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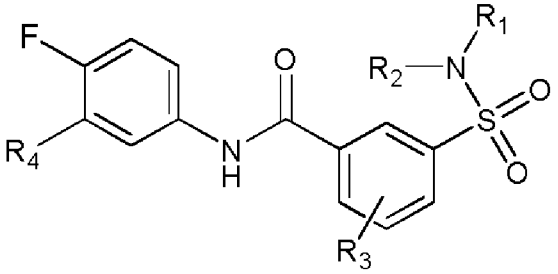

(I)

(57) Abstract: Inhibitors of HBV replication of Formula (I) including stereochemically isomeric forms, salts, hydrates and solvates thereof, wherein R1, R2, R3 and R4 have the meaning as defined herein. The present invention also relates to processes for preparing said compounds, pharmaceutical compositions containing them and their use, alone or in combination with other HBV inhibitors, in HBV therapy.

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

Background Art

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

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

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

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

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

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

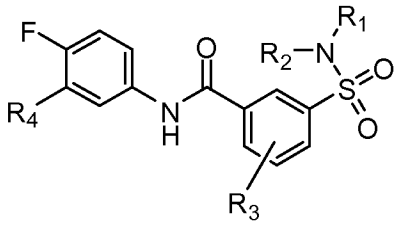
WO/2013/006394, published on January 10 2013, relates to a subclass of Sulphamoyl-arylamides active against HBV.

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

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

Description of the Invention

The present invention relates to compounds of Formula (I):



(I)

or a stereoisomer or tautomeric form thereof, wherein:

R_1 represents hydrogen;

R_2 represents C_1-C_8alkyl substituted with one or more R_5,

R_3 represents Hydrogen or methyl;

R_4 represents methyl;

Each R_5 is independently selected from the group consisting of -C≡CH, -CN, -OH, oxo, C_1-C_4alkyloxy, -C(=O)O-R_6, -C(=O)N(R_6)$_2$, -N(R_6)$_2$, -NR_9C(=O)-R_6, -N R_9C(=O)O-R_6 and SO_2R_9;

Each R_6 independently represents hydrogen or C_1-C_3alkyl;

R_9 represents hydrogen or C_1-C_3alkyl;

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

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

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

C_{1-8}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 8 carbon atoms such as the groups defined for C_{1-6}alkyl and heptyl, octyl, and their branched structural isomers.

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.

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.

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, dodecyl-sulphuric, heptanoic, hexanoic, nicotinic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-amino-salicylic, pamoic and the like acids.

Conversely said acid addition salt forms can be converted by treatment with an appropriate base into the free base form.
The term "salts" also comprises the hydrates and the solvent addition forms that the compounds of the present invention are able to form. Examples of such forms are *e.g.* hydrates, alcoholates and the like.

The present compounds may also exist in their tautomeric forms For example, tautomeric forms of amide (-C(=O)-NH-) groups are iminoalcohols (-C(OH)=N-). Tautomeric forms, although not explicitly indicated in the structural Formulae represented herein, are intended to be included within the scope of the present invention.

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

forms of the compounds of the present invention both in pure form or in admixture with each other are intended to be embraced within the scope of the present invention.

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

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

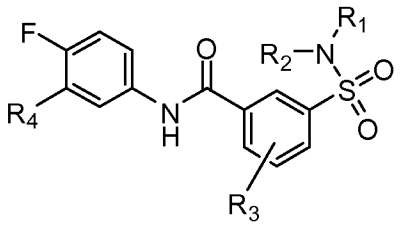
The diastereomeric racemates of Formula (I) can be obtained separately by conventional methods. Appropriate physical separation methods that may advantageously be employed are, for example, selective crystallization and chromatography, e.g. column chromatography.

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

Detailed description of the invention

Whenever used hereinafter, the term "compounds of Formula (I)", or "the present compounds" or similar term is meant to include the compounds of general Formula (I) (Ib) , salts, stereoisomeric forms and racemic mixtures or any subgroups thereof.

The present invention relates to compounds of Formula (I)



(I)

or a stereoisomer or tautomeric form thereof, wherein:

R_1 represents hydrogen;

R_2 represents C_1-C_8alkyl substituted with one or more R_5,

R_3 represents Hydrogen or methyl;

R_4 represents methyl;

Each R_5 is independently selected from the group consisting of -C≡CH, -CN, -OH, oxo, C_1-C_4alkyloxy, -C(=O)O-R_6, -C(=O)N(R_6)$_2$, -N(R_6)$_2$, -NR_9C(=O)-R_6, -N R_9C(=O)O-R_6 and SO_2R_9;

Each R_6 independently represents hydrogen or C_1-C_3alkyl;

R_9 represents hydrogen or C_1-C_3alkyl;

or a pharmaceutically acceptable salt or a solvate thereof.

In one embodiment, compounds of Formula (I) are provided wherein:

R_1 represents hydrogen;

R_2 represents C_1-C_8alkyl substituted with one or more R_5,

R_3 represents Hydrogen or methyl;

R_4 represents methyl;

R_5 is selected from the group consisting of -C≡CH, -CN, -OH, oxo, C_1-C_4alkyloxy, -C(=O)O-R_6, -C(=O)N(R_6)$_2$, -N(R_6)$_2$, -NR_9C(=O)-R_6, -N R_9C(=O)O-R_6 and SO_2R_7;

R_6 represents hydrogen or C_1-C_3alkyl;

R_9 represents hydrogen or C_1-C_3alkyl;

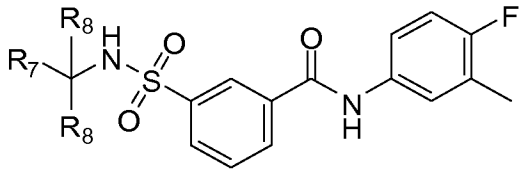
or a pharmaceutically acceptable salt or a solvate thereof.

In a further embodiment, compounds of Formula (I) are provided wherein:

R_1 represents hydrogen;
R_2 represents C_1-C_6alkyl substituted with one R_5,
R_3 represents Hydrogen;
R_4 represents methyl;
R_5 is selected from the group consisting of -C≡CH, -CN, -OH, C_1-C_4alkyloxy, -C(=O)O-R_6, -C(=O)N(R_6)$_2$, -N(R_6)$_2$, -NHC(=O)-R_6 and -NHC(=O)O-R_6;
R_6 represents hydrogen or C_1-C_3alkyl;
or a pharmaceutically acceptable salts or a solvate thereof.

In another embodiment. compounds of Formula (I) are provided wherein the C_1-C_8alkyl group as defined in R_2 represents a branched C_2-C_6alkyl.
In yet another embodiment, at least one R_5 is –OH.

In a subembodiment, such compounds are represented by Formula (Ib):



(Ib)

wherein:
R_7 is selected from the group consisting of -C≡CH, -CN, -C(=O)O-R_6 -C(=O)N(R_6)$_2$ and C_1-C_4alkyl optionally substituted with one or more substituents selected from the group consisting of -C≡CH, -CN, -OH, oxo, C_1-C_4alkyloxy, -C(=O)O-R_6, -C(=O)N(R_6)$_2$, -N(R_6)$_2$, -NR_9C(=O)-R_6, -N R_9C(=O)O-R_6 and SO_2R_9;
R_6 represents hydrogen or C_1-C_3alkyl;
R_9 represents hydrogen or C_1-C_3alkyl and wherein
Each R_8 independently represents hydrogen or C_1-C_2alkyl optionally substituted with OH.

In a sub-embodiment, compounds are according to Formula (Ib) are provided wherein
R_7 is selected from the group consisting of -C≡CH, -CN, -C(=O)O-R_6 -C(=O)N(R_6)$_2$ and C_1-C_4alkyl optionally substituted with one or more substituents selected from the group consisting of -C≡CH, -CN, -OH, C_1-C_4alkyloxy, -C(=O)O-R_6, -C(=O)N(R_6)$_2$, -N(R_6)$_2$, -NHC(=O)-R_6 and -NHC(=O)O-R_6;
R_6 represents hydrogen or C_1-C_3alkyl; and wherein

Each R_8 independently represents hydrogen or C_1-C_2alkyl optionally substituted with OH. In one aspect, one R_8 is C_1-C_2alkyl substituted with OH.

In another subembodiment, compounds according to Formula (Ib) are provided wherein R_7 is selected from the group consisting of C_1-C_4alkyl optionally substituted with -C≡CH, -CN, -OH, C_1-C_4alkyloxy, -C(=O)O-R_6, -C(=O)N(R_6)$_2$, -N(R_6)$_2$, -NHC(=O)-R_6 and -NHC(=O)O-R_6.

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 compound or a stereoisomer or tautomeric form thereof with a Formula selected from table 1.

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

Therefore, the compounds of the present invention or any subgroup thereof may be formulated into various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, optionally in addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, particularly, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like

in the case of oral liquid preparations such as suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules, and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid pharmaceutical carriers are employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations intended to be converted, shortly before use, to liquid form preparations. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin. The compounds of the present invention may also be administered via oral inhalation or insufflation in the form of a solution, a suspension or a dry powder using any art-known delivery system.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, suppositories, powder packets, wafers, injectable solutions or suspensions and the like, and segregated multiples thereof.

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

Due to their antiviral properties, particularly their anti-HBV properties, the compounds of Formula (I) or any subgroup thereof, are useful in the inhibition of the HBV replication cycle, in particular in the treatment of warm-blooded animals, in particular humans, infected with HBV, and for the prophylaxis of HBV infections. The present invention furthermore relates to a method of treating a warm-blooded animal, in

particular human, infected by HBV, or being at risk of infection by HBV, said method comprising the administration of a therapeutically effective amount of a compound of Formula (I).

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

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

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

The combination of previously known anti-HBV agents, such as interferon-α (IFN-α), pegylated interferon-α, 3TC, adefovir or a combination thereof, and, a compound of

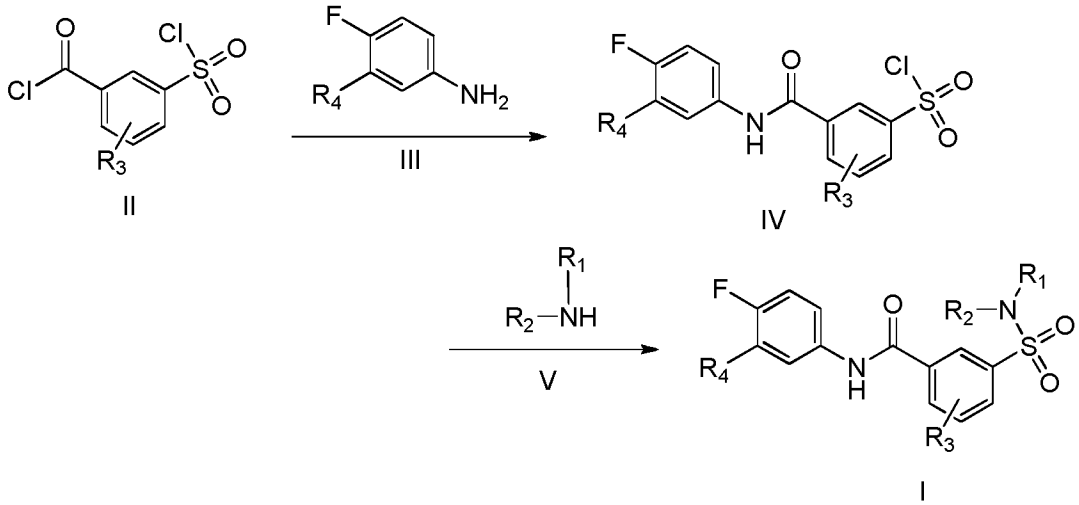
Formula (I) or any subgroup thereof can be used as a medicine in a combination therapy.

