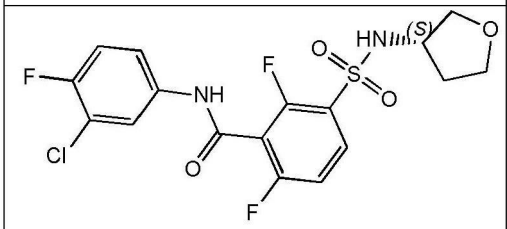
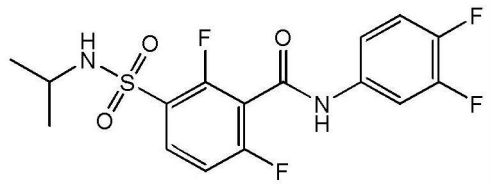
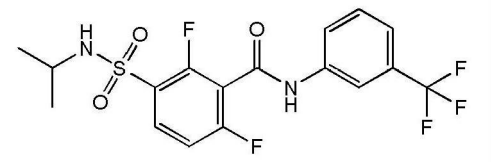
[0757]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**189**			0.35	> 25
	**190**			0.27	> 25
	**191**	0.33		0.36	> 25
	**192**			0.19	> 25
	**193**			0.10	13.5

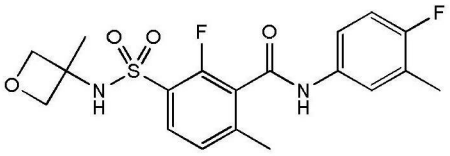
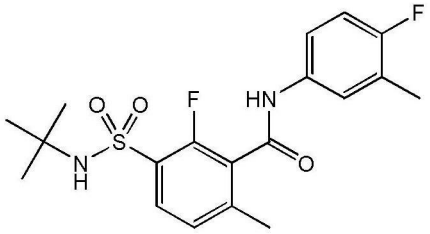
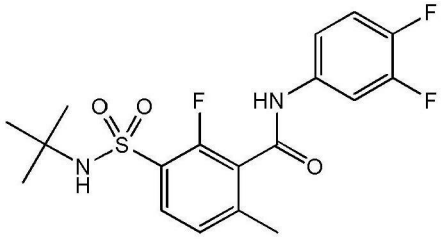
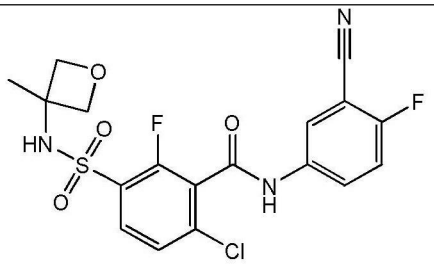
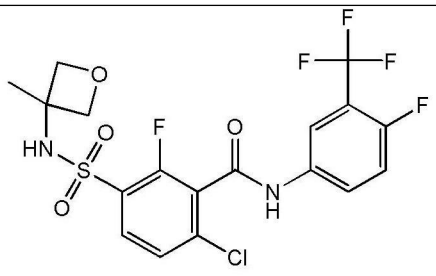
[0758]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**194**	0.38		0.31	> 25
	**195**	0.27		0.18	> 25
	**196**	0.13		0.07	> 25
	**197**			0.09	> 25
	**198**			0.15	> 25

