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Sulfamoyl-arylamides and the use thereof as medicaments for the treatment of Hepatitis B

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(71) Applicant(s)
Janssen Sciences Ireland UC

(72) Inventor(s)
Vandyck, Koen;Last, Stefaan Julien;Rombouts, Geert;Verschueren, Wim Gaston;Raboisson, Pierre Jean-Marie Bernard

(74) Agent / Attorney
Shelston IP Pty Ltd., L 9 60 Margaret St, Sydney, NSW, 2000, AU

(56) Related Art
US 20110009622 A1
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, 2007, vol. 17, no. 1, pages 272 - 277
US 20100016310 A1
WO 02064618 A2
US 20050239833 A1
Nam Doo Kim et al., "Discovery of novel HCV polymerase inhibitors using pharmacophore-based virtual screening", Bioorganic & Medicinal Chemistry Letters, 2011, vol. 21, pages 3329 - 3334
WO 2013006394 A1
WO 2013096744 A1
WO 1992/07835 A1
Carver, D.S., et al, "Polyfunctionalisation of Imidazole via Sequential Imidazolyl Anion Formation". Tetrahedron, 1997, vol. 53, no. 42, pages 14481-14496

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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 present application is a divisional application of Australian Application No. 2013307331, which is incorporated in its entirety herein by reference.

Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of common general knowledge in the field.

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).

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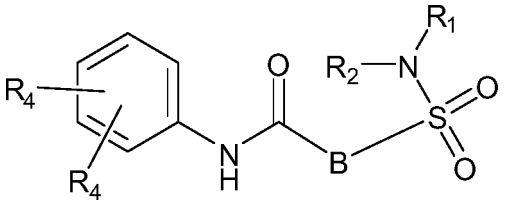
WO2013/006394, published on January 10, 2013, and WO2013/096744, published on June 27, 2013 relate to subclasses of Sulphamoyl-arylamides active against HBV.

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

According to a first aspect, the present invention provides a compound of Formula (Ia)



(Ia)

or a stereoisomer or tautomeric form thereof, wherein:

B represents a monocyclic 6 membered aromatic ring, containing one or more heteroatoms each independently selected from the group consisting of O, S and N, such 6 membered aromatic ring optionally being substituted with one or more substituents each independently selected from the group consisting of 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 carbocyclic ring optionally containing one or more heteroatoms each independently selected from the group consisting of O, S and N, such 3-7 membered saturated carbocyclic ring or C_1-C_6alkyl being substituted with one or more substituents each independently selected from the group consisting of 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 carbocyclic 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 carbocyclic ring containing one or more heteroatoms each independently selected from the group consisting of O, S and N, such 3-7 membered saturated carbocyclic ring optionally being substituted with one or more substituents each independently selected from the group consisting of 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.

According to a second aspect, the present invention provides a compound of Formula (Ia) according to claim 1 or a stereoisomer or tautomeric form thereof, or a pharmaceutically acceptable salt or a solvate thereof, wherein

R_2 represents C_1-C_3alkyl-R_6 or a 4-7 membered saturated carbocyclic 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 carbocyclic ring being substituted with one or more substituents each independently selected from the group consisting of 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 carbocyclic ring optionally containing one or more heteroatoms each independently selected from the group consisting of O and N; and

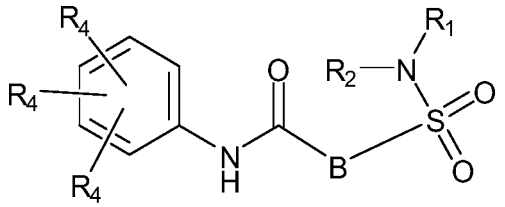
R_6 represents a 4-7 membered saturated carbocyclic ring optionally containing one or more heteroatoms each independently selected from the group consisting of O or S, such 4-7 membered saturated carbocyclic ring optionally being substituted with one or more substituents

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.

According to a third aspect, the present invention provides a pharmaceutical composition comprising a compound according to the invention or a stereoisomer or tautomeric form thereof, or a pharmaceutically acceptable salt or a solvate thereof, and a pharmaceutically acceptable carrier.

Unless the context clearly requires otherwise, throughout the description and the claims, the words "comprise", "comprising", and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of "including, but not limited to".

The present invention also 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;

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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.

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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

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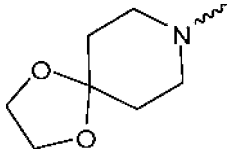
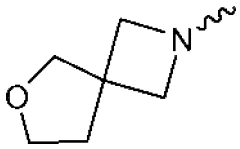
more heteroatoms, such that at least one carbon atom is replaced by a heteroatom selected from N, O and S, in particular from N and O.

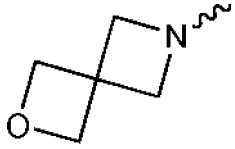
Examples of such 6-10 membered bicyclic ring as used herein arean1,4-dioxa-8-azaspiro[4.5] decyl moiety indicating a group with structural formula



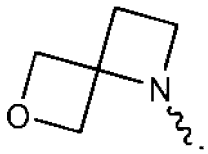
, a 6-Oxa-2-azaspiro[3.4]octane moiety indicating a group with structural formula



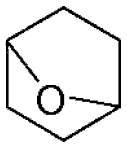
a 2-oxa-6-azaspiro[3.3]heptyl moiety indicating a group with structural formula



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

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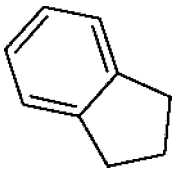
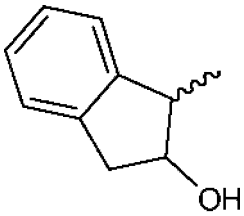
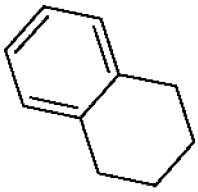
 . Such dihydroindenyl moiety can be optionally substituted with OH. One example as used herein, a 2-hydroxy-2,3-dihydro-1H-indenyl moiety, indicates a group with structural formula



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

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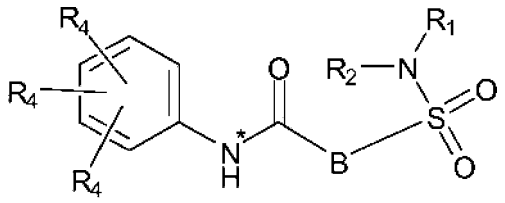
position of R_4, any location is indicated relative to the nitrogen (*) connected to the main structure:



(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

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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

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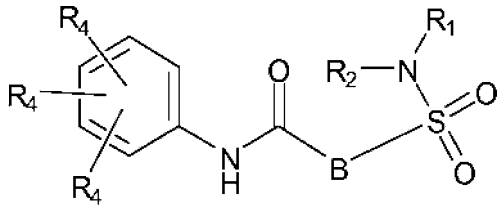
stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

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

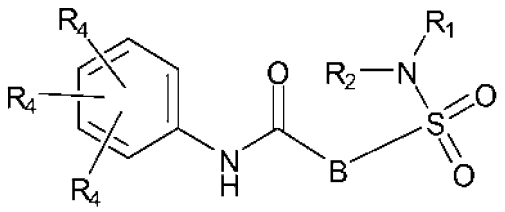
Whenever used hereinafter, the term "compounds of formula (I)",



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:

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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.

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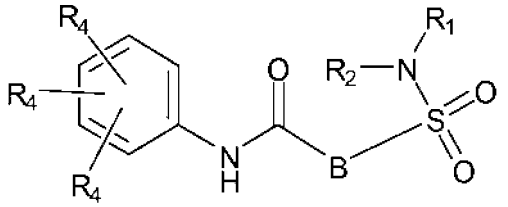
In a first aspect, the invention further provides compound of Formula (I)



(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_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 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;

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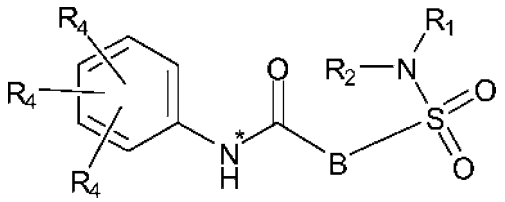
R_5 represents C_1-C_6alkyl, CFH_2, CF_2H, CF_3, phenyl, pyridyl or a 3-7 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O, S and N, such 3-7 membered saturated ring optionally being substituted with one or more substituents 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

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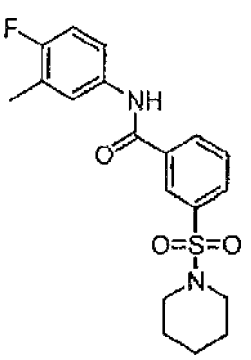
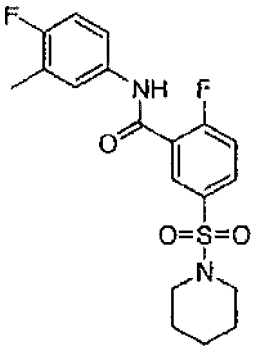


or



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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

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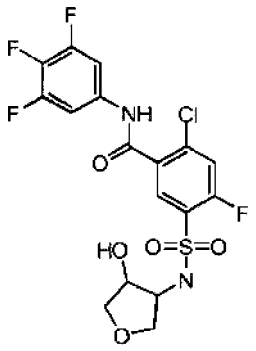
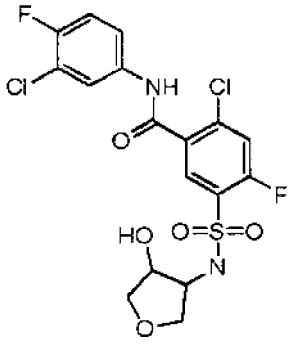


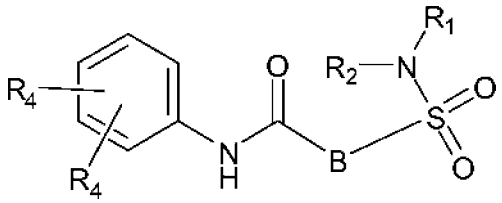
or



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.

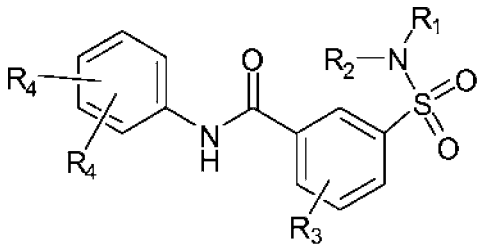
In another embodiment of the present invention, compounds according to Formula (I) are provided wherein B represents phenyl or thiophene, optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halogen, C_1-C_3alkyl, CN, CFH_2, CF_2H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

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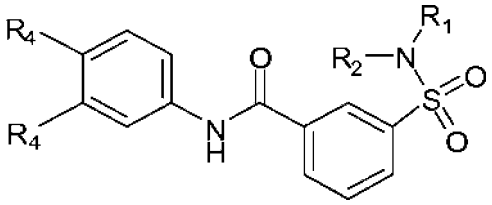
CF_3. In a preferred embodiment, R_3 represents Fluor or hydrogen, more preferably hydrogen.

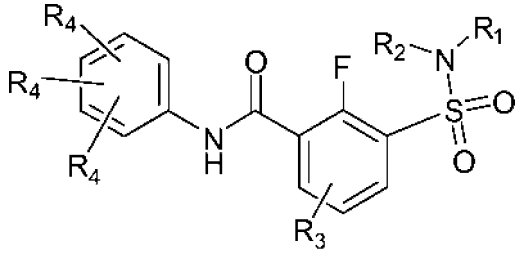
In yet another sub-embodiment, compounds are represented by Formula (Ic):



(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)

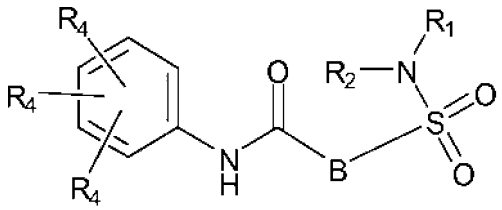


(Id)

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:

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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;

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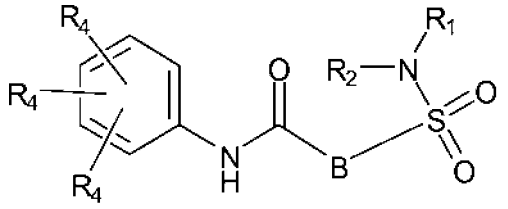
or a pharmaceutically acceptable salt or a solvate thereof. These compounds are especially suited for use in the prevention or treatment of an HBV infection in a mammal.

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)

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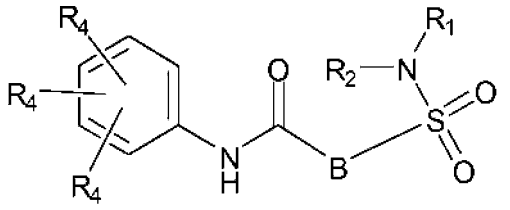

(I)

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;

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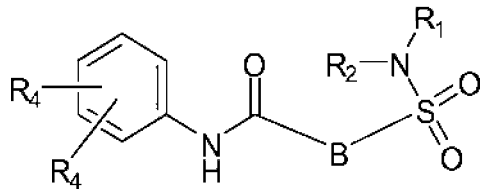
R_5 represents C_1-C_6alkyl, CFH_2, CF_2H, CF_3 or a 3-7 membered saturated ring optionally containing one or more heteroatoms each independently selected from the group consisting of O, S and N, such 3-7 membered saturated ring optionally being substituted with one or more substituents each independently 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.

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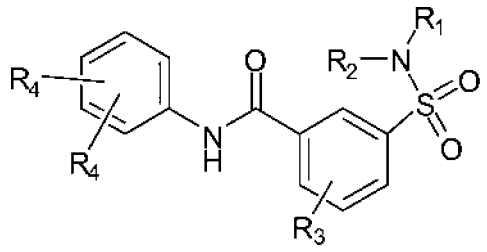
In a preferred embodiment of the invention, B represents phenyl or thiophene, optionally being substituted with one or more substituents each independently selected from the group consisting of hydrogen, halogen, C_1-C_3alkyl, CN, CFH_2, CF_2H and CF_3.

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~).

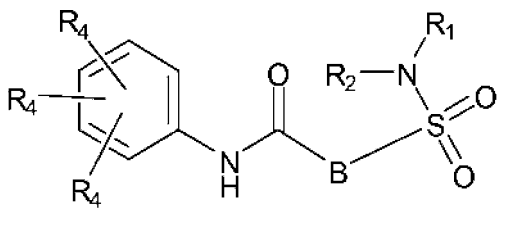
One sub-embodiment of the invention provides compounds which can be represented by formula (Ib)



(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)

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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;

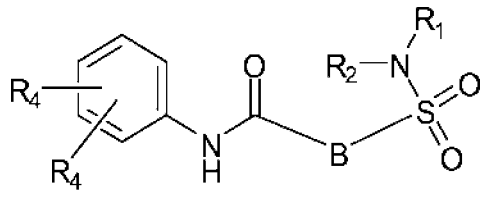
R_2 represents C_1-C_3alkyl-R_6 or a 4-7 membered saturated ring consisting of carbon atoms and one or more heteroatoms each independently selected from the group consisting of O or S, such 4-7 membered saturated ring optionally being substituted with one or more substituents each independently selected 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)

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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.

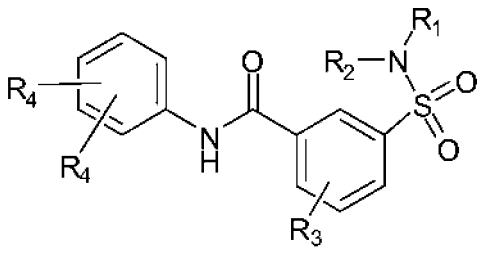
In one embodiment, R_2 represents C_1-C_3alkyl-R_6 or a 4-7 membered saturated ring consisting of carbon atoms and one or more heteroatoms each independently selected from the group consisting of O or S, such 4-7 membered saturated ring optionally being substituted with one or more substituents each 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;

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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:

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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

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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

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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.

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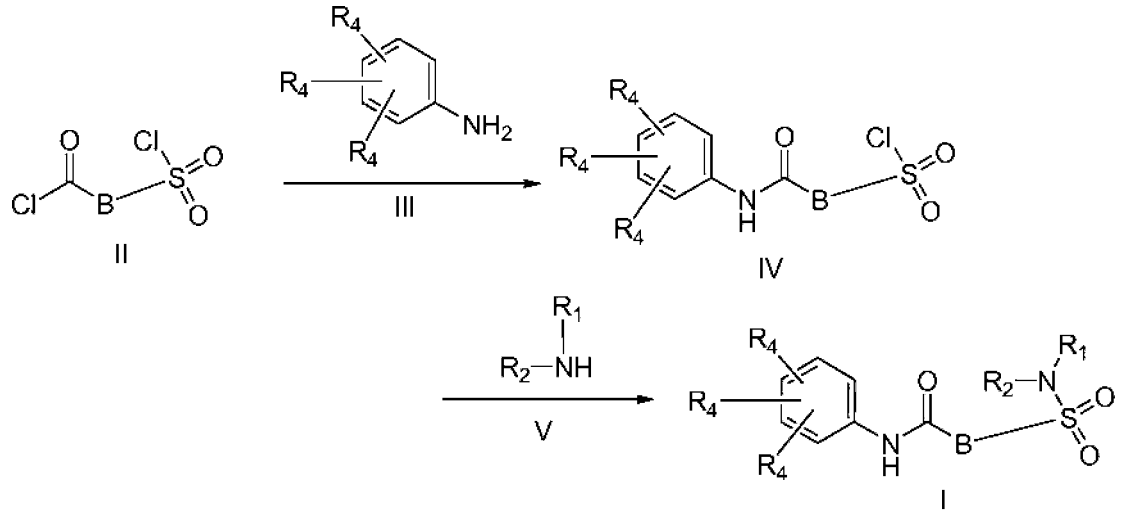
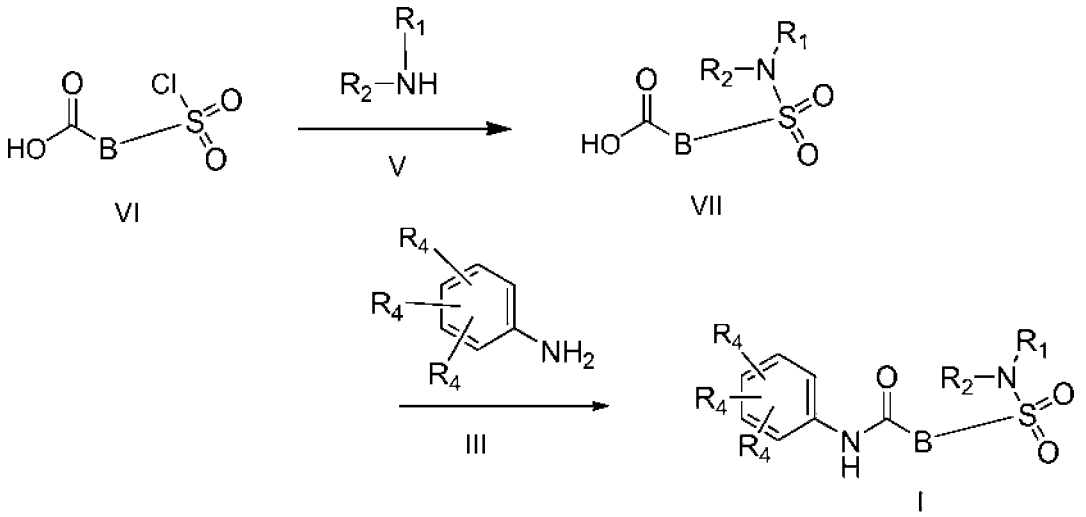


Scheme 1



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 $MeOH/CH_2Cl_2$

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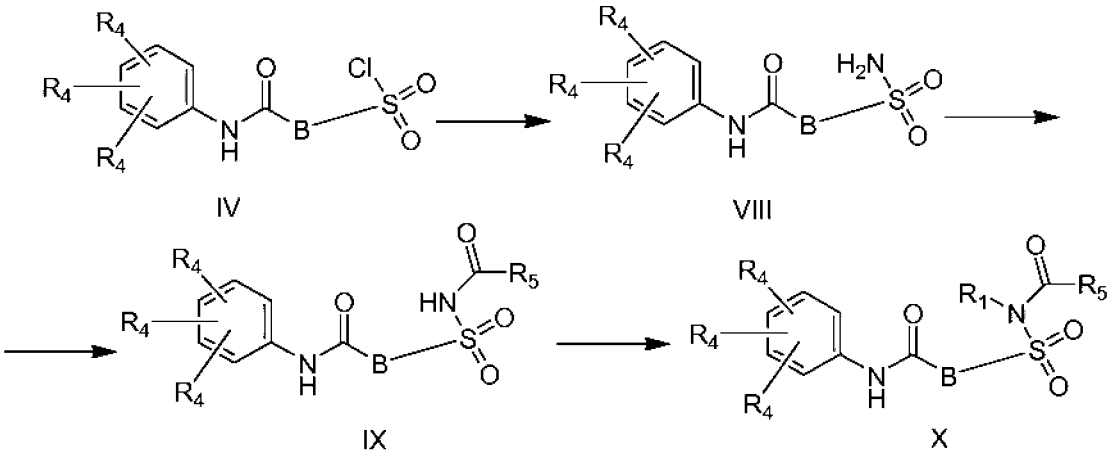
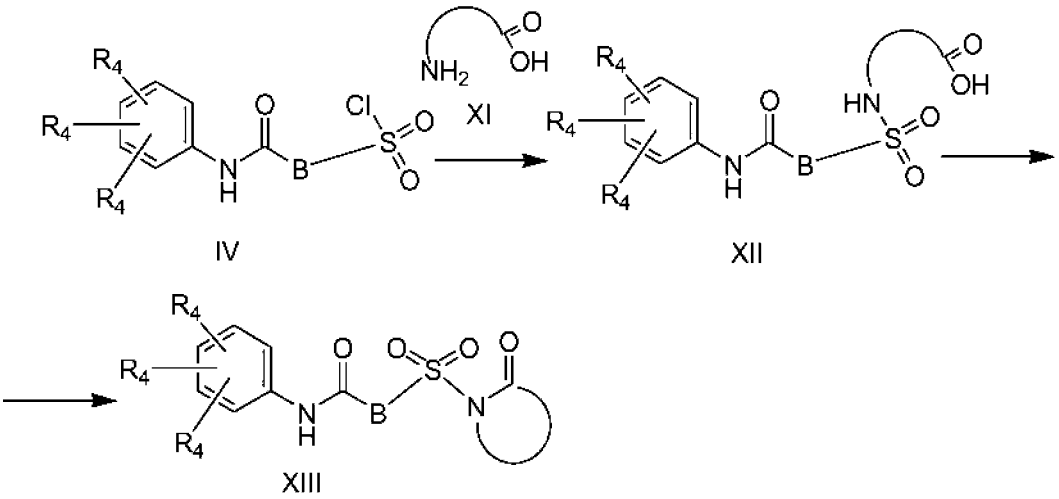


Scheme 3

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

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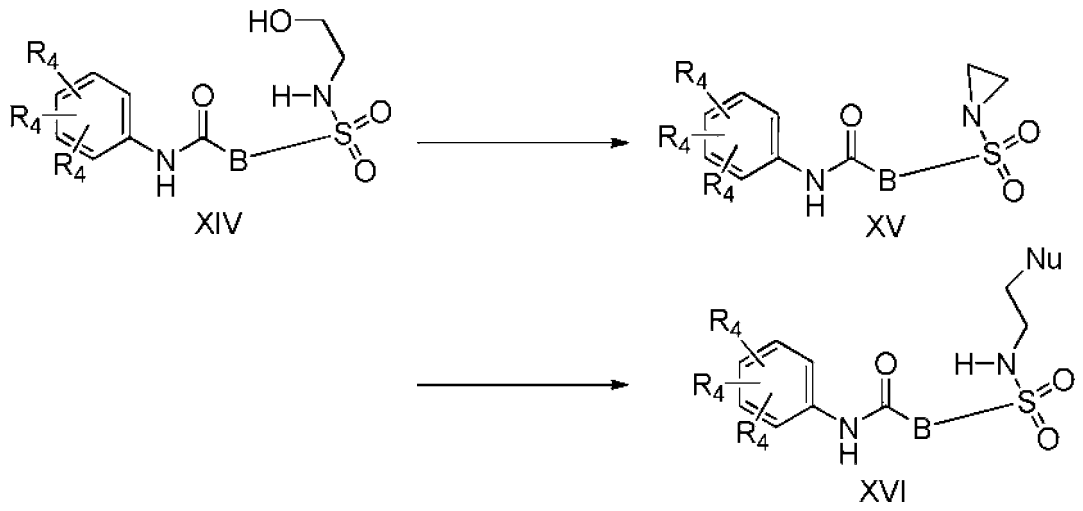
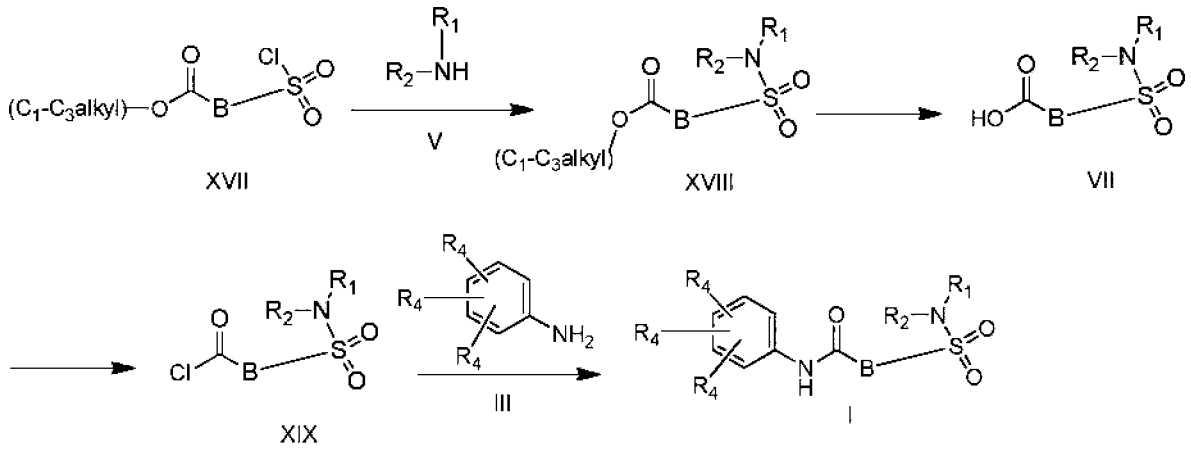


Scheme 5

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 treatment 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

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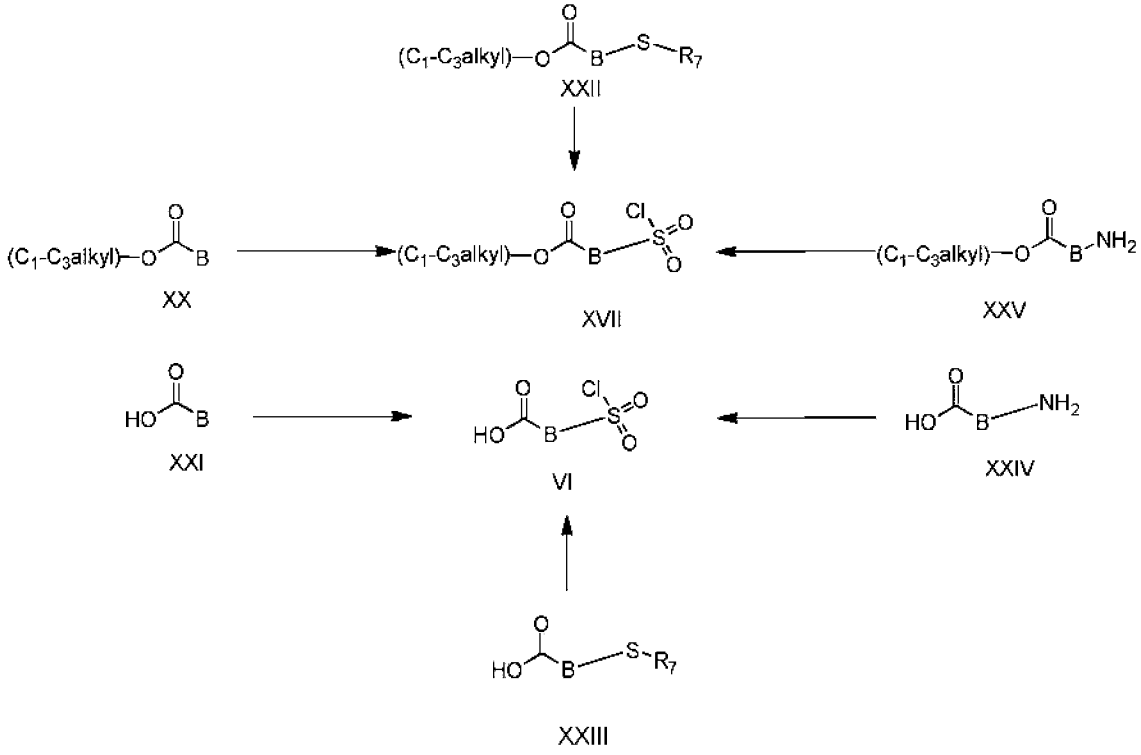
triethylamine or DIPEA, followed by hydrolysis of the ester, for example with LiOH in THF/H_2O, followed by acidification, results in a compound of general formula VII. A compound of general formula VII, obtained via the route in scheme 2 or scheme 6, can be transformed to and acid chloride of formula 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

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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

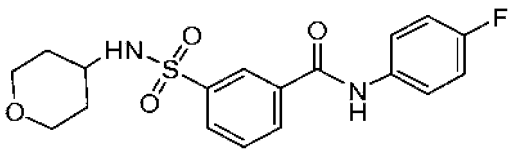
[40/60] to 7.5 [15/85] to 9.5 [100/0]; flow: 0.8 mL/min; column temp.: 50°C, Agilent TC-C18, 50×2.1mm, 5µm

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.