Generic synthesis:

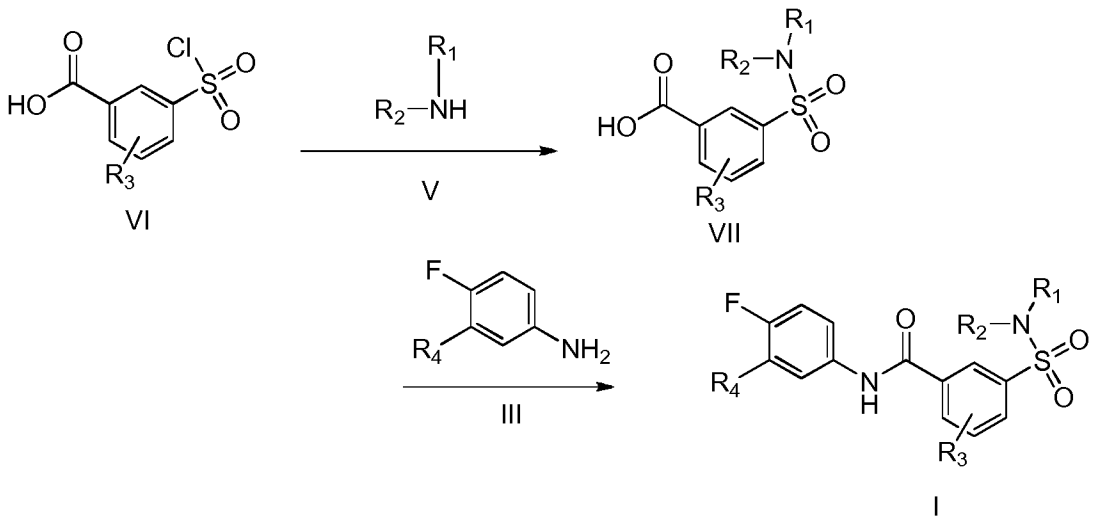
The substituent represented by R^2 in this general synthesis section are meant to include any substituent or reactive species that is suitable for transformation into any R^2 substituent according to the present invention without undue burden for the person skilled in the art.

A possible synthesis of compound of general Formula (I) is described in scheme 1 and 2.

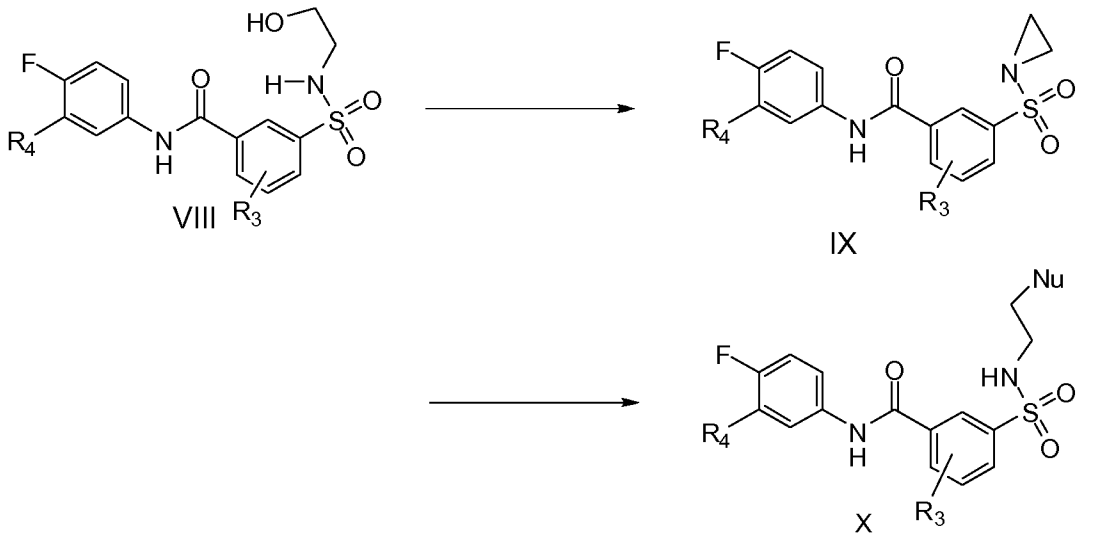
A carboxylic acid chloride of general Formula II can be selectively reacted with an aniline of general Formula III, for example in an organic solvent like CH_2Cl_2 in the presence of an organic base like triethylamine or DIPEA (N,N-diisopropylethylamine), or, as another example, by addition of the aniline 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, as another example, in the presence of Na_2CO_3 in a mixture of H_2O/THF. The resulting compound VII is coupled with aniline of general Formula III in the presence of an activating reagent like for example HATU and an organic base like triethylamine or DIPEA.



Scheme 1



Scheme 2



Scheme 3

A synthetic route to compounds of general Formula X is described in Scheme 3. A aminoethanol derivative VIII, prepared as described in scheme 1 for the compounds of general Formula (I), is transformed in an aziridine derivative IX by treatement with Diethyl diazene-1,2-dicarboxylate and PPh_3 in THF. The aziridine of general Formula IX is reacted with a nucleophile Nu, resulting in a compound of general Formula X. Examples of such nucleophiles (Nu) are, but are not limited to, ammonia, methanamine and dimethylamine. In case ammonia is used, the resulting primary amine can be reacted with for example acetyl chloride, or methyl chloroformate, like for example used in the synthesis of compounds **1** and **9**. Examples of a compounds synthesized according to the route described in scheme 3, are compounds **2** and **3**.

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.

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.

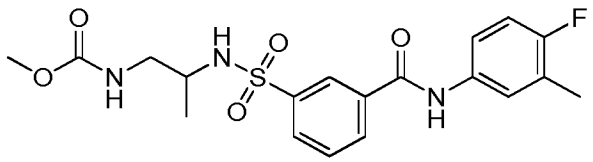
Procedure S4: 3-[(4-fluoro-3-methyl-phenyl)carbamoyl]benzenesulfonyl chloride (250 mg, 0.76 mmol) and DIPEA (329 µL, 1.9 mmol, 2.5 eq) dissolved in CH_2Cl_2 (5 mL) were added to a tube containing an amine (1.1 eq). The reaction mixture was stirred for 3 hours. 1M HCl (5 mL) was added.

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).

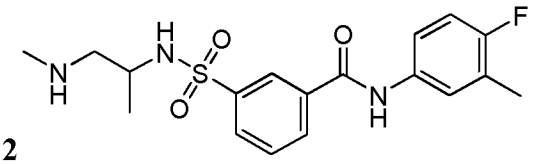
Workup W4: The organic layer was separated and loaded on a silica gel column. The mixture was purified using gradient elution from heptane to EtOAc.



Compound **1**

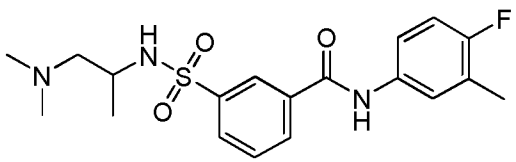
4-fluoro-3-methyl-aniline (9.04 g, 72.2 mmol) was added drop wise to a solution of 3-(chlorosulfonyl) benzoyl chloride (19.0 g, 79.47 mmol) in toluene (300 mL) at 110°C. The resultant mixture was stirred at 110°C for 1 hour and allowed to cool to 20°C over night. The precipitate was filtered and recrystallized 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 over night. 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). To N-(4-fluoro-3-methyl-phenyl)-3-(2-methylaziridin-1-yl)sulfonyl-benzamide (200 mg, 0.574 mmol), NH_3 (NH_3 in methanol, 8 mL) was added drop wise at 0°C. The

mixture was stirred at 20°C over night. The solvent was removed and the obtained residue (170 mg) containing 3-[(2-amino-1-methyl-ethyl)sulfamoyl]-N-(4-fluoro-3-methyl-phenyl)benzamide used as such in the next step. 3-[(2-amino-1-methyl-ethyl)sulfamoyl]-N-(4-fluoro-3-methyl-phenyl)benzamide (0.17 g, 0.465 mmol) and triethylamine (94 mg) were dissolved in anhydrous CH_2Cl_2 (20 mL) and methyl chloroformate (0.5 g, 5.29 mmol) was added drop wise at 0°C. 1 N HCl (10 mL) was added, the organic layer was separated 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 and the obtained residue was purified by reversed phase high performance liquid chromatography (eluent: CH_3CN in water (0.5% NH_3H_2O) from 35% to 65%, v/v). The relevant fractions were concentrated in vacuo and the residual aqueous fraction lyophilized to dryness resulting in compound **1** (70 mg). Method A; Rt: 5.14 min. m/z : 424.3 $(M+H)^+$ Exact mass: 423.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.85 (d, *J*=6.5 Hz, 3 H) 2.24 (s, 3 H) 2.80 - 2.99 (m, 2 H) 3.16 - 3.32 (m, 1 H) 3.44 (s, 3 H) 7.05 (t, *J*=5.8 Hz, 1 H) 7.14 (t, *J*=9.2 Hz, 1 H) 7.51 - 7.63 (m, 1 H) 7.63 - 7.71 (m, 1 H) 7.71 - 7.83 (m, 2 H) 7.99 (d, *J*=7.8 Hz, 1 H) 8.20 (d, *J*=7.8 Hz, 1 H) 8.36 (s, 1 H) 10.47 (s, 1 H).



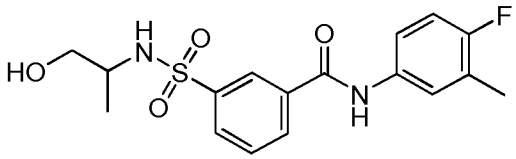
Compound **2**

N-(4-fluoro-3-methyl-phenyl)-3-(2-methylaziridin-1-yl)sulfonyl-benzamide (0.30 g, 0.861 mmol), methanamine (0.134 g, 4.305 mmol) and triethylamine (0.523 g) were dissolved in anhydrous 1,4-dioxane (8 mL). This mixture was stirred at 150°C in an autoclave under argon for 30 minutes. The volatiles were removed in vacuo and the obtained residue was purified by reversed phase high performance liquid chromatography (eluent: CH_3CN in water (0.075 % TFA) from 15% to 45%, 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 concentrated in vacuo and the residual aqueous layer lyophilized to dryness, resulting in compound **2** (130 mg). Method A; Rt: 4.27 min. m/z: 380.3 $(M+H)^+$ Exact mass: 379.1.



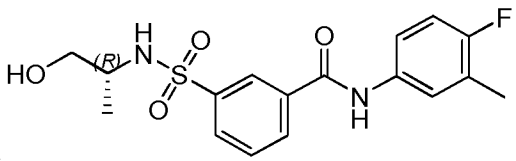
Compound **3**

N-(4-fluoro-3-methyl-phenyl)-3-(2-methylaziridin-1-yl)sulfonyl-benzamide (0.35 g, 1.0 mmol), dimethylamine hydrochloride (0.41 g, 5.025 mmol) and triethylamine (0.61g) were dissolved in anhydrous 1, 4-dioxane (8 mL). This mixture was stirred at 150°C in an autoclave under argon for 30 min. The solvent was removed in vacuo and the obtained residue was purified by reversed phase high performance liquid chromatography r (eluent: CH3CN in water (0.075%TFA) from 20% to 45%, 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 concentrated in vacuo and the residual aqueous lyophilized to dryness, resulting in compound **3**. Method A; Rt: 4.40 min. m/z: 394.3 $(M+H)^+$ Exact mass: 393.2.