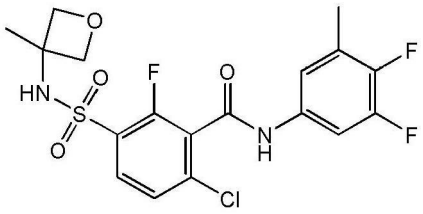
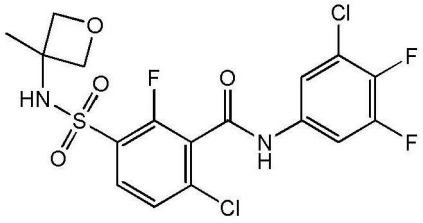
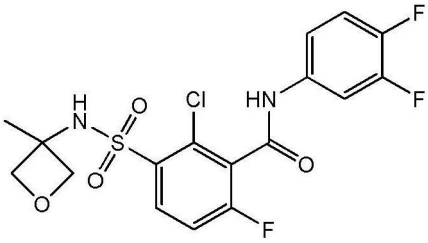
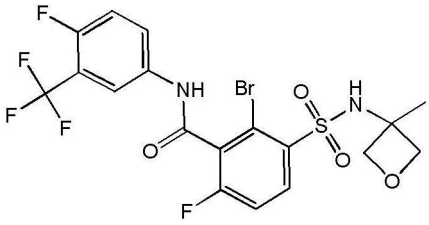
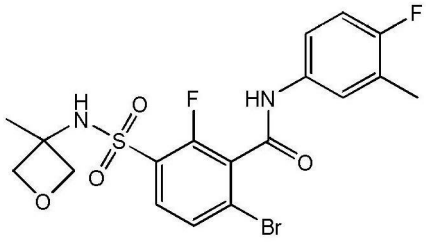
[0759]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	199			0.43	> 25
	200			0.45	> 25
	201	0.06		0.06	> 25
	202			0.11	> 25
	203			0.24	16.7

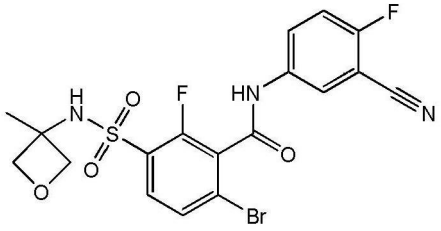
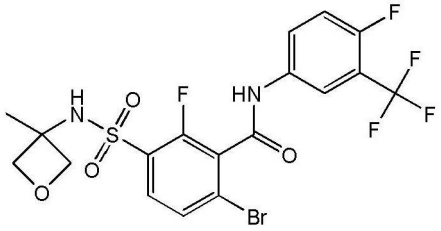
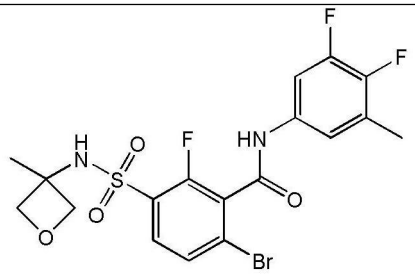
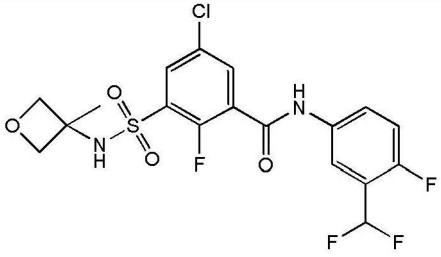
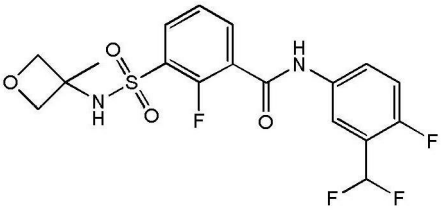
[0760]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**204**			0.09	> 25
	**205**			0.35	> 25
	**206**			0.64	> 25
	**207**			> 1	> 25
	**208**			> 1	> 25

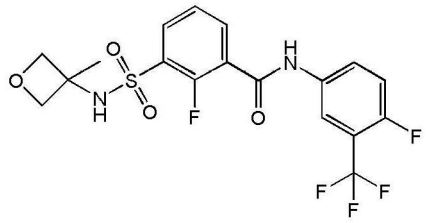
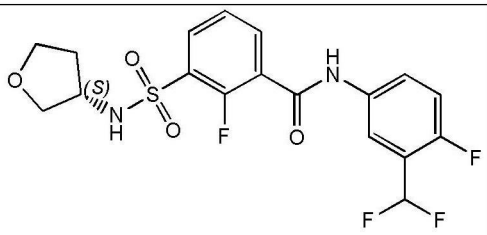
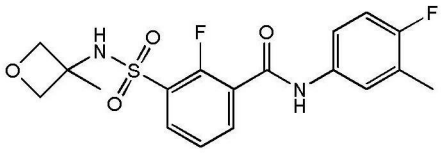
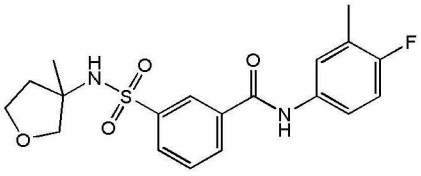
[0761]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	209			0.15	> 25
	210			0.46	> 25
	211			0.65	> 25
	212			7.3	> 25
	213			0.28	> 25