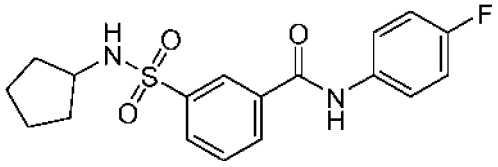
Compounds **21**, **49-55**, **57-62** were purchased from Aurora Fine Chemicals.



Compound **1**

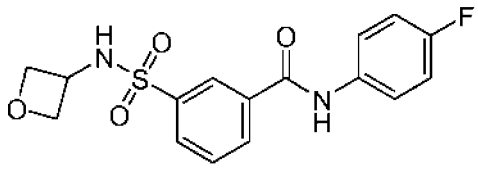
3-(chlorosulfonyl)benzoyl chloride (207 mg, 1 mmol) was dissolved in dichloromethane (3 mL) and 4-fluoroaniline (111 mg, 1.0 mmol) and triethylamine (112 mg, 1.0mmol) in dichloromethane (2 mL) were added to the mixture at 0°C. The mixture was next stirred at 20°C for 1 hour. To this reaction mixture 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:



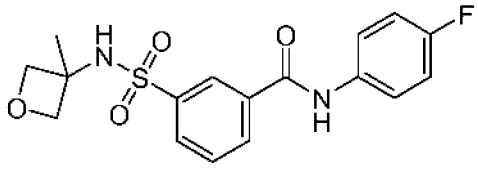
Compound **2**

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



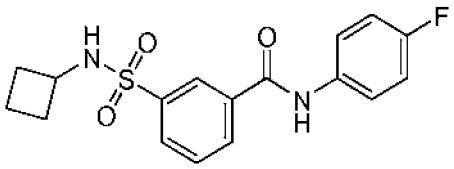
Compound **3**

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



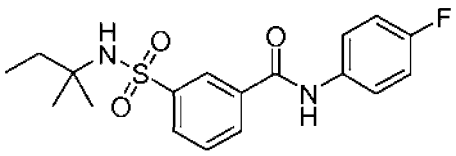
Compound **4**

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



Compound **5**

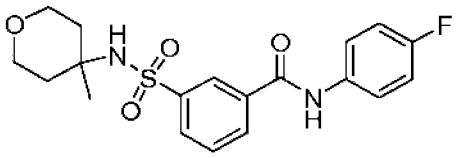
Method A; Rt: 5.32 min. m/z : 349.1 $(M+H)^-$ Exact mass: 348.1



Compound **79**

Method A; Rt: 5.39 min. m/z : 365.2 $(M+H)^+$ Exact mass: 364.1

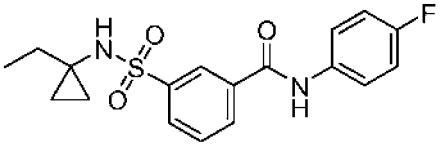
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.37 (1 H, t, *J*=1.5 Hz), 8.16 (1 H, br. s.), 8.11 (1 H, dm, *J*=8.0 Hz), 8.05 (1 H, dm, *J*=8.0 Hz), 7.57 - 7.70 (3 H, m), 7.08 (2 H, t, *J*=8.7 Hz), 4.78 (1 H, s), 1.55 (2 H, q, *J*=7.5 Hz), 1.18 (6 H, s), 0.84 (3 H, t, *J*=7.5 Hz).



Compound **83**

Method A; Rt: 4.20 min. m/z : 415.0 $(M+Na)^+$ Exact mass: 392.1;

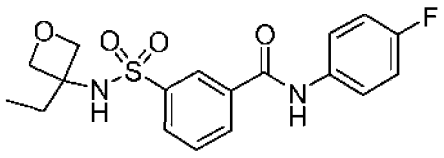
Purified by silica gel chromatography (gradient eluent: petroleum ether/ethyl acetate from 100/1 to 1/1). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.57 (1 H, br. s), 8.33 - 8.47 (1 H, m), 8.19 (1 H, dm, *J*=7.5 Hz), 8.06 (1 H, dm, *J*=7.5 Hz), 7.72 - 7.85 (3 H, m), 7.66 - 7.73 (1 H, br. s), 7.12 - 7.31 (2 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

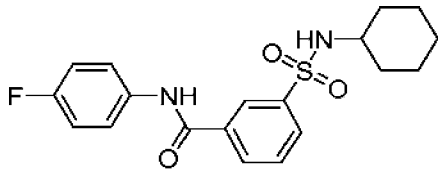
Purified by high performance liquid chromatography over RP-18 (eluent: CH_3CN in water (0.1%TFA) from 25 to 55, v/v). ^{1}H NMR (400 MHz, DMSO-d_6), δ ppm 0.34-0.42 (m, 2 H), 0.46-0.54 (m, 2H), 0.75(t, J=7.3 Hz, 3 H), 1.28 (q, J=7.3 Hz, 2 H), 7.15-7.25 (m,2 H) 7.67-7.83 (m, 3 H), 7.97 (d, J=8.3 Hz; 1 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

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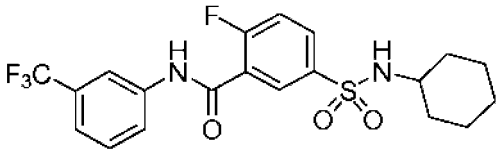
(15 mL) at 5°C, 4-fluoroaniline (0.52 g, 4.66 mmol) and DIPEA (1.64 g, 12.71 mmol) were successively added.. The mixture was stirred for 20 minutes and then HATU (1.93 g, 5.08 mmol) was added. The solution was stirred at room temperature overnight. To the reaction mixture aqueous $NaHCO_3$ (50 mL) was 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

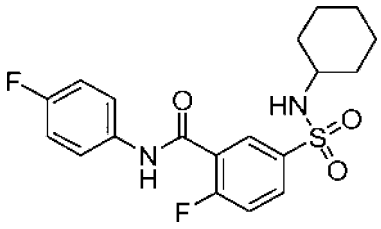
Synthesis of compound **7**



Compound **7**

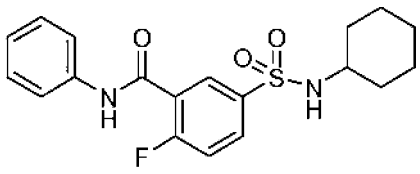
To 5-(chlorosulfonyl)-2-fluorobenzoic acid (10 g, 41.91 mmol) in EtOAc (150 mL) cyclohexanamine (12.47 g, 125.72 mmol) was added at room temperature. The reaction mixture was stirred at room temperature for 10 minutes and washed with 1N HCl (100 mL). The organic phase was dried over $MgSO_4$ and concentrated 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**

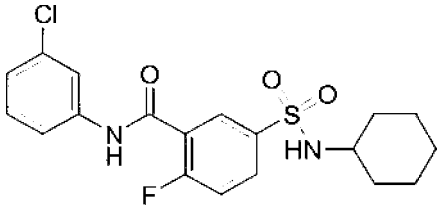
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.68 (1 H, br. s), 8.08 (1 H, dd, *J*=6.0, 2.5 Hz), 8.01 (1 H, ddd, *J*= 8.5, 4.5, 2.5 Hz), 7.83 (1 H, br. s), 7.70 - 7.77 (2 H, m), 7.60 (1 H, app. t, *J*= 9.0 Hz), 7.18 - 7.27 (2H, m), 2.90 - 3.07 (1 H, m), 1.53 - 1.67 (4 H, m), 1.40 - 1.53 (1 H, m), 0.96 - 1.25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



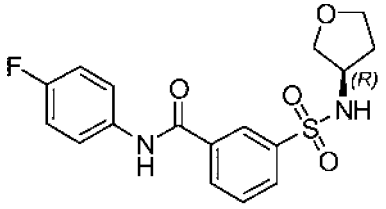
Compound **19**

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

Compound **43**



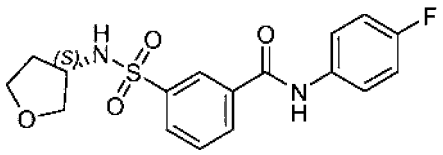
Method C; Rt: 4.53 min. m/z : 411.1 $(M+H)^-$ Exact mass: 410.1



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-(chlorosulfonyl)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) ^{1}H 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).

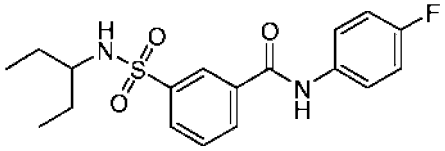


Compound **9**

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.

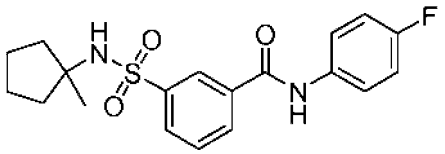
The mixture was washed with saturated aqueous critic acid (10 mL), brine and dried over Na_2SO_4. The solvent was removed in vacuo. The residue was purified by column chromatography over silica gel (gradient eluent: petroleum ether/ethyl acetate from 100/0 to 10/90). The pure fractions were collected 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); ^{1}H 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;



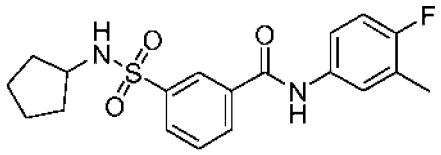
Compound **76**

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

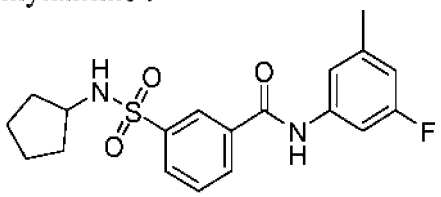
was washed by brine (15 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford 3-(N-cyclopentylsulfamoyl)benzoic acid (4.5 g).



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)

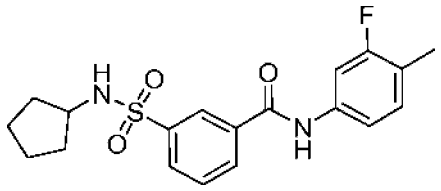
Prepared similarly as compound **11** starting from the corresponding anilines instead of 4-fluoro-3-methylaniline :



Compound **12**

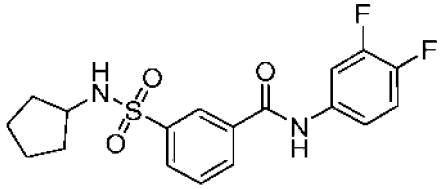
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.60 (1 H, bs), 8.36 (1 H, t, *J*=1.5 Hz), 8.19 (1 H, dm, *J*=7.5 Hz), 8.02 (1 H, dm, *J*=7.5 Hz), 7.81 (1 H, d, *J*=7.5 Hz), 7.78 (1 H, t, *J*=7.5 Hz), 7.55 (1 H, dm, *J*=11.0 Hz), 7.38 - 7.46 (1 H, m), 6.82 (1 H, dm, *J*=9.5 Hz),

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**

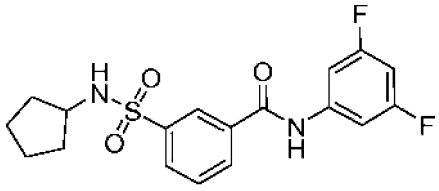
The residue was purified by column chromatography over silica gel (gradient eluent: petroleum ether/ethyl acetate from 100/0 to 40/60). Method B; Rt: 4.41 min. m/z : 377.2 $(M+H)^-$ Exact mass: 376.1



Compound **14**

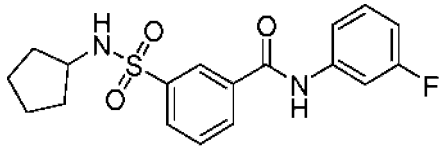
Method B; Rt: 4.34 min. m/z : 381.2 $(M+H)^+$ Exact mass: 380.1

^{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)



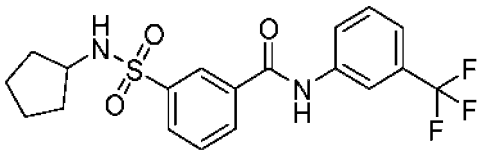
Compound **15**

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



Compound **77**

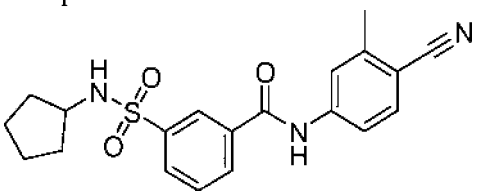
Method B; Rt: 5.45 min. m/z : 363.2 $(M+H)^-$ Exact mass: 362.1



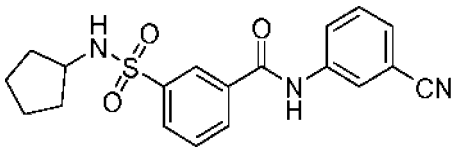
Compound **81**

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**

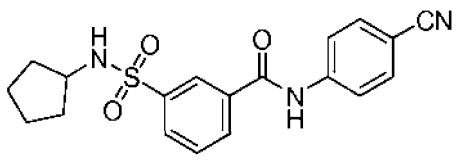


A solution of 3-(N-cyclopentylsulfamoyl)benzoic acid (500 mg, 1.73 mmol) in oxalyl dichloride (10 mL) was stirred at 45°C for 5 hours. The solvent was removed in vacuo. The crude 3-(N-cyclopentylsulfamoyl)benzoyl chloride (600 mg) was used as such in the next step.To an ice cooled mixture of 3-(N-cyclopentylsulfamoyl)benzoyl 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.



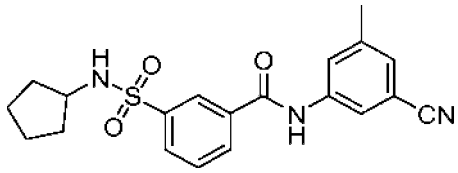
Compound **75**

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.



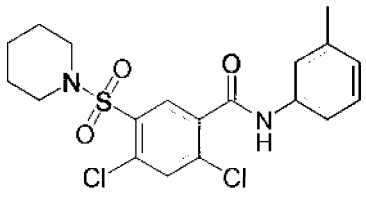
Compound **80**

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.



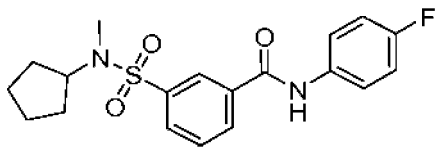
Compound **82**

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

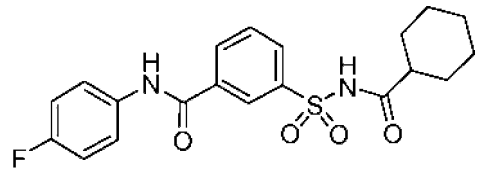


Compound **46**

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

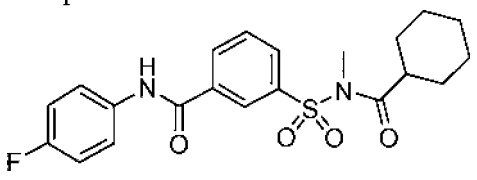
Compound **56**



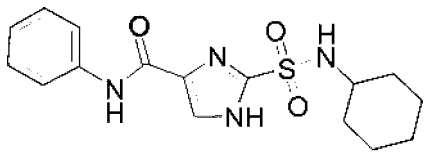
4-fluoroaniline (0.93 g, 8.366 mmol) and DIPEA (2.91 mL, 16.732 mmol) were dissolved in CH_2Cl_2 (20 mL). 3-(chlorosulfonyl)benzoyl chloride (2 g, 8.366 mmol) in CH_2Cl_2 (20 mL) was added in one portion at 0°C. The mixture was stirred for 1 hour at 0°C. The reaction mixture (40 mL) containing 3-(4-fluorophenylcarbamoyl)benzene-1-sulfonyl 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**



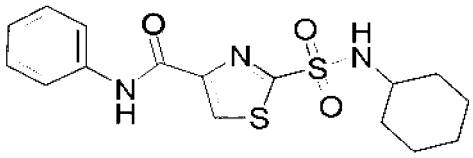
Compound **56** (600 mg) was dissolved in CH_2Cl_2 (6 mL) and MeOH (2 mL) and $TMSCHN_2$ (3.7 mL, 7.415 mmol, 2M in hexane) were added drop wise at 20°C. The mixture was stirred for 2 hours at 20°C. The solvent was removed in vacuo. The residue was purified by flash column (gradient eluent: petroleum 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:

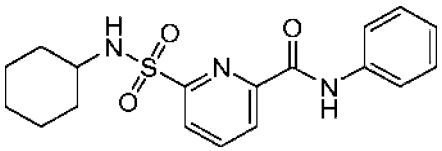
25-55%, 30 min) resulting in ethyl 2-(N-cyclohexylsulfamoyl)-1H-imidazole-4-carboxylate (0.6 g) as a light yellow solid. To a solution of ethyl 2-(N-cyclohexyl-sulfamoyl)-1H-imidazole-4-carboxylate (0.6 g, 1.99 mmol) in EtOH-H_2O (3/1; 20 mL), LiOH (0.145 g, 6.055 mmol) was added. The mixture was stirred 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**

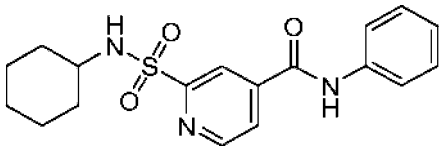
A mixture of ethyl 2-(chlorosulfonyl)thiazole-4-carboxylate (3 g, 11.73 mmol), Et_3N (3.56 g, 35.2 mmol) and cyclohexanamine (1.75 g, 17.65 mmol) in THF (100 mL) was stirred at room temperature for 15 hours. The mixture was concentrated and purified by preparative HPLC resulting in ethyl 2-(N-cyclohexylsulfamoyl)thiazole-4-carboxylate (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)

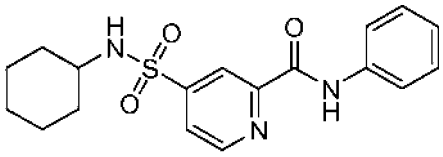


Compound **66**

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. ^{1}H 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)

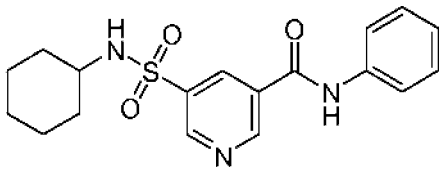
Compound **67**



2-chloro-N-cyclohexylpyridine-4-sulfonamide (540 mg, 1.965 mmol), $PdCl_2$dppf (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

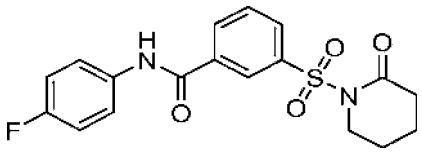
room temperature for 18 hour. The mixture was diluted with water (200 mL), and extracted with EtOAc. The organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The obtained residue was purified by silica gel chromatography (10-20% EtOAc in petroleum ether) resulting 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**



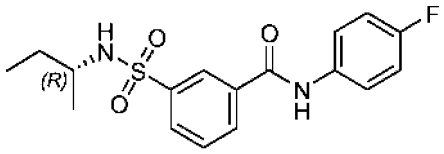
Thionyl chloride (10 mL, 137 mmol) was added drop wise to water (60 mL) at 0-5°C. The mixture was stirred at room temperature for 16 hour. CuCl (40 mg, 0.4 mmol) was added, and the mixture (mixture A) was cooled to -5°C. To a mixture of 5-amino-nicotinic acid in con. HCl (35 mL), a solution of $NaNO_2$ (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**



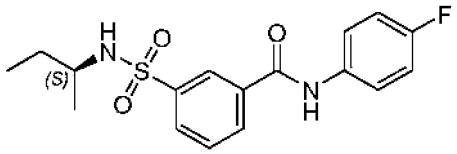
To an ice-cooled solution of 5-aminopentanoic acid (1.2 g, 3.44 mmol) and 1N NaOH (8 mL) in THF (16 mL) was added 3-(4-fluorophenylcarbamoyl)benzene-1-sulfonyl chloride (0.444 g, 3.78mmol). Then the reaction mixture was stirred at 25°C overnight. The resulting mixture was diluted with 1N HCl (10 mL) 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)phenylsulfon-amido) 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**



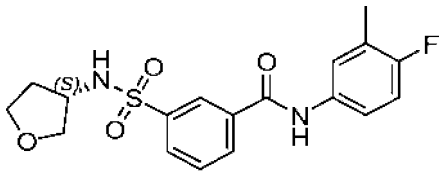
To an iced-cooled mixture of (*R*)-butan-2-amine (0.500 g, 6.837 mmol) and NaOH (0.547 g, 13.67 mmol) in H_2O (15 mL) and THF (15 mL), 3-(chlorosulfonyl)benzoic acid was added (1.508 g, 6.84 mmol) in portions. The reaction mixture was stirred at 20°C for 2 hours. The resulting mixture was diluted with 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**

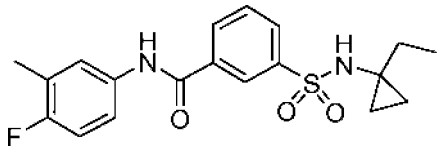
Prepared similar as described for compound **70** starting from (*S*)-butan-2-amine instead of (*R*)-butan-2-amine.Method B; Rt: 4.03 min. m/z : 351.2 $(M+H)^+$ Exact mass: 350.1 ($[\alpha]_D^{20}$ = + (*c*= 0.2, MeOH). $[\alpha]_D^{20}$ = + 9.49 (c 0.611 w/v %, DMF), Column: Chiralpak AD-3 150×4.6mm 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**

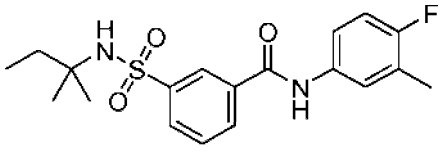
3-(chlorosulfonyl)benzoyl chloride (1200 mg, 5.0 mmol) was dissolved in dichloromethane (15 mL). A solution of 4-fluoro-3-methylaniline (625 mg, 5.0 mmol) and triethylamine (606 mg, 6.0 mmol) in dichloromethane (15 mL) was added to the mixture at 0°C. The mixture was stirred at 25°C for 1 hour. The reaction 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).

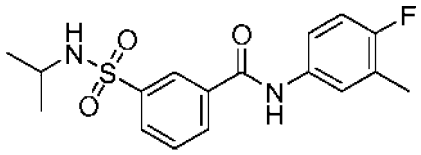
Compound **86**



Prepared similarly as described for compound **72** using 2-methylbutan-2-aminchydrochloride 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**:

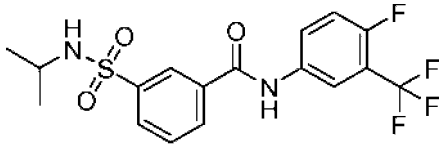
A mixture of 3-(chlorosulfonyl)benzoyl chloride (4.61 g ,19.28mmol) in toluene (45 mL) was refluxed under a gentle flow of nitrogen. 4-fluoro-3-methylaniline (2.19 g, 17.53 mmol) in toluene (15 mL) was added drop wise to the refluxing solution. After addition, the mixture was refluxed for another 30 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**

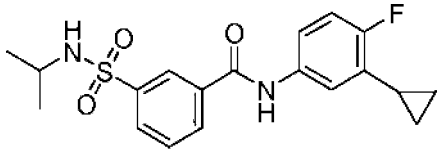
To an iced-cooled solution of 3-(chlorosulfonyl)benzoic acid (50.0 g, 226.6 mmol) in ethylacetate (1000 mL) was added isopropylamine (67.0 g, 1.13 mol) in one portion. The reaction mixture was stirred at 25°C for 3 hours. The resulting mixture was diluted with 1N HCl (500 mL) and extracted with ethyl 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 citric 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**

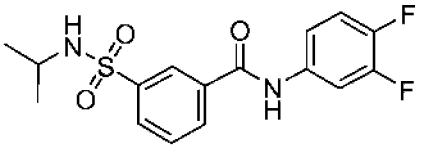
Prepared similarly as described for compound **73**, using 4-fluoro-3-(trifluoromethyl)-aniline instead of 4-fluoro-3-methylaniline. Purified on HPLC Synergi 150x30mmx5u (eluent: CH_3CN in H_2O (0.05% HCl) from 45% to 75%, v/v). Method A; Rt: 5.62 min. m/z : 405.2 $(M+H)^+$ Exact mass: 404.1. ^{1}H NMR (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**

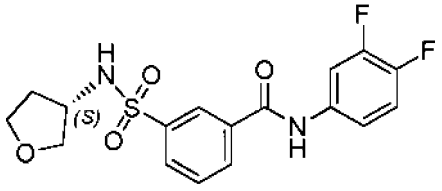
A mixture of N-(3-bromo-4-fluorophenyl)-3-(N-isopropylsulfamoyl)benzamide (prepared similarly as described for compound **73,** using 3-bromo-4-fluoroaniline instead of 4-fluoro-3-methylaniline and purified via preparative high performance liquid chromatography over RP-18 (eluent: CH_3CN in H_2O (0.05% 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; ^{1}H 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).