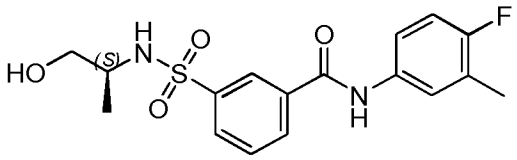
Compound **4**

A mixture of 2-aminopropan-1-ol (229 mg, 3.05 mmol) and DIPEA (1.063 mL, 6.10 mmol) were dissolved in CH_2Cl_2 (10 mL). 3-[(4-fluoro-3-methyl-phenyl)-carbamoyl]benzenesulfonyl chloride (1 g, 3.051 mmol) was added portionwise 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 washed with tert-butyl methyl ether (2 x 5 mL). The solid was suspended in water (10 mL) and acetonitrile (10 mL) and the solution was lyophilized to dryness resulting in compound **4** (780 mg). Method A; Rt: 4.90 min. m/z : 367.3 $(M+H)^+$ Exact mass: 366.1. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 0.90 (d, J=6.3 Hz, 3 H) 2.26 (d, *J*=1.5 Hz, 3 H) 3.07-3.20 (m, 2 H) 3.25-3.32 (m, 1 H) 4.72 (t, J=5.5 Hz, 1 H) 7.15 (t, J=9.3 Hz, 1 H) 7.54 - 7.64 (m, 1 H) 7.64 - 7.72 (m, 2 H) 7.76 (t, J=7.9 Hz, 1 H) 8.02 (d, J=7.8 Hz, 1 H) 8.19 (d, J=7.8 Hz, 1 H) 8.37 (s, 1 H) 10.48 (s, 1 H)



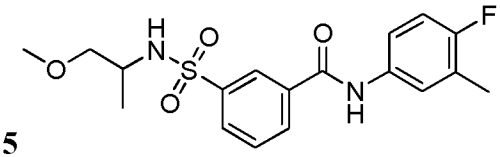
Compound **4a**

Synthesis following procedure S4 (20 hours instead of 3 hours reaction time) with D-alaninol as amine, workup W4. DSC (From 30 to 300 °C at 10°C/min): peak: 152 °C. Method F; Rt: 0.83 min. m/z : 384.2 $(M+NH_4)^+$ Exact mass: 366.1.



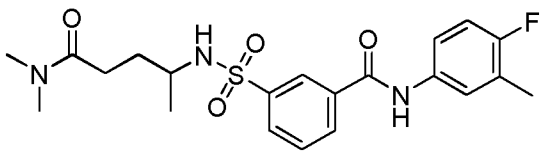
Compound **4b**

Synthesis following procedure S4 (20 hours instead of 3 hours reaction time) with L-alaninol as amine, workup W4. DSC (From 30 to 300°C at 10°C/min): peak: 152°C Method F; Rt: 0.83 min. m/z : 384.1 $(M+NH_4)^+$ Exact mass: 366.1.



Compound **5**

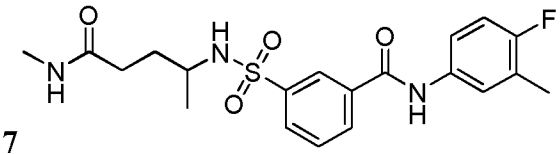
To a solution of 3-[(4-fluoro-3-methyl-phenyl)carbamoyl]benzenesulfonyl chloride (0.20 g, 0.60 mmol) in CH_2Cl_2 (2mL), DIPEA (0.16 g, 1.21 mmol) was added, followed by 1-methoxypropan-2-amine (0.05g, 0.60 mmol). After stirring at 15°C for 1 hour, the resulting mixture was diluted with water (10 mL). The organic layer was separated, washed with 1N HCl (5 mL), aqueous $NaHCO_3$ (5 mL), brine (5 mL) and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo, resulting in compound **5** (123 mg). Method A; Rt: 5.38 min. m/z: 381.3 $(M+H)^+$ Exact mass: 380.1. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 0.89 (d, *J*=6.8 Hz, 3 H) 2.23 (s, 3 H) 3.04 - 3.12 (m, 4 H) 3.16 (dd, *J*=9.5, 5.8 Hz, 1 H) 3.30-3.37 (m, 1 H) 7.13 (t, *J*=9.2 Hz, 1 H) 7.52 - 7.62 (m, 1 H) 7.61 - 7.70 (m, 1 H) 7.73 (t, *J*=7.9 Hz, 1 H) 7.83 (d, *J*=6.5 Hz, 1 H) 7.99 (d, *J*=7.8 Hz, 1 H) 8.17 (d, *J*=7.8 Hz, 1 H) 8.35 (s, 1 H) 10.46 (s, 1 H)



Compound **6**

To a solution of 4-(tert-butoxycarbonylamino)pentanoic acid (2.17 g, 9.99 mmol), N-methylmethanamine hydrochloride (0.82 g, 10.00 mmol), EDC (2.33 g, 15.01 mmol), and HOBt (0.68 g, 5.00 mmol) in CH_2Cl_2 (30 mL), DIPEA (3.88 g, 30.02 mmol) was added. The resulting mixture was stirred at 15° C for 2 hours. The resulting mixture was diluted with water (40 mL), the organic layer was separated, washed with 1 N HCl (10 mL), aqueous $NaHCO_3$ (20 mL), brine (20 mL) and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo resulting in tert-butyl N-[4-(dimethylamino)-1-methyl-4-oxo-butyl]carbamate (1.00 g). To a solution of tert-butyl N-[4-(dimethylamino)-1-methyl-4-oxo-butyl]carbamate(1.00 g, 4.09 mmol) in

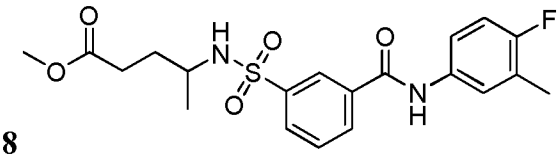
CH_2Cl_2 (30 mL), TFA (30 mL) was added. The resulting mixture was stirred for 2 hours at 15°C. The reaction mixture was concentrated and the obtained residue, containing the TFA salt of 4-amino-N,N-dimethyl-pentanamide, was used directly in the next step. To a solution of the TFA salt of 4-amino-N,N-dimethyl-pentanamide (0.77 g) and 3-[(4-fluoro-3-methyl-phenyl)carbamoyl]benzenesulfonyl chloride (0.98 g, 2.99 mmol) in CH_2Cl_2 (15 mL) DIPEA (1.16 g, 9.00 mmol) was added at 0°C. The resulting mixture was stirred at 15° for 1 hour. The resulting mixture was washed with 1 N HCl (15 mL), aqueous $NaHCO_3$ (15 mL), brine (15 mL) and dried over anhydrous $MgSO_4$. The residue was purified by silica gel column chromatography (gradient eluent: EtOAc/petroleum ether from 0/100 to100/0). The product fractions were collected and the solvent was evaporated resulting in compound **6** (0.62 g). Method A; Rt: 5.18 min. m/z : 436.3 $(M+H)^+$ Exact mass: 435.2. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 0.94 (d, *J*=6.5 Hz, 3 H) 1.40 - 1.59 (m, 2 H) 2.00 - 2.16 (m, 2 H) 2.25 (s, 3 H) 2.73 (s, 3 H) 2.78 (s, 3 H) 3.15-3.28 (m, 1 H) 7.15 (t, *J*=9.2 Hz, 1 H) 7.55 - 7.64 (m, 1 H) 7.65 - 7.84 (m, 3 H) 7.99 (d, *J*=7.8 Hz, 1 H) 8.20 (d, *J*=7.8 Hz, 1 H) 8.36 (s, 1 H) 10.49 (s, 1 H)



Compound **7**

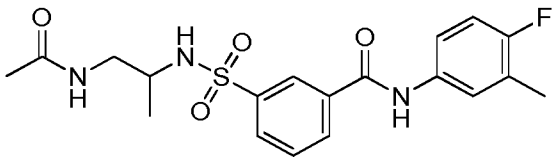
To a solution of 4-(tert-butoxycarbonylamino)pentanoic acid (1.08 g, 4.97 mmol), methanamine hydrochloride (0.68 g, 10.00 mmol), EDC (1.16 g, 7.47 mmol), and HOBt (0.34 g, 2.50 mmol) in CH_2Cl_2 (20 mL), DIPEA (1.94 g, 15.01 mmol) was added. The resulting mixture was stirred at 15°C for 2 hours and then diluted with water (40 mL). The organic layer was separated, washed with 1N HCl (10 mL), aqueous $NaHCO_3$ (20 mL) and brine (20 mL) and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo resulting in tert-butyl N-[1-methyl-4-(methylamino)-4-oxo-butyl]carbamate (1.00 g). To a solution of tert-butyl N-[1-methyl-4-(methyl-amino)-4-oxo-butyl]carbamate (0.50 g, 2.17 mmol) in CH_2Cl_2 (20 mL), TFA (20 mL) was added. The resulting mixture was stirred for 2 hours at 15°C. The reaction mixture was concentrated and the obtained residue was used directly in the next step. To a solution of the above obtained residue and 3-[(4-fluoro-3-methyl-phenyl)carbamoyl]-benzenesulfonyl chloride (0.718 g, 2.71 mmol) in CH_2Cl_2 (12 mL) DIPEA (0.84 g, 6.51 mmol) was added at 0°C. The resulting mixture was stirred at 15°C for 1 hour and then washed with 1N HCl (15 mL), aqueous $NaHCO_3$ (15 mL), brine (15 mL) and dried over anhydrous $MgSO_4$.After removal of the solvent in vacuo, the obtained residue was purified by silica gel column chromatography (gradient eluent:

EtOAc/petroleum ether from 0/100 to 100/0). The product fractions were collected and the solvent was removed in vacuo, resulting in compound **7** (0.33 g). Method A; Rt: 4.98 min. m/z : 422.3 $(M+H)^+$ Exact mass: 421.2.