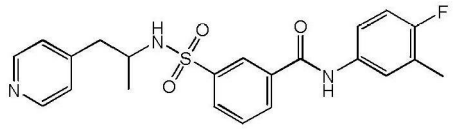
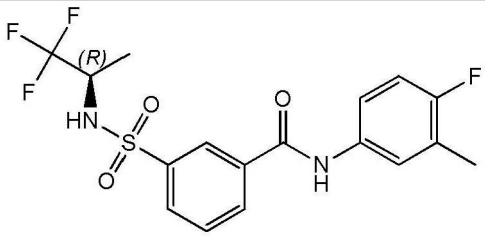
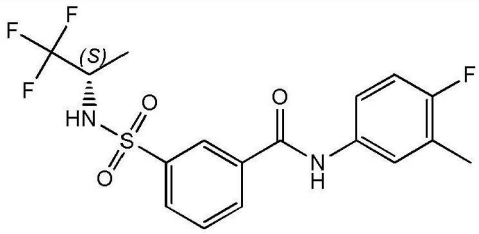
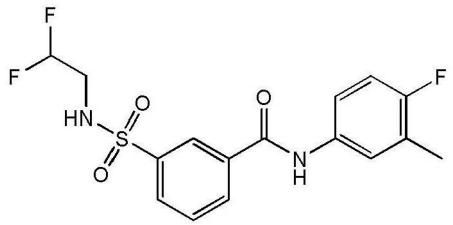
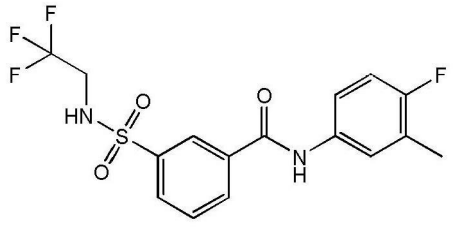
[0762]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**214**			> 1	> 25
	**215**			> 1	> 25
	**216**			0.29	> 25
	**217**	0.20		0.60	> 25
	**218**	0.12		0.10	> 25

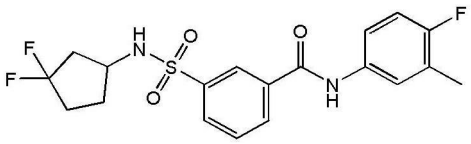
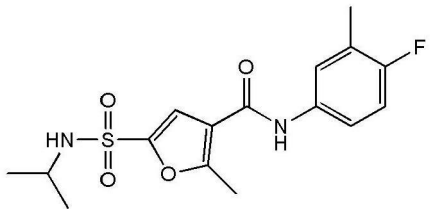
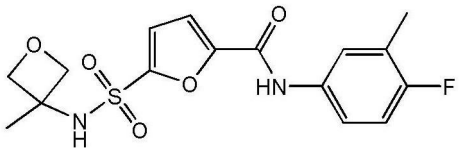
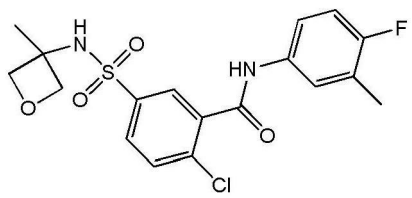
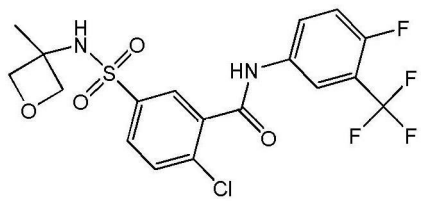
[0763]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**219**			0.46	> 25
	**220**	0.11		0.09	> 25
	**221**			0.13	> 25
	**222**	0.05		0.10	> 25
	**223**			0.21	> 25