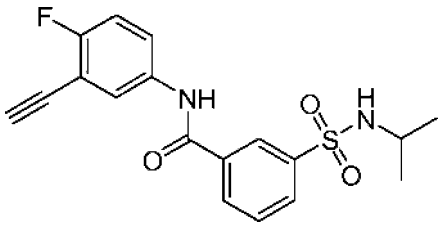
Compound **88**

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; ^{1}H 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**

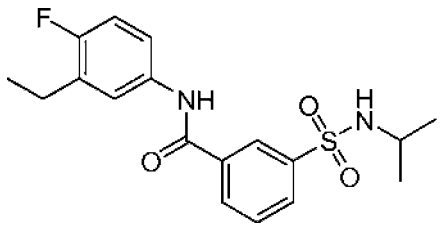
3-(chlorosulfonyl)benzoyl chloride (1200 mg, 5.0 mmol) was dissolved in dichloromethane (15 mL). A solution of 3,4-difluoroaniline (650 mg, 5.0 mmol) and triethylamine (606 mg, 6.0mmol) in dichloromethane (15 mL) was added to the mixture at 0°C. The mixture was stirred at 25°C for 1 hour. To the obtained 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).

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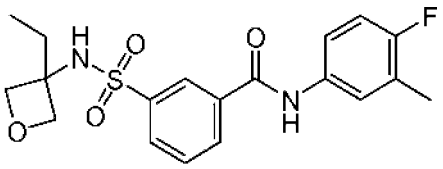
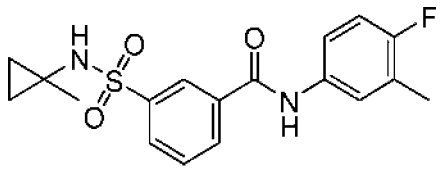


Compound **93**

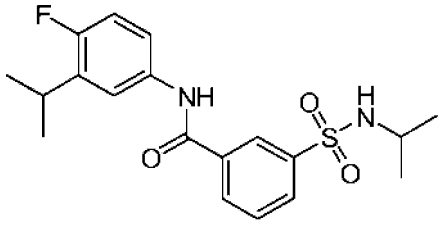
To a solution of 3-(chlorosulfonyl)benzoyl chloride (0.50 g, 2.09 mmol) in CH_2Cl_2 (10 mL), DIPEA was added (1.35 g, 10.45 mmol) followed by slow addition of 4-fluoro-3-methylaniline (0.25 g, 1.99 mmol). After stirring at 25°C for 0.5 hour, 3-ethyloxetan-3-amine (0.21 g, 2.09 mmol) was added. After 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;

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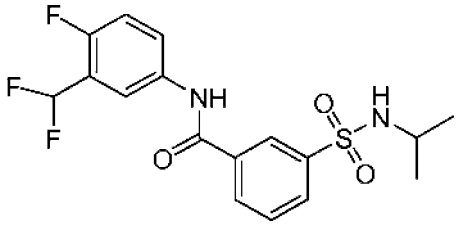
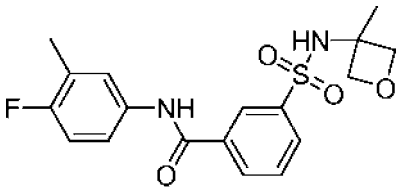


Compound **96**

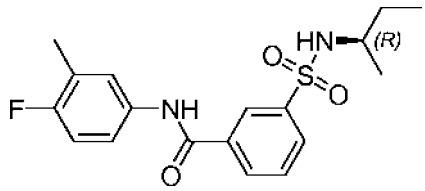
3-(difluoromethyl)-4-fluoroaniline (1.20 g, 7.448 mmol), 3-(N-isopropylsulfamoyl)-benzoic acid (0.90 g, 3.699 mmol) and DIPEA (1.93 mL, 11.10 mmol) were dissolved in CH_2Cl_2 (10 mL) and HATU (1.41 g, 3.699 mmol) was added at 0°C. The mixture was stirred at 20 °C for 2 hours. The mixture was diluted 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; ^1H 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**

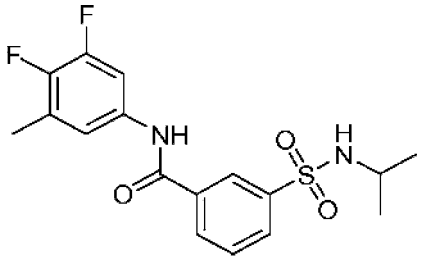
To 3-(4-fluoro-3-methylphenylcarbamoyl)benzene-1-sulfonyl chloride (500 mg, 1.53 mmol) in toluene (10 mL) at room temperature, a solution of diisopropyl-ethylamine (0.657 mL, 141.6 mmol) and 3-methyl-3-oxetanamine hydrochloride (207 mg, 1.68 mmol) in toluene (5 mL) and dichloromethane (10 mL) was added 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; ^1H 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**

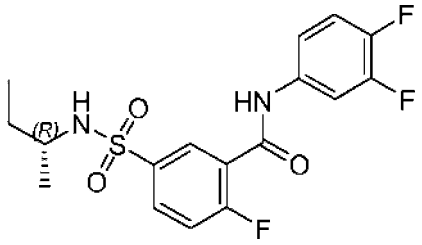
To 3-(4-fluoro-3-methylphenylcarbamoyl)benzene-1-sulfonyl chloride (500 mg, 1.53 mmol) in toluene (10 mL) at room temperature, a solution of diisopropylethylamine (0.657 mL, 141.6 mmol) and (*R*)-(-)-2-aminobutane (130 mg, 1.83 mmol) in toluene (5 mL) and dichloromethane (10 mL) was added drop wise. 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

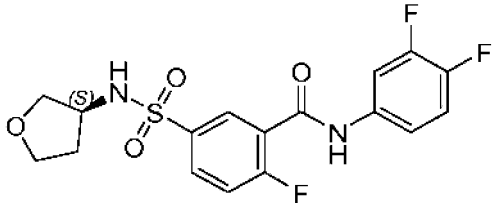
70/30) resulting in crude N-(3-bromo-4,5-difluorophenyl)-3-(N-isopropylsulfamoyl)-benzamide (4 g). A mixture of N-(3-bromo-4,5-difluorophenyl)-3-(N-isopropyl-sulfamoyl)benzamide (1 g, 2.308 mmol), methylboronic acid (1 g, 4.616 mmol), Cs_2CO_3 (2.26 g, 6.924 mmol), 2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl (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 silica 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).

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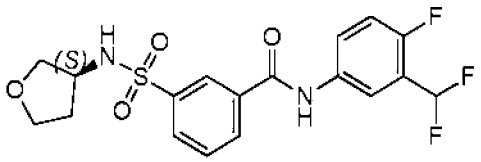
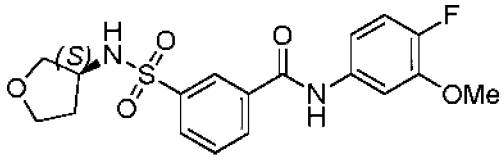


Compound **102**

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).



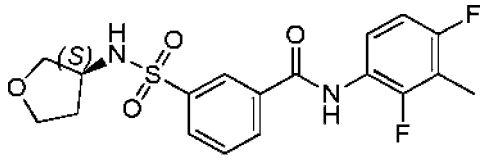
Compound **103**

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

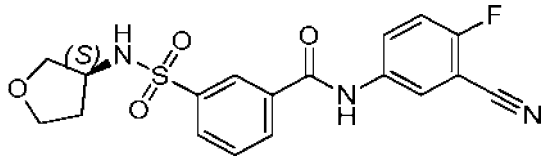
Prepared similarly as described for compound **103:**

Compound **104**



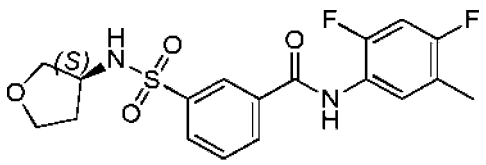
Method A; Rt: 5.17 min. m/z: 397.3 $(M+H)^-$ Exact mass: 396.1

Compound **105**



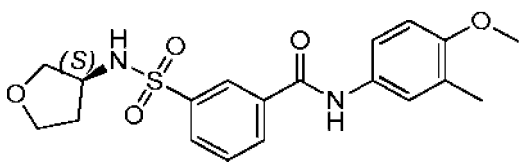
Method A; Rt: 5.10 min. m/z: 389.1 $(M+H)^+$ Exact mass: 390.2

Compound **106**



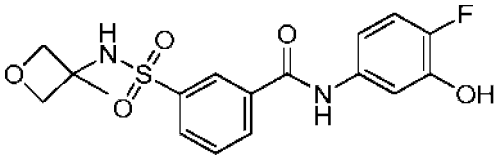
Method A; Rt: 5.18 min. m/z : 397.2 $(M+H)^-$ Exact mass: 396.1

^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)



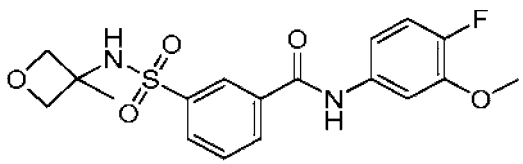
Compound **107**

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 resulting in compound **108** (60 mg). Method A; Rt: 4.47 min. m/z: 381.2 $(M+H)^+$ Exact mass: 380.1



Compound **109**

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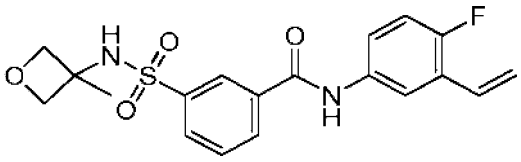
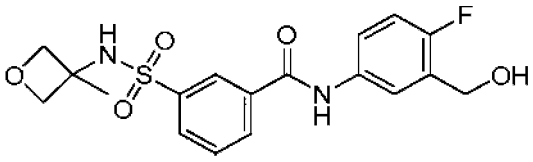
Prepared similarly as described for compound **108**, using 4-fluoro-3-methoxy-aniline instead of 5-amino-2-fluoro-phenol. Method A; Rt: 5.03 min. m/z: 395.2 $(M+H)^+$ Exact mass: 394.1



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

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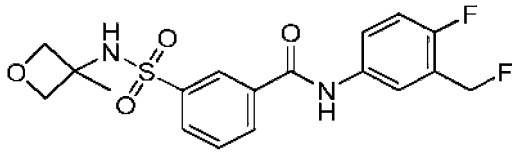
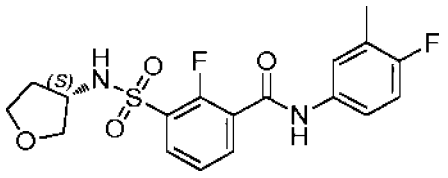
DMF (40 mL). HATU (5.02 g , 13.2 mmol) was added at 0°C. The mixture was stirred at 20°C for 2 hours. The solvent was removed in vacuo and the obtained residue was purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate=3:1) resulting in methyl 2-fluoro-5-[[3-[(3-methyloxetan-3-yl)sulfamoyl]-benzoyl]amino]benzoate (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**



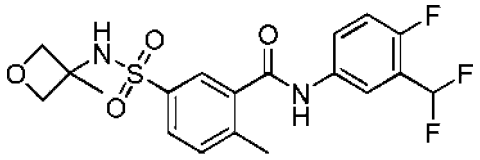
(2-fluoro-5-nitro-phenyl)methanol (4.3 g, 25.1 mmol) was dissolved in dichloro-methane (50 mL). Diethylaminosulfur trifluoride (4.5 g, 27.9 mmol) was added drop wise to the mixture at -30°C. The mixture was stirred at 10° C for 4 hours. Methanol (10 mL) was added to the mixture and the mixture was further 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-

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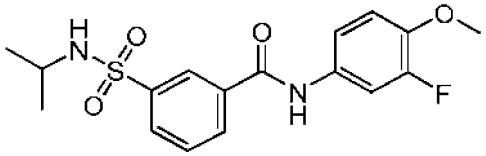
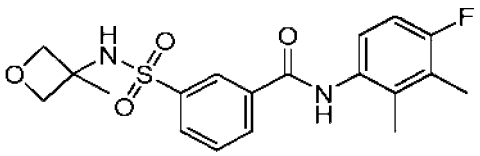
3-yl)sulfamoyl]benzoic acid (250 mg, 0.876 mmol), 3-(difluoromethyl)-4-fluoro-aniline (178 mg, 1.1 mmol) and DIPEA (232 mg, 1.8 mmol) were dissolved in DMF (5 mL). HATU (399 mg , 1.05 mmol) was added at 0°C. The mixture was stirred at 20°C for 2 hours. The solvent was removed in vacuo and the obtained 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

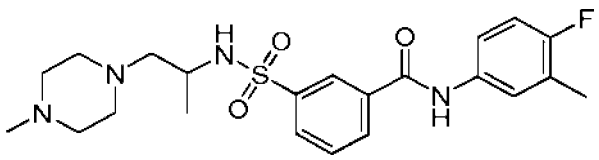


Compound **115**

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.

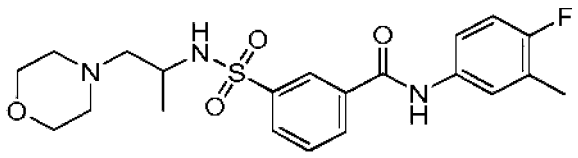
Compound **116**



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

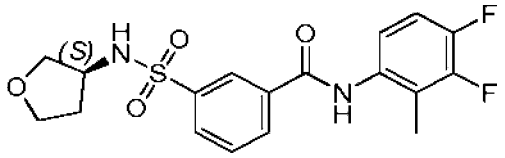
obtained residue was purified by preparative high-performance liquid chromatography (column: Luna 150*30mm*5u, mobile phase: CH_3CN in water (0.1% NH_4HCO_3) from 44% to 74%). The pure fractions were collected, concentrated in vacuo and the residual aqueous solution was lyophilized to dryness resulting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

Compound **117**



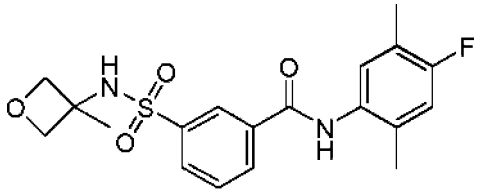
Prepared similarly as desribed for compound **116** using morpholine instead of 1-methylpiperazine. Method A; Rt: 4.45 min. m/z : 436.3 $(M+H)^+$ Exact mass: 435.2

Compound **118**



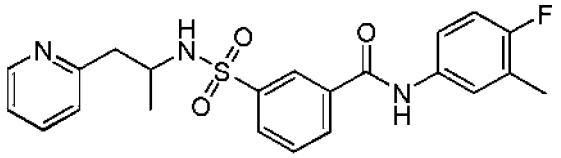
To a stirred solution of 3,4-difluoro-2-methyl-aniline (369 mg, 2.6 mmol), 3-[[(3*S*)-tetrahydrofuran-3-yl]sulfamoyl]benzoic acid (700 mg, 2.58 mmol) and N,N-diisopropylethylamine(1.35 ml, 7.74 mmol) in DMF (10 mL), Pybrop (132705-51-2, 1.82 g, 3.9 mmol) was added at 0° C. The resulting mixture was stirred 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**



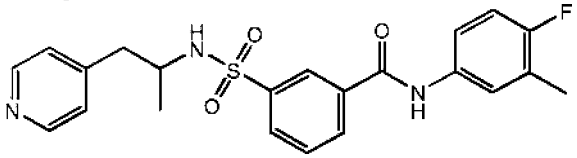
Prepared similarly as described for compound **127** using 4-fluoro-2,5-dimethyl-aniline instead of 4-fluoro-3-(fluoromethyl)aniline, and DIPEA instead of NEt_3. Method A; Rt: 5.27 min. m/z: 393.3 $(M+H)^-$ Exact mass: 392.1

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**



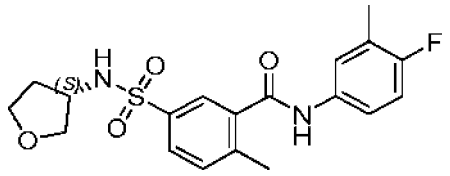
Compound **224** was prepared similarly as described for compound **223**, using 1-(4-pyridyl)propan-2-amine instead of 1-(2-pyridyl)propan-2-amine. Compound **224** was purified by preparative high-performance liquid chromatography (column: Luna 150*30mm*4u, mobile phase: CH_3CN in water (0.05% NH_4HCO_3) 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

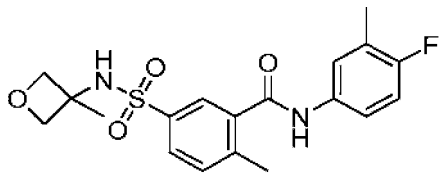
2018204597 25 Jun 2018

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**

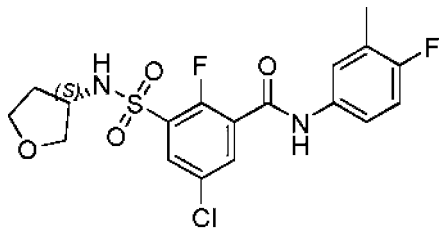


A solution of (*S*)-3-aminotetrahydrofuran tosylate (0.76 g, 2.93 mmol) and diisopropylethylamine (1.26 mL, 7.31 mmol) in dichloromethane (10 mL) was added drop wise to a solution of 3-[(4-fluoro-3-methyl-phenyl)carbamoyl]-4-methyl-benzenesulfonyl chloride (1 g, 2.93 mmol) in dichloromethane (10 mL). 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).

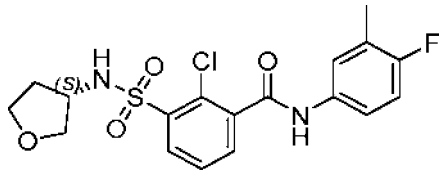


Compound **123**

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,

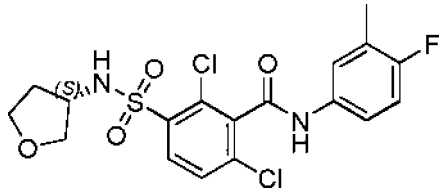
J=6.9, 2.3 Hz, 1 H), 7.91 (dd, J=5.7, 2.6 Hz, 1 H), 8.07 (dd, J=5.2, 2.8 Hz, 1 H), 8.57 (d, J=6.8 Hz, 1 H), 10.68 (s, 1 H)

Compound **124**



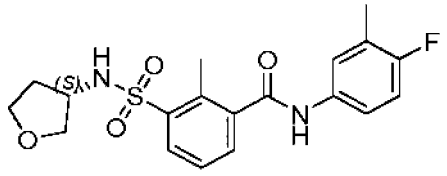
Compound **125** (167 mg,0.371 mmol) and Pd/C (25 mg) were stirred in methanol (19 mL) under hydrogen atmosphere during 80 minutes. The reaction mixture was filtered and concentrated. The obtained residue was purified by preparative SFC (Stationary phase: Chiralpak Diacel AD 30 x 250 mm), Mobile phase: 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.

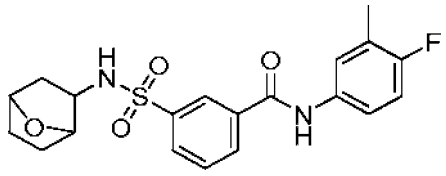
Workup W1: A precipitate was formed. The precipitate was filtered off, rinced with diisopropylether and dried in a vacuum oven at 55 °C.

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).

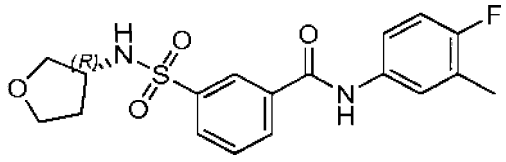
Workup W4: The organic layer was separated and loaded on a silica gel column. The mixture was purified using gradient elution from heptane to EtOAc.

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).

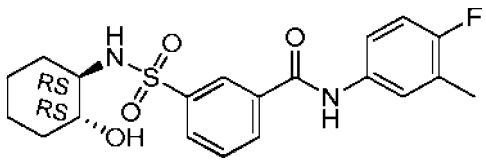
Compound **129**



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

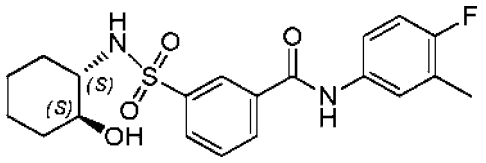
Method F; Rt: 0.89 min. m/z: 396.1 $(M+NH_4)^+$ Exact mass: 378.1. ^{1} H NMR (400 MHz, DMSO-d_6) ppm 1.56 - 1.65 (m, 1 H), 1.85 - 1.94 (m, 1 H), 2.25 (d, J=1.8 Hz, 3 H), 3.36 (dd, J=9.0, 4.4 Hz, 1 H), 3.52 - 3.65 (m, 2 H), 3.65 - 3.73 (m, 1 H), 3.73 - 3.79

(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)



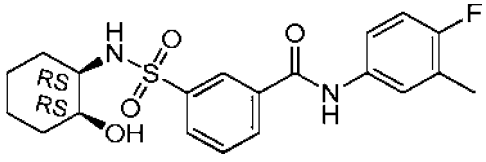
Compound **130**

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.



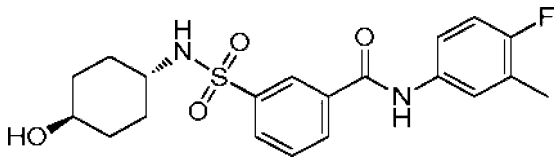
Compound **131**

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**

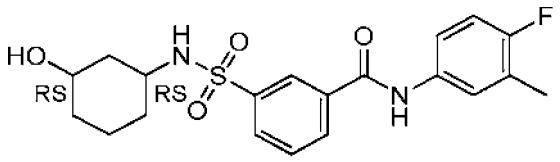
Synthesis following procedure S3 with racemic cis-2-aminocyclohexanol hydrochloride as amine, workup W2. Method F; Rt: 0.96 min. m/z: 424.1 $(M+NH_4)^+$ Exact mass: 406.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.01 - 1.26 (m, 4 H), 1.26 - 1.36 (m, 1 H), 1.38 - 1.62 (m, 3 H), 2.25 (d, J=1.8 Hz, 3 H), 3.03 - 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** 

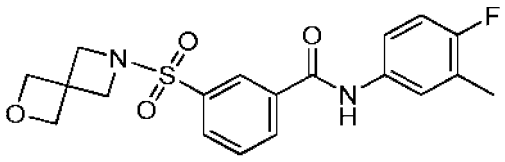
Method F; Rt: 0.89 min. m/z: 424.2 $(M+NH_4)^+$ Exact mass: 406.1.

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)

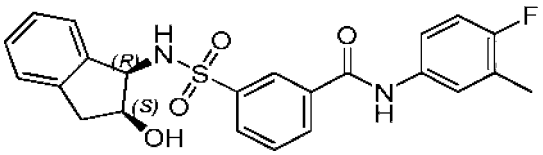
Trans: enantiomers **134c** and **134d** N-(4-fluoro-3-methyl-phenyl)-3-[[(1R,3R)-3 hydroxycyclohexyl]sulfamoyl]benzamide or N-(4-fluoro-3-methyl-phenyl)-3-[[(1S,3S)-3-hydroxycyclohexyl]sulfamoyl]benzamide ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.08 - 1.20 (m, 1 H), 1.25 - 1.42 (m, 4 H), 1.42 - 1.58 (m,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



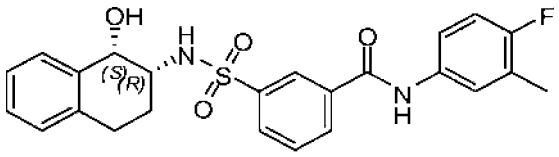
Compound **135**

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)

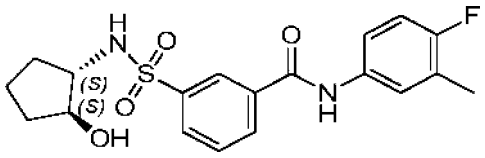


Compound **137**

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

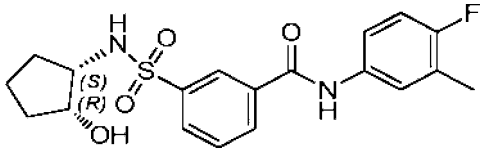
Hz, 1 H), 7.09 - 7.24 (m, 4 H), 7.55 - 7.63 (m, 1 H), 7.62-7.70 (m, 2 H), 7.75 (t, J=7.8 Hz, 1 H), 8.06 - 8.13 (m, 1 H), 8.19 (d, J=8.1 Hz, 1 H), 8.43 (t, J=1.5 Hz, 1 H), 10.44 (s, 1 H), $[\alpha]_D^{20}$: +66 ° (c 0.55 w/v %, DMF). DSC (From 30 to 300 °C at 10°C/min): 170°C.