Compound **8**

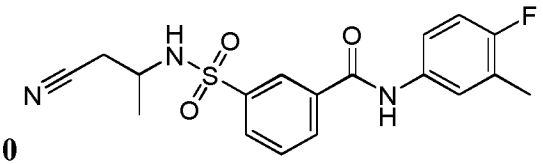
To a solution of methyl 4-aminopentanoate (0.17 g, 1.00 mmol) and 3-[(4-fluoro-3-methyl-phenyl)carbamoyl]benzenesulfonyl chloride (0.33 g, 1.00 mmol) in CH_2Cl_2 (8 mL), DIPEA (0.26 g, 2.02 mmol) was added at 0°C. The resulting mixture was stirred at 15° C for 1 hour. The resulting mixture was washed with 1 N HCl (5 mL), aqueous $NaHCO_3$ (5 mL), brine (5 mL), dried over anhydrous $MgSO_4$ and the volatiles were removed in vacuo. The obtained residue was purified by silica gel column chromatography (gradient eluent: EtOAc/petroleum ether from 0/100 to 58/42). The product fractions were collected and the solvent was removed in vacuo, resulting in compound **8** (0.18 g). Method B; Rt: 4.24 min. m/z: 423.3 $(M+H)^+$ Exact mass: 422.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.88 (d, *J*=6.8 Hz, 3 H) 1.46 - 1.66 (m, 2 H) 2.12 - 2.34 (m, 5 H) 3.14 - 3.29 (m, 1 H) 3.53 (s, 3 H) 7.15 (t, *J*=9.3 Hz, 1 H) 7.56 - 7.64 (m, 1 H) 7.66 - 7.72 (m, 1 H) 7.72 - 7.82 (m, 2 H) 7.99 (d, *J*=8.0 Hz, 1 H) 8.21 (d, *J*=8.0 Hz, 1 H) 8.36 (t, *J*=1.5 Hz, 1 H) 10.48 (s, 1 H)



Compound **9**

N-(4-fluoro-3-methyl-phenyl)-3-(2-methylaziridin-1-yl)sulfonyl-benzamide (3 g, 19.1 mmol) was dissolved in NH_3/MeOH (4 mL). The mixture was stirred for 8 hours at 0°C. The solvent was removed in vacuo an the obtained residue containing 3-[(2-amino-1-methyl-ethyl)sulfamoyl]-N-(4-fluoro-3-methyl-phenyl)benzamidewas used in the next step without further purification. 3-[(2-amino-1-methyl-ethyl)-sulfamoyl]-N-(4-fluoro-3-methyl-phenyl)benzamide (200 mg, 0.491 mmol) and acetyl chloride (77.3 mg, 0.985 mmol) was dissolved in dichloromethane (3 mL). DIPEA (212 mg, 1.64 mmol) was added drop wise at 0°C. The mixture was stirred for 8 hours at 25°C. The mixture was washed with saturated citric acid (10 mL), saturated aqueous $NaHCO_3$ (10 mL)and brine and dried over Na_2SO_4. The solvent was removed in vacuo and the obtained crude was purified by preparative high-performance liquid

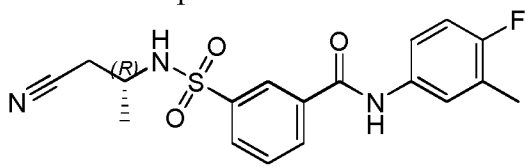
chromatography (column: Luna 150*30mm*5u, mobile phase: CH_3CN in water (0.5% NH_4HCO_3) from 36% to 66%). The pure fractions were collected and the volatiles were removed in vacuo resulting in compound **9** (200 mg). Method A; Rt: 4.92 min. m/z: 408.3 $(M+H)^+$ Exact mass: 407.1.



Compound **10**

3-[(4-fluoro-3-methyl-phenyl)carbamoyl]benzenesulfonyl chloride (400 mg, 1.22 mmol) and 3-aminobutanenitrile (102 mg, 1.22 mmol) were dissolved in CH_2Cl_2 (4 mL). DIPEA was added drop wise at 0°.The mixture was stirred for 8 hours at 25°C and next washed with saturated citric acid (10 mL), saturated aqueous $NaHCO_3$ (10 mL) and brine. After drying over Na_2SO_4, the solvent was removed in vacuo and the obtained crude was purified by preparative high-performance liquid chromatography (column: Luna 150*30mm*5u, mobile phase: CH_3CN in water (0.5% NH_4HCO_3) from 38% to 68%). The relevant fraction were concentrated in vacuo and the residual aqueous layer was lyophilized to dryness resulting in compound **10** (300 mg). Method A; Rt: 5.22 min. m/z: 376.3 $(M+H)^+$ Exact mass: 375.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.98 (d, *J*=6.8 Hz, 3 H) 2.26 (d, *J*=1.3 Hz, 3 H) 2.62 (dd, *J*=16.8, 5.8 Hz, 1 H) 2.71 (dd, *J*=16.6, 5.3 Hz, 1 H) 3.45 - 3.55 (m, 1 H) 7.16 (t, *J*=9.3 Hz, 1 H) 7.56 - 7.62 (m, 1 H) 7.68 (dd, *J*=6.8, 2.3 Hz, 1 H) 7.78 (t, *J*=8.0 Hz, 1 H) 8.00 - 8.07 (m, 1 H) 8.16-8.28 (m, 2 H) 8.38 (t, *J*=1.5 Hz, 1 H) 10.49 (s, 1 H).
Racemic mixture **10** was separated in enantiomers **10a** (Method F; Rt: 0.90 min. m/z: 376.2 $(M+H)^+$ Exact mass: 375.1).and **10b** (Method F; Rt: 0.90 min. m/z: 376.1 $(M+H)^+$ Exact mass: 375.1 by preparative SFC (Stationary phase: Chiralpak Diacel AD 30 x 250 mm), Mobile phase: CO_2, MeOH with 0.4 % $iPrNH_2$). SFC; Column: AD-H (diacel) 250 mm x 4.6 mm, Flow: 5 ml/min; Mobile phase: 35% MeOH (containing 0.2% $iPrNH_2$) hold 4.00 min, up to 50% in 1 minute and hold 2.00 minutes at 50%; Temperature: 40°C. Rt: **10a** (1.7 min), **10b** (2.3 min).

Alternative synthesis of compound **10a**:

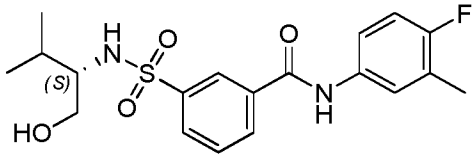


Compound **4a** (1 g, 2.73 mmol) was dissolved in dichloromethane (50 mL) and diisopropylethylamine (941 µL, 5.46 mmol) was added. This mixture was cooled in an

ice bath and stirred for 20 minutes. Then methanesulfonyl chloride (317 µL, 4.09 mmol) in dichloromethane (25 mL) was added slowly and drop wise over 30 minutes. Cooling was continued for another 30 minutes. The mixture was quenched with water (75 mL), the layers were separated and the aqueous layer was extracted with dichloromethane (2 x 75 mL). The combined organics were washed with HCL (1M, 75 mL) and $NaHCO_3$ (sat, 10 mL). The combined organics were 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) yielding [(2*R*)-2-[[3-[(4-fluoro-3-methyl-phenyl)carbamoyl]phenyl]sulfonylamino]propyl] methanesulfonate (916 mg) as a white powder. Sodium cyanide (33.1 mg, 67 mmol) was suspended in DMSO (5 mL) and this was warmed to 40°C. A solution of [(2*R*)-2-[[3-[(4-fluoro-3-methyl-phenyl)carbamoyl]phenyl]sulfonylamino]propyl] methanesulfonate (100 mg, 0.22 mmol) in DMSO (5 mL) was added drop wise. After 1 hour the solution was cooled to room temperature and then water (12 mL) was added. The resulting mixture was extracted using diethylether (2 X 15 mL). The combined extracts were dried on $MgSO_4$, 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 combined fractions were concentrated in vacuo and dried in a vacuum oven at 55°C for 24 hours yielding compound **10a** as a white power (21.4 mg).

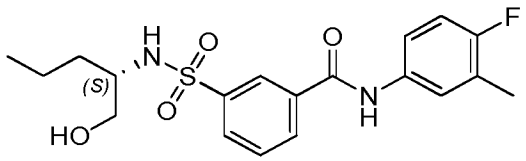
Synthesis of 3-[(4-fluoro-3-methyl-phenyl)carbamoyl]benzenesulfonyl chloride:
3-(chlorosulfonyl)benzoyl chloride (32.4 g, 135.6 mmol) was dissolved in dry toluene (250 mL) in a 1L multi neck flask. The mixture was stirred with an overhead stirrer (240 rpm) and brought to a gentle reflux under a nitrogen flow. 4-fluoro-3-methyl-aniline (15.4 g, 123.3 mmol) dissolved in dry toluene (100 mL) was added drop wise via a syringe pump at a flow of 2 mL/min. After complete addition the reaction was heated for another 30 minutes and then slowly cooled to room temperature. After over night stirring at 60 rpm the reaction mixture was cooled with an ice bath and diisopropylether (100 mL) was added. The precipitate was filtered off, triturated with diisopropylether and dried in a vacuum oven, resulting in a solid (30.9 g) The solid was recrystallized from toluene (200 mL) resulting in 3-[(4-fluoro-3-methyl-phenyl)carbamoyl]benzenesulfonyl chloride (22.9 g).

Compound **11**



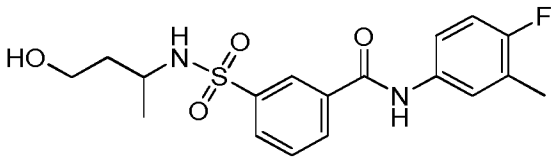
Synthesis following procedure S1 with (*S*)-(+)-2-amino-3-methyl-1-butanol as amine, workup W1. Method G; Rt: 1.66 min. m/z: 395.0 $(M+H)^+$ Exact mass: 394.1. ^{1}H NMR (400 MHz, DMSO-d_6) ppm 0.73 (d, J=6.8 Hz, 3 H), 0.76 (d, J=6.8 Hz, 3 H), 1.77 - 1.91 (m, 1 H), 2.25 (d, J=1.8 Hz, 3 H), 2.93 - 3.06 (m, 1 H), 3.10 - 3.26 (m, 2 H), 4.49 (t, J=5.4 Hz, 1 H), 7.14 (t, J=9.2 Hz, 1 H), 7.49 (d, J=8.6 Hz, 1 H), 7.56 - 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), 7.97 - 8.03 (m, 1 H), 8.13 - 8.20 (m, 1 H), 8.37 (t, J=1.7 Hz, 1 H), 10.44 (s, 1 H)

Compound **12**



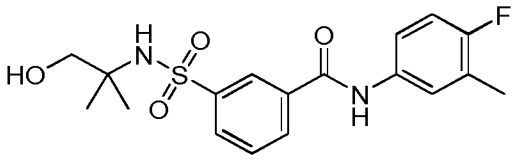
Synthesis following procedure S1 with (S)-(+)-2-amino-1-pentanol as amine, workup W1. Method F; Rt: 0.94 min. m/z: 412.2 $(M+NH_4)^+$ Exact mass: 394.1.

Compound **13**

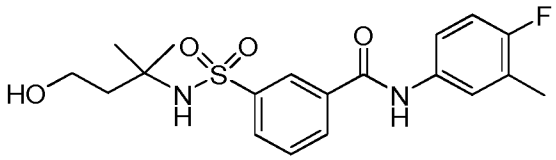


Synthesis following procedure S1 with 3-amino-3-methylpropan-1-ol as amine, workup W2. Method F; Rt: 0.85 min. m/z: 381.1 $(M+H)^+$ Exact mass: 380.1.