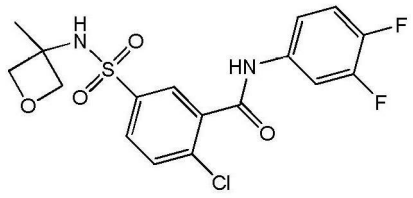
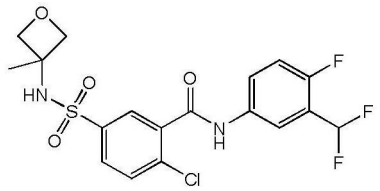
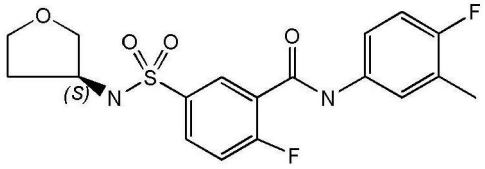
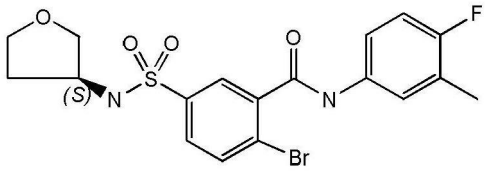
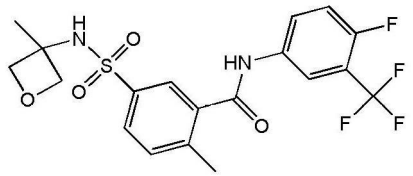
[0764]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**224**	0.16		0.76	> 25
	**225**	0.09		1.34	> 25
	**226**	0.27		1.9	> 25
	**227**	0.16		0.71	> 25
	**228**	0.17		1.19	> 25

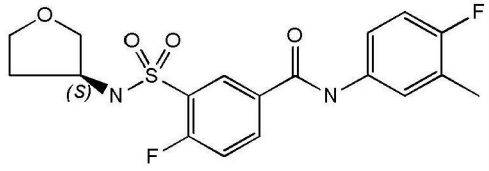
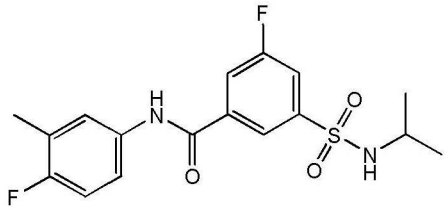
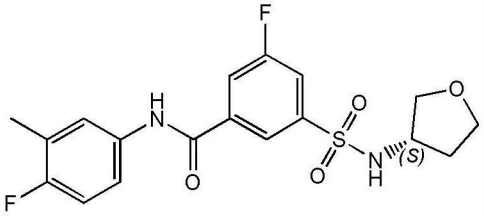
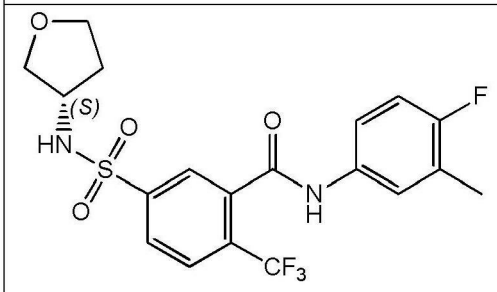
[0765]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**229**	0.20		0.49	>25
	**230**	0.73		1.52	> 25
	**231**	0.21		0.32	> 25
	**232**			0.31	> 25
	**233**	> 1		> 1	> 25

[0766]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**234**	0.72		0.34	> 25
	**235**	0.83		0.33	> 25
	**236**	0.48		1.58	> 25
	**237**	0.43		0.13	> 25
	**238**	0.61		0.50	> 25

[0767]

结构	化合物编号	HepG2 2.15 EC50（μM）	HepG2 6 天 CC50（μM）	HepG2 117 EC50（μM）	HepG2 4 天 CC50（μM）
	**239**	0.48		0.53	> 25
	**240**	0.40		2.86	> 25
	**241**	0.38		1.79	> 25
	**242**	1.91		1.80	> 25