Compound **138**



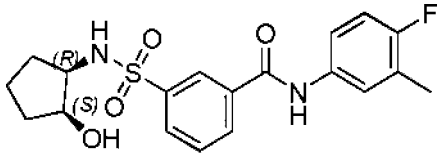
Synthesis following procedure S1 with trans-(1*S*,2*S*)-2-aminocyclopentanol hydrochloride as amine, workup W1. Method F; Rt: 0.88 min. m/z: 410.4 $(M+NH_4)^+$ Exact mass: 392.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.16 - 1.29 (m, 1 H), 1.29 - 1.40 (m, 1 H), 1.50 (quin, J=7.4 Hz, 2 H), 1.61 - 1.78 (m, 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**

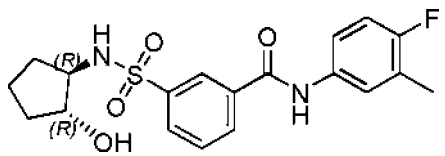


Synthesis following procedure S1 with cis-(1*R*,2*S*)-2-aminocyclopentanol hydrochloride as amine, workup W1. Method F; Rt: 0.92 min. m/z: 410.1 $(M+NH_4)^+$ Exact mass: 392.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.25 - 1.51 (m, 4 H), 1.51 - 1.67 (m, 2 H), 2.25 (d, J=1.5 Hz, 3 H), 3.21 - 3.28 (m, 1 H), 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)

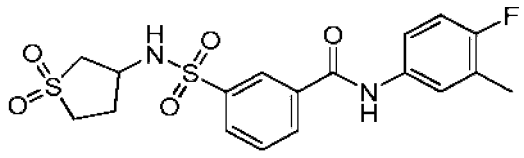
Compound **172**



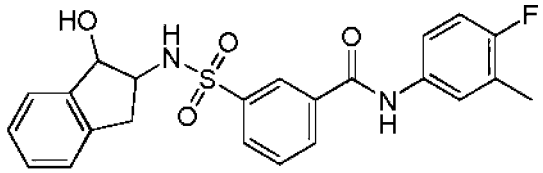
Synthesis following procedure S2 with cis-(1*S*,2*R*)-2-aminocyclopentanol hydrochloride as amine.The formed precipitate was collected on a glassfilter and rinsed with CH_2Cl_2 (2 x 5 mL). The precipitate was further purified using silica gel column chromatography (gradient elution: EtOAc-heptane 0:100 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)

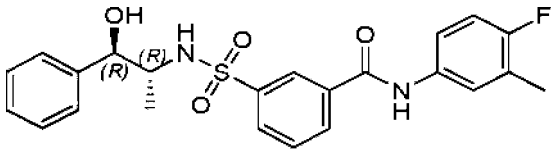
Compound **141** 

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.

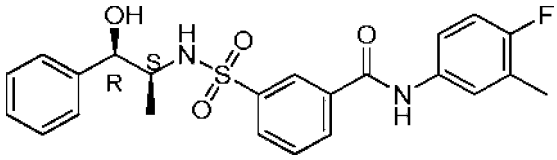
141b, 141d: N-(4-fluoro-3-methyl-phenyl)-3-[[(1*R*,2*S*)-1-hydroxyindan-2-yl]sulfamoyl]benzamide or N-(4-fluoro-3-methyl-phenyl)-3-[[(1S,2R)-1-hydroxyindan-2-yl]sulfamoyl]benzamide. ^{1}H NMR (600 MHz, ACETONE-d_6, -14 °C) δ ppm 2.25 (d, J=1.9 Hz, 3 H), 2.80 - 2.90 (m, 2 H), 3.94 - 3.99 (m, 1 H), 4.72 (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**

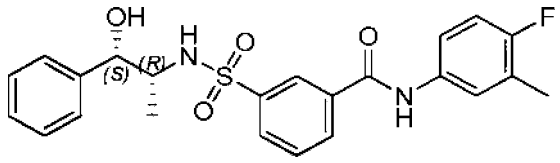


Synthesis following procedure S4 with (1*R*,2*R*)-2-amino-1-phenyl-propan-1-ol as amine, workup W4. Method F; Rt: 1.00 min. m/z: 460.1 $(M+NH_4)^-$ Exact mass: 442.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.76 (d, J=6.8 Hz, 3 H), 2.25 (d, J=1.3 Hz, 3 H), 3.37 - 3.46 (m, 1 H), 4.56 (d, J=4.6 Hz, 1 H), 5.41 (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**

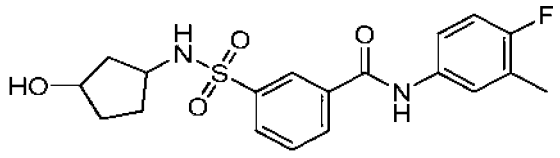


Synthesis following procedure S1 with (1*R*,2*S*)-(-)-norephedrine as amine, workup W1. Method F; Rt: 1.01 min. m/z: 460.1 $(M+NH_4)^+$ Exact mass: 442.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.79 (d, J=6.8 Hz, 3 H), 2.25 (d, J=1.8 Hz, 3 H), 3.33 - 3.37 (m, 1 H), 4.48 (t, J=4.6 Hz, 1 H), 5.42 (d, J=4.6 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)

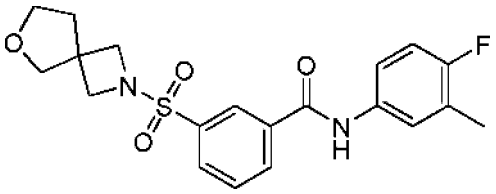


Compound **145**

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-

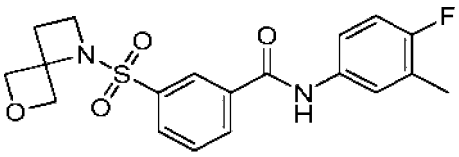
pentyl]sulfamoyl]benzamide. Method F; Rt: 0.82 min. m/z: 410.2 $(M+NH_4)^+$ Exact mass: 392.1.

^{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)



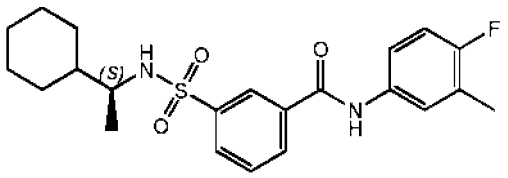
Compound **146**

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).



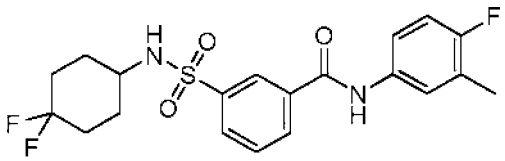
Compound **147**

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)



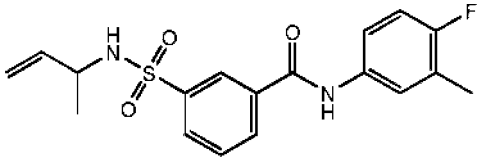
Compound **148**

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



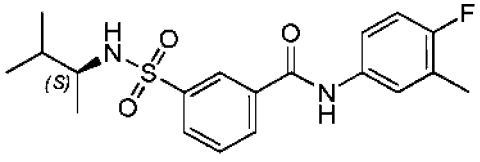
Compound **149**

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.



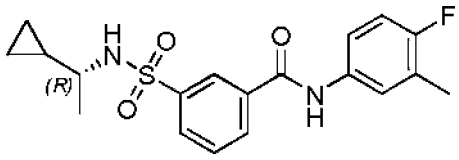
Compound **150**

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).



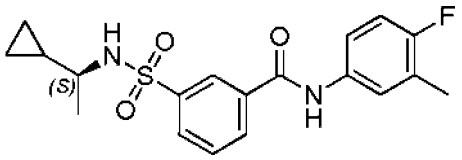
Compound **151**

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).



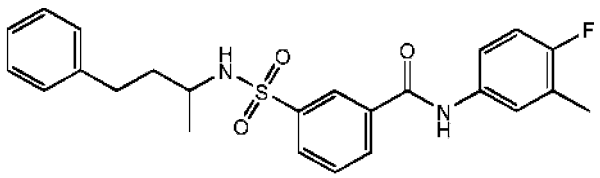
Compound **152**

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 diisopropylether/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)

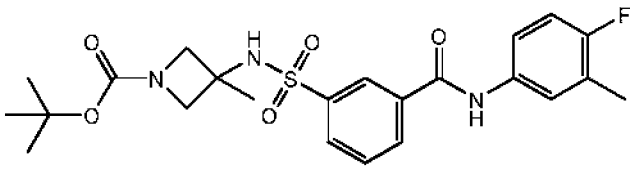


Compound **153**

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

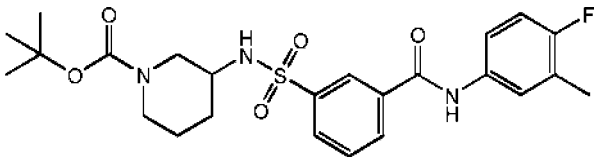
Hz, 1 H), 7.57 (t, J=7.8 Hz, 1 H), 7.95 (m, J=7.8, 1 H), 8.10 (m, J=7.8 Hz, 1 H), 8.25 (s, 1 H), 8.37 (t, J=1.5 Hz, 1 H)

Compound **154**



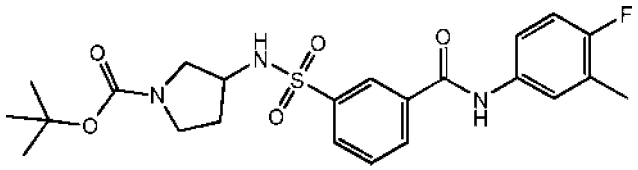
3-[(4-fluoro-3-methyl-phenyl)carbamoyl]benzenesulfonyl chloride (500 mg, 1.53 mmol) and DIPEA (657 µL, 3.8 mmol, 2.5 eq) dissolved in CH_2Cl_2 (15 mL) were added to a tube containing 3-amino-1-Boc-3-methyl-azetidine (1.1 eq). The reaction mixture was stirred for 20 hours. 1M HCl (5 mL) was added and 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**

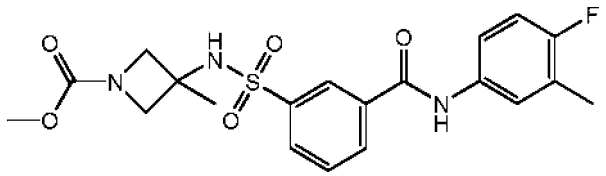


Prepared as described for compound **154** using 1-Boc-3-aminopiperidine instead of 3-amino-1-Boc-3-methyl-azetidine. Method F; Rt: 1.13 min. m/z: 492.1 $(M+H)^+$ Exact mass: 491.2.

Compound **156**

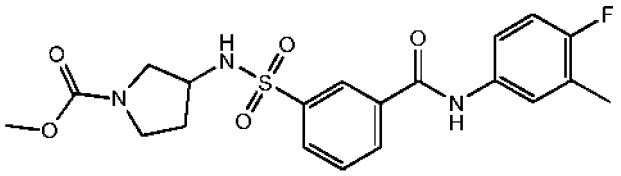


Prepared as described for compound **154** using (+/-)-3-amino-1-N-Boc-pyrrolidine instead of 3-amino-1-Boc-3-methyl-azetidine. Method F; Rt: 1.08 min. m/z: 478.2 $(M+H)^+$ Exact mass: 477.2 ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.36 (s, 9 H), 1.71 - 1.92 (m, 1 H), 1.92 - 2.15 (m, 1 H), 2.28 (d, *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).



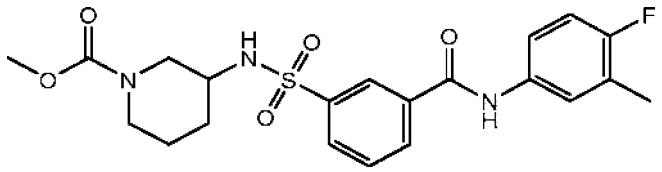
Compound **157**

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)



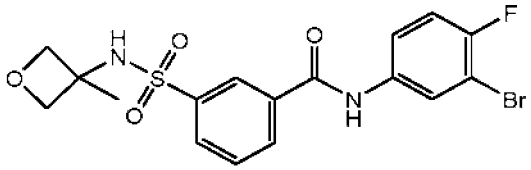
Compound **158**

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)



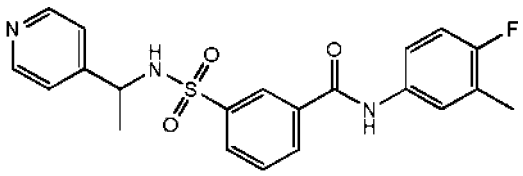
Compound **159**

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**

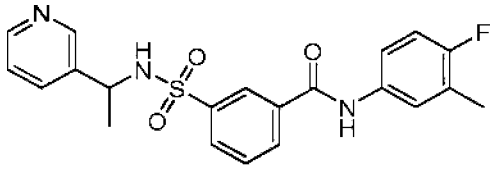
Method B; Rt: 4 min. m/z: 443.1 $(M+H)^+$ Exact mass: 442.0
^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.41 (s, 3 H) 4.14 (d, J= 6.3 Hz, 2 H) 4.56 (d, J=6.0 Hz, 2 H) 7.42 (t, J=8.8 Hz, 1 H) 7.74 - 7.82 (m, 2 H) 8.04 (s, 1 H) 8.15 - 8.24 (m, 2 H) 8.37 (t, J=1.5 Hz, 1 H) 8.54 (br. s, 1 H) 10.67 (br. s, 1 H).



Compound **161**

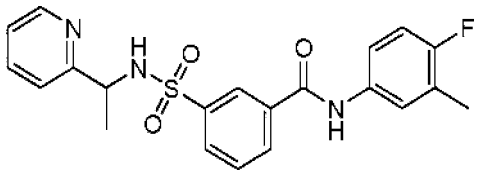
1-pyridin-4-yl-ethylamine (220 mg, 1.8 mmol) and 3-[(4-fluoro-3-methyl-phenyl)-carbamoyl]benzenesulfonyl chloride (500 mg, 1.53 mmol) were dissolved in CH_2Cl_2 (10 mL). DIPEA (6.2 mmol) was added at 0°C and the mixture was stirred at 25°C for 4 hours. The mixture was washed with water (20 mL) and the 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).



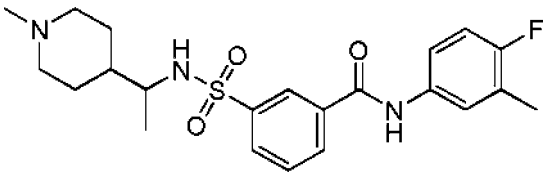
Compound **162**

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.



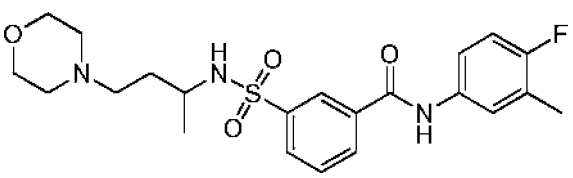
Compound **163**

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.



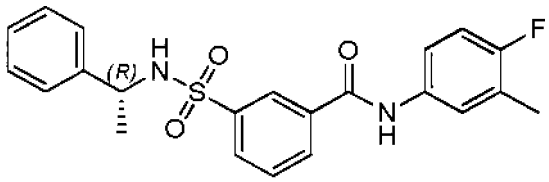
Compound **164**

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.



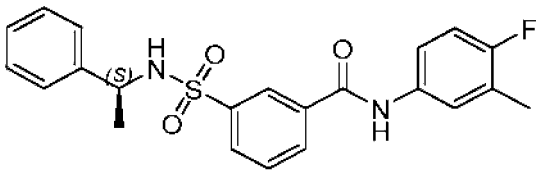
Compound **165**

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.



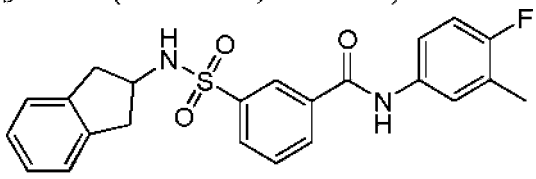
Compound **166**

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)

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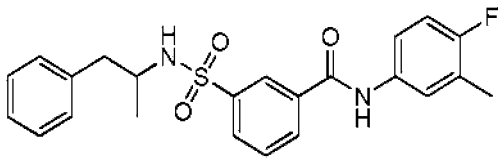
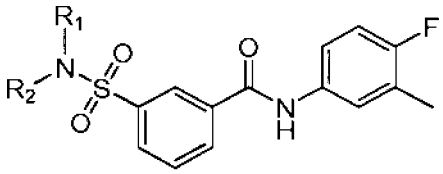
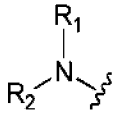
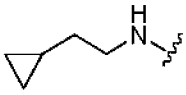
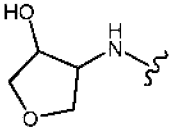
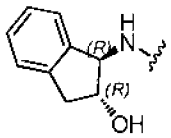
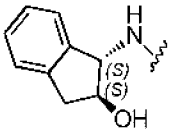
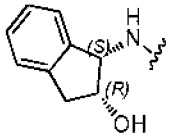
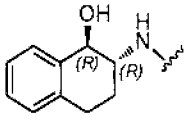
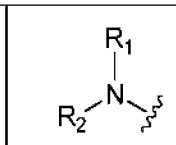
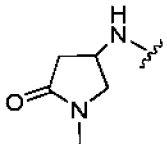
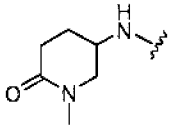
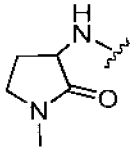
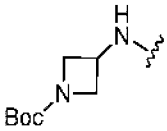
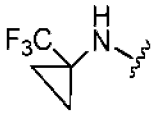
Compound **169**



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).

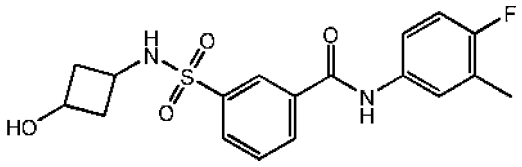
Compound **180**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.55 - 1.79 (m, 2 H), 2.01 - 2.36 (m, 5 H), 2.68 (s, 3 H), 3.06 (dd, J=12.3, 6.8 Hz, 1 H), 3.25 - 3.30 (m, 1 H), 3.46 - 3.58 (m, 1 H), 7.14 (t, J=9.1 Hz, 1 H), 7.52 - 7.63 (m, 1 H), 7.64 - 7.71 (m, 1 H), 7.78 (t, J=7.8 Hz, 1 H), 8.01 - 8.09 (m, 1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

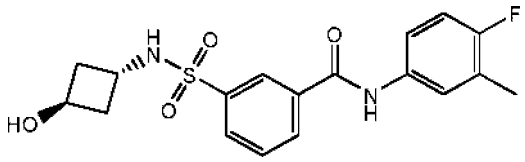
Compound **184**



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

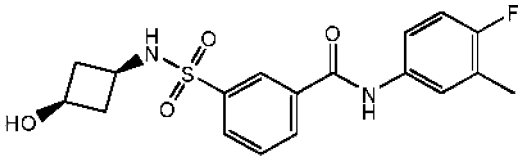
min), **184b** (3.4 min). The diastereomeric mixture of compound **184** was separated in diastereoisomers (Prep SFC (Stationary phase: Chiralpak Diacel AD 30 x 250 mm), Mobile phase: CO_2, MeOH with 0.4% $iPrNH_2$). The obtained fractions were concentrated under reduced pressure and dried in vacuo at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

Compound **184a**



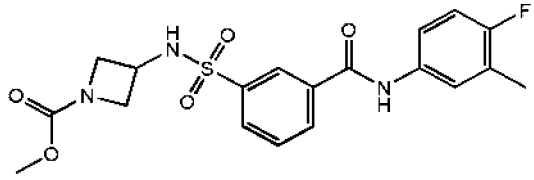
^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.84 - 1.91 (m, 2 H), 1.92 - 1.98 (m, 2 H), 2.25 (d, J=1.8 Hz, 3 H), 3.77 (quin, J=6.9 Hz, 1 H), 4.10 - 4.14 (m, 1 H), 4.93 (d, J=4.9 Hz, 1 H), 7.14 (t, J=9.2 Hz, 1 H), 7.59 (ddd, J=8.8, 4.6, 2.7 Hz, 1 H), 7.68 (dd, J=7.1, 2.7 Hz, 1 H), 7.76 (t, J=7.8 Hz, 1 H), 7.96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

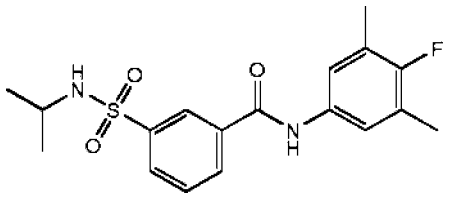


^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.54 - 1.60 (m, 2 H), 2.19 - 2.24 (m, 2 H), 2.25 (d, J=1.8 Hz, 3 H), 3.09 - 3.19 (m, 1 H), 3.62 - 3.68 (m, 1 H), 5.00 (d, J=5.6 Hz, 1 H), 7.14 (t, J=9.2 Hz, 1 H), 7.59 (ddd, J=8.5, 4.5, 2.8 Hz, 1 H), 7.68 (dd, J=7.0, 2.2 Hz, 1 H), 7.75 (t, J=7.8 Hz, 1 H), 7.97 (ddd,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



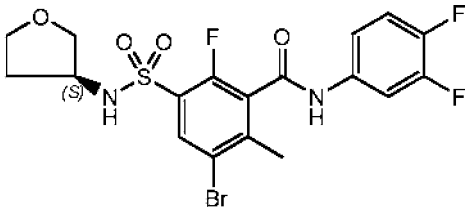
Prepared similarly as described for compound **157**, starting from compound **182** instead of compound **154**, via intermediate 3-(azetidin-3-ylsulfamoyl)-N-(4-fluoro-3-methyl-phenyl)benzamide hydrochloride. Method F; Rt: 0.89 min. m/z: 439.2 $(M+NH_4)^+$ Exact mass: 421.1.^{1}H NMR (400 MHz, DMSO-d_6) 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**

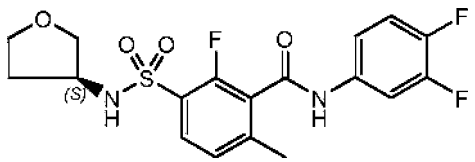


A solution of 2-fluoro-6-methylbenzoic acid (10 g, 0.0649 mol) in HOAc (300 mL) was stirred on a water-bath containing a bit of ice. At ~ 15°C, HNO_3 (65%, 32.7 mL) was added dropwise. After addition, H_2O (30 mL) was added slowly. After addition, Br_2 (3.7 mL) was added dropwise. A solution of silver 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)

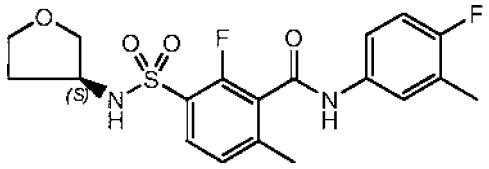
Method F; Rt: 1.06 min. m/z: 491.0 $(M-H)^-$ Exact mass:492.0. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.66 - 1.76 (m, 1 H), 1.94 - 2.05 (m, 1 H), 2.41 (s, 3 H), 3.43 (dd, J=8.9, 4.5 Hz, 1 H), 3.58 - 3.65 (m, 1 H), 3.68 (dd, J=8.9, 6.3 Hz, 1 H), 3.71 - 3.78 (m, 1 H), 3.83 - 3.92 (m, 1 H), 7.36 - 7.42 (m, 1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

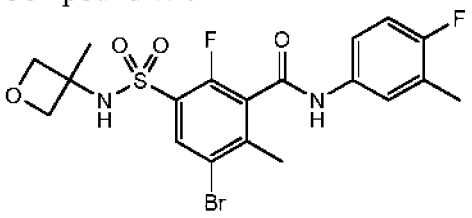
Compound **189**



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**

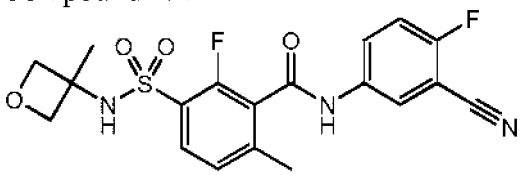


Na_2CO_3 (1.60 g, 0.0151 mol) was dissolved in water (25 mL). A solution of 3-methyloxetan-3-amine (2.63 g, 0.0302 mol) in THF (20 mL) was added, and the reaction mixture was cooled to 0°C on an ice-bath. A solution of crude 5-bromo-3-chlorosulfonyl-2-fluoro-6-methyl-benzoic acid (5 g) in THF (30 mL) 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**



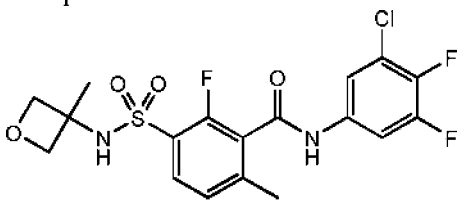
Triethylamine (0.206 mL, 0.00149 mol) was added to a stirring mixture of 2-fluoro-6-methyl-3-[(3-methyloxetan-3-yl)sulfamoyl]benzoic acid (0.15 g, 0.000495 mol) and CH_3CN (10 mL) under N_2-atm. To the resulting solution was added HATU (0.207 g, 0.545 mmol). After stirring for 5 minutes, 5-amino-2-fluorobenzonitrile, (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

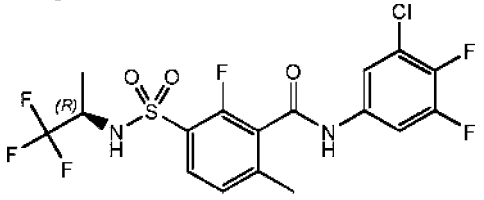
$MgSO_4$, filtered off, and evaporated. The solid residue was stirred in diisopropylether (20 mL), filtered off, washed with diisopropylether (3x) and dried at 50°C, resulting in tert-butyl N-(3-chloro-4,5-difluoro-phenyl)carbamate (8.5 g). The filtrate was concentrated in vacuo. The residue was stirred 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). ^1H 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).