Compound **14**



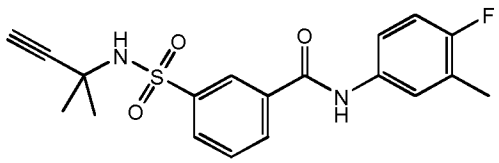
Synthesis following procedure S1 with 2-amino-2-methyl-1-propanol as amine, workup W1. Method F; Rt: 0.88 min. m/z: 398.1 $(M+NH_4)^+$ Exact mass: 380.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.03 (s, 6 H), 2.25 (d, J=1.8 Hz, 3 H), 3.21 (d, J=5.7 Hz, 2 H), 4.77 (t, J=5.8 Hz, 1 H), 7.14 (t, J=9.2 Hz, 1 H), 7.46 (s, 1 H), 7.56 - 7.63 (m, 1 H), 7.68 (dd, J=7.2, 2.3 Hz, 1 H), 7.73 (t, J=7.8 Hz, 1 H), 8.00 - 8.06 (m, 1 H), 8.16 (dt, J=7.8, 1.3 Hz, 1 H), 8.39 (t, J=1.7 Hz, 1 H), 10.44 (s, 1 H)



Compound **15**

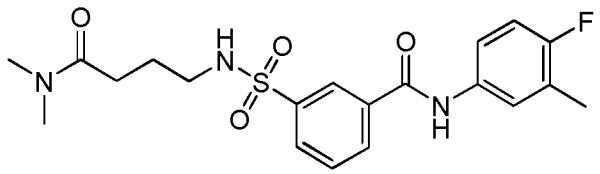
Synthesis following procedure S2 with 3-amino-3-methyl-1-butanol as amine, workup W3. Method F; Rt: 0.90 min. m/z: 412.2 $(M+NH_4)^+$ Exact mass: 394.1.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.28 (s, 6 H), 1.75 (t, J=5.8 Hz, 2 H), 2.07 (t, J=4.5 Hz, 1 H), 2.30 (d, J=1.8 Hz, 3 H), 3.85 (td, *J*=5.8, 4.5 Hz, 2 H), 6.10 (s, 1 H), 7.01 (t, J=8.9 Hz, 1 H), 7.37-7.44 (m, 1 H), 7.53 (dd, J=6.5, 2.5 Hz, 1 H), 7.61 (t, J=7.8 Hz, 1 H), 7.99 - 8.12 (m, 2 H), 8.15 (s, 1 H), 8.37 (t, J=1.7 Hz, 1 H)



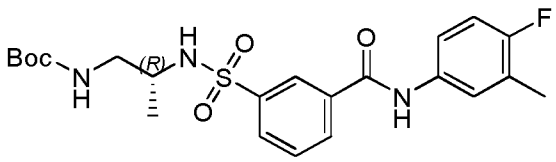
Compound **16**

Synthesis following procedure S4 with 3-amino-3-methyl-1-butyne as amine, workup W4. Method F; Rt: 1.01 min. m/z: 392.3 $(M+NH_4)^+$ Exact mass: 374.1.



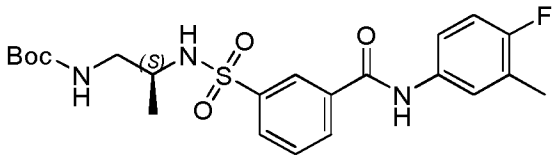
Compound **17**

Synthesis following procedure S2 with 4-amino-N,N-dimethyl-butanamide hydrochloride as amine, workup W3. Method F; Rt: 0.87 min. m/z: 422.2 $(M+H)^+$ Exact mass: 421.2. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.74-1.82 (m, 2 H) 2.29 (d, *J*=2.0 Hz, 3 H) 2.31 - 2.37 (m, 2 H) 2.85 (s, 3 H) 2.94 (s, 3 H) 3.04-3.10 (m, 2 H) 5.70 (t, *J*=5.5 Hz, 1 H) 6.99 (t, *J*=9.0 Hz, 1 H) 7.43 - 7.50 (m, 1 H) 7.58 (dd, *J*=6.7, 2.5 Hz, 1 H) 7.63 (t, *J*= 7.8 Hz, 1 H) 8.02 (ddd, *J*=7.8, 1.8, 1.5 Hz, 1 H) 8.17 (ddd, *J*=7.9, 1.8, 1.5 Hz, 1 H) 8.37 (t, *J*=1.8 Hz, 1 H) 8.80 (bs, 1 H)



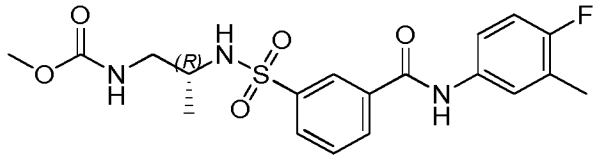
Compound **18**

Synthesis following procedure S4 (reaction time: 20 hours instead of 3 hours) with N-[(2*R*)-2-aminopropyl]-carbamic acid 1,1-dimethylethyl ester hydrochloride as amine, workup W4. Method F; Rt: 1.06 min. m/z: 466.2 $(M+H)^+$ Exact mass: 465.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.86 (d, J=6.6 Hz, 3 H), 1.34 (s, 9 H), 2.26 (d, J=1.8 Hz, 3 H), 2.71 - 3.02 (m, 2 H), 3.17 - 3.33 (m, 1 H), 6.30 - 6.93 (m, 1 H), 7.14 (t, J=9.1 Hzj 1 H), 7.57 - 7.65 (m, 1 H), 7.66 - 7.74 (m, 2 H), 7.76 (t, J=7.7 Hz, 1 H), 7.98 - 8.08 (m, 1 H), 8.16 - 8.27 (m, 1 H), 8.39 (s, 1 H), 10.46 (s, 1 H).



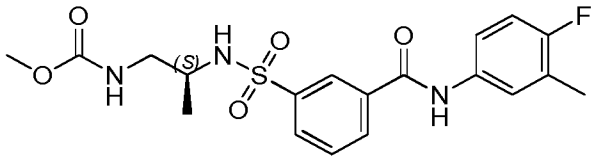
Compound **19**

Synthesis following procedure S4 (reaction time: 20 hours instead of 3 hours) with N-[(2*S*)-2-aminopropyl]-carbamic acid 1,1-dimethylethyl ester hydrochloride as amine, workup W4. Method F; Rt: 1.06 min. m/z: 466.2 $(M+H)^+$ Exact mass: 465.2



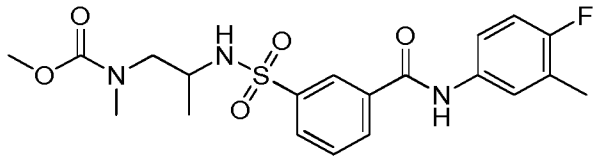
Compound **1a**

Compound **18** (203 mg) was dissolved in dichloromethane (5 mL) and then HCl (6 M in iPrOH) (726 µL) was added. The mixture was stirred at room temperature for 5 hours and next concentrated under reduced pressure. The obtained oil was dissolved in dichloromethane (5 mL). Diisopropylethylamine (309 µL, 1.79 mmol) was added followed methyl chloroformate (52 µL, 0.67 mmol). The resulting mixture was stirred for 1 hour and next injected as such on a silica plug and purified using flash chromatography (gradient elution: EtOAc-heptane 0:100 to 100:0). The fractions were concentrated under reduced pressure and the obtained residue was dried in vacuo at 55°C for 20 hours resulting in compound **1a** as a white powder. Method F; Rt: 0.89 min. m/z: 441.3 $(M+NH_4)^+$ Exact mass: 423.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.84 - 0.89 (m, 3 H), 2.25 (d, J=1.8 Hz, 3 H), 2.78 - 2.99 (m, 2 H), 3.19 - 3.29 (m, 1 H), 3.44 (s, 3 H), 7.02 (t, J=5.8 Hz, 1 H), 7.14 (t, J=9.1 Hz, 1 H), 7.55 - 7.63 (m, 1 H), 7.68 (dd, J=6.8, 2.4 Hz, 1 H), 7.71 - 7.82 (m, 2 H), 7.92 - 8.08 (m, 1 H), 8.15-8.23 (m, 1 H), 8.36 (t, J=1.7 Hz, 1 H), 10.45 (s, 1 H).



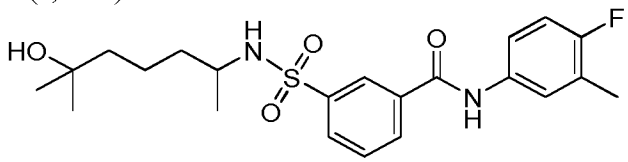
Compound **1b**

Compound **1b** was prepared similarly as described for **1a**, starting from compound **19** instead of compound **18**. Method F; Rt: 0.89 min. m/z: 424.1 $(M+H)^+$ Exact mass: 423.1.



Compound **20**

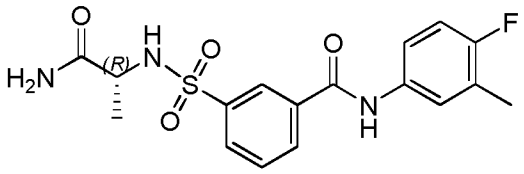
Diisopropylethylamine (92 µL, 0.54 mmol) was added to a solution of compound **2** (52 mg) in dichloromethane (5 mL), followed by methyl chloroformate (15.5 µL, 0.2 mmol).The resulting mixture was stirred for 1 hour. Workup W4. Method F; Rt: 0.95 min. m/z: 455.1 $(M+NH_4)^+$ Exact mass: 437.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.76 - 1.05 (m, 3 H), 2.17 - 2.31 (m, 3 H), 2.61 - 2.79 (m, 3 H), 2.95 - 3.21 (m, 2 H), 3.40-3.55 (m, 4 H), 7.14 (t, J=9.1 Hz, 1 H), 7.56 - 7.64 (m, 1 H), 7.68 (dd, J=6.9, 2.3 Hz, 1 H), 7.71 - 7.91 (m, 2 H), 7.93 - 8.01 (m, 1 H), 8.14 - 8.24 (m, 1 H), 8.34 (t, J=1.5 Hz, 1 H), 10.45 (s, 1 H).



Compound **21**

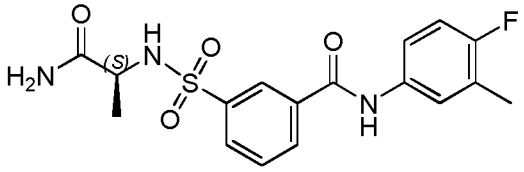
Synthesis following procedure S4 with 6-amino-2-methyl-2-heptanol as amine, workup W4. Method F; Rt: 0.99 min. m/z: 454.2 $(M+NH_4)^+$ Exact mass: 436.2.