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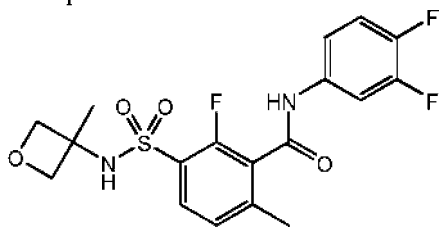
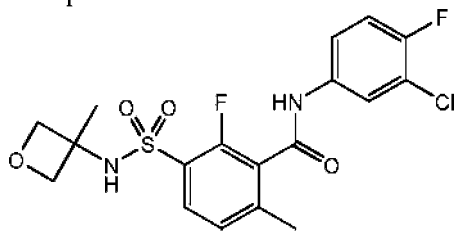
Compound **194**



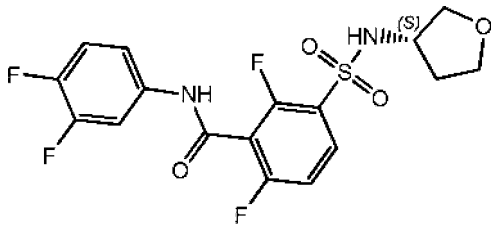
2-fluoro-6-methyl-3-[(3-methyloxetan-3-yl)sulfamoyl]benzoic acid (0.15 g, 0.473 mmol) was dissolved in DMF (5 mL) and triethylamine (0.2 mL) and HATU (233 mg, 0.61 mmol) were added to the reaction mixture. The reaction mixture was stirred for 10 minutes and 3,4-difluoroaniline (123 mg, 0.945 mmol) was 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. ^{1}H 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. ^{1}H 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**

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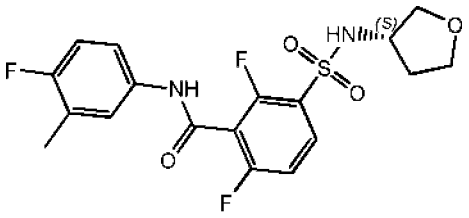
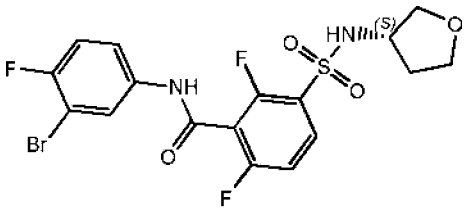


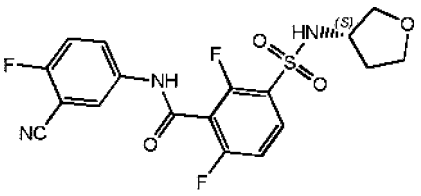
4-fluoro-3-methylaniline was used as aniline. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.64 - 1.76 (m, 1 H), 1.91 - 2.05 (m, 1 H), 2.25 (d, J=1.8 Hz, 3 H), 3.42 (dd, J=8.9, 4.7 Hz, 1 H), 3.56 - 3.78 (m, 3 H), 3.79 - 3.88 (m, 1 H), 7.16 (t, J=9.1 Hz, 1 H), 7.41 - 7.51 (m, 2 H), 7.60 (dd, J=7.0, 2.2 Hz, 1 H), 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)

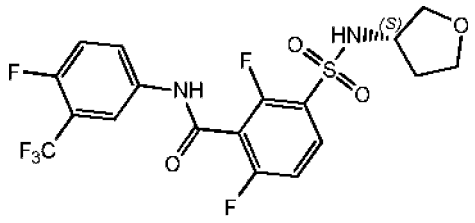
Compound **199**



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).

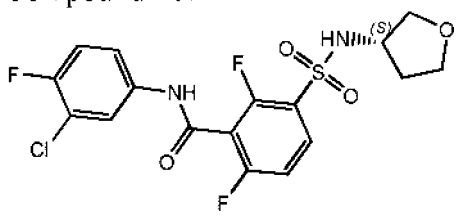
Compound **200**



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**

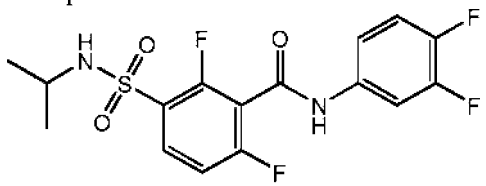


3-chloro-4-fluoroaniline was used as aniline.

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.

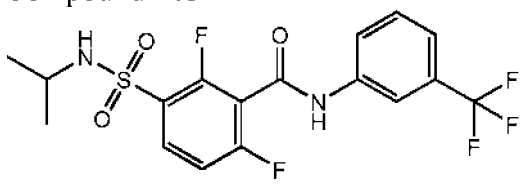
Compound **202**



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

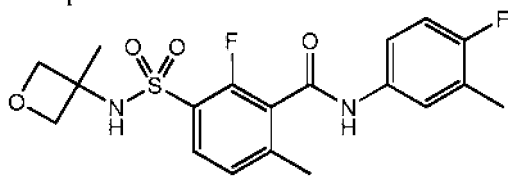
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.03 (d, J=6.6 Hz, 8 H), 3.34 - 3.46 (m, 1 H), 7.36 - 7.53 (m, 3 H), 7.84 (ddd, J=12.7, 7.4, 2.5 Hz, 1 H), 8.00 (td, J=8.6, 6.2 Hz, 1 H), 8.09 (br. s., 1 H), 11.20 (br. s., 1 H)

Compound **203**



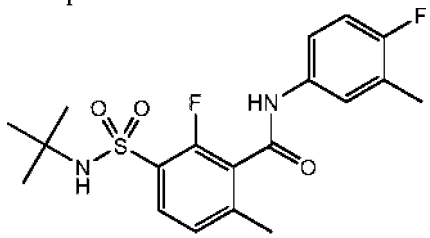
Method G, Rt: 1.82 min. m/z : 421.1 (M-H)- Exact mass: 422.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.04 (d, J=6.6 Hz, 6 H), 3.34 - 3.46 (m, 1 H), 7.47 (t, J=8.6 Hz, 1 H), 7.54 (d, J=7.9 Hz, 1 H), 7.65 (t, J=7.9 Hz, 1 H), 7.87 (d, J=8.4 Hz, 1 H), 8.01 (td, J=8.6, 6.2 Hz, 1 H), 8.11 (d, J=7.5 Hz, 1 H),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

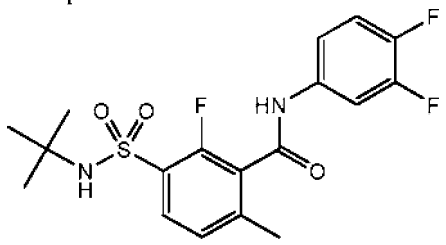
Compound **205**



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)

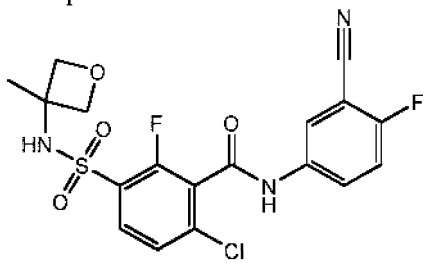
Synthesis of 6-chloro-2-fluoro-3-[(3-methyloxetan-3-yl)sulfamoyl]benzoic acid and 2-chloro-6-fluoro-3-[(3-methyloxetan-3-yl)sulfamoyl]benzoic acid

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

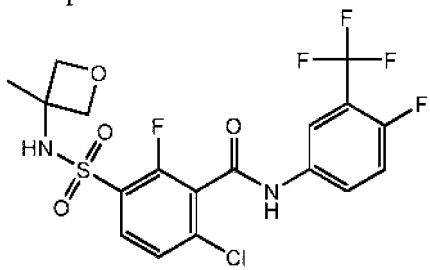
Compound **207** to **210** were prepared similarly as described for compound **196** using 6-chloro-2-fluoro-3-[(3-methyloxetan-3-yl)sulfamoyl]benzoic acid instead of 2,6-difluoro-3-[[(3*S*)-tetrahydrofuran-3-yl]sulfamoyl]benzoic acid and the corresponding aniline instead of 3,4-difluoroaniline.

Compound **207**



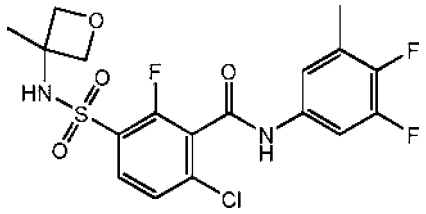
Using 5-amino-2-fluorobenzonitrile as aniline. Method F, Rt: 0.92 min. m/z : 440.0 $(M-H)^-$ Exact mass: 441.0. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.46 (s, 2 H), 4.21 (d, J=6.4 Hz, 2 H), 4.61 (d, J=6.2 Hz, 2 H), 7.59 (t, J=9.1 Hz, 1 H), 7.66 (d, J=8.8 Hz, 1 H), 7.89 - 7.99 (m, 2 H), 8.18 (dd, J=5.6,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

Compound **208**



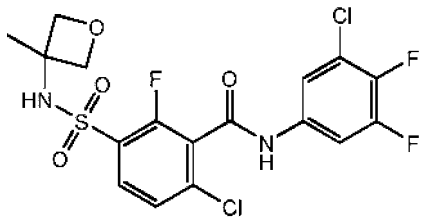
Using 4-fluoro-3-(trifluoromethyl)aniline as aniline. Method F, Rt: 1.06 min. m/z : 483 $(M-H)^-$ Exact mass: 484.0. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.46 (s, 2 H), 4.20 (d, J=6.2 Hz, 2 H), 4.61 (d, J=6.2 Hz, 2 H), 7.58 (t, J=9.9 Hz, 1 H), 7.66 (d, J=8.6 Hz, 1 H), 7.94 (m, J=8.1, 8.1 Hz, 2 H), 8.07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

Compound **209**



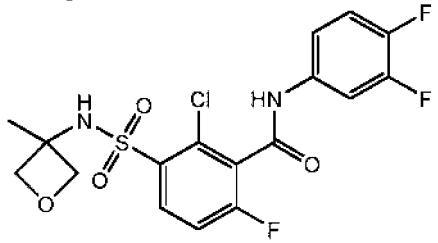
Using 3,4-difluoro-5-methyl-aniline as aniline. Method F, Rt: 1.03 min. m/z : 447.1 $(M-H)^-$ Exact mass: 448.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.45 (s, 3 H), 2.30 (d, J=2.0 Hz, 3 H), 4.20 (d, J=6.4 Hz, 2 H), 4.61 (d, J=6.2 Hz, 2 H), 7.32 (m, J=5.9 Hz, 1 H), 7.54 - 7.69 (m, 2 H), 7.91 (t, J=8.3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

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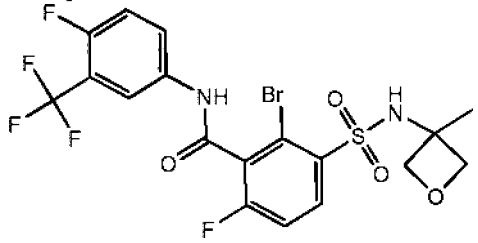
2-bromo-6-fluoro-3-[(3-methyloxetan-3-yl)sulfamoyl]benzoic acid and 6-bromo-2-fluoro-3-[(3-methyloxetan-3-yl)sulfamoyl]benzoic acid were prepared similarly as described for 2-chloro-6-fluoro-3-[(3-methyloxetan-3-yl)sulfamoyl]benzoic acid and 6-chloro-2-fluoro-3-[(3-methyloxetan-3-yl)sulfamoyl]benzoic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

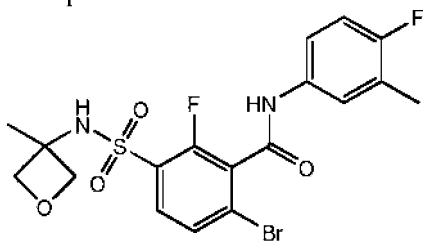
Compound **212**



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).

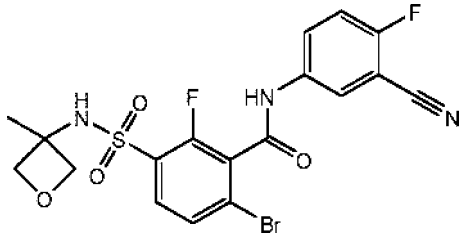
Compound **213** to **216** were prepared similarly as described for compound **196** using 6-bromo-2-fluoro-3-[(3-methyloxetan-3-yl)sulfamoyl]benzoic acid instead of 2,6-difluoro-3-[[(3*S*)-tetrahydrofuran-3-yl]sulfamoyl]benzoic acid the corresponding aniline instead of 3,4-difluoroaniline.

Compound **213**



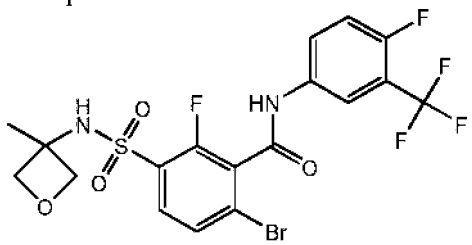
Using 4-fluoro-3-methylaniline as aniline. Method F, Rt: 0.99 min. m/z: 473.0 $(M-H)^-$ Exact mass: 474.0. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.46 (s, 3 H), 2.25 (d, J=1.5 Hz, 3 H), 4.20 (d, J=6.4 Hz, 2 H), 4.62 (d, J=6.2 Hz, 2 H), 7.16 (t, J=9.1 Hz, 1 H), 7.42 - 7.52 (m, 1 H), 7.60 (dd, J=7.0, 2.4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

Compound **214**



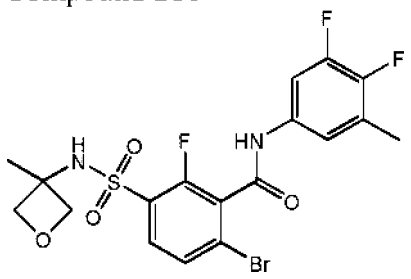
Using 5-amino-2-fluorobenzonitrile as aniline. Method F, Rt: 0.92 min. m/z : 484.0 $(M-H)^-$ Exact mass: 485.0. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.39 - 1.55 (m, 3 H), 4.20 (d, J=6.6 Hz, 2 H), 4.61 (d, J=6.4 Hz, 2 H), 7.59 (t, J=9.1 Hz, 1 H), 7.77 - 7.89 (m, 2 H), 7.95 (ddd, J=9.2, 4.8, 2.8 Hz, 1 H),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



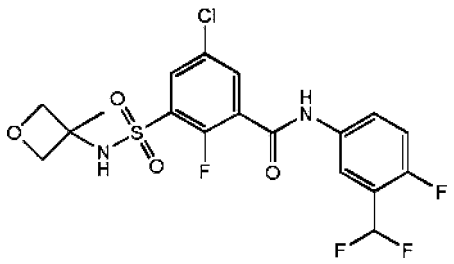
Using 4-fluoro-3-(trifluoromethyl)aniline as aniline. Method F,Rt: 1.07 min. m/z : 527.0 $(M-H)^-$ Exact mass: 528.0. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.46 (s, 3 H), 4.20 (d, J=6.6 Hz, 2 H), 4.61 (d, J=6.2 Hz, 2 H), 7.58 (t, J=9.8 Hz, 1 H), 7.74 - 7.89 (m, 2 H), 7.90 - 7.98 (m, 1 H), 8.16 (dd, J=6.3,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

Compound **216**



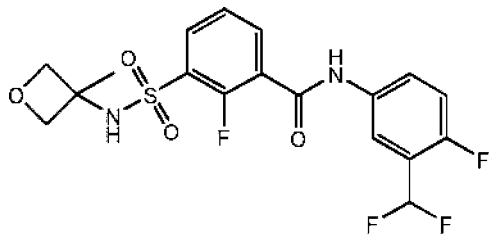
Using 3,4-difluoro-5-methyl-aniline as aniline. Method F, Rt: 1.03 min. m/z : 491.0 $(M-H)^-$ Exact mass: 492.0. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.46 (s, 3 H), 2.30 (d, J=1.8 Hz, 3 H), 4.20 (d, J=6.6 Hz, 2 H), 4.61 (d, J=6.4 Hz, 2 H), 7.32 (m, J=5.7 Hz, 1 H), 7.61 (ddd, J=12.3, 6.9, 2.6 Hz, 1 H),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

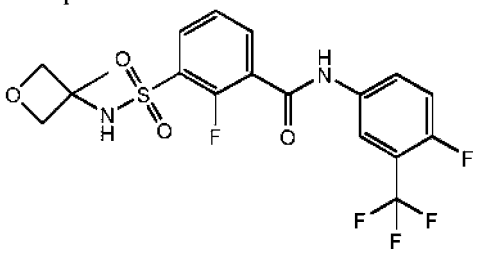


Pd/C (10%) (716 mg) was suspended in a solution of compound **217** (345 mg, 0.673 mmol) and Et_3N (0.467 mL) in MeOH (100 mL) at room temperature under nitrogen atmosphere.The reaction mixture was next stirred at room temperature under an

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.

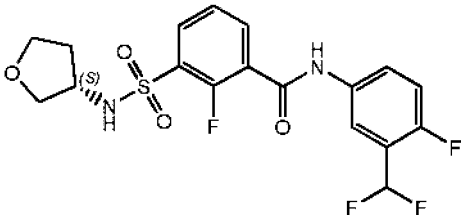
Compound **219**



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.

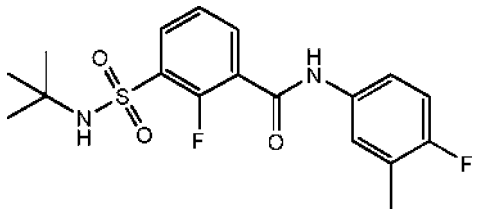
^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 1.44 (s, 3 H) 4.19 (d, J=5.9 Hz, 2 H) 4.62 (d, J=6.2 Hz, 2 H) 7.53 (t, J=7.9 Hz, 1 H) 7.57 (t, J=9.9 Hz, 1 H) 7.94 - 8.02 (m, 3 H) 8.20 (dd, J=6.4, 2.7 Hz, 1 H) 8.78 (s, 1 H) 11.02 (s, 1 H).

Compound **220**



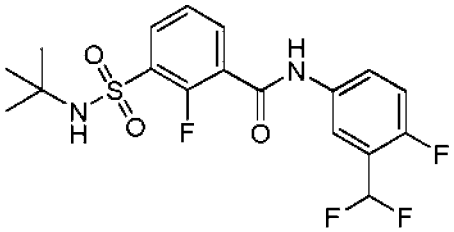
Compound **220** was prepared similar as described for compound **217** and **218**, using (*S*)-3-aminotetrahydrofuran instead of 3-methyl-3-oxetanamine. Method F, Rt: 0.90 min. m/z : 431.1 $(M-H)^-$ Exact mass: 432.1. ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 1.66 - 1.77 (m, 1 H) 1.91 - 2.03 (m, 1 H) 3.43 (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**



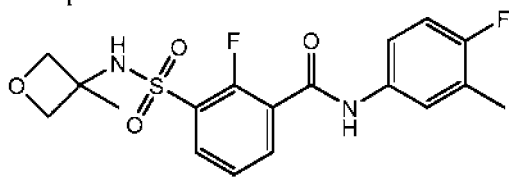
Compound **221** was prepared similar as described for compound **217** and **218**, using 2-methylpropan-2-amine instead of 3-methyl-3-oxetanamine, and 4-fluoro-3-methyl-aniline instead of 3-(difluoromethyl)-4-fluoro-aniline Method F, Rt: 1.06 min. m/z : 381.2 $(M-H)^-$ Exact mass: 382.1. 1 H NMR (360 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**



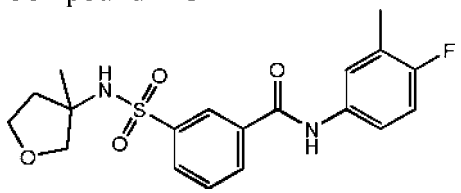
Compound **243** was prepared similar as described for compound **217** and **218**, using tert-butylamine instead of 3-methyl-3-oxetanamine. Method G, Rt: 1.76 min. m/z : 417.1 $(M-H)^-$ Exact mass: 418.1. ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 1.15 (s, 9 H) 7.41 (t, J=9.7 Hz, 1 H) 7.26 (t, J=54.5 Hz,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



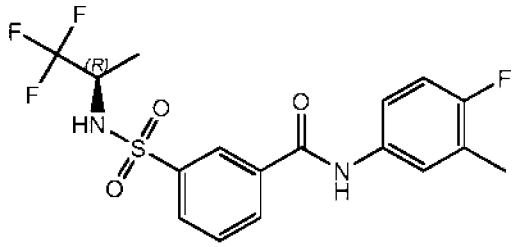
Compound **222** was prepared similar as described for compound **221**, using 3-methyl-3-oxetanamine instead of 2-methylpropan-2-amine. Method F, Rt: 0.91 min. m/z : 395.1 $(M-H)^-$ Exact mass: 396.1. ^{1} H NMR (360 MHz, DMSO-d_6) δ ppm 1.44 (s, 3 H) 2.24 (d, J=1.5 Hz, 3 H) 4.19 (d, J=6.6 Hz, 2 H)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

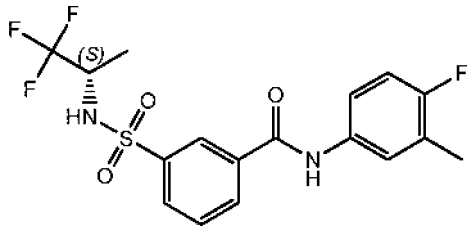
Compound **225**



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.

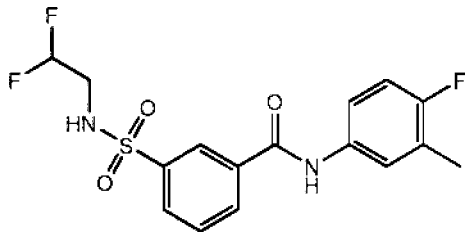
m/z : 403.1 $(M-H)^-$ Exact mass: 404.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.01 (d, J=6.8 Hz, 3 H), 2.25 (d, J=1.8 Hz, 3 H), 4.06 - 4.22 (m, 1 H), 7.15 (t, J=9.2 Hz, 1 H), 7.51 - 7.63 (m, 1 H), 7.67 (dd, J=7.2, 2.3 Hz, 1 H), 7.78 (t, J=7.8 Hz, 1 H), 8.00 - 8.10 (m, 1 H), 8.16 - 8.28 (m, 1 H), 8.40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

Compound **226**



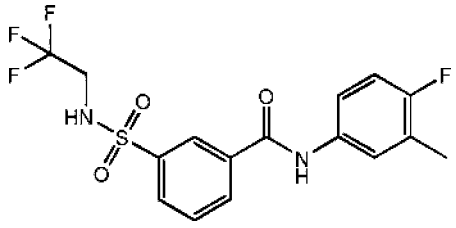
Compound **226** (416 mg) was prepared as described for compound **225**, using (*S*)-1,1,1-trifluoro-2-propylamine instead of (*R*)-1,1,1-trifluoro-2-propylamine. Method F, Rt: 1.05 min. m/z : 403.1 $(M-H)^-$ Exact mass: 404.1.

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. ^{1}H 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)

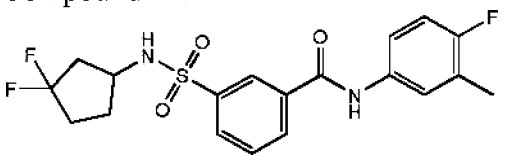
Compound **228**



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

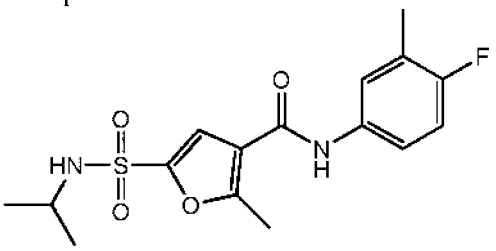
(using 2,2-difluoroethylamine as amine), workup W4, followed by preparative HPLC (SunFire Prep C18 OBD-10µm,30x150mm). Mobile phase (0.25% NH_4HCO_3 solution in water, MeOH). Method F, Rt: 0.97 min. m/z : 389.1 $(M-H)^-$ Exact mass: 390.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.25 (d, J=1.8 Hz, 3 H), 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).

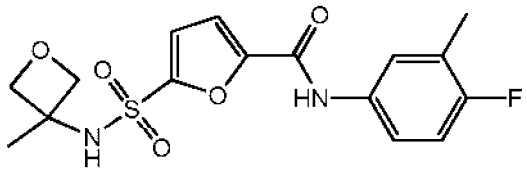
Compound **230**



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).

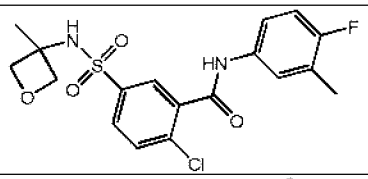
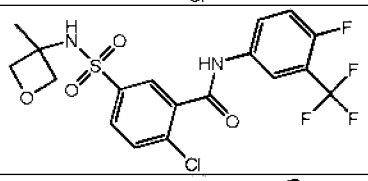
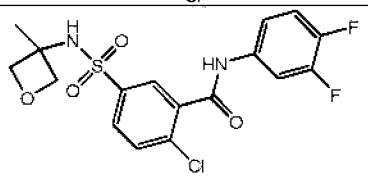
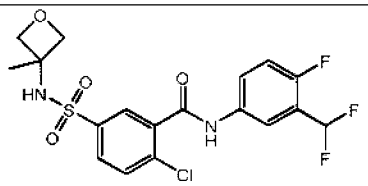
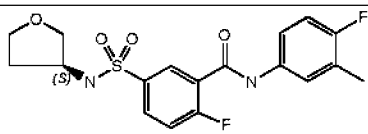
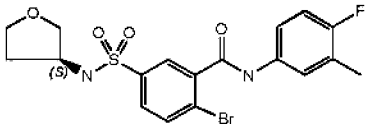
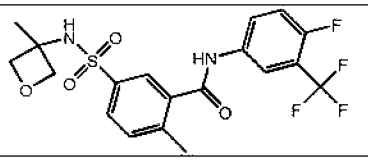
Compound **231**

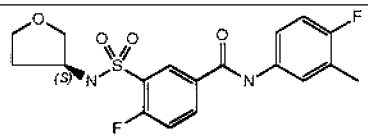


3-methyl-3-oxetanamine hydrochloride (302.6 mg, 2.45 mmol) and Hunig's base (1.15 mL, 6.68 mmol) dissolved in CH_2Cl_2 (2 mL) were added to a solution of methyl 5-(chlorosulfonyl)-2-furoate (thermo scientific, 500 mg, 2.23 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred overnight at room 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

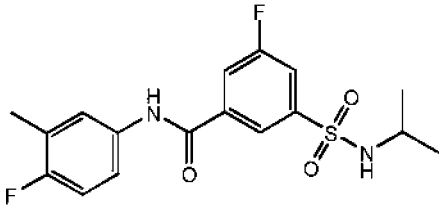
Compound	^{1}H-NMR
232	^{1}H NMR (360MHz , DMSO-d_6) δ ppm 10.67 (s, 1 H), 8.57 (s, 1 H), 7.96 - 7.88 (m, 2 H), 7.84 - 7.79 (m, 1 H), 7.62 (dd, J = 2.6, 7.0 Hz, 1 H), 7.54 - 7.46 (m, 1 H), 7.15 (t, J = 9.1 Hz, 1 H), 4.56 (d, J = 6.2 Hz, 2 H), 4.17 (d, J = 6.2 Hz, 2 H), 2.24 (d, J = 1.8 Hz, 3 H), 1.43 (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

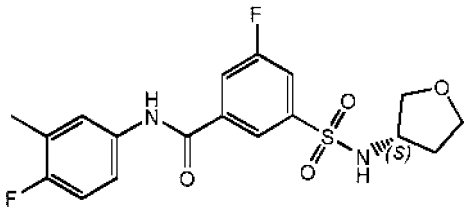
Optical rotation:
Compound **236**: $[\alpha]_D^{20}$= - 5.83 (c 0.67 w/v %, MeOH).

Compound **240**



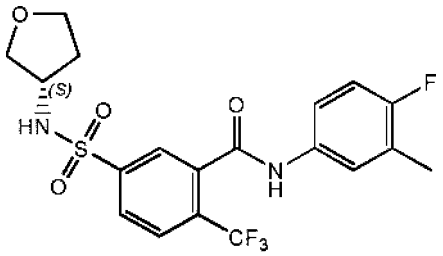
$SOCl_2$ (20.1 mL, 277.2 mmol) was added slowly to water (125 mL) cooled to 5 °C, maintaining the temperature between 4 and 7 °C (addition took about 1.5 hour). The solution was then kept stirring overnight while the temperature was allowed to slowly reach room temperature. Copper(I) chloride (76.6 mg, 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.

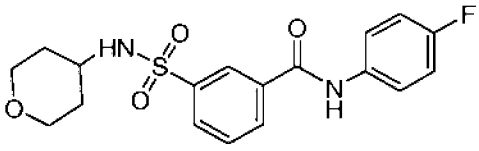
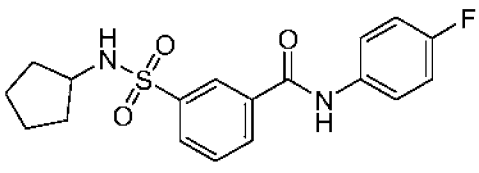
For the antiviral, assay cells were treated twice for three days with serially diluted compound in 96-well plates in duplicate. After 6 days of tretament the antiviral activity was determined by quantification of purified HBV DNA from secreted virions using realtime PCR and an HBV specific primer set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

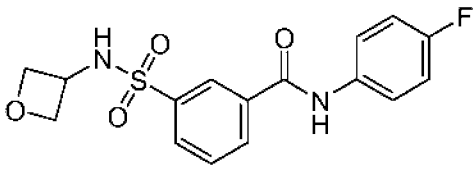
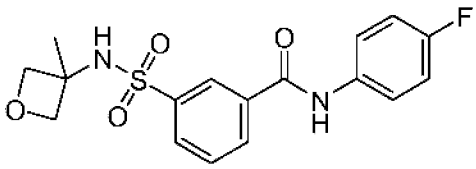
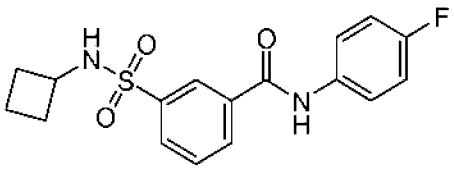
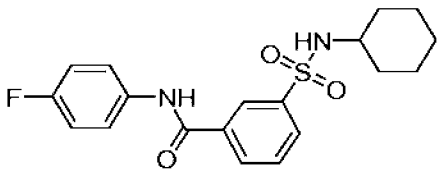
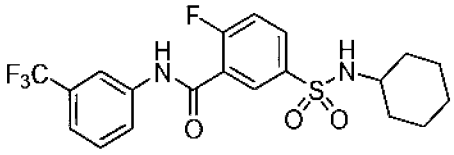
Cytotoxicity of the compounds was tested in HepG2 cells using CellTiter-Blue, with the same incubation period and dose range as in the HepG2.2.15 assay.

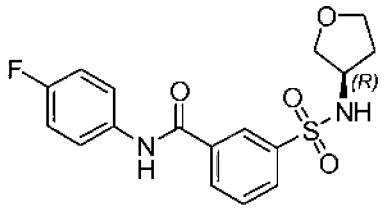
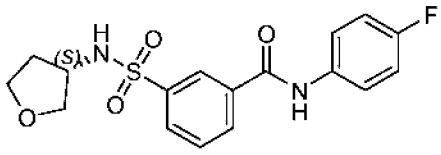
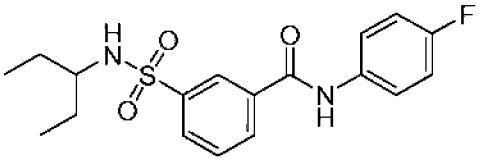
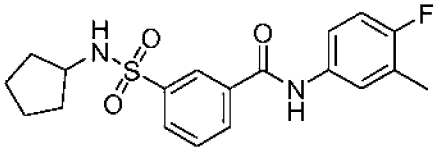
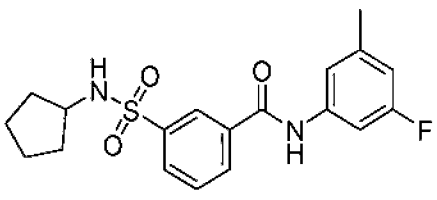
The anti HBV activity was also measured using the HepG2.117 cell line, a stable, inducibly HBV producing cell line, which replicates HBV in the absence of doxicycline (Tet-off system). For the antiviral assay, HBV replication was induced, followed by a treatment with serially diluted compound in 96-well 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.

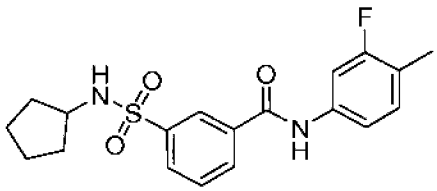
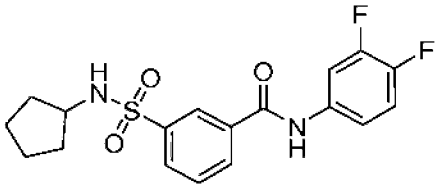
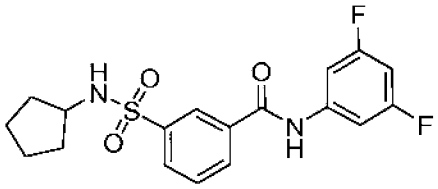
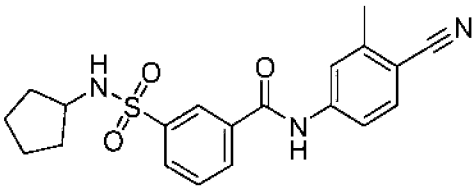
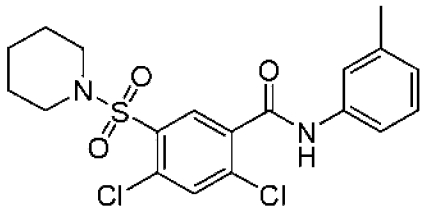
Cytotoxicity of the compounds was tested using HepG2 cells, incubated for 4 days in the presence of compounds. The viability of the cells was assessed using a Resazurin assay. Results are displayed in Table 1.

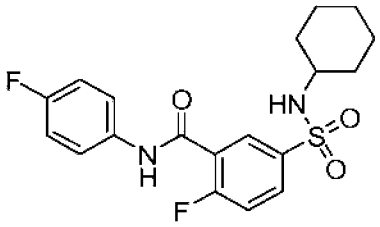
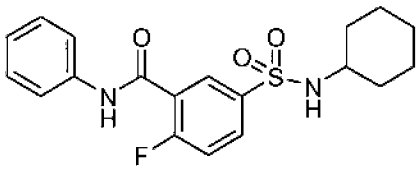
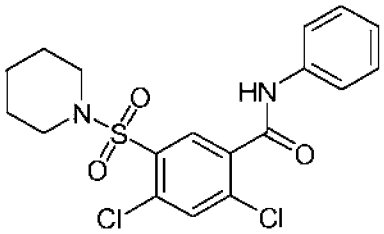
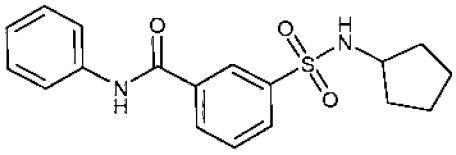
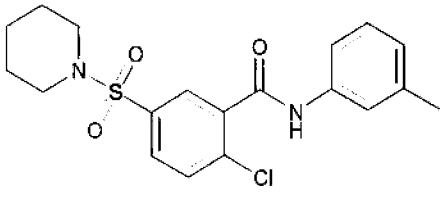
Table 1.

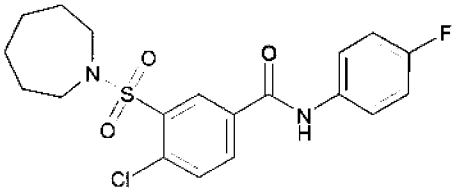
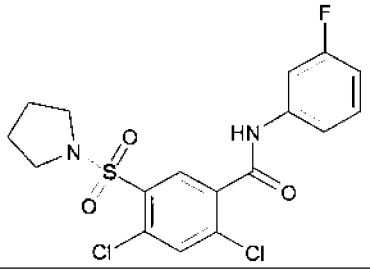
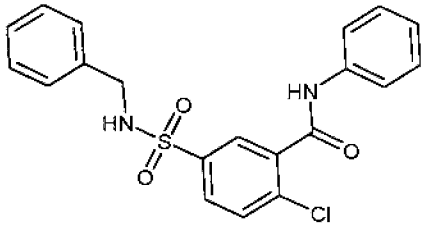
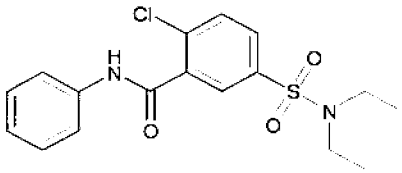
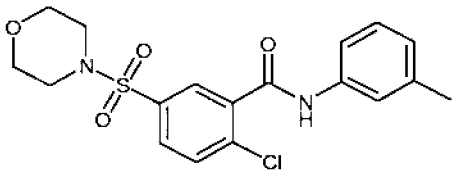
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	1	0.93		1.67	>100
	2	0.47		0.56	32.7

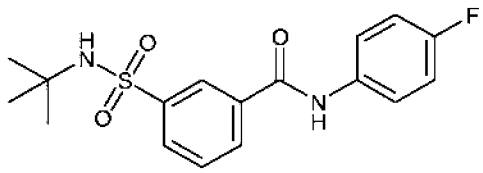
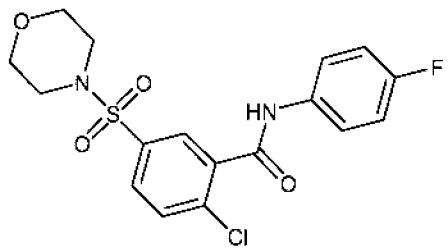
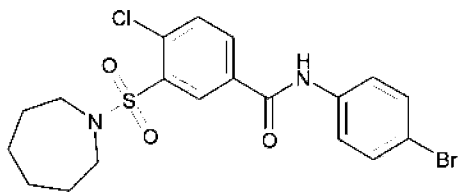
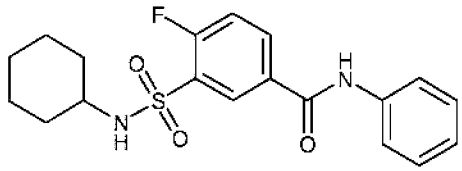
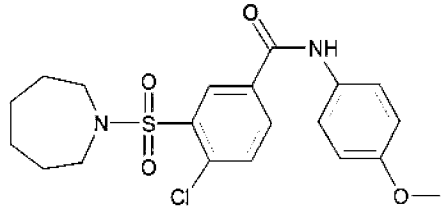
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**3**	2.10		3.05	>100
	**4**	0.96		0.93	>100
	**5**	0.83		0.90	57.7
	**6**			0.58	>25
	**7**	0.66	-	0.56	11.4

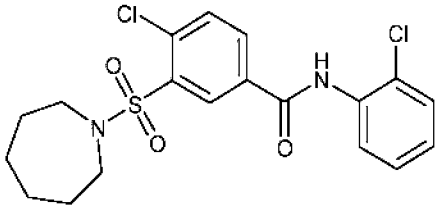
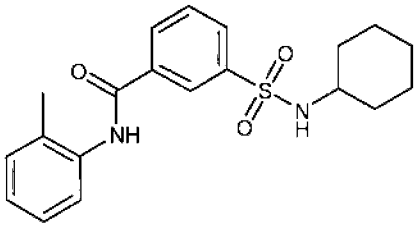
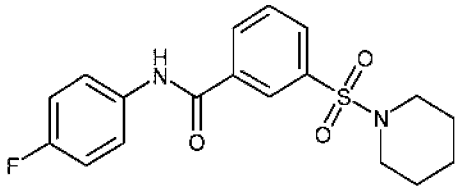
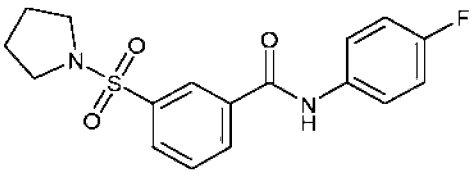
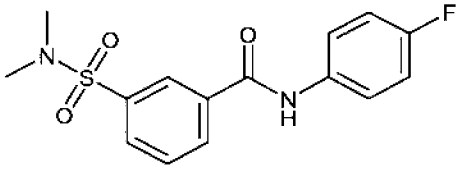
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**8**	1.18		2.03	>100
	**9**	0.54		1.36	>100
	**10**	0.75		3.63	40.3
	**11**	0.10		0.42	19.6
	**12**	0.11		1.51	13.3

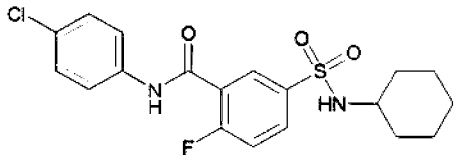
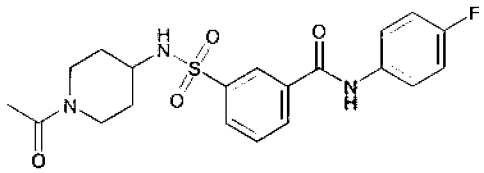
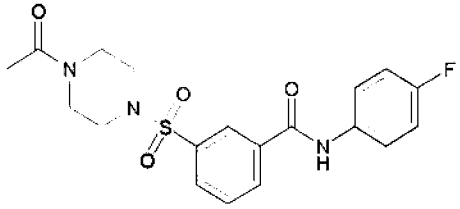
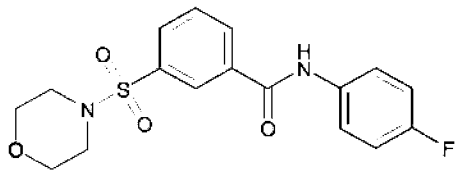
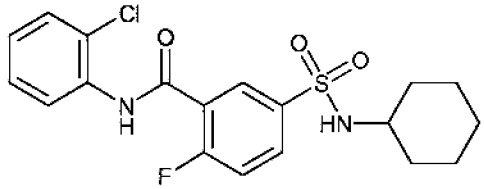
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**13**	1.99		15.31	13.8
	**14**	0.09		0.36	11.7
	**15**	0.28		0.78	10.1
	**16**	1.21		2.8	10.3
	**17**	0.56		2.65	>100

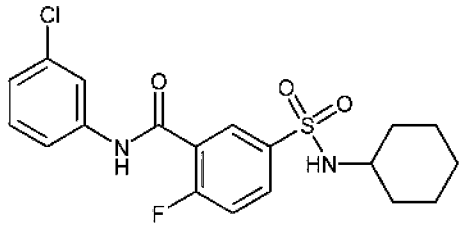
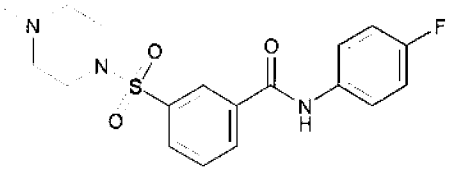
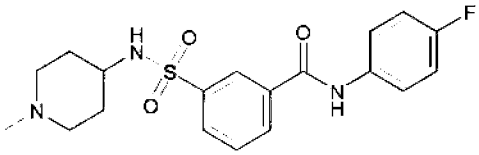
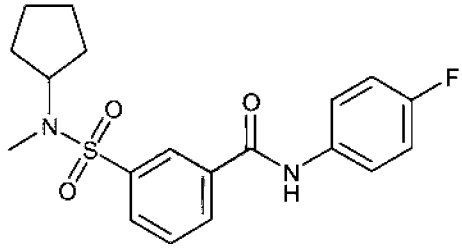
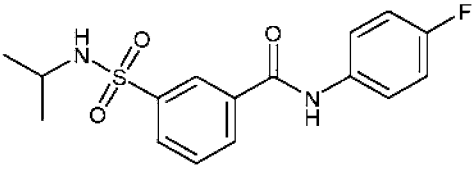
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**18**	0.78	51.6	1.30	>50
	**19**	0.66	42.5	0.60	>25
	**20**	0.50	>25	1.00	79.6
	**21**	0.60	27.2	0.76	41.1
	**22**	0.52	>25		

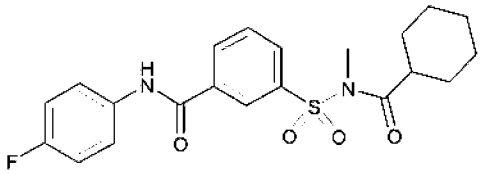
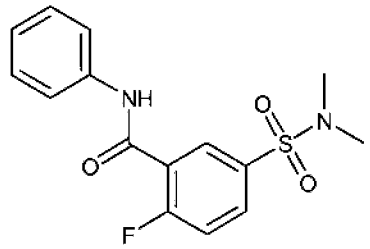
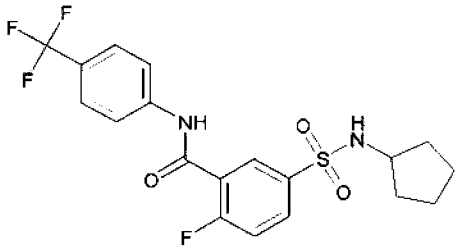
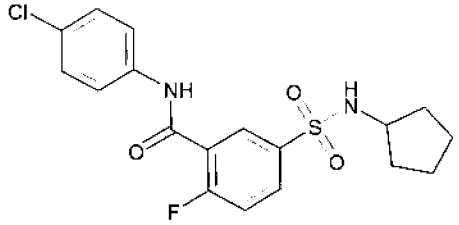
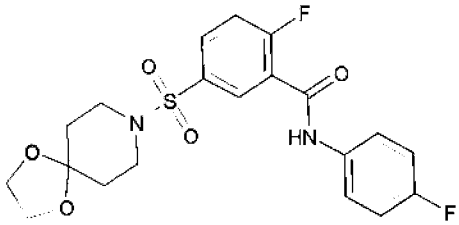
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**23**	0.66	17.0	1.30	19.6
	**24**	0.79	>25		
	**25**	0.80	>25	1.02	>6.25
	**26**	1.04	>25		
	**27**	1.13	>25		

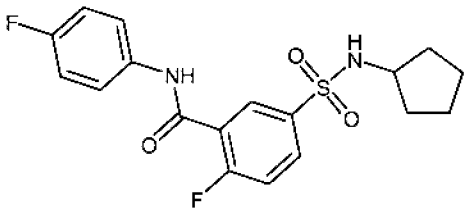
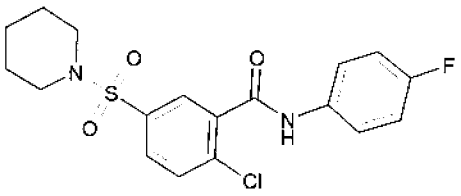
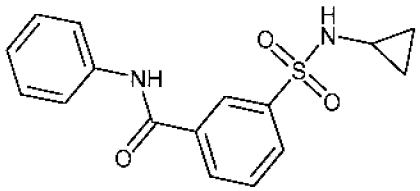
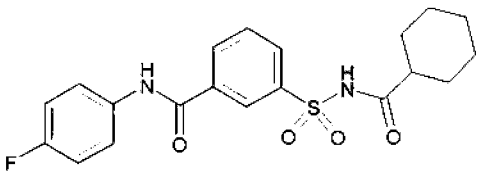
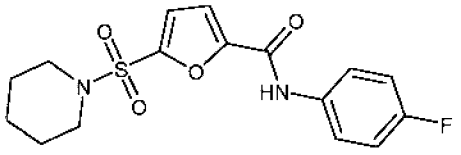
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**28**	1.24		2.28	52.5
	**29**	1.39	>25		
	**30**	1.67	>25		
	**31**	2.23	16.4		
	**32**	2.59	9.9	4.58	>25

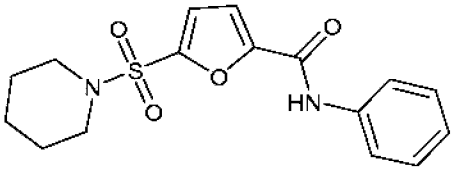
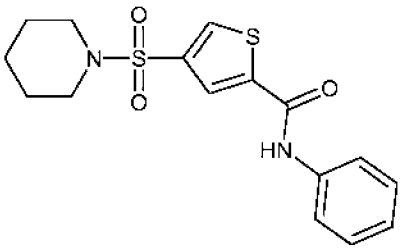
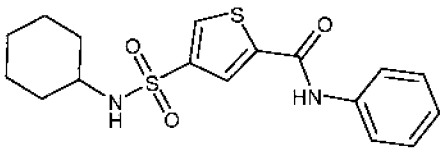
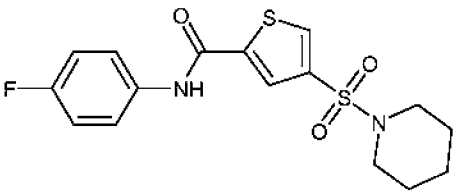
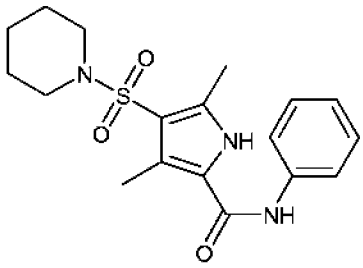
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**33**	3.56	>25		
	**34**	4.18	>25		
	**35**	4.50		2.70	70.4
	**36**	4.53		3.03	97.0
	**37**	5.02		2.99	>100

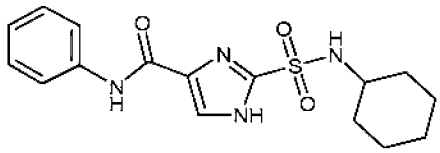
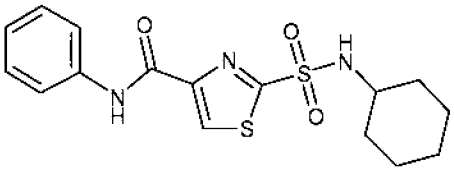
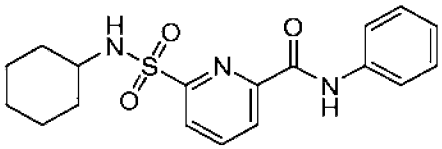
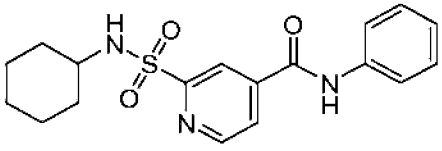
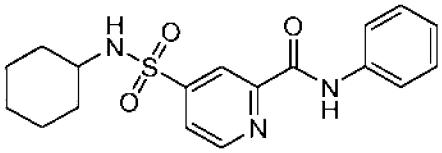
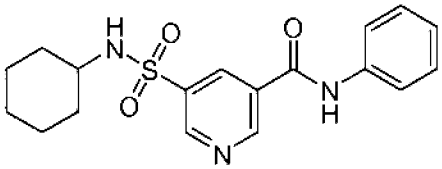
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**38**	<6.25	18.4	15.54	22.10
	**39**	6.77		4.68	>100
	**40**	7.10		6.29	>100
	**41**	8.49	-	10.95	>100
	**42**	11.64	37.2	>25	

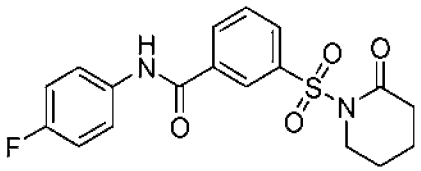
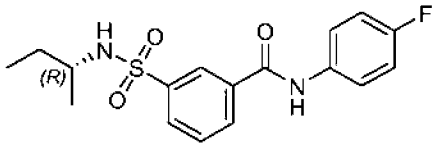
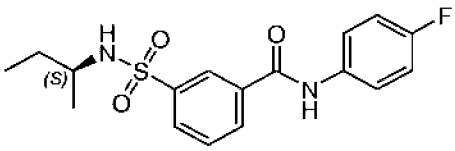
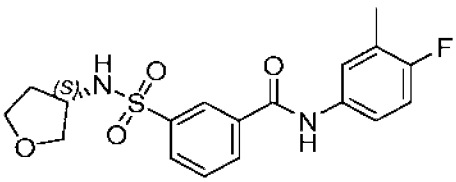
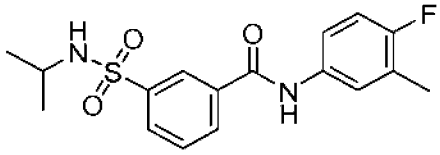
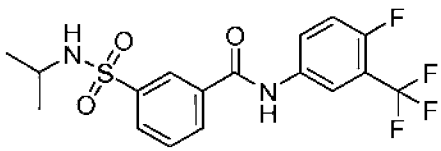
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**43**	15.13	36.3	>25	>25
	**44**	26.49		11.08	>100
	**45**	59.33		16.03	>100
	**46**	2.61		11.09	23.8
	**47**	0.74		0.96	57.5