The racemic compound **21** was separated in enantiomers **21a** and **21b** by preparative SFC (Stationary phase: Chiralpak Diacel AD 30 x 250 mm), Mobile phase: CO_2, MeOH with 0.4% $iPrNH_2$) , SFC: Column: AD-H 250 mm x 4.6 mm, Flow: 5 mL/min, Mobile phase: 25 % EtOH (containing 0.2% $iPrNH_2$) hold 4 min, increased to 50 % in 1 min, hold 2 min at 50%, Temperature: 40°C Rt: **21a** (1.9 min; (Method G; Rt: 1.76 min. m/z: 437.1 $(M+H)^+$ Exact mass: 436.2)); **21b** (2.6 min; (Method G; Rt: 1.76 min. m/z: 437.0 $(M+H)^+$ Exact mass: 436.2)). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.90 (d, J=6.6 Hz, 3 H), 0.97 (s, 6 H), 1.04 - 1.31 (m, 6 H), 2.25 (d, J=1.8 Hz, 3 H), 3.13 - 3.24 (m, 1 H), 3.98 (s, 1 H), 7.14 (t, J=9.2 Hz, 1 H), 7.55 - 7.63 (m, 1 H), 7.63-7.69 (m, 2 H), 7.75 (t, J=7.8 Hz, 1 H), 7.96 - 8.03 (m, 1 H), 8.19 (dt, J=7.9, 1.2 Hz, 1 H), 8.37 (t, J=1.7 Hz, 1 H), 10.45 (s, 1 H)



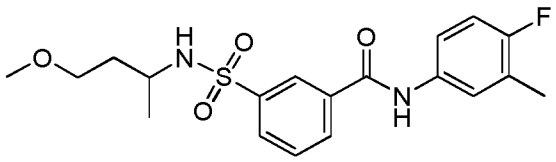
Compound **22**

Synthesis following procedure S4 with (2*R*)-2-aminopropanamide as amine, workup W1. Method F; Rt: 0.77 min. m/z: 397.2 $(M+NH_4)^+$ Exact mass: 379.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.08 (d, J=7.0 Hz, 3 H), 2.25 (d, J=1.8 Hz, 3 H), 3.75 (q, J=7.0 Hz, 1 H), 6.97 (br. s., 1 H), 7.14 (t, J=9.1 Hz, 1 H), 7.26 (br. s., 1 H), 7.55 - 7.64 (m, 1 H), 7.68 (dd, J=7.0, 2.4 Hz, 1 H), 7.73 (t, J=7.8 Hz, 1 H), 7.96 - 8.01 (m, 1 H), 8.05 (br. s., 1 H), 8.17 (dt, J=8.0, 1.2 Hz, 1 H), 8.36 (t, J=1.7 Hz, 1 H), 10.42 (s, 1 H).



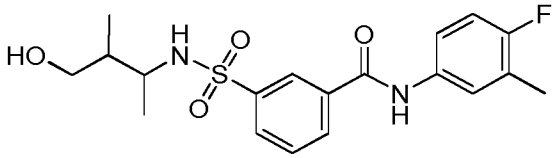
Compound **23**

Synthesis following procedure S4 with (2*S*)-2-aminopropanamide as amine, workup W1. Method F; Rt: 0.78 min. m/z: 397.1 $(M+NH_4)^+$ Exact mass: 379.1.



Compound **24**

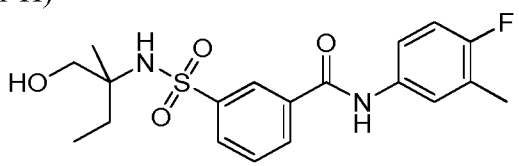
Synthesis following procedure S4 with 4-methoxy-2-butanamine as amine, workup W4. Method F; Rt: 0.98 min. m/z: 412.2 $(M+NH_4)^+$ Exact mass: 394.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.92 (d, J=6.6 Hz, 3 H), 1.43 - 1.61 (m, 2 H), 2.25 (d, J=1.8 Hz, 3 H), 3.05 (s, 3 H), 3.10 - 3.24 (m, 2 H), 3.24 - 3.31 (m, 1 H), 7.14 (t, J=9.2 Hz, 1 H), 7.54 - 7.64 (m, 1 H), 7.64 - 7.73 (m, 2 H), 7.76 (t, J=7.8 Hz, 1 H), 7.96 - 8.03 (m, 1 H), 8.20 (dt, J=7.9, 1.3 Hz, 1 H), 8.36 (t, J=1.7 Hz, 1 H), 10.47 (s, 1 H)



Compound **25**

Synthesis following procedure S4 with 3-amino-2-methyl-1-butanol as amine, workup W4. Method F; Rt: 0.89 min. m/z: 412.2 $(M+NH_4)^+$ Exact mass: 394.1

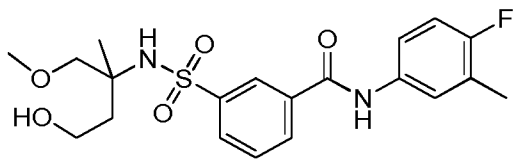
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.68 - 0.87 (m, 6 H), 1.54 - 1.68 (m, 1 H), 2.25 (d, J=1.8 Hz, 3 H), 3.09 - 3.30 (m, 2 H), 3.30-3.40 (m, 1 H), 4.26 - 4.55 (m, 1 H), 7.14 (t, J=9.2 Hz, 1 H), 7.44 - 7.65 (m, 1 H), 7.56 - 7.63 (m, 1 H), 7.68 (dd, J=7.2, 2.5 Hz, 1 H), 7.75 (t, J=7.8 Hz, 1 H), 7.97 - 8.04 (m, 1 H), 8.19 (d, J=7.7 Hz, 1 H), 8.36 (t, J=1.5 Hz, 1 H), 10.46 (br. s., 1 H)



Compound **26**

Synthesis following procedure S4 with 2-amino-2-methyl-1-butanol as amine, workup W4. Method F; Rt: 0.92 min. m/z: 412.2 $(M+NH_4)^+$ Exact mass: 394.1.

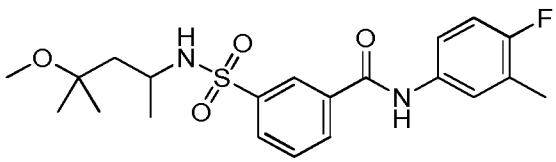
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.71 (t, J=7.4 Hz, 3 H), 0.98 (s, 3 H), 1.47 (q, J=7.3 Hz, 2 H), 2.25 (d, J=1.5 Hz, 3 H), 3.19 - 3.27 (m, 2 H), 4.66 (t, J=5.5 Hz, 1 H), 7.14 (t, J=9.1 Hz, 1 H), 7.34 (s, 1 H), 7.55 - 7.62 (m, 1 H), 7.68 (dd, J=7.2, 2.3 Hz, 1 H), 7.72 (t, J=7.8 Hz, 1 H), 8.00 - 8.06 (m, 1 H), 8.12 - 8.18 (m, 1 H), 8.38 (t, J=1.7 Hz, 1 H), 10.44 (s, 1 H)



Compound **27**

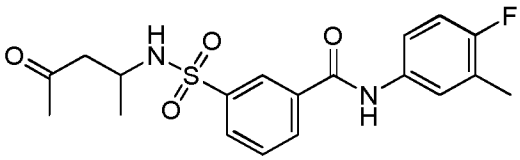
Synthesis following procedure S4 with 3-amino-4-methoxy-3-methyl-1-butanol as amine, workup W4. Method F; Rt: 0.89 min. m/z: 425.2 $(M+H)^+$ Exact mass: 424.2.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.07 (s, 3 H), 1.58 - 1.79 (m, 2 H), 2.25 (d, J=1.5 Hz, 3 H), 2.99 (s, 3 H), 3.12 - 3.19 (m, 2 H), 3.40 - 3.49 (m, 2 H), 4.42 (t, J=4.6 Hz, 1 H), 7.14 (t, J=9.1 Hz, 1 H), 7.53 - 7.63 (m, 2 H), 7.68 (dd, J=7.0, 2.4 Hz, 1 H), 7.72 (t, J=7.8 Hz, 1 H), 7.99 - 8.05 (m, 1 H), 8.13 - 8.19 (m, 1 H), 8.38 (t, J=1.7 Hz, 1 H), 10.44 (s, 1 H)



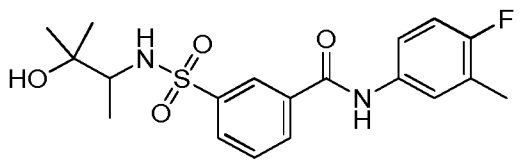
Compound **28**

Synthesis following procedure S4 with 4-methoxy-4-methyl-2-pentanamine as amine, workup W4. Method F; Rt: 1.09 min. m/z: 423.2 $(M+H)^+$ Exact mass: 422.2.
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.93 (d, J=6.4 Hz, 3 H), 0.96 (s, 3 H), 1.01 (s, 3 H), 1.44 - 1.58 (m, 2 H), 2.25 (d, J=1.8 Hz, 3 H), 2.98 (s, 3 H), 3.32 - 3.41 (m, 1 H), 7.14 (t, J=9.2 Hz, 1 H), 7.53 - 7.64 (m, 2 H), 7.68 (dd, J=7.0, 2.4 Hz, 1 H), 7.76 (t, J=7.8 Hz, 1 H), 7.97 - 8.03 (m, 1 H), 8.20 (dt, J=7.9, 1.3 Hz, 1 H), 8.34 - 8.39 (m, 1 H), 10.47 (s, 1 H)



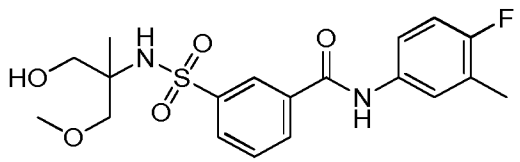
Compound **29**

Synthesis following procedure S4 with 4-aminopentan-2-one hydrochloride as amine, workup W4. Method F; Rt: 0.92 min. m/z: 410.2 $(M+NH_4)^+$ Exact mass: 392.1.
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.89 (d, J=6.6 Hz, 3 H), 2.01 (s, 3 H), 2.25 (d, J=1.8 Hz, 3 H), 2.52 (d, J=7.7 Hz, 2 H), 3.53 - 3.66 (m, 1 H), 7.14 (t, J=9.2 Hz, 1 H), 7.55 - 7.65 (m, 1 H), 7.68 (dd, J=7.2, 2.3 Hz, 1 H), 7.76 (t, J=7.8 Hz, 1 H), 7.82 (d, J=5.9 Hz, 1 H), 7.95 - 8.01 (m, 1 H), 8.20 (dt, J=8.0, 1.2 Hz, 1 H), 8.35 (t, J=1.7 Hz, 1 H), 10.46 (s, 1 H)



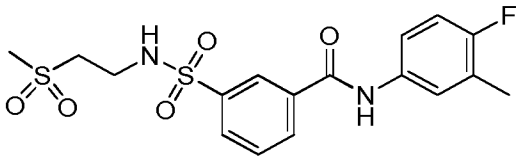
Compound **30**

Synthesis following procedure S4 with 3-amino-2-methyl-2-butanol as amine, workup W4. Method F; Rt: 0.90 min. m/z: 412.2 $(M+NH_4)^+$ Exact mass: 394.1.
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.76 (d, J=6.6 Hz, 3 H), 0.99 (s, 3 H), 1.06 (s, 3 H), 2.26 (d, J=1.8 Hz, 3 H), 3.00-3.12 (m, 1 H), 4.29 (s, 1 H), 7.14 (t, J=9.1 Hz, 1 H), 7.45 (br. s., 1 H), 7.56 - 7.65 (m, 1 H), 7.69 (dd, J=7.2, 2.3 Hz, 1 H), 7.76 (t, J=7.8 Hz, 1 H), 7.99 - 8.07 (m, 1 H), 8.19 (dt, J=7.9, 1.2 Hz, 1 H), 8.39 (t, J=1.7 Hz, 1 H), 10.47 (s, 1 H)



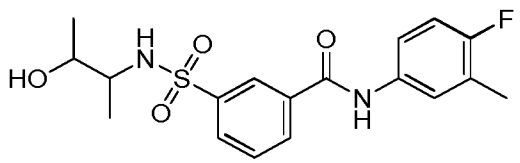
Compound **31**

Synthesis following procedure S4 with 2-amino-3-methoxy-2-methyl-1-propanol as amine, workup W4. Method F; Rt: 0.89 min. m/z: 428.1 $(M+NH_4)^+$ Exact mass: 410.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.02 (s, 3 H), 2.25 (d, J=1.8 Hz, 3 H), 3.01 (s, 3 H), 3.10-3.24 (m, 2 H), 3.24 - 3.30 (m, 1 H), 3.33 - 3.39 (m, 1 H), 4.73 (t, J=5.7 Hz, 1 H), 7.14 (t, J=9.1 Hz, 1 H), 7.42 (s, 1 H), 7.54 - 7.63 (m, 1 H), 7.64 - 7.69 (m, 1 H), 7.72 (t, J=7.9 Hz, 1 H), 8.02 - 8.07 (m, 1 H), 8.15 (dt, J=8.1, 1.2 Hz, 1 H), 8.39 (t, J=1.7 Hz, 1 H), 10.43 (s, 1 H)



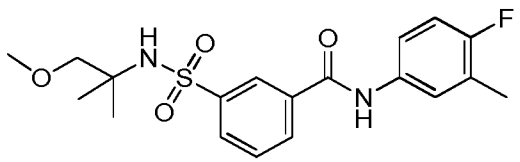
Compound **32**

Synthesis following procedure S4 with 2-amino ethylmethylsulfone hydrochloride as amine, workup W4. Method F; Rt: 0.83min. m/z: 415.3 $(M+H)^+$ Exact mass: 414.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.25 (d, J=1.8 Hz, 3 H), 3.01 (s, 3 H), 3.15 - 3.22 (m, 2 H), 3.24 - 3.29 (m, 2 H), 7.14 (t, J=9.1 Hz, 1 H), 7.55 - 7.64 (m, 1 H), 7.67 (dd, J=7.0, 2.2 Hz, 1 H), 7.79 (t, J=7.8 Hz, 1 H), 7.99 - 8.04 (m, 1 H), 8.09 (br. s., 1 H), 8.23 (dt, J=8.1, 1.2 Hz, 1 H), 8.36 (t, J=1.7 Hz, 1 H), 10.48 (s, 1 H)



Compound **33**

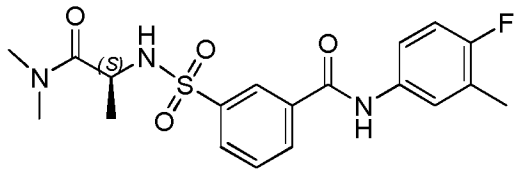
Synthesis following procedure S4 with 3-aminobutan-2-ol as amine, workup W4. Method F; Rt: 0.86 min. m/z: 398.2 $(M+NH_4)^+$ Exact mass: 380.1.
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.77 - 0.86 (m, 3 H), 0.90 - 0.99 (m, 3 H), 2.25 (d, J=1.8 Hz, 3 H), 2.96 - 3.20 (m, 1 H), 3.37 - 3.61 (m, 1 H), 4.54 - 4.65 (m, 1 H), 7.14 (t, J=9.2 Hz, 1 H), 7.50 - 7.64 (m, 2 H), 7.68 (dd, J=7.0, 2.2 Hz, 1 H), 7.72 - 7.79 (m, 1 H), 7.99 - 8.06 (m, 1 H), 8.19 (dt, J=7.9, 1.2 Hz, 1 H), 8.35 - 8.41 (m, 1 H), 10.46 (br. s., 1 H)



Compound **34**

Synthesis following procedure S4 with 1-methoxy-2-methyl-2-propanamine

as amine, workup W4. Method F; Rt: 1.02 min. m/z: 412.2 $(M+NH_4)^+$ Exact mass: 394.1.^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.08 (s, 6 H), 2.25 (d, J=1.8 Hz, 3 H), 3.05 (s, 3 H), 3.13 (s, 2 H), 7.14 (t, J=9.2 Hz, 1 H), 7.55 - 7.63 (m, 1 H), 7.63 - 7.70 (m, 2 H), 7.73 (t, J=7.8 Hz, 1 H), 8.00 - 8.06 (m, 1 H), 8.13 - 8.19 (m, 1 H), 8.39 (t, J=1.7 Hz, 1 H), 10.44 (s, 1 H)

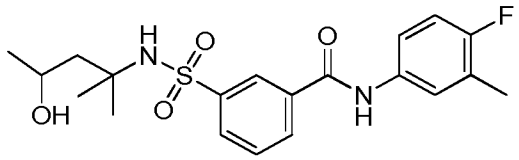


Compound **35**

To a solution of L-alanine (130.5 mg, 1.46 mmol) in NaOH (1M in H_2O) (1.53 mL, 1.53 mmol) at 0°C, acetone (11.5 mL, 156.1 mmol) was added, followed by 3-[(4-fluoro-3-methyl-phenyl)carbamoyl]benzenesulfonyl chloride (500 mg, 1.53 mmol) and DIPEA (788.65 µl, 4.58 mmol). The mixture was stirred for 30 minutes at room temperature. The resulting mixture was washed with diethylether (3 x 10 mL) and the combined organic washings were extracted with NaOH (1M / 2 x 10 mL). The combined basic aqueous layers were acidified to pH 1 using concentrated hydrochloric acid. A precipitation was formed. The mixture was extracted with ethyl acetate (3 x 25 mL). The combined extracts were washed with brine, dried on $MgSO_4$, filtered and concentrated under reduced pressure. (2*S*)-2-[[3-[(4-fluoro-3-methyl-phenyl)carbamoyl]phenyl]sulfonylamino]propanoic acid (0.577 g) was obtained as a slightly pink powder and was used as such. Method G; Rt: 1.16 min. m/z: 381.0 $(M+H)^+$ Exact mass: 380.1.

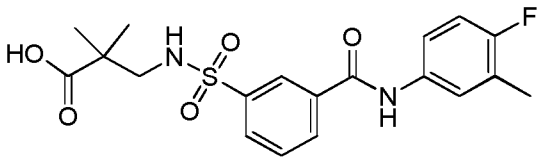
(2*S*)-2-[[3-[(4-fluoro-3-methyl-phenyl)carbamoyl]phenyl]sulfonylamino]propanoic acid (0.2 g, 0.49 mmol), HATU (0.21 g, 0.54 mmol), DIPEA (0.26 mL, 1.48 mmol) and dichloromethane (10 mL) were stirred in a closed vessel at room temperature. 3 drops of dimethylamine were added and the vessel was closed. The mixture was stirred at room temperature for 2 hours. An extra equivalent of HATU, 2 extra equivalents of DIPEA, and 3 drops of dimethylamine were added and the mixture was stirred for another 2 hours. Then the mixture was heated to 50°C and stirred for 2 hours. The mixture was concentrated to dryness under reduced pressure and purified by Prep HPLC on (RP SunFire Prep C18 OBD-10µm, 30x150mm). Mobile phase (0.25% NH_4HCO_3 solution in water, acetonitrile). The desired fractions were concentrated under reduced pressure, co-evaporated with methanol (2 x 10 mL) and dried in vacuo, resulting in compound **35** (40 mg) as a white powder. Method F; Rt: 0.88 min. m/z: 425.2 $(M+NH_4)^+$ Exact mass: 407.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.07 (d,

J=6.8 Hz, 3 H), 2.25 (d, J=1.8 Hz, 3 H), 2.57 (s, 3 H), 2.94 (s, 3 H), 4.31 - 4.40 (m, 1 H), 7.15 (t, J=9.2 Hz, 1 H), 7.57 - 7.64 (m, 1 H), 7.65 - 7.70 (m, 1 H), 7.72 (t, J=7.8 Hz, 1 H), 7.90 - 8.00 (m, 1 H), 8.07 (br. s., 1 H), 8.12 - 8.21 (m, 1 H), 8.31 (t, J=1.7 Hz, 1 H), 10.43 (s, 1 H)



Compound **36**

Synthesis following procedure S4 (20 hours instead of 3 hours reaction time) with 4-amino-4-methyl-2-pentanol as amine, workup W4. Method F; Rt: 0.99 min. m/z: 426.2 $(M+NH_4)^+$ Exact mass: 408.2. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 0.99 - 1.07 (m, 3 H), 1.13 (s, 3 H), 1.15 - 1.22 (m, 3 H), 1.43 - 1.58 (m, 2 H), 2.20 - 2.31 (m, 3 H), 3.75-3.95 (br. s., 1 H), 4.73 (d, J=4.2 Hz, 1 H), 7.14 (t, J=9.1 Hz, 1 H), 7.55 - 7.66 (m, 2 H), 7.70 (dd, J=7.2, 2.3 Hz, 1 H), 7.74 (t, J=7.8 Hz, 1 H), 7.95 - 8.09 (m, 1 H), 8.15 - 8.23 (m, 1 H), 8.39 (t, J=1.7 Hz, 1 H), 10.46 (s, 1 H)



Compound **37**

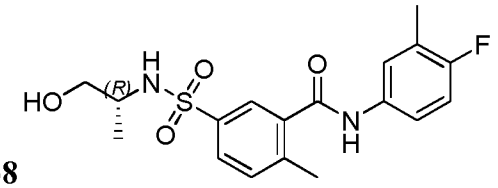
Synthesis following procedure S4 (reaction time: 20 hours instead of 3 hours) with 3-amino-2,2-dimethyl-propanoic acid as amine, workup W4. Method F; Rt: 0.70 min. m/z: 426.2 $(M+NH_4)^+$ Exact mass: 408.1. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.07 (s, 6 H), 2.27 (d, J=1.0 Hz, 3 H), 2.80 (s, 2 H), 2.97 - 3.54 (br. s, 2 H), 7.13 (t, J=9.2 Hz, 1 H), 7.55-7.65 (m, 1 H), 7.67 - 7.83 (m, 2 H), 7.99 (m, J=8.1 Hz, 1 H), 8.17 (m, J=7.9 Hz, 1 H), 8.37 (s, 1 H), 10.67 (br. s., 1 H).

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

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.