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

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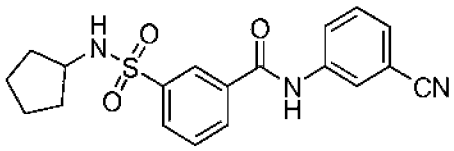
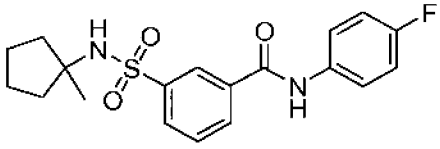
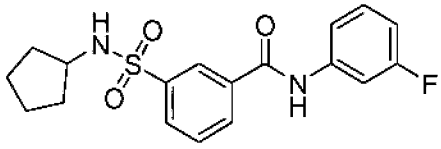
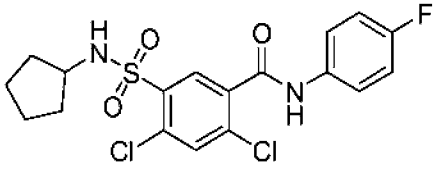
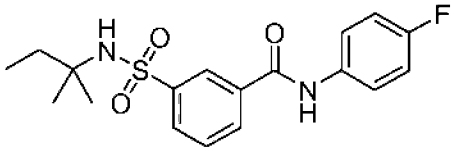
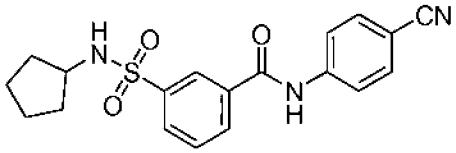
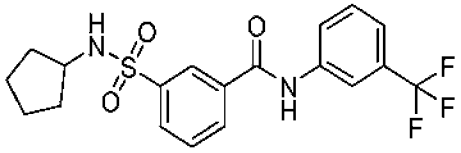
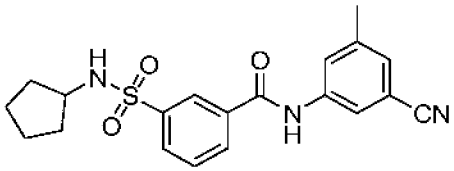
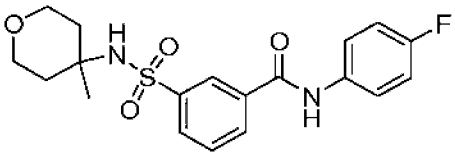
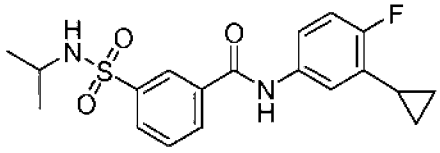
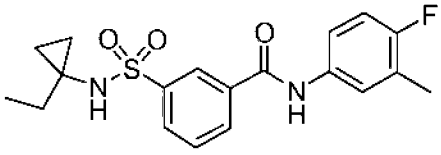
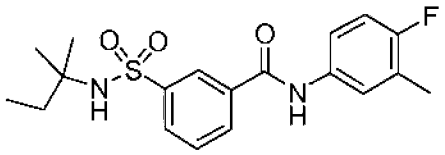
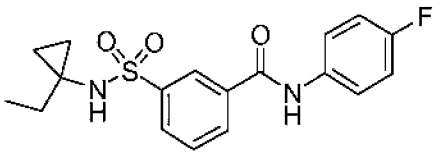
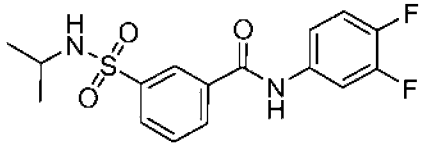
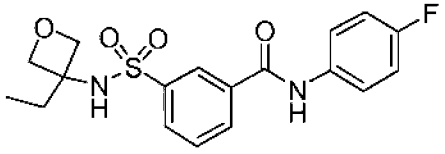
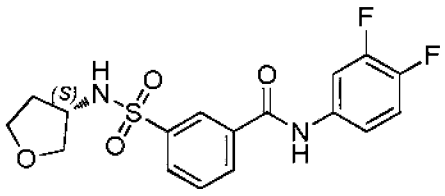
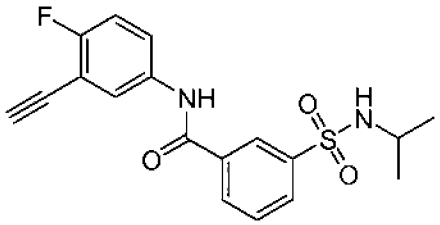
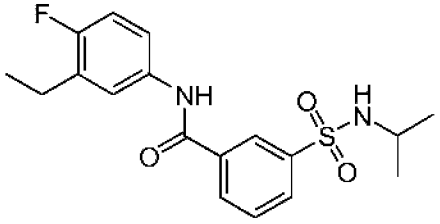
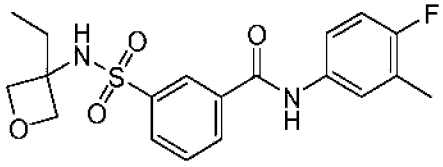
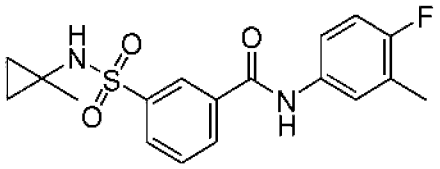
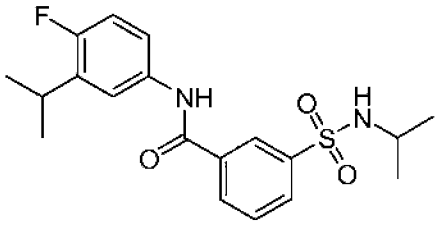
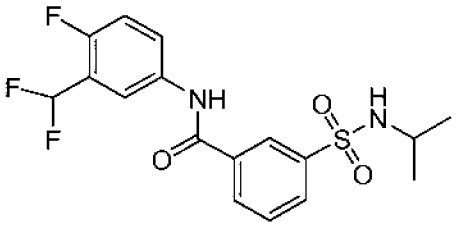
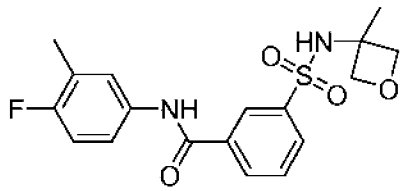
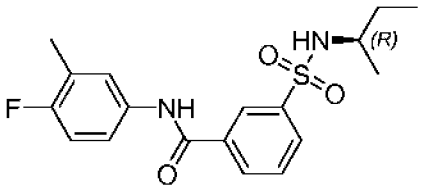
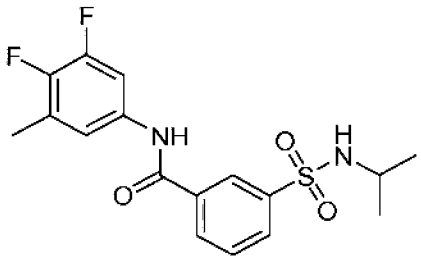
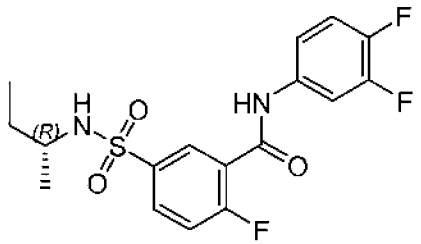
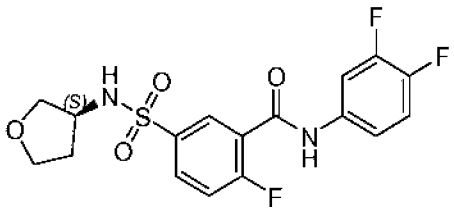
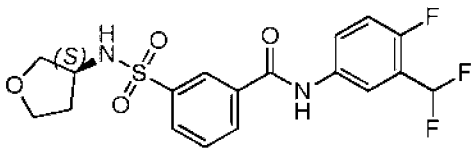
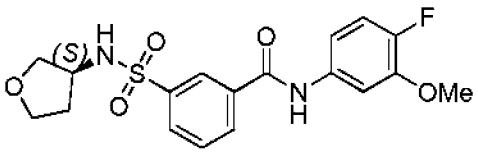
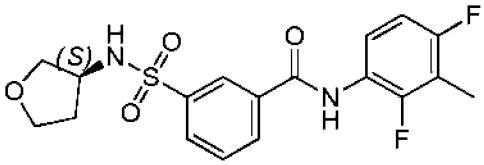
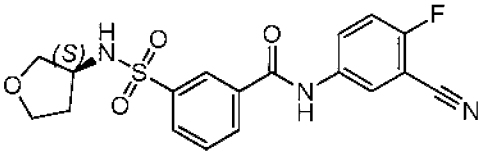
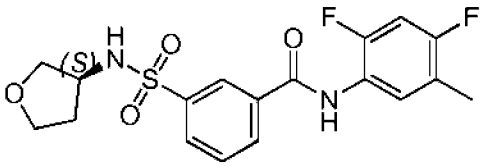
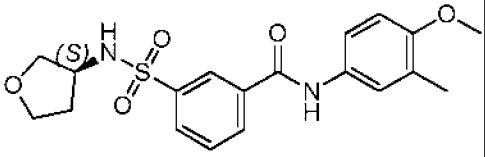
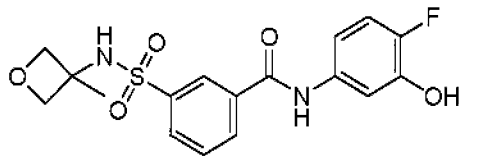
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**75**	0.39		0.82	>25
	**76**	0.72		2.5	>25
	**77**	0.27		0.43	>25
	**78**	0.90		0.65	>25
	**79**	0.96		1.69	>25
	**80**	8.4		17.9	>25

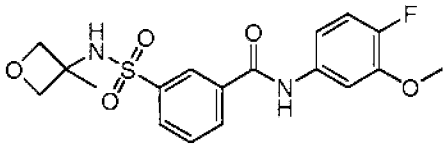
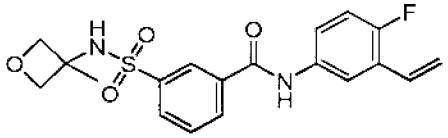
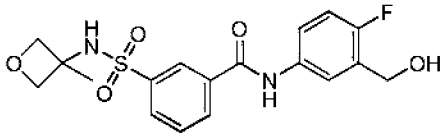
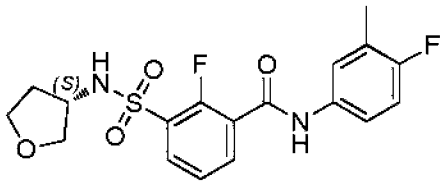
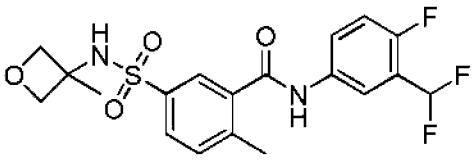
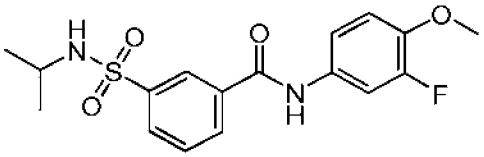
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**81**	0.24		0.81	15.3
	**82**	1.20		3.13	>25
	**83**	1.04		1.23	>25
	**84**	0.32		0.91	>25
	**85**	0.05		0.38	>25

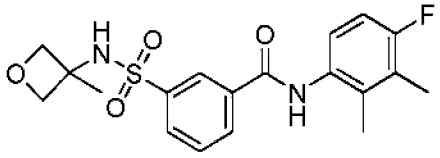
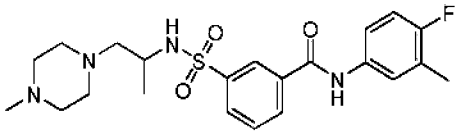
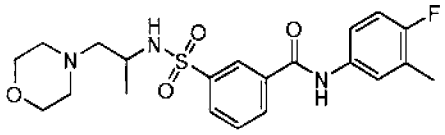
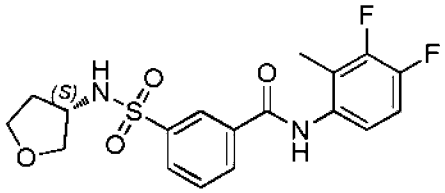
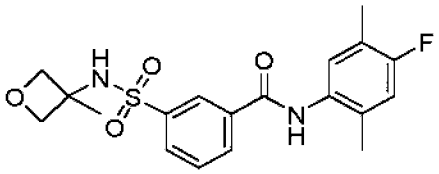
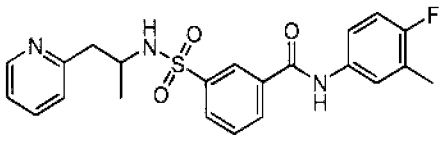
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**86**	0.14		0.11	>25
	**87**	0.41		0.89	>25
	**88**	0.21		0.40	>25
	**89**	0.54		0.72	>25
	**90**	0.38		0.51	>25

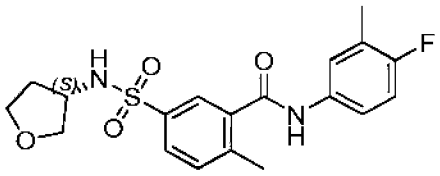
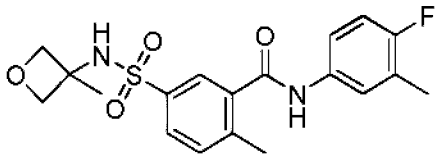
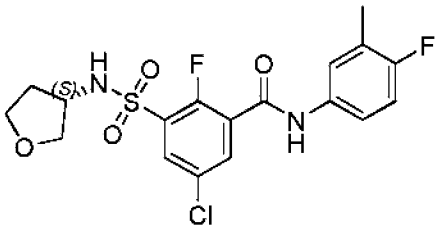
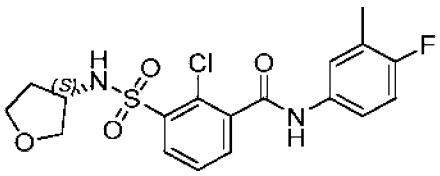
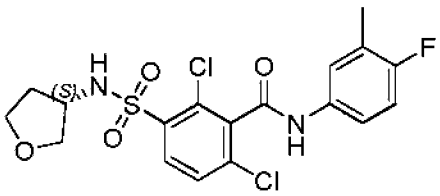
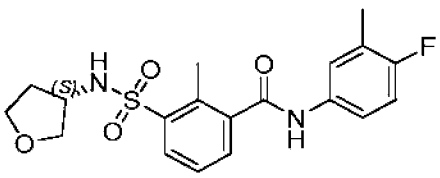
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**91**	0.53		0.77	>25
	**92**	0.31		2.59	>25
	**93**	0.07		0.22	>25
	**94**	0.15		0.23	>25
	**95**	1.4		2.79	>25
	**96**	0.10		0.29	>25

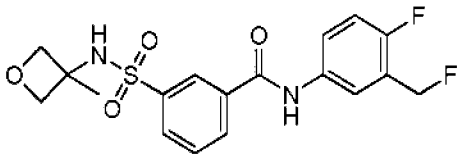
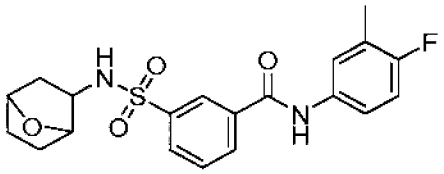
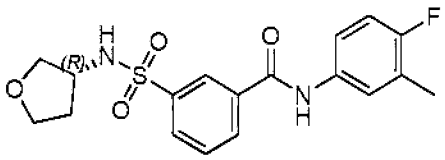
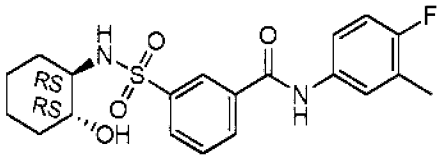
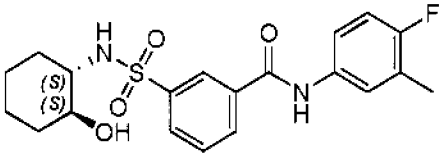
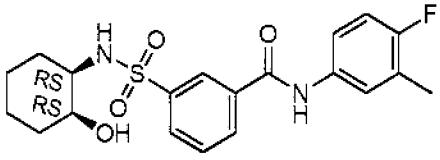
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**97**	0.12		0.37	>25
	**98**	0.10		0.31	>25
	**99**	0.09		0.46	>25
	**100**	0.13		0.43	>25
	**101**	0.43		1.51	>25
	**102**	0.18		0.33	>25

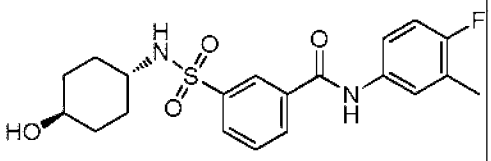
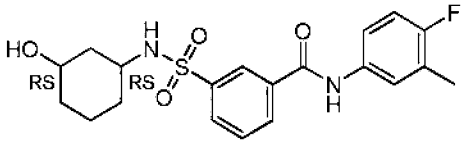
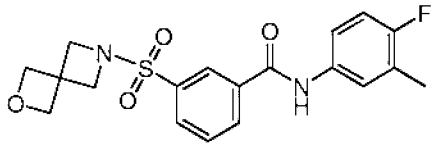
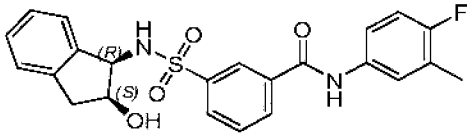
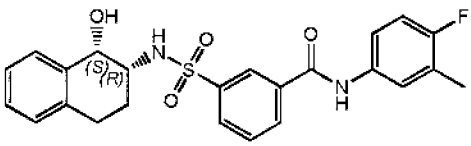
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**103**	2.33		2.66	>25
	**104**	0.29		0.78	>25
	**105**	0.81		0.98	>25
	**106**	2.22		3.30	>25
	**107**	7.82		13.82	>25
	**108**	7.20		9.27	>25

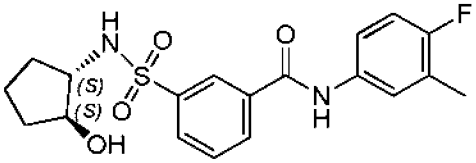
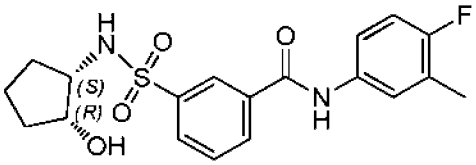
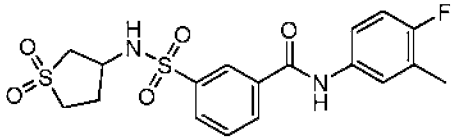
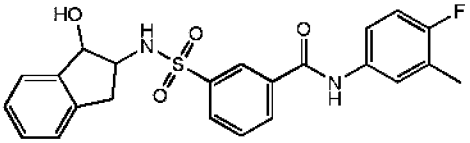
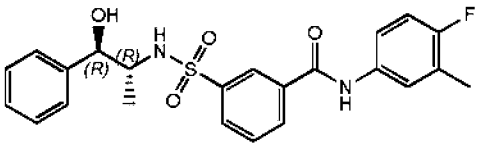
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**109**	1.23		2.53	>25
	**110**	0.66		0.85	>25
	**111**	4.48		1.48	>25
	**112**	0.03		0.14	>25
	**113**	0.15		0.18	>25
	**114**	1.35		3.15	>25

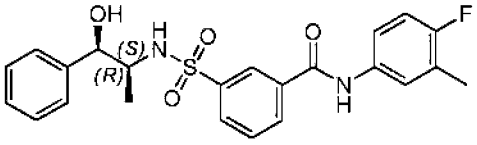
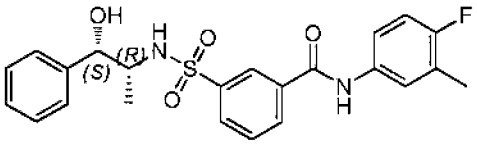
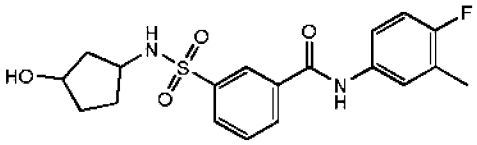
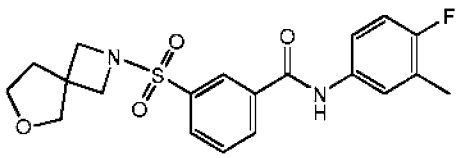
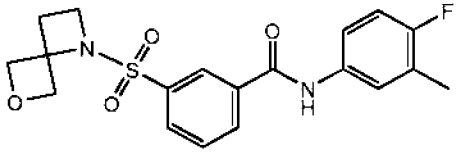
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**115**	2.74		1.65	>25
	**116**	1.94		0.90	>25
	**117**	0.88		0.50	>25
	**118**	3.63		1.91	>25
	**119**	3.06		1.91	>25
	**120**	0.53		0.51	>25

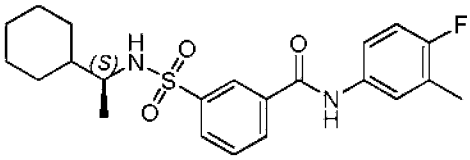
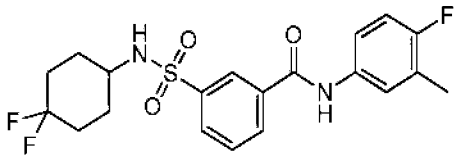
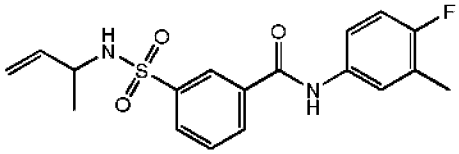
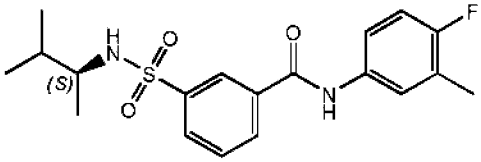
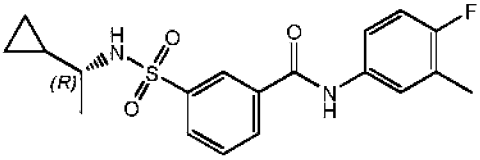
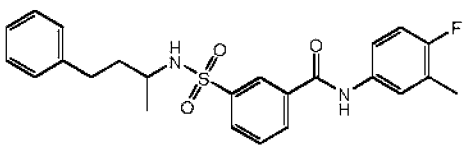
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**121**	0.16		0.13	>25
	**122**	0.13		0.18	>25
	**123**	0.15		0.3	>25
	**124**	0.33		0.68	>25
	**125**	1.44		1.15	>25
	**126**	1.38		0.89	>25

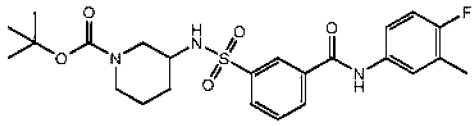
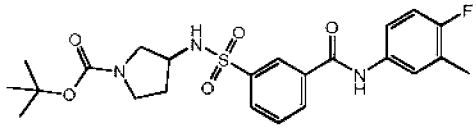
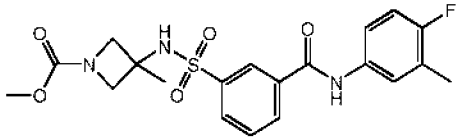
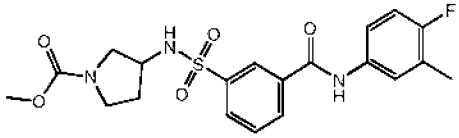
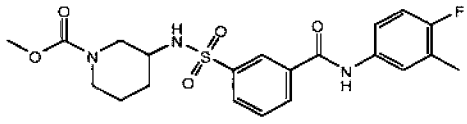
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**127**	0.23		0.58	>25
	**128**	0.23		0.54	>25
	**129**	0.35		0.78	>25
	**130**	0.88		1.03	>25
	**131**	2.63		1.74	>25
	**132**	0.59		0.73	>25

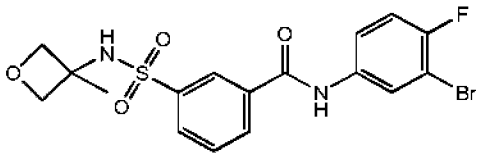
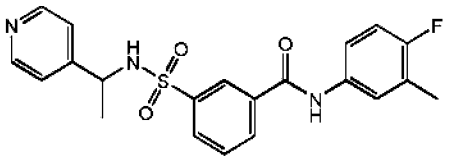
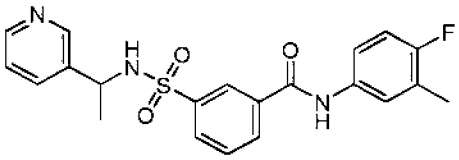
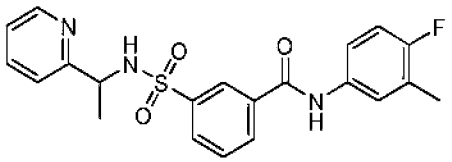
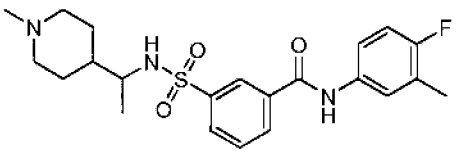
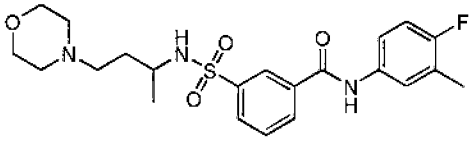
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**133**	0.60		1.69	>25
	**134**	0.18		0.57	>25
	134a	0.66		0.72	
	134b	0.57		0.20	
	134c	0.49		0.38	
	134d	0.25		1.22	
	**135**	0.56		0.36	>25
	**136**	0.47		0.81	>25
	**137**	0.66		0.92	23.7

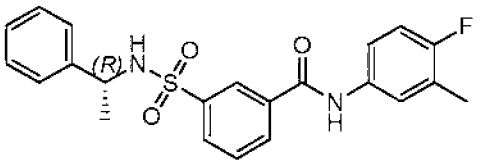
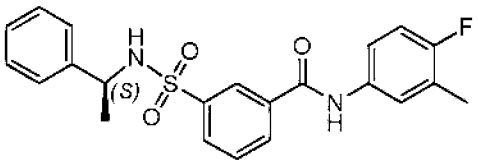
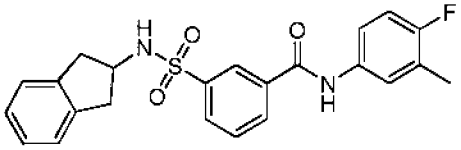
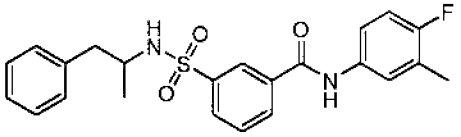
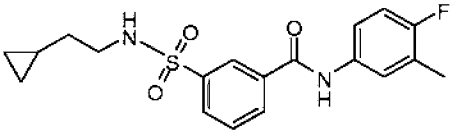
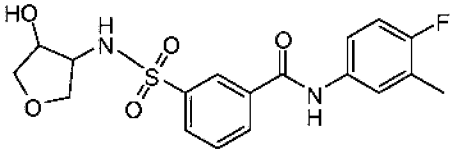
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**138**	1.28		2.27	>25
	**139**	1.00		1.75	>25
	**140**	1.10		1.12	>25
	**141**	0.36		0.60	>25
	141a	0.70		1.65	>25
	141b	0.27		0.23	>25
	141c	0.17		0.29	>25
	141d	0.56		1.14	>25
	**142**	0.14		0.56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

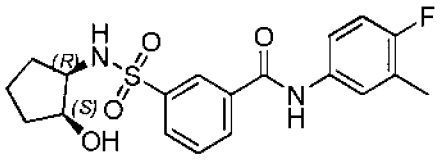
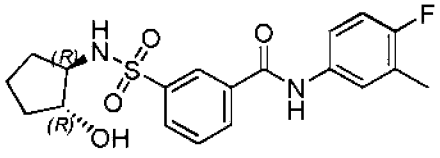
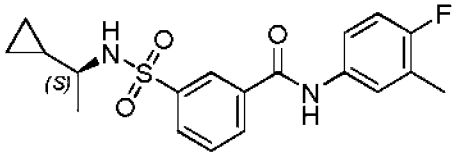
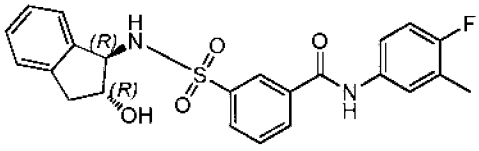
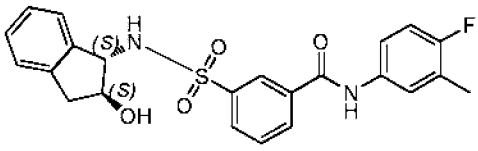
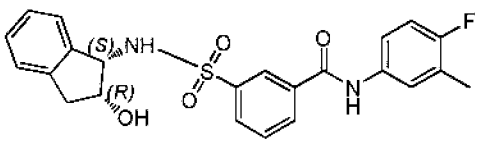
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**143**	0.91		2.66	>25
	**144**	0.13		0.24	>25
	**145**	0.22		0.27	>25
	145a	0.14		0.21	>25
	145b	0.44		0.58	>25
	145c	0.34		0.34	>25
	145d	0.40		0.64	>25
	**146**	0.45		0.42	>25
	**147**	0.26		0.15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