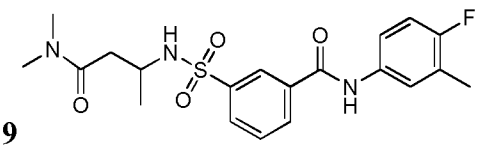
The resulting mixture was stirred for one hour at room temperature. The mixture was concentrated in vacuo and co-evaporated twice using toluene (2 x 100 mL) yielding 5-chlorosulfonyl-2-methyl-benzoyl chloride as a yellow oil which was used as such. 5-chlorosulfonyl-2-methyl-benzoyl chloride (10.7 g, 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 **38**

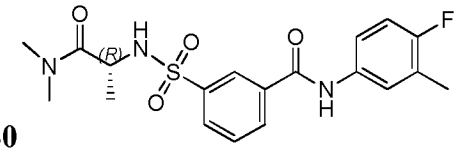
A solution of D-alaninol (0.33 g, 4.39 mmol) and diisopropylethylamine (1.26 mL, 7.31 mmol) in dichloromethane (10 mL) was added to a solution of 3-[(4-fluoro-3-methyl-phenyl)carbamoyl]-4-methyl-benzenesulfonyl chloride (1 g, 2.93 mmol) in dichloromethane (10 mL). The resulting mixture was stirred for 1 hour at room temperature. The mixture was quenched using HCl (aq, 14.6 mL, 14.6 mmol). A precipitation was formed between the two layers. This precipitation was collected on a glass filter and recrystallised from Diisopropylether/acetonitrile. The crystals were collected and dried in a vacuum oven at 55°C for 24 hours yielding compound **38** (643 mg) as bright white crystals. Method F; Rt: 0.85 min. m/z: 398.2 $(M+NH_4)^+$ Exact mass: 380.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.92 (d, J=6.2 Hz, 3 H), 2.24 (d, J=1.5 Hz, 3 H), 2.44 (s, 3 H), 3.05-3.18 (m, 2 H), 3.25 - 3.38 (m, 1 H), 4.60 - 4.78 (m, 1 H), 7.13 (t, J=9.2 Hz, 1 H), 7.45 - 7.61 (m, 3 H), 7.60-7.70 (m, 1 H), 7.77 - 7.86 (m, 2 H), 10.44 (s, 1 H)



Compound **39**

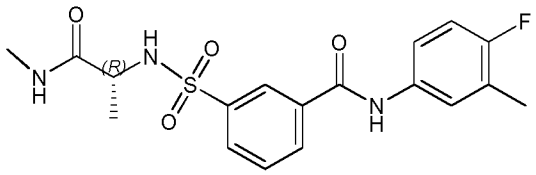
Compound **39** was prepared similarly as described for compound **6**, using 3-amino-N,N-dimethyl-butanamide hydrochloride instead of the TFA salt of 4-amino-N,N-dimethyl-pentanamide. Method E; Rt: 4.81 min. m/z: 422.1 $(M+H)^+$ Exact mass: 421.1.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.96 (d, J=6.5 Hz, 3 H) 2.25 (d, J=1.5 Hz, 3 H) 2.33 (dd, J=15.8, 8.0 Hz, 1 H) 2.44 (dd, J=15.8, 5.0Hz, 1 H) 2.71 (s, 3 H) 2.86 (s, 3 H) 3.50 - 3.65 (m, 1 H) 7.15 (t, J=9.2 Hz, 1 H) 7.55 - 7.64 (m, 1 H) 7.68 (m, J=6.8 Hz, 1 H) 7.76 (t, J=7.8 Hz, 1 H) 7.84 (d, J=7.8 Hz, 1 H) 7.95 - 8.02 (m, 1 H) 8.16 - 8.21 (m, 1 H) 8.34 (t, J=1.5 Hz, 1 H) 10.49 (s, 1 H).



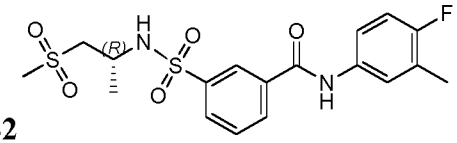
Compound **40**

Compound **40** was prepared similarly as described for compound **35** using, D-alanine instead of L-alanine and 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide instead of HATU. Method F; Rt: 0.90 min. m/z: 406.1 $(M-H)^-$ Exact mass: 407.1.



Compound **41**

Compound **41** was prepared similarly as compound **40**, using methylamine (2M in THF) instead of dimethylamine. Method F; Rt: 0.83 min. m/z: 392.2 $(M-H)^-$ Exact mass: 393.1.



Compound **42**

NaSMe (0.213 g , 3.04 mmol) was added to a stirring solution of [(2*R*)-2-[[3-[(4-fluoro-3-methyl-phenyl)carbamoyl]phenyl]sulfonylamino]propyl] methanesulfonate (0.9 g, 0.00203 mol) in DMF (25 mL). The reaction mixture was stirred at 65°C under N_2-atm for 1 h 30 minutes. The reaction mixture was allowed to reach room temperature, and poured into H_2O (125 mL). The product was extracted with EtOAc. The separated organic layer was dried with Na_2SO_4, filtered off, evaporated, and co-evaporated with toluene, resulting in crude N-(4-fluoro-3-methyl-phenyl)-3-[[(1R)-1-methyl-2-methylsulfanyl-ethyl]sulfamoyl]benzamide (0.76 g). m-CPBA (0.66 g) was added to a stirring solution of crude N-(4-fluoro-3-methyl-phenyl)-3-[[(1R)-1-methyl-2-methylsulfanyl-ethyl]sulfamoyl]benzamide (0.76 g) in CH_2Cl_2 (15 mL). The reaction mixture was stirred at room temperature for 3 hours. More mCPBA (0.125 g) was

added, and the reaction was continued at room temperature for 4 hours. The reaction mixture was quenched with MeOH (15 mL), stirred for 15 minutes, and evaporated. The residue was stirred in CH_2Cl_2 (10 mL) for 15 minutes, then left standing for 1 hour. The solid was filtered and washed with CH_2Cl_2 (3 x). The filtrate was concentrated in vacuo and the obtained residue was purified by silica gel chromatography heptane-EtOAc 100/0 to 0/100. The desired fractions were combined and evaporated. The white solid residue was stirred in CH_2Cl_2 (4 mL), filtered off, washed with CH_2Cl_2 (3 x), and dried at 50°C, resulting in compound **42** (0.218 g). Method G; Rt: 1.60 min. m/z: 427.0 $(M-H)^-$ Exact mass: 428.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.02 (d, J=6.6 Hz, 3 H), 2.25 (d, J=1.5 Hz, 3 H), 2.99 (s, 3 H), 3.17 - 3.28 (m, 2 H), 3.72 - 3.82 (m, 1 H), 7.14 (t, J=9.2 Hz, 1 H), 7.56 - 7.62 (m, 1 H), 7.68 (dd, J=7.2, 2.3 Hz, 1 H), 7.78 (t, J=7.8 Hz, 1 H), 8.01 - 8.05 (m, 1 H), 8.12 (br. s, 1 H), 8.20 - 8.24 (m, 1 H), 8.38 (t, J=1.7 Hz, 1 H), 10.47 (s, 1 H).

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.

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

Compound	HepG2 2.15 EC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
1	0.13	0.37	>25
1a	0.18	0.11	>25
1b	1.85	1.57	>25
2	9.4	2.4	>25
3	7.5	1.1	>25
4	0.28	0.32	>25
4a	0.21	0.26	>25
4b	0.40	0.94	>25
5	0.24	0.84	>25
6	0.18	0.11	>25
7	0.54	0.24	>25
8	1.4	2.8	>25
9	1.3	0.56	>25
10	0.22	0.19	>25
10a	0.10	0.14	>25
10b	0.67	0.68	>25
11	0.55	0.83	>25
12	0.65	0.82	>25
13	0.21	0.71	>25
14	0.38	0.53	>25
15	0.22	0.32	>25

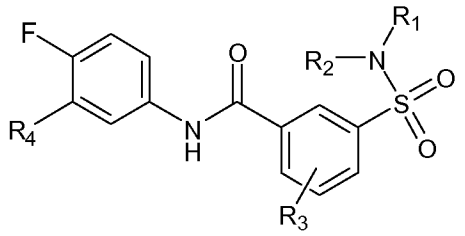
Compound	HepG2 2.15 EC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
16	0.19	0.59	>25
17	0.26	0.61	>25
18	0.20	0.19	>25
19	0.74	0.50	>25
20	0.55	0.56	>25
21	0.17	1.71	>25
21a	0.65	2.36	>25
21b	0.13	0.20	>25
22	0.55	0.50	>25
23	1.10	1.43	>25
24	0.21	1.37	>25
25	0.25	0.57	>25
26	0.39	0.34	>25
27	1.16	0.96	>25
28	0.27	1.41	>25
29	0.19	0.23	>25
30	0.26	0.17	>25
31	0.48	0.47	>25
32	0.19	0.64	>25
33	0.32	0.26	>25
34	0.54	0.64	>25

Compound	HepG2 2.15 EC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
35	2.70	3.62	>25
36	0.27	0.15	>25
37	2.68	3.03	>25
38	0.16	0.18	>25
39	1.05	0.86	>25

Compound	HepG2 2.15 EC50 (μM)	HepG2 117 EC50 (μM)	HepG2 4 days CC50 (μM)
40	2.28	2.66	>25
41	2.22	1.35	>25
42	0.25	0.15	>25

Claims

1. A compound of Formula (I)



(I)

or a stereoisomer or tautomeric form thereof, wherein:

R_1 represents hydrogen;

R_2 represents C_1- C_8alkyl substituted with one or more R_5,

R_3 represents Hydrogen or methyl;

R_4 represents methyl;

Each R_5 is independently selected from the group consisting of -C≡CH, -CN, -OH, oxo, C_1-C_4alkyloxy, -C(=O)O-R_6, -C(=O)N(R_6)$_2$, -N(R_6)$_2$, -NR_9C(=O)-R_6, -NR_9C(=O)O-R_6 and SO_2R_9;

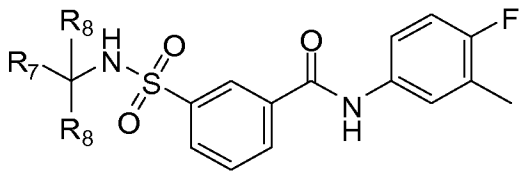
Each R_6 independently represents hydrogen or C_1-C_3alkyl;

R_9 represents hydrogen or C_1-C_3alkyl;

or a pharmaceutically acceptable salt or a solvate thereof.

2. The compound according to claim 1, wherein the C_1-C_8alkyl group as defined in R_2 represents a branched C_2-C_6alkyl.

3. A compound according to claim 1 or 2 of Formula (Ib)



(Ib)

wherein:

R_7 is selected from the group consisting of -C≡CH, -CN, -C(=O)O-R_6 , -C(=O)N(R_6)$_2$ and C_1-C_4alkyl optionally substituted with one or more substituents selected from the group consisting of -C≡CH, -CN, -OH, C_1-C_4alkyloxy, -C(=O)O-R_6, -C(=O)N(R_6)$_2$, -N(R_6)$_2$, -NHC(=O)-R_6 and -NHC(=O)O-R_6;

Each R_6 independently represents hydrogen or C_1-C_3alkyl; and wherein

Each R_8 independently represents hydrogen or C_1-C_2alkyl optionally substituted with OH.

4. A compound according to claim 3, wherein R_7 is selected from the group consisting of C_1-C_4alkyl optionally substituted with -C≡CH, -CN, -OH, C_1-C_4alkyloxy, -C(=O)O-R_6, -C(=O)N(R_6)$_2$, -N(R_6)$_2$, -NHC(=O)-R_6 and -NHC(=O)O-R_6.

5. A compound according to claim 1 or 2, wherein at least one R_5 is –OH.

6. A compound accoding to claim 3 or 4, wherein at least one R_8 is C_1-C_2alkyl substituted with OH.

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

8. A pharmaceutical composition comprising a compound according to any of claims 1 to 6, and a pharmaceutically acceptable carrier.

9. A product containing (a) a compound of Formula (I) as defined in any one of claims 1 to 6, and (b) another HBV inhibitor, as a combined preparation for simultaneous, separate or sequential use in the treatment of HBV infections.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/053858

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C311/16 A61K31/18 A61P31/20
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2013/006394 A1 (INST HEPATITIS AND VIRUS RES [US]; GUO JU-TAO [US]; XU XIAODONG [US];) 10 January 2013 (2013-01-10) cited in the application the whole document -----	1-9

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 May 2014	28/05/2014

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2014/053858

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2013006394 A1	10-01-2013	EP 2726459 A1	07-05-2014
		WO 2013006394 A1	10-01-2013