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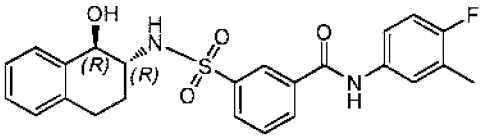
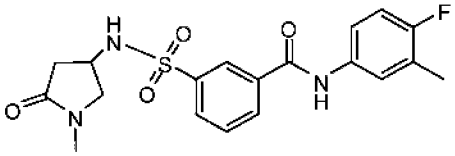
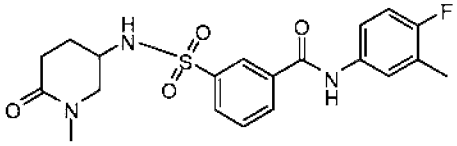
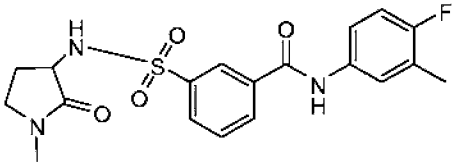
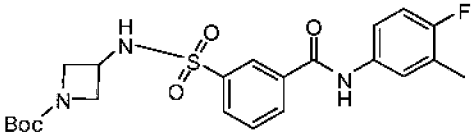
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**178**	0.75		2.54	>25
	**179**	0.21		0.44	>25
	179a	0.38		0.25	>25
	179b	1.11		1.84	>25
	**180**	0.76		1.30	>25
	**181**	2.59		2.04	>25
	**182**	0.31		0.88	>25

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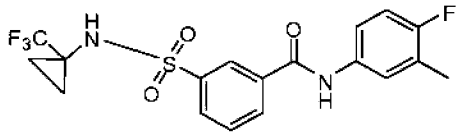
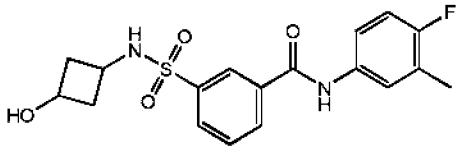
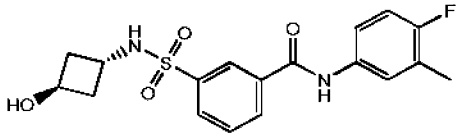
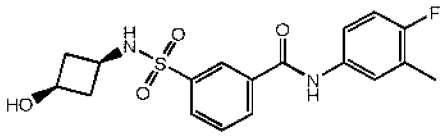
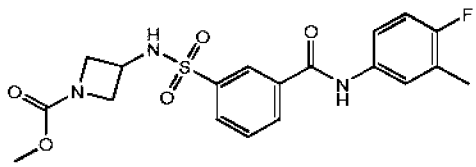
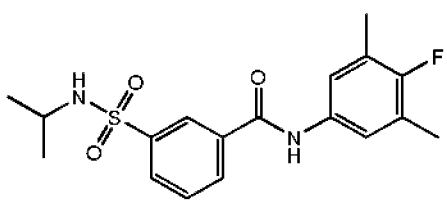
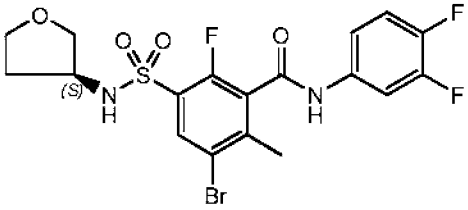
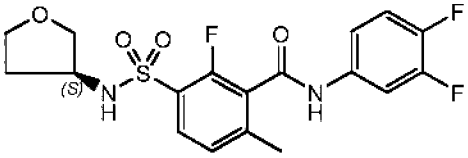
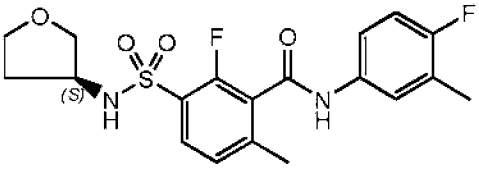
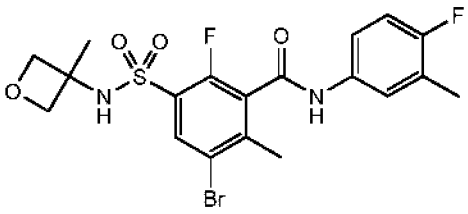
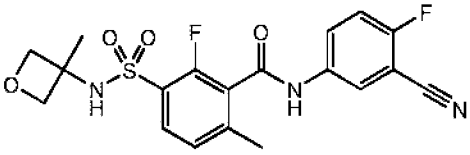
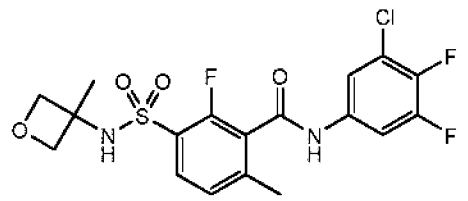
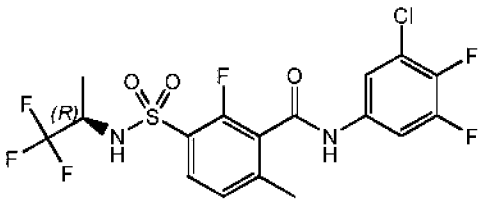
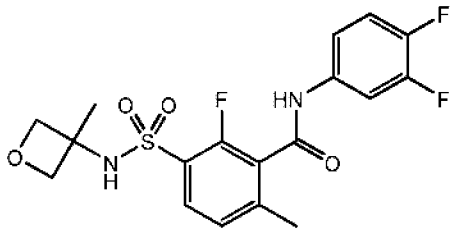
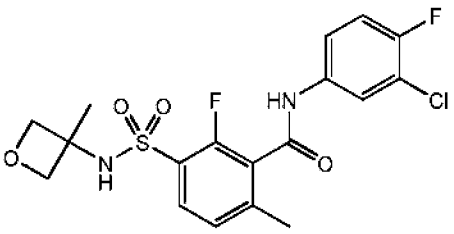
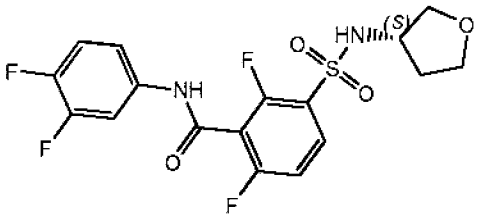
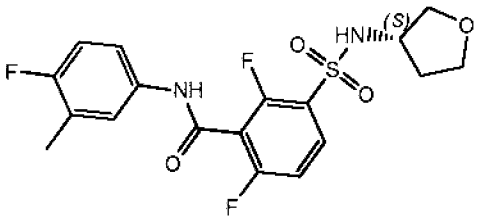
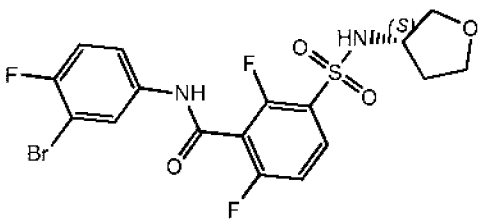
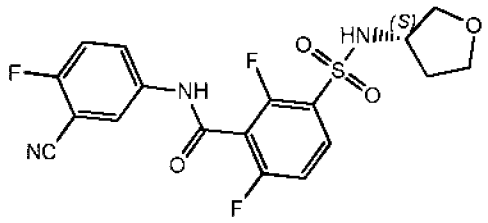
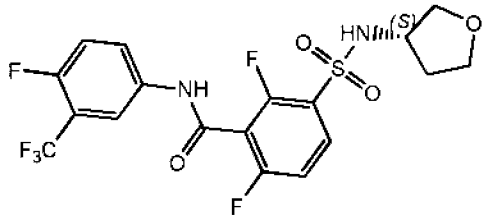
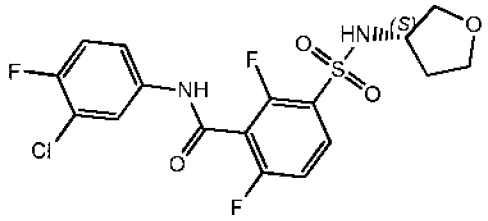
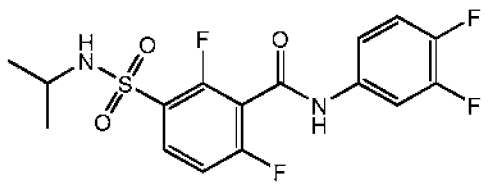
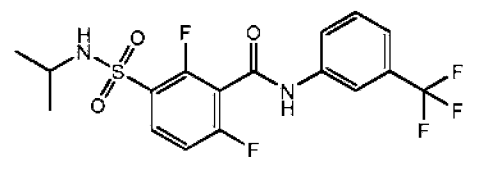
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**183**	0.08		0.84	>25
	**184**	0.15		0.40	>25
	**184a**	0.31		0.77	>25
	**184b**	0.30		0.33	>25
	**185**	0.22		0.62	>25
	**186**	0.20		1.34	>25

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

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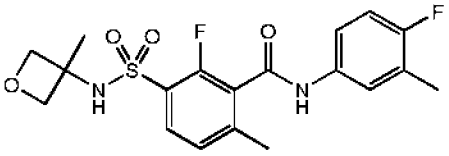
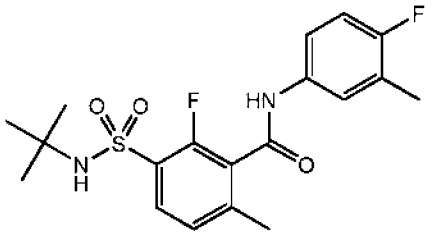
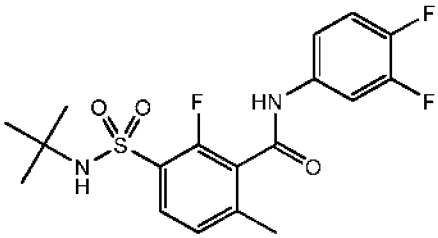
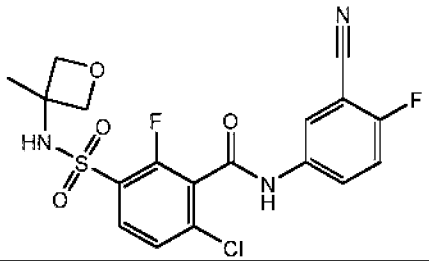
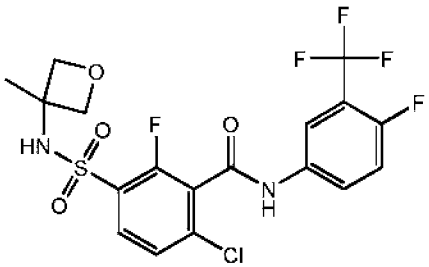
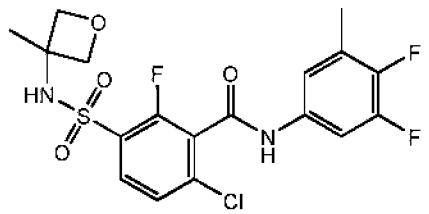
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**204**			0.09	>25
	**205**			0.35	>25
	**206**			0.64	>25
	**207**			>1	>25
	**208**			>1	>25
	**209**			0.15	>25

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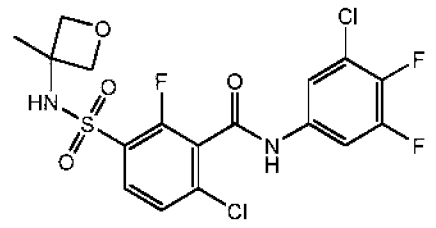
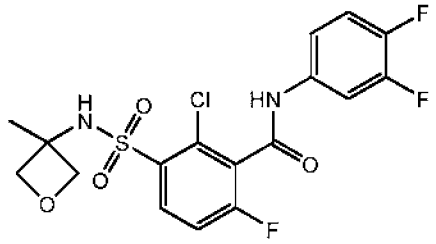
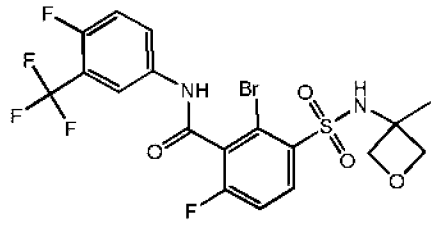
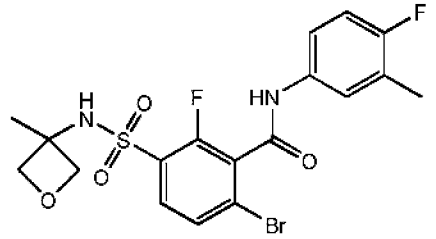
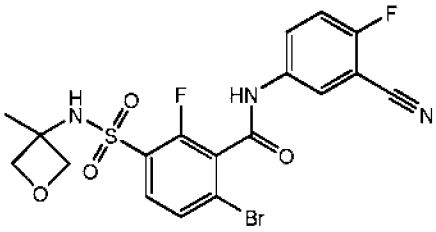
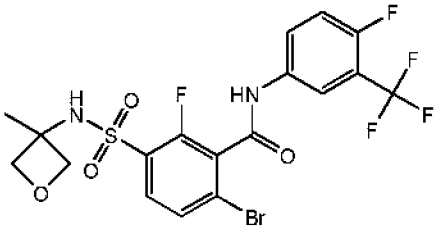
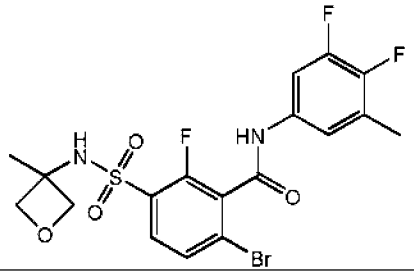
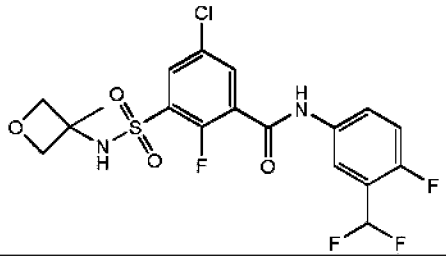
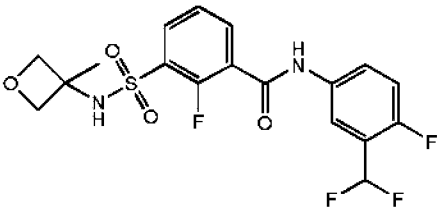
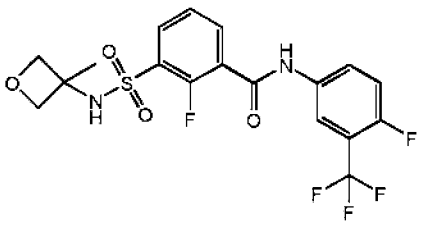
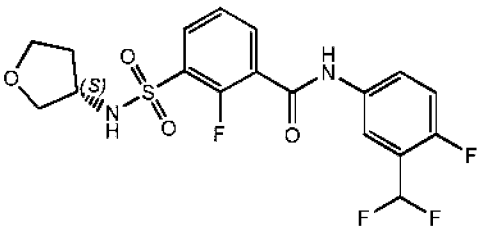
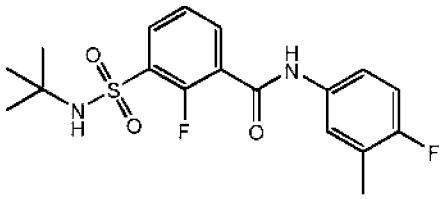
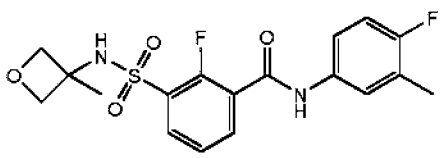
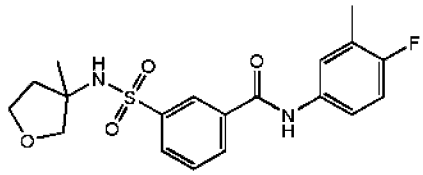
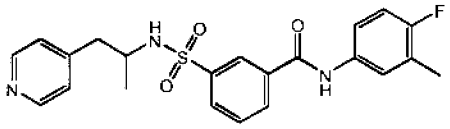
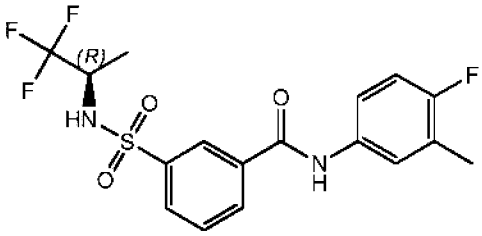
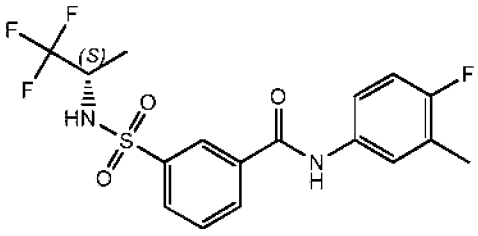
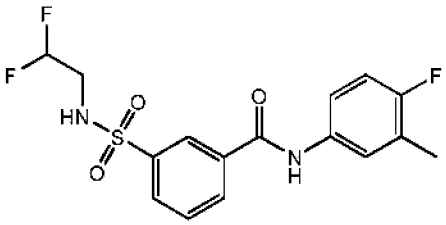
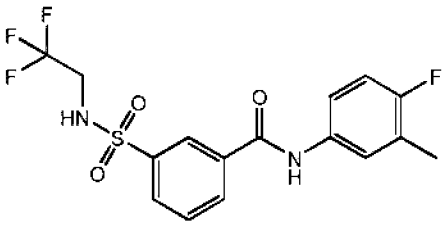
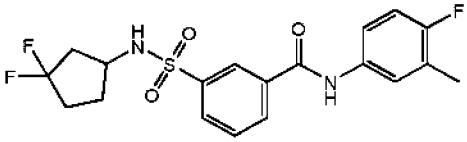
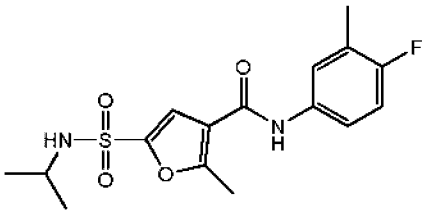
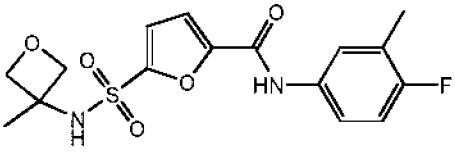
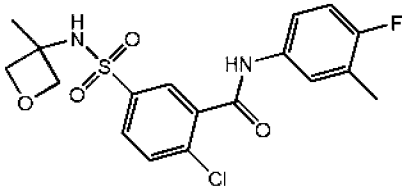
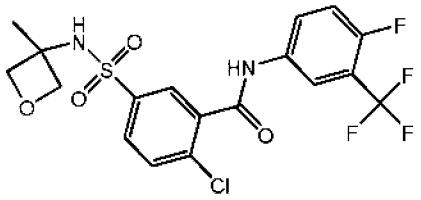
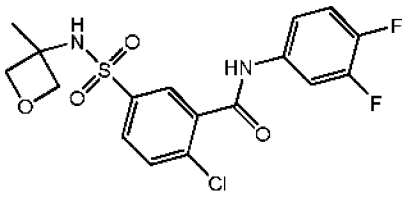
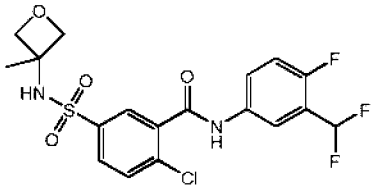
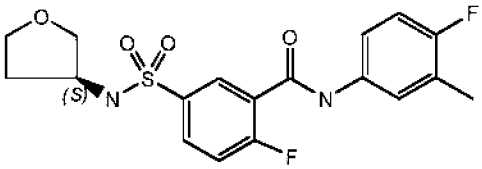
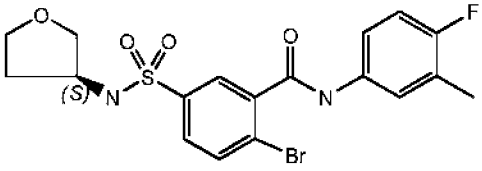
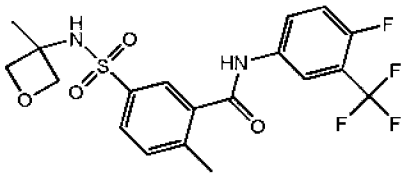
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**210**			0.46	>25
	**211**			0.65	>25
	**212**			7.3	>25
	**213**			0.28	>25
	**214**			>1	>25
	**215**			>1	>25

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

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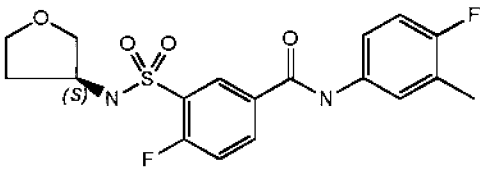
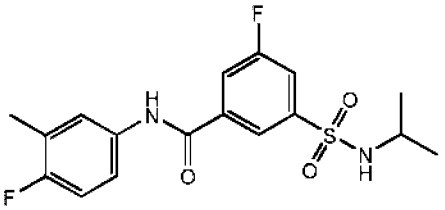
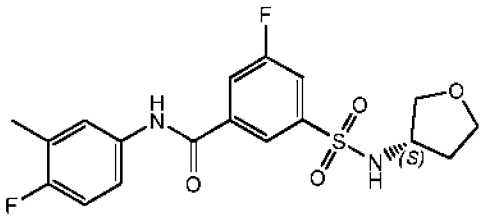
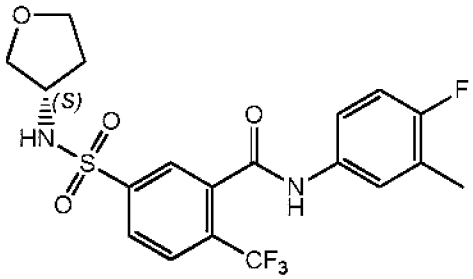
STRUCTURE	Co. No.	HepG2 2.15 EC50 (μM)	HepG2 6 days CC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
	**239**	0.48		0.53	>25
	**240**	0.40		2.86	>25
	**241**	0.38		1.79	>25
	**242**	1.91		1.80	>25

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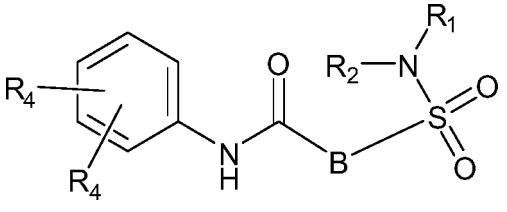
Claims

1. A compound of Formula (Ia)



(Ia)

or a stereoisomer or tautomeric form thereof, wherein:

B represents a monocyclic 6 membered aromatic ring, containing one or more heteroatoms each independently selected from the group consisting of O, S and N, such 6 membered aromatic ring optionally being substituted with one or more substituents each independently selected from the group consisting of 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 carbocyclic ring optionally containing one or more heteroatoms each independently selected from the group consisting of O, S and N, such 3-7 membered saturated carbocyclic ring or C_1-C_6alkyl being substituted with one or more substituents each independently selected from the group consisting of 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 carbocyclic 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 carbocyclic ring containing one or more heteroatoms each independently selected from the group consisting of O, S and N, such 3-7 membered saturated carbocyclic ring optionally being substituted with one or more substituents each independently selected from the group consisting of 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 or a stereoisomer or tautomeric form thereof, or a pharmaceutically acceptable salt or a solvate thereof, wherein R_2 represents a 3-7 membered saturated carbocyclic ring, containing one or more heteroatoms each independently selected from the group consisting of O, S and N, such 3-7 membered saturated carbocyclic ring being substituted with one or more substituents each independently selected from the group consisting of 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 carbocyclic 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 carbocyclic ring optionally being substituted with one or more substituents each independently selected from the group consisting of 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 claim 2 or a stereoisomer or tautomeric form thereof, or a pharmaceutically acceptable salt or a solvate thereof, wherein R_2 represents a 4-7 membered saturated carbocyclic ring containing carbon and one or more oxygen atoms, such 4-7 membered saturated carbocyclic ring being substituted with one or more substituents each independently selected from the group consisting of 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. The compound according to claim 1 or a stereoisomer or tautomeric form thereof, or a pharmaceutically acceptable salt or a solvate thereof, wherein B represents a monocyclic 6 membered aromatic ring containing one or more heteroatoms each independently selected from the group consisting of O, S and N, such 6 membered aromatic ring, optionally being substituted with one or more substituents each independently selected from the group consisting of halo, C_1-C_3alkyl, CN, CFH_2, CF_2H and CF_3.

5. A compound of Formula (Ia) according to claim 1 or a stereoisomer or tautomeric form thereof, or a pharmaceutically acceptable salt or a solvate thereof, wherein

R_2 represents C_1-C_3alkyl-R_6 or a 4-7 membered saturated carbocyclic 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 carbocyclic ring being substituted with one or more substituents each independently selected from the group consisting of 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 carbocyclic 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 carbocyclic ring optionally containing one or more heteroatoms each independently selected from the group consisting of O or S, such 4-7 membered saturated carbocyclic 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 claims 1 to 5 or a stereoisomer or tautomeric form thereof, or a pharmaceutically acceptable salt or a solvate thereof, wherein at least one R_4 represents Fluoro, C_1-C_3alkyl or cyclopropyl.

7. A compound according to any one of claims 1 to 6 or a stereoisomer or tautomeric form thereof, or a pharmaceutically acceptable salt or a solvate thereof, wherein one R_4 on the *para* position represents Fluoro and the other one R_4 on the *meta* position represents methyl.

8. A compound according to any one of claims 1-7 or a stereoisomer or tautomeric form thereof, or a pharmaceutically acceptable salt or a solvate thereof, wherein halogen is chosen from among fluoro and chloro.

9. A compound according to claim 1 or a stereoisomer or tautomeric form thereof, or a pharmaceutically acceptable salt or a solvate thereof, wherein 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 carbocyclic ring, optionally containing one or more additional heteroatoms each independently selected from the group consisting of S and N, such 5-7 membered saturated carbocyclic ring being substituted with one or more substituents each independently selected from the group consisting of 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.

10. A pharmaceutical composition comprising a compound according to any one of claims 1 to 9 or a stereoisomer or tautomeric form thereof, or a pharmaceutically acceptable salt or a solvate thereof, and a pharmaceutically acceptable carrier.